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Activity description	Practicing evidence-based medicine (EBM) is important in today's health care environment because this model of care offers clinicians a way to enrich quality, provide patient satisfaction, reduce costs and improve outcomes. A common implementation of EBM involves the use of clinical practice algorithms during medical decision-making to encourage optimal care. This widely recognized practice is designed to address the persistent problem of clinical practice variation with the help of actionable information at the point of care. These e-newsletters will enable health care professionals (HCPs) to put new EBM into practice.
Learning objectives	• Discuss primary screening for colorectal cancer and its effectiveness. • Examine pharmacological evidence from the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study including the outcome trials for individuals with type 2 diabetes mellitus (DM). • Apply medical management regarding spinal cord stimulator use in chronic low back pain treatment and/or cancer treatment (in the last month of life).

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Primary screening for colorectal cancer – Important update on effectiveness of colonoscopy

Results from the Nordic-European Initiative on Colorectal Cancer (NordICC) trial recently published in the New England Journal of Medicine revealed a surprisingly modest benefit of being invited for colonoscopy for colorectal cancer (CRC) screening.[1] This large (~84,500 patients) randomized controlled trial compared adults invited for screening colonoscopy versus those not invited on the outcomes of CRC incidence and death from CRC. Using an intention-to-screen analysis, over a 10-year period, the colonoscopy group had an absolute risk reduction of 0.22% and a relative risk reduction of 18% in the incidence of CRC (risk ratio, 0.82; 95% confidence interval [CI], 0.70 to 0.93) compared to the control group. The risk of dying from CRC was not significantly different between the two groups. Since only 42% of those in the colonoscopy-invited group ultimately underwent a screening colonoscopy, additional per-protocol analyses were done looking only at patients who actually underwent colonoscopy. These showed a 0.38% absolute risk reduction (31% relative risk reduction) in CRC and 0.15% absolute risk reduction (50% relative reduction) in death from CRC.

Previous articles, based on evidence from less-robust cohort studies, estimated the benefit of primary colonoscopy screening to prevent CRC at up to 69% and to prevent death from CRC at up to 88%.[2] In light of the results from the NordICC trial, these estimates need to be adjusted downwards by quite a bit. The exact numbers are unclear as there are many caveats to the NordICC trial results as summarized in the editorial in the same issue of the New England Journal.[3] The most obvious caveat is that for colonoscopy to be effective as a CRC screening tool, patients who are invited must actually undergo the procedure for it to have the desired effect. The intention-to-screen analysis revealed only a very modest benefit with regards to developing CRC and no benefit for death from CRC. This can be partially explained by the low rate of screening in the 'invited' group. That said, even the per-protocol analyses of those who ultimately underwent screening showed an unexpectedly low benefit. Another point to consider when weighing the results of this study is the adenoma detection rate (ADR) of the colonoscopists. ADR is considered a surrogate for quality of the procedure, with a minimum threshold of at least 25% considered to be adequate.[4] In the United States, the average ADR is estimated at over 39%.[5] In the NordICC trial, conducted in countries that don't use colonoscopy as much as in the U.S., almost one third of the colonoscopists had an ADR below the 25% threshold for quality.[6] This could reflect overall lower quality colonoscopies that missed potential problematic adenomas and therefore could have attenuated the benefits of screening colonoscopies in this study. In other words, if the ADR was higher (as in the U.S.), there could have been a larger effect observed.

Even with these caveats, these recent findings do call into question the prevailing preference by the medical establishment in the U.S. to recommend primary screening for CRC with colonoscopy. Compared to non-invasive stool-based tests, colonoscopy does carry a risk of significant adverse events. Colonoscopy complication rates are higher in the elderly for GI complications (e.g.; perforation, bleeding) and non-GI complications (e.g.; myocardial infarction, stroke).[7,8]

Patient preference is also important to consider. A pilot study conducted in the U.S. between 2019 and 2020 showed 76% of patients who chose to have CRC screening underwent colonoscopy. This was likely based on the recommendation of their physician. After a shared decision-making intervention provided to 207 patients, those patients chose colonoscopy only 29% of the time, with the majority choosing stool-based methods.[9] Another recent study involving 1,000 patients revealed most (~75%) preferred a stool-based test over colonoscopy for CRC screening.[10] Table 1 shows estimates of some CRC screening methods on reducing CRC and death from CRC. This table does not show all available screening methods nor differences when using multiple screening methods in a given patient (e.g.; sigmoidoscopy every five years plus FIT test in between). A comprehensive review of available CRC screening methods, indications, possible harms and benefits are beyond the scope of this article summary.

These findings reinforce the key messages in a previous edition of this publication.[11] Those key messages are:

- Colonoscopy may not be the most cost-effective primary screening tool for CRC for average risk adults.
- When patient goals and preferences are taken into consideration and shared decision-making is used, stool-based testing is often the screening tool of choice.

Of note, there is good evidence that endoscopist adenoma detection rate (ADR) improves for patients with known positive stool-based screening tests.[12] This supports use of colonoscopy as a secondary test following a positive primary stool-based CRC screening test in average-risk adults. With the new evidence from the NordICC trial, added to previous evidence of patient preference for stool-based tests, involving the patient in shared decision-making is essential, as routinely recommending only colonoscopy for CRC screening is no longer appropriate for many patients.

Table 1. Estimates of some common colorectal cancer (CRC) screening methods on reducing CRC and death from CRC, vs no screening.[13]

Method	Estimated reduction in CRC	Estimated reduction in death from CRC	Notes
Colonoscopy	• Absolute risk reduction of 0.22% • Relative risk reduction of 18%	No difference	Based on NordICC intention-to-screen
Sigmoidoscopy	22%	26%	Based on systematic review[1]
Fecal Immunochemical Test (FIT)	Not reported	10%	Based on systematic review[5]

The GRADE studies – Major new outcome trials for patients with Type 2 DM

As the therapeutic options for patients with Type 2 diabetes (DM2) have expanded, it has become more challenging to determine, for any given level of glycemic control, the balance between prevention of secondary outcomes and the cost of the drug regimen. The yearly cost of glycemic control can vary from a few hundred dollars on an all-generic regimen to over $20,000 when combining multiple branded drugs. The critical question therefore becomes – when do the higher costs of a drug regimen provide a cost-effective benefit in any given patient with respect to cardiovascular and microvascular outcomes? To help answer this question, two important companion studies, known as the GRADE studies, were published.[14,15] The GRADE studies used the same population of over 5,000 patients and examined both the glycemic outcomes, and the CV and microvascular outcomes of four different drug classes added to a background of metformin therapy.

The authors chose insulin glargine, glimepiride (sulfonylurea), liraglutide (GLP-1 RA), and sitagliptin- (DPP-IV inhibitor/gliptin) as the four comparators. Due to safety concerns at the time of randomization in 2013, the SGLT-2i's were unfortunately not included as a study arm. Patients were followed for a median of five years. It is noteworthy that, unlike the CV and renal outcomes trials that have been recently published with the SGLT2i's and GLP-1 RA's, this patient population was not selected based on established CV disease, very high CV risk, or high levels of proteinuria, and therefore is generally representative of the broader population of patients with DM2 seen in most primary care settings.

With respect to glycemic control, overall, the median HbA1c at four years into the study was 7.1% in both the glargine and liraglutide groups, as compared with 7.2% in the sitagliptin group and 7.3% in the glimepiride group. As the primary outcome, the authors looked at the percentage of patients who had an HbA1c >7% during the study. This was highest (worst control) in the sitagliptin group at 77%, next was glimepiride at 72%, with liraglutide and glargine being similar at 68% and 67% respectively. The improved glycemic control of glargine and liraglutide were both statistically significant compared to the other two comparators. However, it is important to note that these differences were small. Particularly in a senior population where guidelines suggest less stringent HbA1c control, these differences will be less significant. Severe hypoglycemia was uncommon in all four groups. It occurred in 2.2% of patients with glimepiride over the five years, 1.3 % with glargine, 1% with liraglutide, and 0.7% with sitagliptin. Weight gain was only seen with glimepiride and glargine but was minor in both groups at 0.73 kg and 0.61 kg over the five years, respectively.

In terms of CV outcomes, at baseline, 96% of patients had dyslipidemia and 77% had hypertension. In the small population of patients unaffected by these two comorbidities at baseline, most developed both conditions by the end of the study. At study entry, 6% had a prior stroke or myocardial infarction.

Major CV events (MACE) occurred in 6-8% of the aggregate population by the end of study, and there were no clinically significant differences between any of the four drug groups.

With respect to microvascular outcomes, there were also no major differences among the four treatment groups in the cumulative incidence of moderately increased or severely increased albuminuria level or other renal outcomes. Similarly, there were no major differences among the groups in the incidence of diabetic peripheral neuropathy.

So where does this leave us with respect to pharmacotherapies for DM2? The omission of the SGLT2i group is unfortunate, however the role of this drug class has been well defined in other trials as reviewed in prior editions of this Forum. In the setting of established CHF with reduced ejection fraction, established CVD, or diabetic nephropathy with significant proteinuria, patients should be treated with SGLT2i's based on established benefits and likely cost effectiveness. Importantly, this should be in lieu of or in addition to metformin. Next, one might question whether there is any role at all for the DPP-IV class. They do not reduce CV or renal outcomes, are not associated with significant weight loss, are not of high potency with respect to glycemic control, and they are expensive at ~$6,000 yearly. Rather than initiating a DPP-IV, patients might be considered instead for an GLP-1 RA, with its significantly greater glycemic-lowering potency, documented benefits in obesity, and reductions in secondary DM2 outcomes including myocardial infarction. Lastly, in an average risk population of patients with DM2, there is not established cost effectiveness for expensive branded agents. A recent cost effectiveness modeling study suggested that the incremental cost per quality-adjusted life-year (QALY) of first line SGLT2i use compared to first line metformin use in an average population of patients with DM2 was $478,000 or close to 5 times the accepted cost-effective threshold of $100,000. The QALY for the injectable GLP1-RA class could not be calculated as there was no overall benefit compared to first line metformin use, and the QALY for the oral GLP-1 RA class was over $1 million.[16] Lastly, a recent cost effectiveness analysis was done looking at the impact of the SGLT-2i's in the patient population of the EMPEROR-Preserved trial. This is the only prospective RCT showing a clinical benefit to the SGLIT-2i class in patients with heart failure with preserved ejection fraction.[17] The cost per QALY using Medicare Part D costs was over $510,000.

Perhaps the best algorithm to help determine when expensive branded agents should be considered is the BMJ meta-analysis[18] that evaluated all of the GLP-1 RA and SGLT2i CV and renal outcomes studies. Based on the CV risk burden and renal risk profile of any given patient with DM2, it makes recommendations for generic regimens, or the above two drug classes, and includes the strength of the recommendation. A formal cost effectiveness analysis was not done as part of the meta-analysis as the studies were conducted across the globe with a wide variation in drug costs from county to country. It was reviewed in the July 2021 edition of this Forum and the algorithm can be accessed at this URL.[18] bmj.com/content/373/bmj.n1091

Spinal cord stimulator use in chronic low back pain

Spinal cord stimulators (SCS's) are neuromodulation devices implanted into the epidural space with the intent of treating chronic pain that has failed conventional management. Long term studies of the outcomes of SCS implantation are lacking – a recent Cochrane review found only one small study of 44 patients that looked at pain relief at greater than one year post implantation.[19] This is problematic since over 50,000 are implanted yearly at a cost of over $3.5 billion. Among 4,000 medical devices tracked by the FDA, SCS's had the third highest rate of device related adverse events.[20]

A recent study published in JAMA Neurology describes work done by our Optum Care Research Institute in collaboration with researchers from UCSF. [21] We used the large Optum Labs Data Warehouse to conduct a "synthetic" RCT of over 1,400 patients with SCS implantation and compared them to over 6,300 patients without SCS implantation that were propensity matched on 65 variables to assure closely matched groups. This design allows for a large well-matched observational study that can approximate the results of a prospective RCT. All patients had at least two years of follow-up. By months 13-24 post implantation, the SCS group showed no reductions in opioid utilization or dosage and had increased utilization of anti-depressants and gabapentinoids. They also had no reductions in epidural steroid injections, radiofrequency ablations, or spine surgeries. Over the two years of the study, there were no reductions in ED or hospital utilization. In the year of SCS implantation, the SCS group had a $33,000 higher cost for Medicare, and a $60,000 higher cost for commercial insurance, which was almost entirely related to the cost of the implant and the surgery. The costs were no different between the two groups for the second year of the study. Over the two years of the study, 18% of patients had significant complications related to the device and 22% of patients needed a second surgery for device removal.

Given that we were unable to demonstrate a clinical benefit to SCS implantation in this large observational study, and given the observed significant complication rate and need for device removal, the routine use of SCS should be questioned. If SCS's use is to continue, a large RCT that includes a sham control limb is needed to assess whether there is any clinical benefit that outweighs the known harms of SCS implantation.

Cancer treatment in the last month of life

The use of chemo and biological therapies at the end of life is problematic. It results in potential negative impacts on both the quality and duration of life, including delays in palliative care and hospice enrollment, and is associated with increased costs of care. The median cost of a course of cancer treatment now is just under $200,000. In 2012, the American Society of Clinical Oncology and the National Quality Forum developed a quality measure that looked at the proportion of patients receiving chemotherapy in the last 14 days of life to promote reduction in chemotherapy and earlier use of palliative care and hospice. [22]

A recent study looked at data in over two million cancer patients treated between 2015 and 2019, to examine the use of chemo and biological therapies in the 30 days and 14 days before death. Despite this new quality metric, there was no reduction in treatment over the four-year study period, with 39% of patients receiving treatment within the last 30 days of life and 17% receiving treatment within the last 14 days of life. As would be expected, the percentage of patients treated with chemotherapy declined while the percentage of patients treated with biological therapies increased.

These data suggest that we need new models of oncology reimbursement which include appropriate quality and utilization metrics to improve the outcomes of our cancer patients at the end of life.

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Kenneth Roy Cohen, MD, FACP

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

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Dr. Hitt is the evidence-based medicine implementation sage and Senior National Medical Director for Optimal Care. He has been a physician executive for more than 25 years in several academic teaching hospitals, national home care companies and Vizient. He received his Medical Doctorate from the Medical College of Georgia (AOA honors), completed his Internal Medicine and Infectious Disease Fellowship at the University of Minnesota Hospital and Clinics and his MBA at the Carlson School of Management at the University of Minnesota. 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.

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.

Joshua Jacobs, MD, FAAFP

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

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Learning objectives	• Discuss migraine diagnosis and treatment in the age of gepants, ditans, and CGRP monoclonal antibodies. • Examine pharmacological evidence of pemafibrate for hypertriglyceridemia/diabetic dyslipidemia, viscosupplementation and stopping RAS inhibitors in advanced chronic kidney disease. • Apply medical management for PSA screening in men over 69, stopping cancer screening based on life expectancy, osteoarthritis of the ankle, and inguinal hernia repair.

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Migraine diagnosis and treatment in the era of gepants, ditans and CGRP monoclonal antibodies

Migraine impacts over 37 million people in the United States.[1] Women are three times more susceptible than men, with an estimated 30% of women affected by migraine over a lifetime. Migraine can lead to substantial disability, interfering with daily activities, school, work and social interactions. The 2019 Global Burden of Diseases, Injuries, and Risk Factors Study ranked headache disorders 14th among global causes of disability (based on disability-adjusted life-years).[2,3] When evaluating years lived with disability, headache disorders ranked third globally, just below low back pain and depressive disorders.[2]

The costs of migraine include the direct medical expenses related to diagnosis and treatment as well as the loss of productivity during migraine attacks. Over the past few years, the FDA has approved several newer migraine medications including CGRP monoclonal antibodies, gepants (CGRP receptor antagonists), and ditans (5-HT1f receptor antagonists). These medications are much more expensive than standard treatments, but are not generally more effective. This article will provide a brief overview of migraine diagnosis and treatment, with a particular focus on the costs, effectiveness, and clinical indications of these newer medications.

Diagnosis

As a primary headache disorder, migraine is a clinical diagnosis. The initial evaluation of the patient with headache should include diagnostic features, potential red flags and the degree of headache-related disability. The International Classification of Headache Disorders-3 diagnostic criteria[4] for migraine without and with aura are listed in Table 1.

Table 1. Summary of the ICHD-3 diagnostic criteria for migraine without and with aura

Migraine without aura	Migraine with aura
A. At least 5 headache attacks fulfilling criteria B–D B. Headaches lasting 4-72 hours C. Headache has ≥2 of the following: • Unilateral location • Pulsating quality • Moderate or severe pain intensity • Aggravation by routine activity D. During headache ≥1 of the following • Nausea and/or vomiting • Photophobia and phonophobia E. Not better accounted for by other ICHD-3 diagnosis	A At least two migraine attacks fulfill criteria B and C B. One or more of the following fully reversible aura symptoms: • Visual • Sensory • Speech and/or language • Motor • Brainstem • Retinal C At least three of the following characteristics: • At least one aura symptom spreads gradually, ≥5 minutes • Two or more aura symptoms occur in succession • Each individual aura symptom lasts 5-60 minute • At least one aura symptom is unilateral • At least one aura symptom is positive • The aura is accompanied, or followed within 60 minutes, by headache

There are validated tools that can help determine migraine-related disability, including the MIDAS and HIT-6. Absent a validated questionnaire, basic elements of disability include migraine frequency, severity and the number of days where activities, school, work and/or social interactions are impaired. In the absence of any red flags, imaging and other laboratory testing are not indicated in the diagnostic evaluation.

Initial treatment

The goal of migraine treatment is to lower the frequency and severity of headaches, reducing related disability. The degree of disability should inform initial treatment. For example, the patient with occasional migraines that are brief in duration and rarely interfere with daily activities may benefit from lifestyle changes (described below) and a trial of over-the-counter analgesics taken at headache onset. In contrast, the patient with more severe migraines that halt activities and occur more frequently may need lifestyle changes, a migraine-specific abortive medicine to treat headaches acutely, as well as a daily medicine to help prevent headaches.

All patients with migraine should consider lifestyle changes as part of their treatment regimen. The American Migraine Foundation describes five key lifestyle changes that may improve migraine outcomes:[5]

- **Sleep:** Recommend and discuss good sleep hygiene. Migraines can interfere with sleep, while poor sleep may serve as a migraine trigger.
- **Exercise:** At least 30-50 minutes of moderate-intensity aerobic activity, several days per week, is recommended to reduce migraine frequency and severity.
- **Eating:** The role of dietary triggers (such as chocolate) for migraine is not clear, but maintaining a balanced, nutritious diet and good daily hydration are important for migraine care. Minimizing daily caffeine intake may also help.
- **Diary:** Keeping a headache diary is an important tool for monitoring headache trends, although research suggests that diary compliance can be challenging.
- **Stress:** Stress can trigger migraine attacks, and managing stress may help improve headache outcome.

Abortive treatment

The abortive treatments for migraine comprise all medication(s) taken acutely at headache onset. These range from simple analgesics to the various migraine-specific prescription drugs such as triptans, ergots, antiemetics, and the newer 5-HT_{1f} inhibitors and CRGP receptor antagonists. When choosing the appropriate abortive medication, consider the following approach:

- Use evidence-based treatments.
- Recommend that medication be used immediately at headache onset (not at aura onset, for those with aura).
- If nausea is present early in the migraine course, choose a non-oral formulation and consider adding an antiemetic.
- When migraines are severe, use a migraine-specific medication. Simple analgesics can be tried for milder migraines.
- When appropriate, advance the medication dose before switching to a new medication.
- Use scheduled dosing strategies where appropriate, such as menstrual-related migraine. Frovatriptan, due to its 26-hour half-life, is preferred for this indication.
- Consider cost. Generic options tend to be as effective as non-generics and much less expensive for the patient.
- Avoid opioids and barbiturates.
- Guard against medication overuse.

Medication-overuse headache is an important cause of chronic headache, that is thought to result from the cumulative rebound effect of abortive medication overuse. The diagnostic criteria include (1) ≥15 headache days per month in a patient with a pre-existing headache disorder, (2) regular overuse of an abortive medication, and (3) the headaches are not better accounted for by another diagnosis.[4] Limiting prescriptions can help to prevent the overuse of medication. For example, a triptan can be prescribed to allow for the treatment of two headache days per week on average, but no more. Patient education and avoidance of opioids and barbiturates can also be helpful.

Triptans are regarded as the standard of care for acute migraine treatment.[6] The triptan class (5-$HT_{1B/1D}$ receptor agonists) includes several medication options, each with various half-lives and routes of administration. Many triptans have low-cost generic versions. Triptans can be combined with simple analgesics to optimize their effects for some patients. The contraindications for triptan use include significant coronary artery disease, a history of stroke, peripheral vascular disease and refractory hypertension.

Lasmiditan (Reyvow®) is the first "ditan" approved by the FDA for the abortive treatment of migraine. In a phase-3 clinical trial, lasmiditan improved headache outcomes significantly better than placebo.[7] The 200 mg lasmiditan dose led to 32.2% of patients reporting headache freedom at two hours compared to 15.3% with placebo. With the 100 mg dose, 28.2% of patients reported headache freedom.[7] In the absence of head-to-head treatment trials, odds ratios have been used to compare the effectiveness of various migraine treatments. In a meta-analysis, the odds ratios for pain freedom and for pain relief at two hours for lasmiditan versus placebo was lower than the odds ratios for most triptans.[8] Consequently, the current indication for lasmiditan remains as a second-line treatment for patients who do not benefit from several trials of triptans or who have absolute cardiovascular contraindications. According to GoodRx®, the retail price for lasmiditan is over $700 for a month's supply (8 tablets), while generic sumatriptan costs about $12 for a similar supply.

In 2019, the FDA approved the first gepant, ubrogepant (Ubrelvy™), for the acute treatment of migraine in adults. An open-label study of 50 mg and 100 mg (up to two doses per headache attack) demonstrated good safety and tolerability,[9] and several clinical trials have shown efficacy. In a 1:1:1 (50 mg: 100 mg: placebo) randomized trial (n=16,720), 27.8% of participants reported freedom from the most bothersome migraine symptom at 2 hours in the placebo group, 38.6% in the 50-mg group, and 37.7% in the 100-mg group.[10] Comparing odds ratios, ubrogepant was not more effective than commonly used triptans.[8] The gepant drug class does not constrict blood vessels, so these medications can be used when triptans are contraindicated due to cardiovascular disease. The average retail price for Ubrelvy is $1,764 per month according to GoodRx.

A second gepant, rimegepant (Nurtec®) followed ubrogepant with FDA approval for the acute treatment of migraine in 2020. Similar to ubrogepant, rimegepant can be used in patients with cardiovascular disease. In a comparison of the odds ratios, rimegepant versus placebo was not more effective than the commonly used triptans.[8] The average retail price for Nurtec ODT (oral dissolvable tablet) is $1,057 per month according to GoodRx.

Among patients who require a migraine-specific abortive medication, triptans remain first-line. Lasmiditan, rimegepant and ubrogepant cost much more than triptans but are not clearly more effective. The American Headache Society discourages the use of ditans and gepants as abortives unless (1) the patient has a contraindication or cannot tolerate triptans or (2) has had an inadequate clinical response to at least two triptan trials.[6] If a patient has not had an adequate response to two triptans, referral to a headache specialist may be reasonable.

Preventative treatment

Preventative medications are prescribed for daily use and are intended to decrease migraine frequency and severity. The American Headache Society provides examples where a patient with migraine may benefit from preventative medication(s):[6]

- Migraines interfere with the daily routine despite abortive treatment(s).
- Attacks are frequent (≥6 per month) or disabling (but less frequent, ≥2 per month)
- Abortive treatments are not tolerated or are contraindicated.
- The patient prefers a preventative medication.

Although implied by the 2nd and 3rd bullets, but not explicitly stated, patients with medication-overuse headache may benefit from a preventative medication during withdrawal of the overused abortive medication(s).

Once the decision is made to start a preventative medication, the pros and cons of the various options can be weighed. A given drug may be more suitable based on a patient's comorbidities. For example, topiramate has an appetite suppression effect, so patients with migraine who are also overweight may benefit two-fold from a topiramate trial. Although certain antidepressant medications can be effective migraine preventative therapies, the preventative dose of amitriptyline, for example, is typically lower than the antidepressant dose. These lower doses may not be adequate to treat depression. The sedation effect of amitriptyline, however, may be helpful for patients with migraine and insomnia.

Regardless of which preventative medication is selected, a few basic principles should be followed:

1. Start at a low dose and advance slowly to help avoid intolerable side effects.
2. Aim to reach a therapeutic dose. The ideal dose of any medication is one that effectively treats headaches without causing intolerable side effects.
3. Give an adequate treatment trial, allowing for at least 8 weeks at the target therapeutic dose before switching medications.
4. Establish realistic expectations. Preventative medications rarely eliminate migraines. The goal is to decrease frequency and severity, improving migraine-related disability.
5. Continue abortive treatments during preventative medication trials.

There are several migraine preventative medications with established efficacy (≥2 Class I trials) or probable efficacy (One Class I or ≥2 Class II trials) as well as long-standing use. Table 3 lists examples of these drugs, potential side effects, and dosing strategiesprobable efficacy (One Class I or ≥2 Class II trials) as well as long-standing use. Table 3 lists examples of these drugs, potential side effects, and dosing strategies.

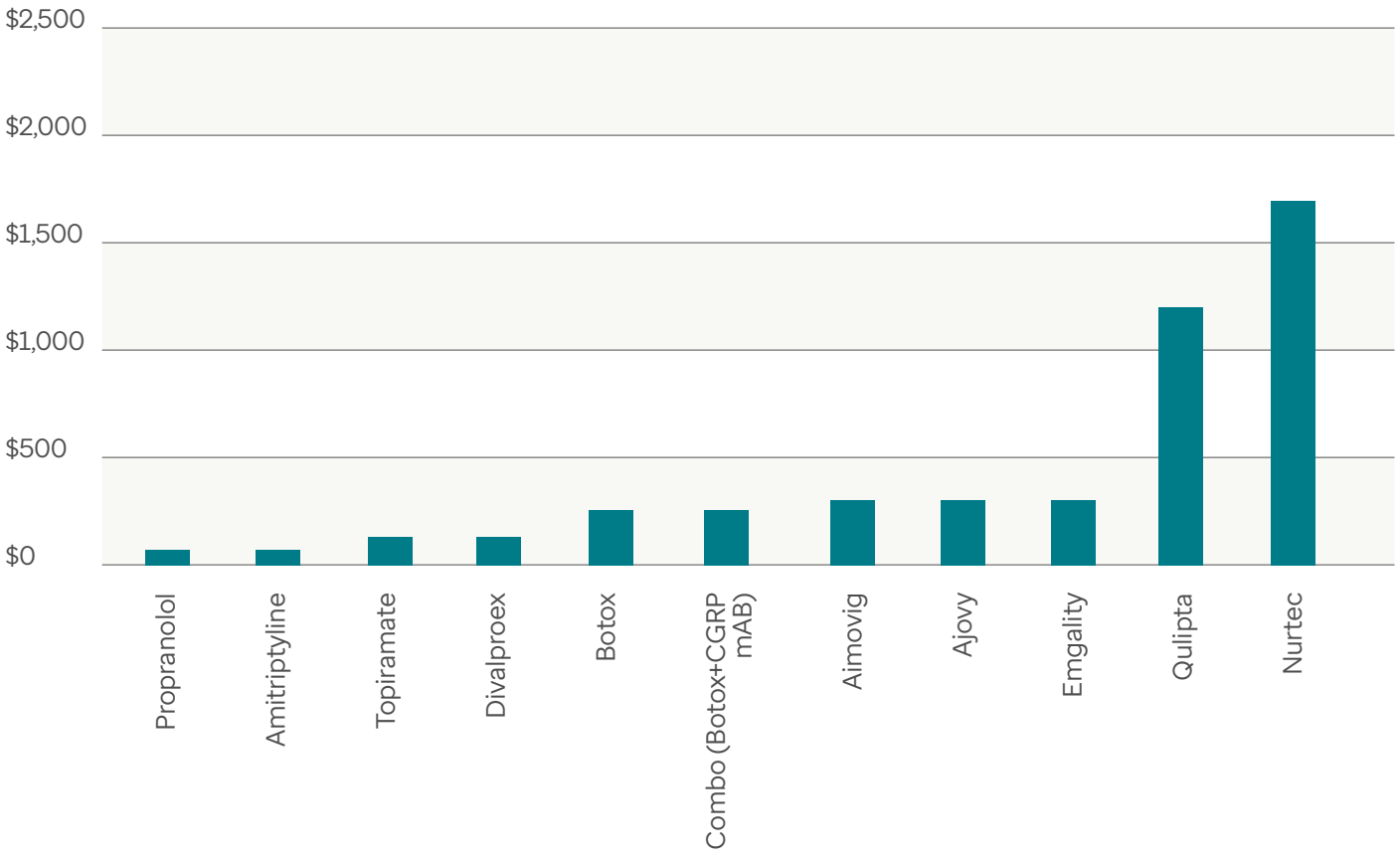
Table 3: Commonly used migraine preventive medications

Medications	Common side effects	Starting dose	Reasonable target dose*
Topirimate	Weight loss, tingling sensations, diarrhea, and dizziness are often self-resolving; lower doses used for migraine rarely cause cognitive complaints	25 mg once daily	100 mg in divided doses
Divalproex sodium/ valpoate sodium	Avoid with pregnancy and use with caution in women of child-bearing age; can cause weight gain, hair loss, sleepiness; understand common and rare side effects before prescribing.	Immediate release (IR): 250 mg orally twice daily Extended release (ER): 500 mg orally once daily	IR/ER: 1,000 mg/day
Beta-blocker	Weight gain, sexual dysfunction, fatigue, upset stomach, coldness/ tingling of hands and feet	Metoprolol tartrate: 25 mg BID Propranolol: 20 mg BID Timolol: 20 mg daily Atenolol: 50 mg daily Nadolol: 40 mg daily	50 to 100 mg 120-240 mg in 2-3 divided doses 20-30 mg 1-2 times daily 100 mg daily 80-240 mg daily
Tricyclic antidepressant	Sedation, nausea/vomiting, dry mouth, constipation, weight gain	Amitriptyline: 10 mg at bedtime Nortriptyline: 10 mg at bedtime	30-75 mg/day
Serotonin-norepinephrine reuptake inhibitor	Difficulty sleeping, dizziness, constipation or diarrhea, nausea/ vomiting, dry mouth, sweating, nervousness. Prolonged withdrawal syndrome	Venlafaxine: 37.5 mg in the morning Duloxetine: 30 mg per day	75-150 mg 1-2 times daily 30-60 mg daily
Magnesium	Diarrhea, nausea, abdominal bloating; can interact with other medications	400 mg daily	400-600 mg daily
Riboflavin	Can cause discoloration of urine; other side effects are rare.	400 mg daily	400 mg daily

* Advance medications slowly. The true target dose is that which effectively treats headaches without intolerable side effects. An example for medication advance: topiramate should be started at 25 mg once daily x 1 week and increased by 25 mg weekly (BID dosing) until target dose achieved.

Newer medications have been FDA-approved for the prevention of migraine, including a group of monoclonal antibody medications and gepants. However, similar to the abortive medications described above, the newer preventatives are much more expensive than the drugs listed in Table 3, but do not appear to be more effective. Using published clinical trial data, the figure below highlights the cost versus efficacy of a group of drugs by plotting the costs to avoid one migraine day per month.

Cost to avoid 1 migraine day monthly



Notably, medications such as propranolol, amitriptyline and topiramate have very favorable cost data based on efficacy, while the newer drugs (right-hand side of the x-axis) are much more expensive, yet not more effective. For these reasons, the newer gepant and monoclonal antibody treatments are considered 3rd-line options for migraine preventatives. Onabotulinumtoxin A (Botox®) is considered 2nd-line as it is well-tolerated and effective, but more expensive than the oral 1st-line drugs.

Summary

The newer migraine medications will help some patients with migraine who cannot take 1st-line treatments because of a lack of effect, intolerable side effects or absolute contraindications. Absent these factors, 1st-line treatments should always be trialed first. The newer agents are much more expensive, without providing added efficacy. Since many factors can affect a patient's response to migraine treatment, when at least two 1st-line medication trials fail, some patients will have greater benefit from referral to a headache specialist than from a trial with a gepant, ditan or monoclonal CGRP antibody.

Pemafibrate for hypertriglyceridemia/diabetic dyslipidemia

This was a in a long-term CV outcomes study managed by Paul Ridker of the Harvard Vascular Biology Lab. [11] It was a study of a new fibrate, pemafibrate. Elevated triglycerides (TG) and low HDL are associated with adverse cardiovascular (CV) outcomes in patients with Type 2 diabetes and others with the metabolic syndrome. However therapeutic options for this condition have not shown improved CV outcomes. These include multiple studies of niacin and other fibrates including gemfibrozil and fenofibrate, the latter of which continues in widespread use. [12,13,14] A recent study of EPA fish oil showed a 4.8% reduction in CV risk over 5 years, but it was later shown that the control product, mineral oil, increased LDL and LDL oxidation and therefore casts these results in doubt. [15]

The current trial was a double blind randomized controlled trial (DBRCT) looking at 10,497 patients with Type 2 diabetes, triglyceride levels between 200 and 499 mg/dL, and HDL cholesterol levels of 40 mg/dL or less. The primary endpoint was a composite of nonfatal myocardial infarction, ischemic stroke, coronary revascularization or death from cardiovascular causes (major adverse cardiovascular events (MACE)). The median baseline fasting triglyceride level was 271 mg/dL, HDL cholesterol level 33 mg/dL, and LDL cholesterol level 78 mg/dL. At four months into the trial, there were approximate 25% reductions in TG and VLDL levels, an 8% increase in HDL levels, but also a 14% increase in LDL levels. At the trial completion, a primary endpoint event occurred in 572 patients in the pemafibrate group and in 560 of those in the placebo group (hazard ratio, 1.03; 95% confidence interval, 0.91 to 1.15), with no apparent improvement in any prespecified subgroup. There was an observed decrease in GFR in the pemafibrate group, as is also seen with fenofibrate. 12% more patients in the pemafibrate group compared to the control group had a decrease in GFR, which returned to baseline after drug discontinuation.

We now have one more large, well conducted DBRCT showing that fibrate therapy, while significantly reducing TG levels and to a lesser extent increasing HDL levels, was not associated with any improvement in long term CV outcomes. Looking at a representative sample of 30% of the Optum Health pharmacy claims, we have estimated that over 45,000 patients are taking fenofibrate, at a cost of $4.3 million. It is likely that a small portion of these patients have baseline TG levels over 500 and are using fenofibrate for the prevention of pancreatitis. The use of fenofibrate for the purpose of improving CV outcomes should be questioned.

Viscosupplementation meta-analysis

In the September 2022 issue of the Forum, we reviewed a paper showing that the use of hyaluronic acid viscosupplementation (Visco) has not decreased despite the American Academy of Orthopedic Surgeons recommending against its use. [16] With this background, a recent meta-analysis of Visco use was published in the British Medical Journal. [17] The analysis focused on large, placebo based randomized controlled trials with at least 100 participants. 169 trials provided data on over 21,000 patients. Overall, there was an insignificant reduction in pain scores of approximately 2% (0.2 on a ten-point VAS score). The accepted minimally important difference on a VAS score is 1.3, or greater than six times the observed magnitude of effect in this meta-analysis. Similar non-clinically meaningful benefits were seen for functional outcomes. In the studies published since 2009, the authors stated, “strong evidence has shown that the pain reduction associated with viscosupplementation is clinically equivalent to the pain reduction associated with placebo when the equivalence margin is 0.2 SMD units (or a margin of 5 mm on a 100 mm visual analogue scale)”. The risk of serious adverse events (SAE) was 49% higher in the Visco group with an overall incidence of 3.7%.

Importantly, the analysis included studies where the placebo group had no intervention (as opposed to placebo injection). Prior studies of DJD trials showed a very large placebo effect size when the intervention group received injection therapy and the placebo group received no intervention. [18] Also, the authors discovered at least 15 industry-funded trials enrolling over 5,000 patients that were never published. They raised the ethical issue of continuing to enroll Visco trials when the serious adverse event rate is appreciable and overwhelming evidence points to a lack of clinical benefit. The major limitation of the study is that the findings represent summary estimates and do not exclude the possibility that selected osteoarthritis patient populations could benefit from Visco.

The authors conclude that “Strong conclusive evidence indicates that, among patients with knee osteoarthritis, viscosupplementation is associated with a clinically irrelevant reduction in pain intensity and with an increased risk of serious adverse events compared with placebo. Our findings do not support the broad use of viscosupplementation for the treatment of knee osteoarthritis.”

Stopping RAS inhibitors in advanced chronic kidney disease does not help eGFR

One goal of management of chronic kidney disease (CKD) is to halt or slow progression to later stages and to avoid end-stage renal disease (ESRD). The use of renin-angiotensin system inhibitors (RAS-I), which includes angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), has been shown to slow the progression of mild or moderate CKD. Despite the beneficial effect of these drugs in early CKD, some studies suggested that discontinuing these medications in more advanced CKD may be indicated, and may slow decline in eGFR. [19] With a recent study published in the New England Journal of Medicine, we now have high-level evidence that this is not the case. [20] In this multi-center study in the United Kingdom, 411 patients with advanced CKD (at least stage 4, not on dialysis) were randomized to continue or discontinue RAS-I drugs and followed prospectively. Outcomes included eGRF, progression to ESRD, initiation of dialysis, hospitalization, blood pressure, exercise capacity, quality of life, cardiovascular events and death. At three years, there were no differences in measured outcomes between the groups or any subgroups. RAS inhibition is a mainstay of prevention and treatment of early CKD. Continuation of this category of medications in later stages of the disease should be decided using a shared decision-making approach, as there is now evidence that discontinuation does not increase the likelihood of the negative outcomes studied.

Cost of low value PSA screening in men over age 69

The American Urological Society, the American College of Physicians, and the USPSTF all recommend the discontinuation of PSA screening at age 69. No published studies have shown benefit in PSA screening of men over age 69. PSA screening for men aged 70 years and older could lead to greater harms from false-positive results for cancers, invasive diagnostic biopsy, and treatment related to overdiagnosis and overtreatment of indolent tumors, including costly procedures, such as biopsy, imaging, prostatectomy and radiation therapy. A recent study in JAMA used the Optum Labs Data Warehouse to look at men over age 69 in a national sample of Medicare Advantage plans who received PSA screening from 2016-2018.[21] These data included, but were not limited to, Optum Health practices.

Strikingly, 39% of the men over age 69 received a PSA and the percentage increased from 2016 to 2018, reaching 42% in 2018. In 2018, fully 68% of men who had a PSA had a subsequent diagnostic cascade. Overall, the most common follow-up service was additional PSA testing (50%), followed by prostate biopsy (5.5%), imaging (4.5%), prostatectomy (2.4%), and prostate radiation (0.2%). The cost of the diagnostic cascade was over tenfold higher than the costs of the initial screening, and 7% of the patients incurred high-cost invasive procedures with potential harm. The conservative estimate on total spend in this population related to non-recommended PSA screening was $275 million.

The authors closed the paper by stating "Because guideline recommendations alone might not lead to long-term sustained effects of reducing low-value PSA cancer screening, innovative and perhaps harsher efforts to reduce both initial unneeded care and avoidable cascading effects—such as the implementation of Section 4105 of the Patient Protection and Affordable Care Act, which provides the Secretary of Health and Human Services the authority to provide no payment for USPSTF grade D services—may be warranted to decrease harm, enhance equity, and improve efficiency of medical spending"

We took this occasion to look at our internal data since PSA screening over age 69 is an Optimal Care low value care measure that is tracked monthly. In 2018 we screened 36% of our population over age 69, compared to 42% in this study. Since 2018, we have reduced this rate to 30%, however it has not further declined in the past two years.

Physician attitudes and reasons for hesitancy on stopping cancer screening based on life expectancy

An important area of cognitive dissonance among physicians and APC's is a significant overestimation of the benefit of medical interventions and an underestimation of the harms. This is particularly true when it comes to cancer screening. A recent survey of almost 1,900 U.S. primary care physicians (791 eligible respondents) showed various reasons why physicians may not be following national guidelines to stop routine cancer screenings when life expectancy is less than ten years.[22] The survey revealed even among physicians who agree that life expectancy should be used to guide stopping cancer screening, almost half worry that stopping cancer screening may be perceived as bias against those of low socioeconomic status against minority groups. About a third of respondents expressed doubt over the accuracy of life-expectancy prediction tools. The majority (64.4%) of respondents agreed patient care is better when over-screening is reduced.[23] A clinical decision-support algorithm based on these guidelines is available to help decrease low-value care, over-diagnosis and potentially harmful cascades of care.[24]

Osteoarthritis of the ankle – Ankle fusion versus arthroplasty

Total ankle arthroplasty (TAA) is increasingly being offered without literature supporting a clear advantage over the standard of care, ankle fusion (AF). TAA is over three times the cost of fusion and randomized trials (RCTs) comparing the two are lacking. The first ever large RCT comparing TAA with ankle fusion was recently published in the Ann of Internal Medicine.[25] This was a pragmatic, randomized, open label trial in 303 patients with end stage DJD of the ankle, conducted in the UK. Patients were randomized 1:1 and followed for one year post surgery. The primary outcome was performance on the Manchester– Oxford Foot Questionnaire walking/standing survey. There were multiple secondary outcomes focused on pain and function. 21 patients withdrew prior to surgery and only four patients crossed over from fusion to TAA.

The TAA group improved on average by 49.9 points compared with 44.4 points in the AF group, with a mean MOXFQ-W/S domain score at 52 weeks of 31.4 (SD, 30.4) in the TAR group and 36.8 (SD, 30.6) in the AF group. This difference was not clinically or statistically significant. Importantly for a surgical trial, findings were similar on the per protocol and intention to treat analyses. Secondary outcomes largely mirrored the primary outcome with the expected exception that joint range of motion increased in the TAA group and decreased in the fusion group. Overall, adverse events were of similar frequency in the two groups, however 12 more patients had wound healing issues including infection in the TAA group and 10 patients had symptomatic nonunion in the fusion group. Thromboembolic complications were slightly more frequent in the fusion group.

Prior non-randomized trials have shown results similar to the above trial.[26,27] There has been a gradual change in practice of TAA from mobile-bearing implants to fixed-bearing implants and approximately half of the TAA patients in this study had each of the implant types. Further study will be needed on long term outcomes of the newer fixed-bearing implants, as in this study, the outcomes were slightly better with the newer implant type. In summary, both procedures broadly offered similar one-year outcomes and complication rates, however TAA is about 2.5 times more expensive than ankle fusion, therefore ankle fusion may be more cost effective.

Inguinal hernia repair operating time reduced with open approach under local anesthesia

Inguinal hernia repair is one of the most common general surgery procedures in the U.S. and can be achieved with robotic assistance, laparoscopically, or the traditional open approach. The open approach can be done under local anesthesia, whereas the others are done under general anesthesia. Previous studies described in this Forum suggest recommending laparoscopic inguinal hernia repair over the robotic-assisted approach as the laparoscopic approach takes less time, but with no increase in complication rates.[28,29] Laparoscopic repair is also done in the ASC whereas, due to the complexity of the robotic equipment, robotic repair is only done in the hospital outpatient setting and has markedly higher costs due to the robotic charge and the higher facility fees. A recent study adds to our understanding of the impact on operating time and on complications within 30 days of the various approaches. This retrospective cohort study examined over 100,000 patients, almost all men, with an average age of 63 and compared outcomes among patients undergoing initial unilateral inguinal hernia repair using an open approach under general or local anesthesia versus a laparoscopic approach.[30] Results showed the duration of surgery using the open approach with local anesthesia was significantly shorter (by over 10 minutes) than the laparoscopic approach. There was no significant time difference between the open approach with general anesthesia and the laparoscopic approach. There were no significant differences in complications among the three procedure types. The accompanying invited commentary suggests these findings support use of the open approach with local anesthesia in select patients, with less exposure to anesthesia and its concomitant potential complications.[31] Individual patient and surgeon factors should further guide the decision of the type of approach used, although at this time there are no data favoring a robotic approach.

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

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Learning objectives	• Discuss primary osteoporosis and low bone mass pharmacologic treatment recommendations. • Examine pharmacological evidence for recurrent renal stones not impacted by HCTZ therapy, and the use of Glucagon in insulin dependent DM 2011 to 2021. • Apply medical management regarding prostate cancer of active surveillance vs. surgery or radiation with a 15-year follow up of the ProtecT Trial, address hearing impairment and cognitive decline and frailty in the elderly using physical activity.

Accreditation statement

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No commercial support was received for this activity.

Primary osteoporosis and low bone mass pharmacologic treatment recommendations update

Primary osteoporosis in adults, particularly in post-menopausal women, has a high prevalence, estimated at over 10 million in the U.S. alone. Low bone mass (osteopenia), associated with high risk of progression to osteoporosis, may be present in over 40% of older adults in the U.S.[1] These conditions greatly increase the risk of fracture with resultant associated morbidity and mortality. Several interventions have demonstrated effectiveness to reduce the risk of fracture in these groups and include both pharmacologic and nonpharmacologic treatment. The American College of Physicians recently published an update to its clinical practice guideline for pharmacologic treatment to prevent fracture in patients with these conditions, and are summarized in **Figures 1-3**.[2] The recommendations are based primarily on a network meta-analysis and systematic review published in the same issue of the Annals of Internal Medicine.[3]

Bisphosphonates remain the first-line therapy to prevent fracture for all patients with primary osteoporosis with average risk of fracture, with high-certainty of evidence in females. One of the primary reasons for discontinuation of bisphosphonates is gastrointestinal side effects caused by oral agents. This is avoided with the use of the intravenous preparation of yearly zoledronic acid. A less-strong recommendation, based on moderate-certainty evidence, is to use the RANK ligand inhibitor denosumab as second-line pharmacotherapy in females who cannot use bisphosphonates . In males, the certainty of evidence of benefit of denosumab as second line is even lower. For patients with low bone mass, the recommendation is to take an individualized approach whether to start pharmacologic treatment with bisphosphonates. Since the evidence of effectiveness is of low certainty for this situation, shared decision-making should be central to the conversation. Clinician treatment thresholds may not be the same as patient thresholds, so use of a tool like the Fracture Risk Assessment Tool (FRAX®[4]), plus conversations around the 10-year risk of a major osteoporotic fracture should be encouraged.[5] The guideline included reporting evidence of patient preferences. These preferences include consideration of the medication profile of benefits and harms, costs, administration frequencies and routes. Other agents and classes to treat primary osteoporosis or low bone mass to prevent fracture in those with average risk of fracture were evaluated, but did not have evidence of effectiveness, long term safety or both, to be recommended for routine use over bisphosphonates or denosumab.

The guideline also provides a recommendation for patients with primary osteoporosis and very high risk of fracture. These are patients who are older (>74 years), have had a fracture within the previous year, a history of multiple fractures or failure of other therapies. For this smaller subset of patients, a conditional recommendation based on moderate and low certainty of evidence is to use a sclerostin inhibitor or recombinant PTH, followed by a bisphosphonate.

Compared with placebo, bisphosphonate use is estimated to reduce risk of any clinical fracture by 24 fewer events per 1,000 patients after three or more years of treatment for a number needed to treat (NNT) of 42. This number drops to an NNT of 18 to prevent one radiographic vertebral fracture. In the high-certainty of evidence randomized controlled trials examined, there was no increase in serious adverse events or withdrawals due to adverse events from use of bisphosphonates. There were observational cohort studies that suggest there may be a higher risk of osteonecrosis of the jaw (ONJ) or atypical femoral fractures (AFF). Based on the included observational studies, the risk of ONJ was estimated at between 1 to 3 in 10,000 bisphosphonate users. Risk of AFF was estimated between 11 to 60 per 10,000 patient years. Since these estimates are based on observational data, the evidence is considered of low certainty. Another study demonstrated that treatment with bisphosphonates for three years prevented up to 149 hip fractures from osteoporosis and was associated with as few as 2 AFF.[6] This suggests that over 70 osteoporotic hip fractures are prevented for every AFF induced with bisphosphonate treatment. To reduce risk of ONJ or AFF further, discontinuing bisphosphonate therapy should be considered as early as feasible once risk of fracture has been reduced. After three years of use, risk of fracture remains lowered even after discontinuation of bisphosphonates.[7] Guidelines suggest a drug holiday after five years of bisphosphonate therapy. For example, the American Assoc. of Clinical Endocrinologist 2020 guideline states “For oral bisphosphonates, consider a bisphosphonate holiday after five years of treatment if fracture risk is no longer high (such as when the T score is greater than -2.5, or the patient has remained fracture free), but continue treatment up to an additional five years if fracture risk remains high (Grade B; BEL 2).[8] Denosumab had similar benefits to bisphosphonates, but with larger NNTs and much higher costs. Average spending per Medicare beneficiary for a bisphosphonate (generic zoledronic acid in this example) is about $50 for the drug plus the infusion cost, whereas the average spending for denosumab for one year can be ~$3,200 (goodrx.com).

When determining which pharmacological agents to use in treating patients with primary osteoporosis or low bone mass, an individualized approach is recommended, with use of shared decision-making when indicated.

Figure 1. Treatments to reduce fractures in postmenopausal females with primary osteoporosis.

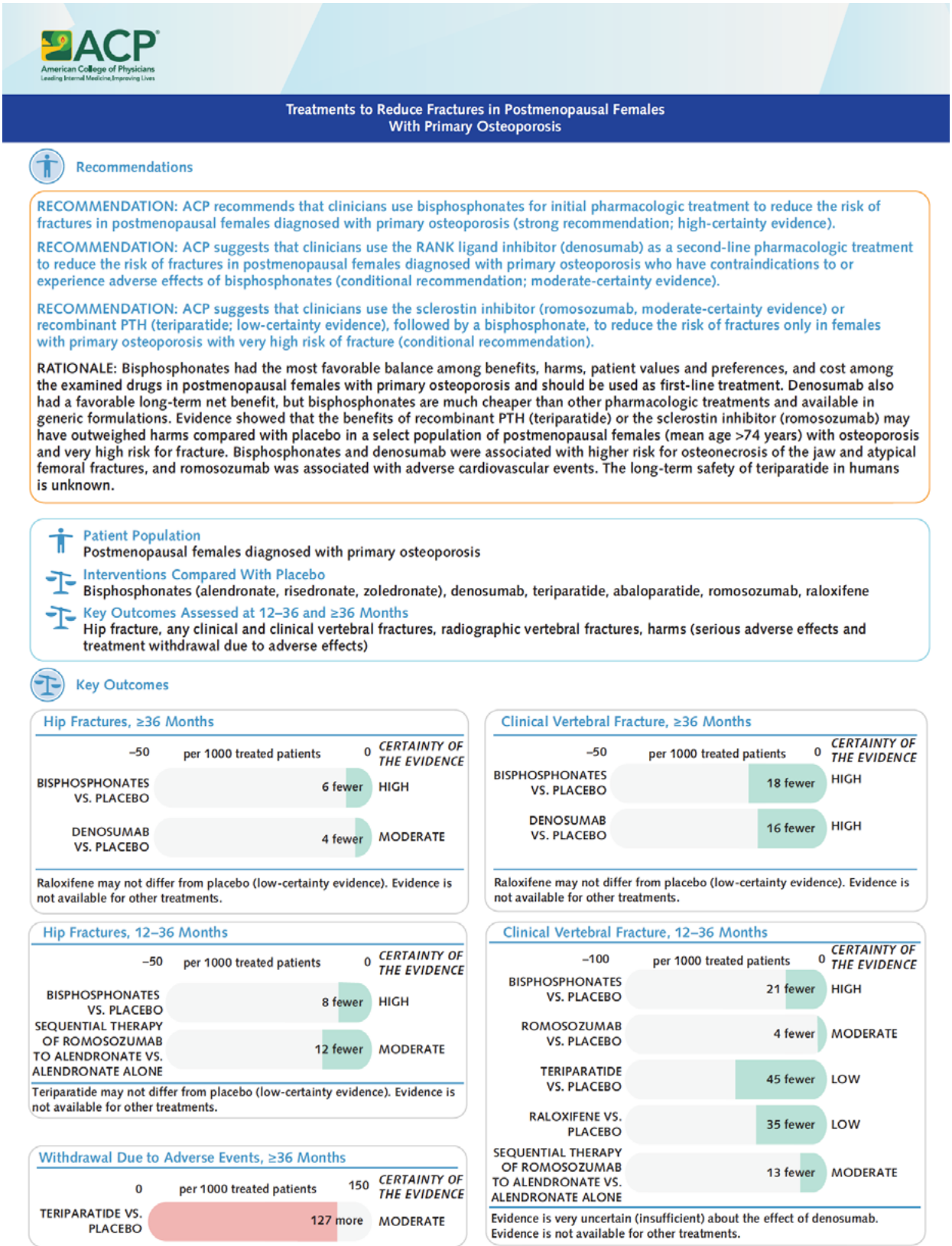

Figure 1. continued. Treatments to reduce fractures in postmenopausal females with primary osteoporosis.

Serious Adverse Events, ≥36 Months

	CERTAINTY OF THE EVIDENCE
Bisphosphonates and denosumab resulted in no differences in serious adverse events and withdrawals due to adverse events in RCTs.	HIGH
Bisphosphonates and denosumab were associated with higher risk for osteonecrosis of the jaw and atypical femoral or subtrochanteric fractures in observational studies, with higher risk after longer treatment duration.	LOW
Romosozumab followed by alendronate probably did not increase risk for serious harms or withdrawal due to adverse effects compared with bisphosphonate alone at 12- to 36-month outcome assessment in an RCT.	MODERATE
Romosozumab was associated with higher risk for adverse cardiovascular events and raloxifene was associated with thromboembolism in observational studies.	LOW
Long-term safety of teriparatide in humans is unknown.	INSUFFICIENT

Clinical Considerations

- Clinicians should prescribe generic medications if possible rather than more expensive brand-name medications.
- Clinicians treating postmenopausal females with osteoporosis should encourage adherence to recommended drug treatments and healthy lifestyle modifications, including exercise, and counseling for evaluation and prevention of falls.
- Adequate calcium and vitamin D intake should be part of fracture prevention in all postmenopausal females with low bone mass or osteoporosis.
- Clinicians should assess baseline risk for fracture based on individualized assessment of bone density, history of fractures, response to prior treatments for osteoporosis, and multiple risk factors for fractures in postmenopausal females with primary osteoporosis.
- Current evidence suggests that increasing the duration of bisphosphonate therapy to longer than 5 years probably reduced risk for new vertebral fractures but not risk for other fractures at the expense of increased risk for long-term harms. Therefore, clinicians should consider stopping bisphosphonate treatment after 5 years unless the patient has a strong indication for treatment continuation.
- The decision of a temporary treatment discontinuation (holidays) should be individualized and based on baseline risk for fractures, type of medication and its half-life in bone, duration of discontinuation, benefits and harms of discontinuation, and higher risk for fracture due to drug discontinuation.
- Females initially treated with an anabolic agent should be offered an antiresorptive agent after discontinuation to preserve gains and because of serious risk for rebound and multiple vertebral fractures.
- Older postmenopausal females with primary osteoporosis who are at increased risk for falls and other adverse events due to polypharmacy or drug interactions need individualized treatment selection based on comorbidities and concomitant medications associated with higher risk for falls/fractures.tt

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Figure 2. Treatments to reduce fractures in males with primary osteoporosis.

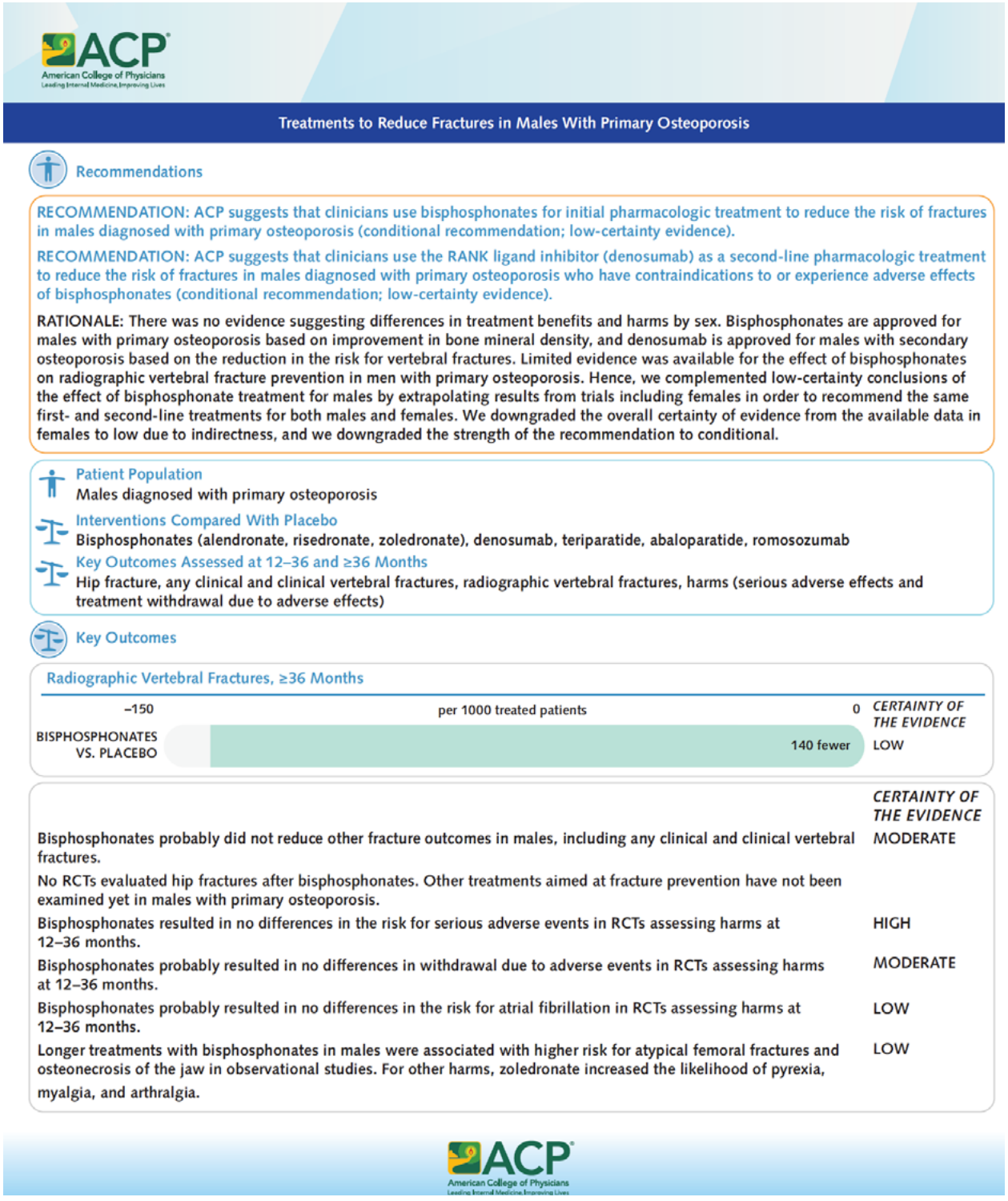
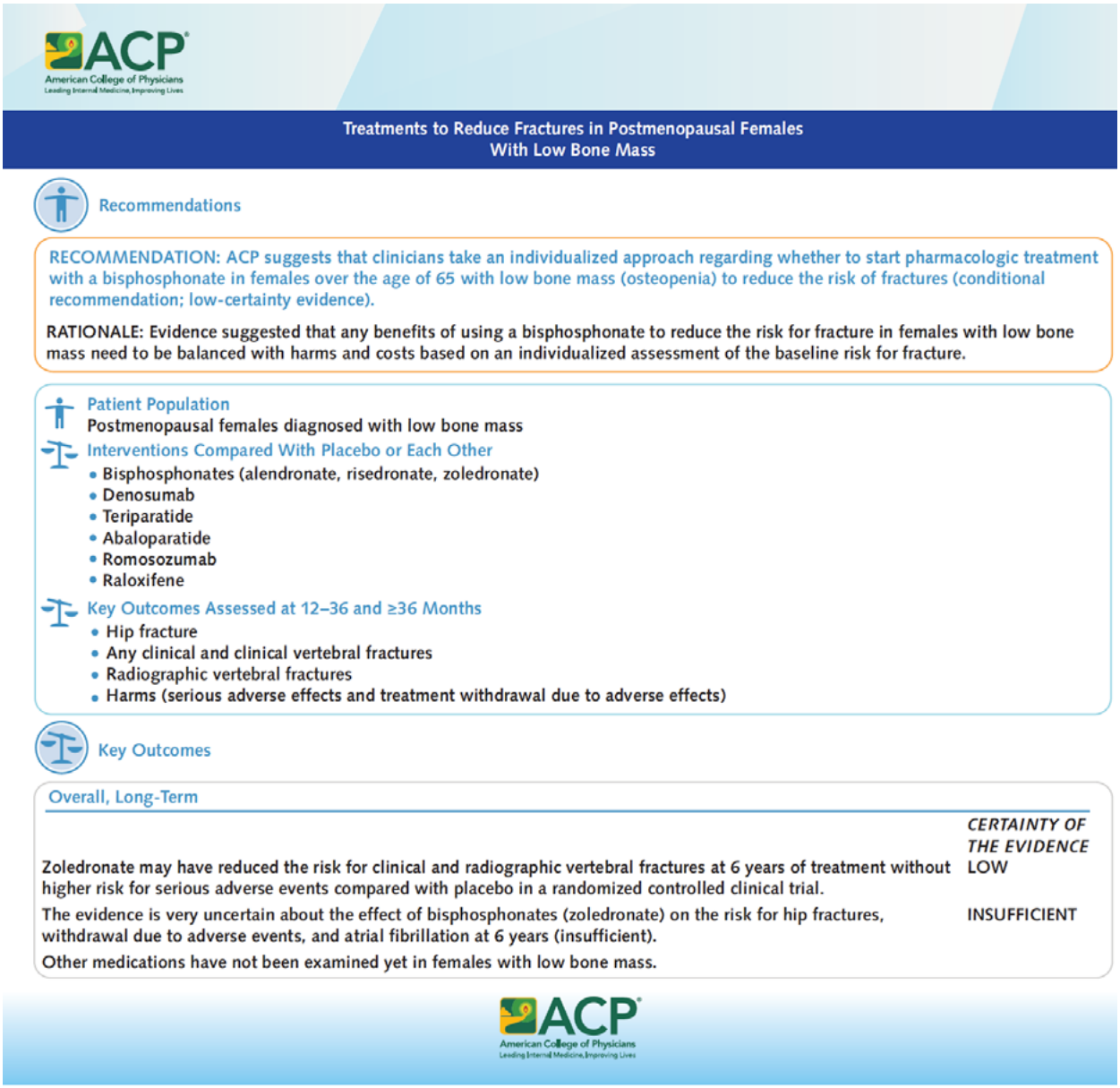


Figure 3. Treatments to reduce fractures in postmenopausal females with low bone mass.



Recurrent renal stones not impacted by HCTZ therapy

For decades, the cornerstone of treatment for recurrent calcium oxalate/phosphate stones has been treatment with HCTZ. This is related to the fact that hypercalciuria is commonly associated with recurrent renal stones and there are good data demonstrating a reduction in urinary calcium excretion with HCTZ use. There are prior studies showing efficacy in reducing recurrent stones, but there have been methodological flaws with many of these studies, and the HCTZ doses were often in the 50-100 mg/day range and therefore often associated with side effects of treatment.

To that end, a group of investigators studied 416 patients with recurrent calcium oxalate stones and randomized them to placebo or three doses of HCTZ 12.5 mg/day, 25 mg/day, or 50 mg/day.[9] Patients were followed for a mean of 2.9 years, and follow up included both symptomatic recurrence and CT discovered new or enlarging stones. A recurrent stone or significant growth of an existing stone occurred in 60 of 102 patients (59%) in the placebo group, in 62 of 105 patients (59%) in the 12.5-mg hydrochlorothiazide group (rate ratio vs. placebo, 1.33; 95% confidence interval [CI], 0.92 to 1.93), in 61 of 108 patients (56%) in the 25-mg group (rate ratio, 1.24; 95% CI, 0.86 to 1.79), and in 49 of 101 patients (49%) in the 50-mg group (rate ratio, 0.92; 95% CI, 0.63 to 1.36). There was no relation between the hydrochlorothiazide dose and the occurrence of a primary end-point event (P=0.66). There was a trend toward lower symptomatic recurrence in the 50 mg HCTZ/day group that did not reach statistical significance. Although generally well tolerated, in the 25 mg HCTZ/day and 50 mg HCTZ/day groups, there were increased rates of hypokalemia, gout, and new onset DM2, seen in the range of 3-5% of patients.

So how can we integrate these data into our treatment algorithms? Interestingly, the patients receiving hydrochlorothiazide had the expected decrease in urinary calcium excretion. However, urine relative supersaturation ratios for calcium oxalate and calcium phosphate, an excellent proxy for stone formation, were not lower among patients receiving hydrochlorothiazide. Additionally, urinary citrate levels were reduced on treatment which might also counteract the effect of the reduced urinary calcium. Given that the treatment non-adherence rate was about 25%, this could have affected results. If patients are successfully treated with HCTZ therapy for recurrent stones and have no side effects on therapy, treatment might be continued. These data would weigh against new initiation of treatment for recurrent calcium stones.

Glucagon use in insulin dependent DM 2011 to 2021

Severe hypoglycemia in patients with insulin dependent DM is common and dangerous.[10] Consequences include an increased rate of hospital admission, readmission and mortality. Guidelines therefore recommend that these patients have a prescription available for glucagon use in the event of severe hypoglycemia.

To assess the use of glucagon in this patient population, researchers used the Optum Labs Data Warehouse to examine the prescription rate for glucagon.[11] The study population included over 2.8 million Medicare Advantage and commercial patients with DM. Of the ~308,000 patients using short acting insulin, only 8,7% of patients were prescribed glucagon, and of the ~236,000 on only long-acting insulin, only 2.3% of patients were prescribed glucagon. Moreover, during the ten years of the study, prescription rates dropped by 22%. Even in the subpopulation of patients who required ED evaluation or hospital admission, only 25% were prescribed glucagon.

Interestingly, despite the availability of nasal glucagon that can easily be administered by family members and caretakers, most of the prescriptions were of the cumbersome vial and syringe kits, despite price parity between the various products. The cost of a glucagon kit is in the range of ~$275, however several commercial and MA plans, including UHC, offer this at zero copay. Patients with diabetes using multi-dose insulin regimens and those using long-acting insulin only who have had severe hypoglycemia should be prescribed glucagon with instructions for appropriate use.

Prostate cancer – active surveillance vs. surgery or radiation – 15–year follow up of the ProtecT Trial

Based upon the results of prior studies, active surveillance (AS) for low-risk prostate cancer has been shown to have equal survival compared to treatment with radical prostatectomy or radiation therapy.[12] Due to the ubiquitous serious side effects of treatment, AS is the preferred management in both the NCCN and AUA guidelines. However, rates of AS remain at only 60% across the U.S., despite other countries in the world, and the urologist MUSIC collaborative in Michigan, reaching AS rates above 90%.

Adding to this body of literature is the ProtecT Trial, a UK trial now reports the 15-year follow up of 1,643 men who were diagnosed with localized prostate cancer and randomized to AS, radical prostatectomy or radiation therapy.[13] 77.2% of the men were in Gleason grade group 1 (Gleason score, 3+3=6) and would qualify for AS today. However, 24% had intermediate disease, some of whom might qualify for AS, and 9.6% had high-risk disease. The primary outcome was death from prostate cancer, and the secondary outcomes were death from any cause, metastases, disease progression, and initiation of long-term androgen-deprivation therapy.

Death from prostate cancer occurred in 2.7%: 3.1% in the AS group, 2.2% in the prostatectomy group, 2.9% in the radiotherapy group (P=0.53 for the overall comparison). Death from any cause occurred in 356 men (21.7%), with similar numbers in all three groups. Metastases developed in 9.4% in the active-surveillance group, 4.7% in the prostatectomy group, and in 5.0% in the radiotherapy group. Long-term androgen-deprivation therapy was initiated 12.7%, 7.2%, 7.7%, respectively; clinical progression occurred in 25.9%, 10.5%, and 11.0%, respectively. In the active-surveillance group, 24.4% were alive without any prostate cancer treatment at the end of follow-up. Interestingly, no differential effects on cancer-specific mortality were noted in relation to the baseline PSA level, tumor stage or grade, or risk-stratification score.

So how does this help us in our AS discussions with our patients? The primary endpoint of prostate cancer death was no different with AS compared to treatment. With respect to disease progression needing treatment, because 23% of the patients in this trial would not have met current guidelines for AS, it is expected that the rates of treatment over time would be higher than in trials that focused only on low-risk prostate cancers. The largest such trial showed that at ten years from diagnosis, in a population of 993 men with low to intermediate risk cancers, 63% of patients remained on AS with a survival of 98.5%. We now have strong data from multiple sources that AS versus treatment does not impact prostate cancer survival, and patients can thus be reassured that enrolling in an AS program is safe and will avoid the toxicities of prostatectomy and radiation therapy. A minority of these patients will evolve over time and thus require treatment, but this is safely monitored in AS programs. If these patients do go on to need treatment, they still would have avoided the toxicity of treatment during the years that they spent on AS.

To improve our current rates of AS, this spring we will launch the "Prostate Cancer – Improving Active Surveillance" (ProCIAS) program. This will entail two key elements. The first is a sophisticated, web based, interactive shared decision-making program to teach patients about their options for low-risk prostate cancer. The second element will be a reporting program that will measure the AS rates for the urologists in your market such that you can refer to urologists who appropriately utilize AS in lieu of prostatectomy and radiation therapy in your patients with low-risk prostate cancer.

Addressing hearing impairment to address cognitive decline

Recent drug development suggests therapies for certain types of dementia may be in the pipeline (e.g.; donanemab, lecanemab). However, some pharmaceutical treatments are often associated with high direct (cost of drug) and indirect (cost of MRI surveillance, adverse drug events, etc.) costs with uncertain clinical benefit, resulting in poor cost-effectiveness and value.[14] Given the high incidence and burden of dementia, treatment options are imperative. There are effective lower-cost interventions available. Prevention of hearing loss can result in a substantial risk reduction for dementia.[15] Hearing loss is highly prevalent in the aging population. A recent systematic review and meta-analysis suggests that addressing hearing impairment after it has already occurred may also decrease risk of cognitive decline in the long term and may even improve cognitive test scores in the short term.[16] Eight of the studies included, representing almost 127,000 patients, examined the association between hearing aid use and long-term cognitive decline, with the pooled analysis showed almost a 20% lower hazard ratio compared to those with uncorrected hearing loss. The risk of bias among the studies was deemed moderate to low. The costs and complications associated with hearing aids are much lower than current and proposed medication interventions and should be considered as a part of initial prevention and therapy for those at risk and who have hearing impairment.

Addressing frailty in the elderly using physical activity

A recent systematic review and network meta-analysis reveals that resistance training may be the most effective non-pharmacologic intervention to reduce frailty. [17] Although 69 randomized-controlled trials were included, the certainty of the evidence from the findings was determined to be moderate at best. That said, the findings can provide some guidance on effective and feasible interventions for frailty. Frailty is common in the elderly and is often considered a 'pre-disability state' characterized by decreased physiologic reserve and increase susceptibility to the detriments of stress. Frailty is often a precursor to cognitive decline, lower quality of life, mood disorders, and other poor health-related outcomes. Effective prevention and treatment, therefore, are important clinical interventions within a value-based framework of care, and contribute directly toward the quadruple aim.

The recent article found evidence of effectiveness for physical activity and for nutrition intervention in reducing frailty, versus usual care. Physical activity was found more effective, with the most effective being resistance training followed by mind-body exercise, mixed physical training, and finally aerobic training. Treatment of comorbid conditions that often accompany frailty, such as diabetes mellitus, chronic kidney disease, or heart disease, will often involve medication as part of medical management. The current study highlights the importance and effectiveness of non-pharmacologic treatment of frailty itself.

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Learning objectives	• Discuss the screening, diagnostic and monitoring approaches to non-alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH). • Examine the updated Chest guidelines for anticoagulation perioperative bridging and anticoagulation in patients with atrial fibrillation. • Utilize medical management strategies regarding prostate cancer screening over age 69, and recognize the high prevalence of colonoscopy in the elderly without improved outcomes.

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Approach to non-alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH)

This article is an updated version of the 2018 summary of non-alcoholic fatty liver disease (NAFLD), including non-alcoholic steatohepatitis (NASH) previously published in this newsletter in 2018.[1,2,3] Updates include screening, diagnostic and monitoring approaches[4] and upcoming pharmacotherapeutic interventions.

Introduction

Now that close to 70% of Americans are overweight or obese, NAFLD has become the most common chronic liver disease in the U.S., representing ~75% of all cases. The annual direct cost attributable to NAFLD/NASH in the U.S. exceeds $100 billion. In a study of over 10,500 patients with biopsy-confirmed NAFLD, their risk of death over an average 14.2-year follow-up period was 41% higher than matched controls from the general population (16.9 vs. 28.6/1000 person-years [PY]; aHR=1.93).[5] This excess mortality was present in varying degrees in all categories of NAFLD (simple steatosis, NASH, and cirrhosis), but increased with increasing degrees of inflammation and fibrosis. However, because a large proportion of patients with NAFLD also have metabolic syndrome, it is still cardiovascular disease and not chronic liver disease that is the most common cause of death in these patients. It is estimated that 24% of the U.S. population has NAFLD and up to 6.5% has NASH, which is the next step in the evolution towards cirrhosis. Cirrhosis due to NASH will ultimately occur in 2% of the American population and will soon become the most common reason for liver transplantation. NASH is defined by the presence of hepatocyte damage with inflammation. The progression of NAFLD to NASH is linked to insulin resistance causing accumulation of toxic lipid metabolites and activation of inflammatory mediators, including TNF alpha. There may also be important contributions from an abnormal gut microbiome. Histologically, NASH is indistinguishable from alcohol related liver damage. Importantly, the most potent risk factors that predict the transition from NAFLD to NASH are Type 2 diabetes and the various components of the metabolic syndrome. The risk of hepatocellular carcinoma is similar to that from other causes of cirrhosis; therefore, patients with cirrhosis need yearly ultrasound surveillance for the development of hepatocellular carcinoma (HCC).

Diagnosis

Since it is impractical and inappropriate to perform liver biopsy on all patients with NAFLD to assess for NASH, a more focused approach to assessing for this condition has recently been put forth by the American Association for the Study of Liver Diseases (AASLD).[6] Patients with two metabolic risk factors or with Type 2 diabetes mellitus should be screened for NASH. Metabolic risk factors include central obesity, high triglycerides, low HDL cholesterol, hypertension, and insulin resistance. In addition to a detailed alcohol history, the following studies will exclude the vast majority of alternative diagnoses.

- Iron studies for hemochromatosis
- Hepatitis B and C serologies for chronic viral hepatitis
- ANA and anti-smooth muscle antibody for autoimmune hepatitis
- Anti-mitochondrial antibody for primary biliary cirrhosis
- Alpha-1 antitrypsin level for alpha-1 antitrypsin deficiency

Because alcohol excess causes identical histologic changes, it may be either the primary etiology or contributory depending on the level of alcohol intake. Moderate alcohol intake at one to two drinks daily has not been found to cause or adversely affect NAFLD.

Although the specificity of an elevated alanine aminotransferase (ALT) level for the diagnosis of NAFLD is 85%, the sensitivity is only 45% and patients can progress to cirrhosis with normal liver function tests (LFTs). The AST/ALT ratio is typically < 1. Clinical signs suggesting the progression to cirrhosis include progressive elevations of the AST/ALT with a ratio >1, increased bilirubin levels, thrombocytopenia, or exam stigmata of advanced liver disease.

The Fibrosis-4 index (FIB-4) is a rigorously studied score for NASH that uses age, AST, ALT, and platelet count to calculate. While it requires minimal and readily available data to calculate and has a high negative predictive value, it has a low positive predictive value and is less accurate in those >65 or <35 years of age. Additionally, roughly 30% of individuals have a score in the 'indeterminate' range, requiring further testing, such as with one of the direct serum fibrosis biomarker tests, or an imaging test for liver stiffness. Imaging includes vibration controlled transient elastography (VCTE – FibroScan®) and magnetic resonance elastography (MRE). Of the two imaging tests, MRE has slightly more favorable performance measures but may not be as widely available and is about 4 times more expensive than the FibroScan. All that said, a FIB-4 score in a person at risk for NASH of <1.3 likely has low risk of progression and can be safely managed in the primary care setting with regular follow-up. Scores in the indeterminate range of 1.3-2.67 should have a FibroScan performed. If this shows significant fibrosis, GI referral should be obtained. Scores >2.67 suggest more advanced fibrosis and likely would benefit from GI specialist management.

Management

Pharmacotherapy is not recommended in the absence of NASH, other than treatment that would otherwise be indicated for DM2 or obesity. There is ample data to support weight loss to reverse NAFLD/NASH and since there are available therapies for this, including drugs and bariatric surgery, weight loss should be considered the cornerstone of treatment. Sustained weight loss of at least 3-5% of body weight is needed to reduce steatosis, and 7-10% for patients with NASH. Additionally, Type 2 diabetes should be aggressively managed. Low carbohydrate diets have shown greater improvement in NAFLD compared to other types of diets. Bariatric surgery in 766 patients with paired liver biopsies showed improvement in NAFLD in 91%, NASH in 81%, and fibrosis in 65% of patients. There are no FDA approved drugs, and the best data to date show improvements in only ~50% of patients with any intervention other than weight loss. The Institute for Clinical and Economic Review (ICER), a non-profit research institute that examines value including cost-effectiveness for existing and emerging therapeutics, recently published a report on two new pharmaceuticals soon to be available (anticipated FDA decision in 2023) for the treatment of NASH.[7] Resmetirom is a small molecule agonist for the thyroid hormone receptor beta. Obeticholic acid is a bile acid analog. This group concluded that the two new agents improve liver histology but there is not yet evidence demonstrating improved long-term outcomes. As the pharmaceutical companies have not yet disclosed the intended price, it is not yet clear if these drugs will be cost-effective.

- **Vitamin E** at a dose of 800 IU daily has been shown in a randomized trial to improve both liver tests and histologic changes of both NAFLD and NASH including resolution of NASH in 36% of patients. However, fibrosis scores were not improved with vitamin E treatment.

- **Pioglitazone** also improves insulin sensitivity and is the best studied of the pharmacologic agents and has demonstrated clear benefits. This may be related to the fact that unlike metformin, pioglitazone improves adipocyte function, and thus increases fatty acid uptake in adipose tissue, decreasing the fatty acid load to the liver and thereby decreasing deposition of fat in the liver. This improves insulin sensitivity at the expense of the expansion of peripheral fat mass (thus the weight gain seen with this drug class). Improvements in the 35-50% range in liver functions and histologic changes have been seen in both diabetic and non-diabetic populations with the use of pioglitazone. The number needed to treat with pioglitazone for resolution of NASH ranges from 2-12, which makes it a reasonable treatment strategy if there are no contraindications.

- Importantly, **metformin** improves insulin sensitivity but has not been shown to improve liver histologic changes. This may be related to the fact that its main effects are on increasing muscle uptake of glucose and decreasing hepatic glucose production, with lesser effects on fat metabolism. If however, patients treated with metformin have significant weight loss and/or improvement in Type 2 diabetes, liver function is likely to secondarily improve.

- Phase II trials have shown improvements in NASH using the **GLP-1 agonist** class and phase III trials are ongoing. Smaller trials have shown benefits using probiotics and fish oil supplements, both of which have been shown to improve insulin sensitivity.

- Lastly, there are small trials showing benefits, including improved histologic changes with use of pentoxifylline which is a TNF alpha antagonist.

Summary

We are under diagnosing both NAFLD as well as NASH. Increased vigilance is required to screen and identify the subset of our patients with NAFLD who are progressing towards NASH and cirrhosis. Once identified by the FIB-4 test and Fibroscan when indicated, the first efforts should be directed at lifestyle modification including, when indicated, pharmacologic or surgical approaches to weight loss, and optimal control of Type 2 DM when present. Given the available data from the Phase II trials, GLP1-RA therapy is the preferred pharmacotherapy for obesity in the setting of NASH. If unsuccessful, the options are to initiate supplement therapies using probiotics, Vitamin E, and/or fish oils, versus initiation of pharmacotherapy using pioglitazone. Bariatric surgery has a clear role when obesity is resulting in the progression of NAFLD to NASH and cirrhosis and continues to be underutilized. NAFLD progressing to cirrhosis will likely be the most common form of cirrhosis and the most common reason for liver transplantation in the near future.

Evidence in favor of bariatric surgery to treat NASH

Recent publication of results from the BRAVES trial (bariatric-metabolic surgery vs. lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (NASH)) provides strong evidence for preferential treatment with surgery to treat NASH.[8] In this randomized controlled trial including 288 patients with biopsy-confirmed NASH, a third were randomized to intensive lifestyle intervention plus medications, a third to Roux-en Y gastric bypass and a third to sleeve gastrectomy. Intention-to-treat analysis showed that patients in both surgical groups had over 3.6 times greater chance of NASH resolution with no worsening fibrosis compared to the intensive lifestyle intervention with medication group at 1-year follow-up. This was even more favorable for the surgery groups when using a per-protocol analysis. The complications in the surgery groups were managed medically or endoscopically, and there were no serious adverse events reported. These findings comport with the 2017 publication of a study looking at the use of these bariatric surgeries in the treatment of patients with Type 2 diabetes mellitus and obesity in which the surgery arms had significantly better outcomes than the medical therapy arm.[9] In this report of a 5-year follow-up after randomization of the 150 patients, all relevant laboratory parameters (HgbA1c; lipid profile), body weight, and measured quality of life (QOL) were significantly better in the surgery groups. For HgbA1c, there was an average reduction of 2.1% in the surgery groups compared with 0.3% in the medical therapy group. For the other outcomes of interest, the numbers are as follows: body weight (-23%, -19%, and -5% in the gastric-bypass, sleeve-gastrectomy, and medical-therapy groups, respectively), triglyceride level (-40%, -29%, and -8%), use of insulin (-35%, -34%, and -13%), and QOL (general health score increases of 17, 16, and 0.3; scores on the RAND 36-item health survey ranged from 0 to 100, with higher scores indicating better health) ($P<0.05$ for all comparisons).

While bariatric surgery appears to perform better than intensive lifestyle intervention plus medical therapy, study limitations make the generalizability of the findings less robust. As always, individual patient factors must be considered when applying the evidence to an individual case. The results of the BRAVES trial add to our understanding of effective treatments of this disease.

Anticoagulation perioperative bridging guideline – Chest update

The updated Chest guideline includes 44 new recommendations of which only a subset is relevant to primary care.[10] Of note, almost all of the previous indications for heparin bridging have been removed. There are still circumstances where heparin bridging may be indicated based on a high risk of perioperative thromboembolism. See the accompanying **Table 1,** which is helpful in identifying this high-risk population. Below are the most important updates.

- Perioperative heparin bridging is no longer recommended in patients receiving vitamin K antagonists (VKA) therapy for atrial fibrillation, mechanical heart valves, or for VTE. The recommendation is to hold VKA therapy at least 5 days prior to the procedure.
- VKA interruption is not recommended for minor dermatologic, minor ophthalmologic procedures, or for colonoscopy with anticipated polypectomy.
- Heparin bridging is not recommended when DOAC therapy is temporarily held perioperatively. The recommendations for stopping specific DOAC therapies preoperatively are:
  - Apixiban, edoxaban, and rivaroxaban - stop 1-2 days before procedure
  - Dabigatran – stop 1-4 days before procedure
- In patients who require DOAC interruption for an elective surgery/procedure, perioperative heparin bridging is not recommended. Resumption of DOAC therapy is recommended not earlier than 24 hours post procedure.
- In patients receiving ASA for secondary prevention of stroke or MI, who are undergoing elective non-cardiac surgery, ASA continuation is recommended.

Table 1: Adapted American College of Chest Physicians (CHEST) Suggested Risk Stratification for Patient-Specific Periprocedural Thromboembolism

Risk Category	Mechanical Heart Valve	Atrial Fibrillation	VTE
High (> 10%/y risk of ATE or > 10%/mo risk of VTE)	Mitral valve with major risk factors for stroke[b] Caged ball or tilting-disc valve in mitral/aortic position Recent (< 3 mo) stroke or TIA or other highrisk stroke situations[c]	CHA_2DS_2VASc score ≥ 7or $CHADS_2$ score of 5 or 6 Recent (< 3 mo) stroke or TIA Rheumatic valvular heart disease	Recent (< 3 mo and especially 1 mo) VTE Severe thrombophilia (deficiency of protein C, protein S or antithrombin; homozygous factor V Leiden or prothrombin gene G20210A mutation or double heterozygous for each mutation, multiple thrombophilias) Antiphospholipid antibodies Active cancer associated with high VTE risk[a]
Moderate (4%-10%/y risk of ATE or 4%-10%/mo risk of VTE)	Bileaflet AVR with major risk factors for $stroke_b$	CHA_2DS_2VASc score of 5 or 6 or $CHADS_2$ score of 3 or 4	VTE within past 3–12 mo Recurrent VTE Non-severe thrombophilia (heterozygous factor V Leiden or prothrombin gene G20210A mutation) Active cancer or recent history of cancer[c]
Low (< 4%/y risk of ATE or < 2%/mo risk of VTE)	Bileaflet AVR without major risk factors for $stroke_b$	CHA_2DS_2VASc score of 1–4 or $CHADS_2$ score of 0–2 (and no prior stroke or TIA)	VTE > 12 mo ago

This was an empiric risk classification, not prospectively validated. ATE = arterial thromboembolism; AVR = aortic valve replacement; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack; CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease history, age ≥ 65 years, female sex.

[a]Includes pancreatic cancer, myeloproliferative disorders, primary brain cancer, gastric cancer, and esophageal cancer.

[b]Includes multiple prior strokes, prior perioperative stroke, or prior valve thrombosis.

[c]Atrial fibrillation, prior stroke or transient ischemic attack (TIA), hypertension, diabetes, congestive heart failure, and age > 75 years.

Evidence of over and under anticoagulation in patients with atrial fibrillation

The Optum Center for Research and Innovation (OCRI), along with colleagues at the Mayo Clinic, published a study in the International Journal of Cardiology[11] looking at patterns of anticoagulation use in 339,000 patients with non-valvular atrial fibrillation (AF). An algorithm was created to estimate CHA_2DS_2-VASc scores from patient claims and applied to the multi-payor Optum Labs data warehouse database using a retrospective cohort design.

The findings of note included:

- In the ~14,000 patients who had scores of 0 in men or 1 in women, 29.6% of patients were on anticoagulation therapy which was potentially inappropriate.
- In the ~297,000 patients who had scores ≥ 2 in men or ≥3 in women, 52.2% were not taking anticoagulants, suggesting possible undertreatment of stroke prevention in this large group of patients.
- In the year prior to the index date, there was an increase in ER and hospitalization use in the high-risk patients who were not anticoagulated. Also, within the previous 3 months of the index date, patients in the non-OAC group had a slightly higher number of ischemic strokes/systemic embolization, major bleeding, and intracranial bleeding episodes.

These data suggest that there is a significant opportunity to improve anticoagulation prescribing based on the CHA_2DS_2-VASc score in non-valvular AF in both low risk and high-risk groups of patients.

Prostate cancer screening not indicated in those over age 69 years, though potentially helpful for younger cohorts

The 21-year follow-up of the Dutch arm of the European Randomised Study of Screening for Prostate Cancer (ERSPC) trial again highlights the lack of benefit of treatment for prostate cancer (CA) over age 70.[12] These findings comport with the USPSTF recommendation to avoid screening for prostate CA in those age 70 and older (grade D).[13] This update on a subset of the ERSPC patients from the Netherlands included over 42,000 men aged 55-74 years who were offered PSA-based screening for prostate CA every 4 years. Those invited for screening who were over 69 years at the time of randomization had no improvement in prostate-specific mortality compared with those not invited for screening (RR of 1.18 [95% CI: 0.87–1.62]). The reason for this likely is due to the fact that aggressive prostate cancers manifest well before age 70, so those of that age and above who do have prostate cancer usually have a more indolent form of the disease; one that does not affect mortality statistics. The 21-year follow-up study does reinforce the potential benefit of screening those in the 55–69-year age group, with a number needed to invite (NNI) of 246 and number needed to diagnose (NND) of 14, to prevent one death from prostate cancer. For the outcome of metastatic disease, the NNI was 121 and the NND was 7. These numbers are similar in magnitude to the Göteborg (Sweden) arm of the ERSPC study 22-year follow-up, in which the NNI was 221 and NND was 9.[14] In that arm of the study, 20,000 men were randomized into a screening invite group and a control group. Screening was offered using PSA every other year. For both studies, there was a noted tradeoff between potentially lower mortality in exchange for higher rates of identification of indolent disease that would not substantively have impacted the patient's health.

For those of our patients who choose to be screened and who are subsequently diagnosed with low-grade prostate CA, patient education and shared decision-making around the beneficial use of active surveillance should be pursued.[15]

Low-value prostate cancer screening in those over age 69 associated with clinician behaviors

Based on robust evidence, the U.S. Preventive Services Task Force (USPSTF) recommends against screening for prostate cancer with a serum prostate-specific antigen (PSA) test in those over age 69 due to the risk of false positives and of overdiagnosis with resultant overtreatment.[16] Treatment of clinically localized prostate cancer in those over age 69 has not been shown to improve outcomes,[17] while it causes harm in virtually all men.[18] Despite this, screening in this age group remains common in clinical practice. A recent cohort study included over 32,000 males aged 70 and older who had a PSA, to better characterize factors associated with this low-value practice.[19] One of the factors associated with this over screening was a clinician discussing the advantages of PSA testing with their patient (odds ratio [OR], 9.09; 95% CI, 7.60-11.40; P<.001). This increased odds of having had a PSA test was not present when the clinician discussed the disadvantages of PSA testing (OR, 0.95; 95% CI, 0.77-1.17; P=.60). These findings suggest a central role of the clinician in providing evidence-based guidance in the shared decision-making discussion to decrease this low-value practice. Screening with serum PSA for prostate cancer is not indicated for average risk patients over age 69. Patient education and shared decision-making should be employed for those wanting screening.

High prevalence of colonoscopy in the elderly without improved outcomes

A recent article by Halabi et al. highlights the continued high prevalence of screening colonoscopies in patients who are asymptomatic for colorectal cancer (CRC), over 75 years old, and with a life expectancy of <10 years.[20] This may be evidence of ongoing low value care. The benefits of CRC screening take 10-15 years to manifest due to the time it takes for typical adenomas to progress to CRC, [21] and therefore would not benefit patients with a life expectancy <10 years. The study by Halabi et al. was a cross-sectional design with a nested cohort that included 7,067 patients over 75 years old and demonstrated a high percentage of those with life expectancy <10 years undergoing colonoscopy, with a very low percentage of actionable findings. Adverse events requiring hospitalization within 10 days of colonoscopy occurred in 13.58 per 1,000 patients in all patients. Those with life expectancy <10 years had double the complication rate compared with those with longer life expectancy. Only 2 per 1,000 patients were found to have invasive colorectal cancer. Of those 9 patients with life expectancy <10 years who were discovered to have colorectal cancer, only 1 out of the total screened population elected to undergo cancer treatment. Even with including the other 6 patients found to have cancer for a total of 15, at an estimated $1,000 per colonoscopy this means roughly $470,000 per cancer found, which is clearly not cost effective.

Colonoscopy complication rates are higher in the elderly for GI complications (e.g., perforation, bleeding) and non-GI complications (e.g., myocardial infarction, stroke).[22,23] Stool-based tests are safer in this population and are preferred for those in whom ongoing screening is indicated. For those with a life expectancy less than 10 years, there are no data supporting improved outcomes with CRC screening. The U.S. Preventive Services Task Force (USPSTF) 2021 guideline recommends discontinuing screening after age 85, and for those age 76-84, the decision to screen or not should be individualized, as the benefits are small.[24] Even if colorectal cancer is found, patients may elect for palliative, rather than attempting curative care.

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Learning objectives	• Discuss Alzheimer's disease diagnosis, screening tools and novel monoclonal antibody treatments. • Examine testosterone replacement therapy and the associated cardiovascular and prostate cancer risks, COPD exacerbations and bacterial pneumonia rates with LAMA-LABA, and the anti-depressant duloxetine, for treating chronic pain. • Utilize medical management strategies regarding the use of canalith repositioning maneuver (CRM) for benign paroxysmal positional vertigo (BPPV), patient preferences for total knee arthroplasty, and nonoperative management of acute Achilles tendon rupture.

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Alzheimer's disease diagnosis and novel monoclonal antibody treatments

Dementia is a general term used to describe a chronic impairment in cognitive function that is severe enough to interfere with an individual's ability to carry out daily activities. Mild cognitive impairment (MCI) similarly causes a loss of cognitive function, but activities of daily living are minimally affected.[1] Individuals with MCI can progress to dementia, but some remain stable and others return to their previously normal neurologic status. Although several diseases can cause MCI and dementia, this article focuses on Alzheimer's disease: its diagnosis, various screening tools, and an overview of the monoclonal antibody treatment trials for aducanumab, lecanemab, donanemab and gantenerumab.

Worldwide, more than 55 million people have dementia, and Alzheimer's disease accounts for 60%-70% of all dementia diagnoses.[2] Older age is the most important risk factor for Alzheimer's disease. The number of patients with Alzheimer's disease doubles about every 5 years beyond the age of 65.[3] By the age of 85 years, about one-third of all people have Alzheimer's disease.

Alzheimer's disease diagnosis

Previous treatments for Alzheimer's disease, namely cholinesterase inhibitors and memantine, have had limited clinical benefit and adverse effects. Because of the limited clinical benefit and adverse effects of these early treatments, there was no urgency to establish a diagnosis, and symptom progression could be observed over time while alternative causes of dementia were excluded. However, with the advent of amyloid-directed monoclonal antibody treatments, this diagnostic approach may be upended. Monoclonal antibodies must be initiated during the early phases of disease. Thus, if the newer treatments become the clinical standard, patients with cognitive complaints will require early diagnoses, including objective evidence of cognitive impairment and a measure of cerebral amyloid burden, each posing several potential clinical hurdles. The current diagnostic approach, absent an assessment for antibody therapy, is described below.

A patient may present for medical evaluation with complaints of cognitive impairment or if family members, friends, or caregivers perceive cognitive changes. Routine screening for cognitive impairments (see below) also may lead to an evaluation for dementia. The initial evaluation should include a thorough history, assessment of daily functioning and independence, review of medications, screening for depression and other relevant psychiatric disorders, assessment of alcohol and illicit drug use, and a complete physical examination. Common cognitive complaints include memory loss, challenges with planning or with problem solving, difficulty completing familiar tasks, confusion about time or place, trouble interpreting visual images or spatial relationships, difficulty speaking or writing, poor judgement, mood or personality changes, and social withdrawal.[4] Evidence of lower performance is needed in one or more cognitive domains, and such change(s) must be greater than would be expected for the patient's age and educational background.[5] As dementia is a progressive disease, continued cognitive decline over time provides further evidence of the diagnosis. Early in its course, focal neurologic impairments are not typically present with the exception of anosmia , which is non-specific.

Since other illnesses can cause cognitive changes, laboratory and neuroimaging evaluations may be considered. Laboratory testing can help to exclude B12 deficiency, hypothyroidism, liver disease, kidney disease, hyperglycemia, infectious diseases such as HIV and neurosyphilis, and other relevant illnesses. Previous guidelines have recommended structural imaging with a non-contrast CT scan or MRI in the initial evaluation of dementia, but not MCI in the absence of other neurological symptoms.[6] CT scans are easily obtained and can be done rapidly, but have considerable radiation exposure. In contrast, MRI better detects subtle vascular changes and hippocampal atrophy, but requires that the patient remains still during prolonged imaging sequences. Neuroimaging can help to characterize associated brain atrophy and distinguish the various causes of dementia, while excluding structural brain disorders such as stroke, hemorrhage, normal pressure hydrocephalus, and tumor. Electroencephalography (EEG) is not routinely recommended in the diagnostic evaluation of cognitive impairment, but may be considered in a secondary evaluation by a dementia specialist.

Some patients with Alzheimer's disease have an early onset and/or a strong family history. In those patients, genetic testing for a familial form of Alzheimer's disease (amyloid precursor protein [APP], presenilin 1 [PSEN1], presenilin 2 [PSEN2]) may be reasonable. However, genetic testing should not be done routinely or without the assistance of a dementia or genetics specialist. Similarly, although the apolipoprotein E (APOE) gene variants confer Alzheimer's risk, APOE testing is not routinely recommended because it has limited clinical utility and poor predictive value

Dementia screening tools

Several brief cognitive screening tools have been validated. Table 1 lists examples of specific screening tools, how they are scored, and their copyright information.

Table 1. Examples of Brief Cognitive Screening Tools

Screening tool	Scoring ranges	Download instructions and copyright information
Saint Louis University Mental Status exam© (SLUMS)	Normal: 27-30 (25-30 with less than high school education) Mild disorder: 21-26 (20-24 with less than high school education) Dementia: 1-20 (1-19 with less than high school education)	Free to use clinically with training: https://www.slu.edu/medicine/internalmedicine/geriatric-medicine/agingsuccessfully/assessment-tools/mental-status-exam.php
Montreal Cognitive Assessment© (MoCA)	MoCA scoring details are provided with training and certification (see download instructions)	Training and certification are required to use the MoCA. Although the screening test can be used freely, there is a fee for training: http://mocacognition. com/
Mini-Cog©	Scoring detailed in website. Total scores of 0, 1 or 2 indicate higher likelihood of cognitive impairment. When greater screening sensitivity is desired, a score of 3 may indicate cognitive impairment.	Free to use clinically with training: https://minicog.com
Mini-Mental Status Examination© (MMSE)	MMSE scoring details are provided purchase (see download instructions)	The MMSE requires purchases for use: https://www.parinc.com/Products/Pkey/237

Importantly, many of these tools can be downloaded directly from the internet, but they are not all free to use. Some have licensing fees; others have specific training requirements. Additionally, the sensitivities and specificities of a screening tool can vary across individual patients based on age, educational background, and culture. A highly educated person, for example, may perceive cognitive changes, but have a normal score on a standardized screening tool. Such an individual may require further evaluation to establish objective evidence of cognitive impairment.

Monoclonal antibody treatments for Alzheimer's disease

The amyloid hypothesis: Alzheimer's disease is characterized by deposition of amyloid-ß peptide in the brain. The amyloid hypothesis posits amyloid-ß aggregation as the primary cause of disease. Based on this hypothesis, monoclonal antibody treatments have been developed that target brain amyloid. However, not all research supports the amyloid hypothesis. For example, some genome-wide association studies have implicated risk genes that are not involved in amyloid-ß processing.[7,8] Many older adults have brain amyloid-ß that fulfills Alzheimer's disease criteria, but the individuals lack symptoms. Additionally, the monoclonal antibodies described below target cerebral amyloid and effectively lower it, but lower amyloid burden did not clearly correlate with improved clinical outcomes. Neurofibrillary tangles and neuron numbers may predict cognitive status in Alzheimer's disease better than amyloid burden.[9]

- **Aducanumab:** June 2021, aducanumab was the first monoclonal antibody directed against amyloid to receive accelerated FDA approval. Two phase-3 trials were conducted, EMERGE and ENGAGE.[10] Study patients had either MCI or mild dementia attributed to Alzheimer's disease. Amyloid-PET scans were used to determine brain amyloid burden. Patients with later stages of disease progression were not studied.

  The primary outcome was measured by the Clinical Dementia Rating Scale Sum of Boxes [CDR-SB]. The EMERGE trial showed statistically significant benefits with high-dose aducanumab therapy, but the difference may not be clinically meaningful (mean change in CDR-SB of -0.39 compared to placebo).[10] Clinically meaningful change for the progression of Alzheimer's disease has been estimated as a CDR-SB change of 1-2.5 points.[11] In contrast to EMERGE, the ENGAGE trial failed to demonstrate any significant differences in the primary outcome. Both trials led to decreases in amyloid burden on amyloid-PET imaging, but changes in amyloid did not directly correlate with clinical outcomes. Adverse events were common, including amyloid-related imaging abnormalities (ARIA). ARIA-E, cerebral edema, occurred in 35% of the treatment cohort versus 3% of the placebo cohort; ARIA-H, cerebral microhemorrhage, occurred in 19% versus 7%; and ARIA-H, siderosis due to cerebral microhemorrhages occurred in 15% versus 2%.[10] Based on the conflicting results between the two trials, the Centers for Medicare & Medicaid Services (CMS) proposed coverage criteria that included mandatory participation in an approved clinical trial.[12] Aducanumab has not yet received traditional FDA approval.

- **Lecanemab:** The phase-3 trial for lecanemab included patients with either MCI or mild dementia due to Alzheimer's disease.[13] The researchers found that treatment led to moderately less decline on the CDR-SB scale among treated patients. The adjusted mean change in CDR-SB scores was 1.21 for lecanemab and 1.66 for placebo (mean difference of -0.45, again not meeting the 1-2.5 point range of minimal clinically important difference).[11] There were greater reductions in amyloid burden with lecanemab compared to placebo. Adverse events were more common with treatment versus placebo: ARIA-H occurred in 14% versus 7.7%, and ARIA-E occurred in 12.6% versus 1.7%.[13]

  In January 2023, the FDA granted accelerated approval for lecanemab, and traditional FDA approval followed in July 2023. CMS will cover lecanemab for people on Medicare who meet the following criteria: 1) be diagnosed with mild cognitive impairment or mild Alzheimer's disease dementia, with documented evidence of beta-amyloid plaque on the brain, and 2) have a physician who participates in a qualifying registry with an appropriate clinical team and follow-up care.[14]

- **Donanemab:** A phase-2 clinical trial of donanemab enrolled 257 patients with MCI or mild dementia attributed to early Alzheimer's disease.[15] The primary outcome was change in the Integrated Alzheimer's Disease Rating Scale (iADRS) at 76 weeks. The study demonstrated a significant change in iADRS (-6.86 with treatment and -10.06 with placebo, p=0.004). At the patient level, interpretation of this result can be difficult. Clinically meaningful change on the iADRS has been estimated at 5 points for MCI, but 9 points for mild dementia.[16]

Phase-3 data were very recently published.[17] Similar to previous trials, patients were included if they had MCI or mild dementia attributed to Alzheimer's disease. Groups were also stratified as low/medium or high tau pathology based on PET imaging. Significant differences between study groups were found for the iADRS (-3.25 in the low/medium tau cohorts; -2.92 in the combined population) and the CDR-SB (-0.67 in the low/medium tau cohorts; -0.7 in the combined population). Brain amyloid decreased significantly in the treatment group compared to placebo. ARIA-E was found in 24% of the treatment group and 1.9% of the placebo group; ARIA-H was found in 19.7% versus 7.4%.[17]

- **Gantenerumab:** In a November 2022 press release, Roche reported that gantenerumab did not meet its primary endpoint in two phase-3 studies.[18] Study participants who received gantenerumab showed slowing of clinical progression of -0.31 and -0.19 points on the CDR-SB compared to the placebo group. Neither result was statistically significant.

Summary

If monoclonal antibodies directed against cerebral amyloid become the treatment standard for Alzheimer's disease, the diagnostic approach to the most common cause of dementia worldwide may be upended. As antibody therapy must be initiated in the early stages of disease, patients with new cognitive complaints will require early clinical evaluations that include objective evidence of both cognitive impairment and high cerebral amyloid burden.

Several screening tools for cognitive impairment are available. As clinicians choose one or more of these tools for their practices, they should learn the various pitfalls and biases in scoring as well as any copyright/licensing requirements.

Lecanemab is the first monoclonal antibody to receive traditional FDA approval, with other similar treatments in the pipeline. Based on the phase-3 trial, lecanemab effectively removed amyloid plaque, but the finding was not directly correlated with cognitive outcomes. If lecanemab therapy is considered, a shared decision-making conversation with the patient, family, and other caregivers must address the high rate of adverse events, including cerebral edema and cerebral hemorrhage, and the limited potential benefit. Lecanemab does not stop progression of Alzheimer's disease, but it may help to slow progression for some patients. The extent that disease progression is slowed, for the individual patient, is difficult to quantify from a mean CDR-SB change of -0.45. Further research on real-world outcomes (RWO) is needed. Optum Health (OCRI) is in late discussions with Lilly around plans to launch a phase IV, RWO trial for MCI and mild dementia using donanemab. If this moves forward, the study would enroll 3600 patients and provide drug therapy for the active treatment patients and imaging for the entire cohort at no cost to the patient or the health system.

Testosterone replacement therapy – cardiovascular and prostate cancer risks

The long-awaited TRAVERSE study was published in the NEJM 7/23. [19] The NIH Testosterone Trials had confirmed modest symptomatic improvement in older men treated with testosterone replacement therapy (TRT) along with improvements in bone density and anemia. [20] Prior to this study, smaller trials and observational studies showed conflicting results on whether TRT increased cardiovascular disease (CVD) risk and no randomized controlled trials had evaluated the risk of prostate cancer. [21] TRAVERSE enrolled 5246 men, ages 45-80 years, who had established CVD or were at high CVD risk and randomized them to TRT vs. placebo. They had symptomatic hypogonadism with two consecutive testosterone levels <300 ng/dL, and the treatment group received transdermal testosterone titrated to the normal male range. The primary endpoint was the occurrence of one or more major adverse cardiac events (MACE).

There was no increase in MACE in the treatment group compared to placebo (7% vs. 7.3%) nor were there differences in any of the MACE sub-components. There was also no difference in prostate cancer incidence (12 cases in the TRT group vs. 11 in the placebo group). Overall, there was a slight (0.2 ng/ml) increase in PSA levels in the TRT group. In the TRT group, there was a slight increase in the rates of pulmonary embolus (0.9% vs. 0.5%), atrial fibrillation (3.5% vs 2.4%) and acute kidney injury (2.3% vs. 1.5%). All of these were statistically significant with p values of <0.05.

Overall, the results of this study are reassuring in terms of CVD and prostate cancer risks. Given the slight increase in pulmonary embolus, atrial fibrillation and acute kidney injury rates, shared decision-making is needed in men with, or at risk of these conditions. Because the Testosterone Trials showed only modest symptomatic improvement in a portion of the men on TRT, treatment should only be continued when there is clear clinical benefit.

COPD exacerbations and bacterial pneumonia rates are less with LAMA-LABA than with ICS-LABA

A recent report of a propensity score-matched cohort study of almost 140,000 patients over age 40 with COPD showed the use of a LAMA-LABA combination inhaler for maintenance therapy, compared with ICS-LABA combination resulted in 8% lower rate of first moderate or severe exacerbations, and a 20% lower rate of first pneumonia hospitalizations. [22] These findings, that long-acting muscarinic antagonists (LAMAs) plus long-acting beta agonists (LABAs), are preferred over inhaled corticosteroid (ICS) plus LABA combinations comport with the GOLD guidelines. [23]

The cohort study excluded patients with a history of asthma, as there is evidence that patients with COPD and eosinophilia such as that often found with asthma, may benefit from an ICS-LABA combo. [24] Data was extracted from the Optum Clinformatics Data Mart on patients who filled a new prescription for either of the two types of combo inhalers from 2014-2019, without having been on either therapy (or triple therapy) in the preceding 12 months. The hazard ratio for first moderate or severe COPD exacerbation in those using LAMA-LABA compared with ICS-LABA was 0.92 (95% CI, 0.89-0.96) and for first pneumonia hospitalization was 0.80 (95% CI, 0.75-0.86).

Study findings reinforce the use of LAMA-LABA therapy over ICS-LABA therapy in patients with COPD and without a history consistent with asthma or eosinophilia and is concordant with the Optum Health COPD algorithm. [25] Patients with asthma, or those with a blood eosinophil count >100 should continue to receive an ICS-LABA combination as initial therapy.

Duloxetine is the only anti-depressant with demonstrated efficacy in treating chronic pain

A recent comprehensive 485-page network meta-analysis (NMA) published in the Cochrane Library examined the evidence of effectiveness of the use of 25 different anti-depressant medications in adults for the treatment of pain across many common chronic pain conditions (except headache). [26] Primary outcomes included pain relief of 50% or more, pain intensity, mood, and adverse events. Secondary outcomes included 30% or more pain relief, physical function, sleep, quality of life, Patient Global Impression of Change (PGIC), serious adverse events, and withdrawal from the study. There were 176 studies included in the analysis, with a total of 28,664 participants. Common pain conditions examined were fibromyalgia, neuropathic pain and musculoskeletal pain.

Duloxetine at the standard dose of 60 mg had a small to moderate effect for the outcome of 50% or greater pain relief (odds ratio (OR) 1.91, 95% confidence interval (CI) 1.69 to 2.17; 16 studies, 4490 participants; moderate-certainty evidence) and continuous pain intensity (standardized mean difference (SMD) −0.31, 95% CI −0.39 to −0.24; 18 studies, 4959 participants; moderate-certainty evidence). In the remaining primary outcomes and all secondary outcomes, the effect size was small, with moderate-certainty evidence. This drug was equally efficacious at the standard dose compared with high dose for most outcomes. Milnacipran was the next most effective, but the certainty of evidence was lower than that for duloxetine. There was insufficient evidence to draw conclusions about effectiveness for any other antidepressant for chronic pain. There was also insufficient evidence to draw conclusions about safety of antidepressants for chronic pain.

Given the thoroughness of the NMA, it is reasonable to consider duloxetine as adjunctive treatment of chronic pain conditions when indicated. As the side effects of duloxetine are dose related and higher doses were not more efficacious, 60 mg daily should be the preferred dose. Use of other antidepressants for this indication are not supported by the current evidence. The studies examined as part of the NMA excluded participants with low mood, so conclusions about effect on mood in those with chronic pain could not be generated.

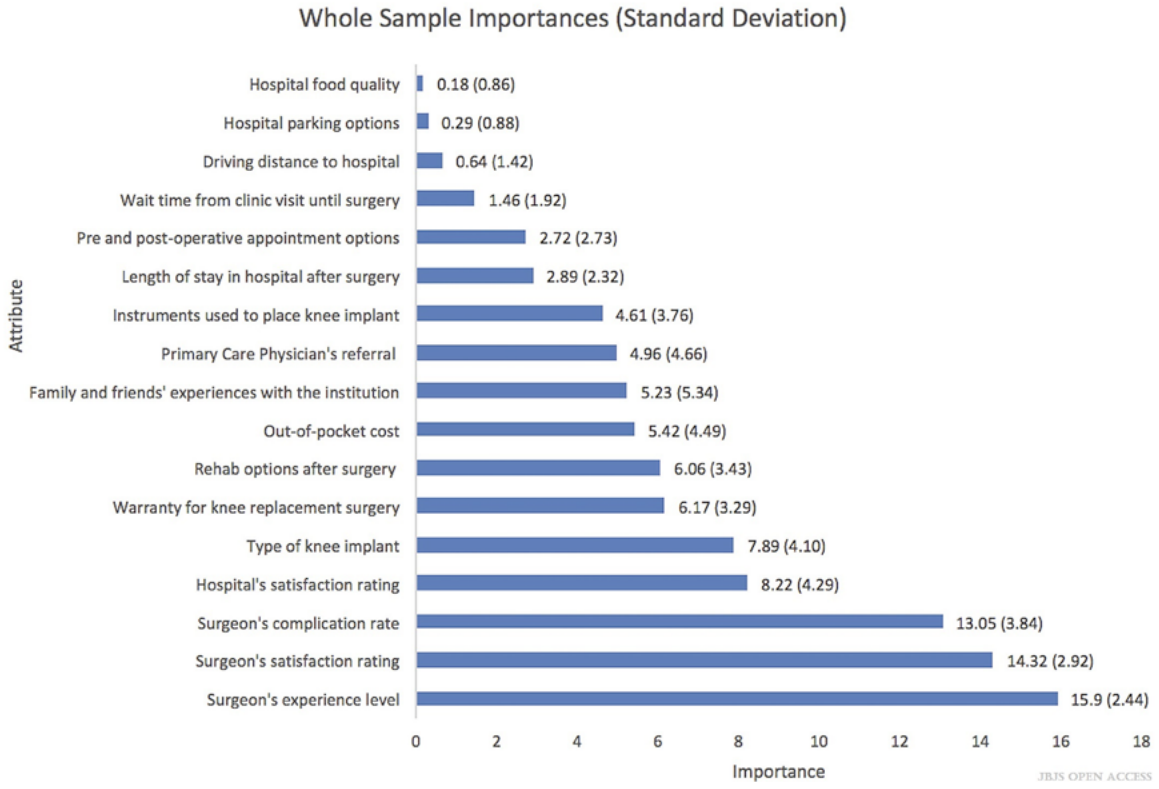
Use of the canalith repositioning maneuver (CRM) for benign paroxysmal positional vertigo (BPPV)

BPPV accounts for almost one million ER visits yearly in the U.S. It presents with vertigo triggered by changes in head position, generally lasting < 60 seconds, and often accompanied by nausea.[27] The majority of cases are related to free floating canaliths in the posterior semicircular canal. Diagnosis of posterior canal BPPV can be confirmed with the Dix-Hallpike maneuver. A recent evidence review examined the literature on the efficacy of the CRM (compared to control) and showed it was associated with higher complete resolution of vertigo at 1 week (OR 7.19). Meta-analysis of three randomized controlled trials in 195 patients showed the use of the CRM was associated with higher conversion to negative Dix–Hallpike at 1 week (OR 6.67). The number-needed-to-treat (NNT) was three. These odds ratios would be even higher were it not for the 64% spontaneous resolution of BPPV within one month. After a successful maneuver, up to 37% of patients may experience mild non-positional vague dizziness for 2–3 weeks (with a negative Dix–Hallpike). This is more common in older patients, those with anxiety, and those whose BPPV had been present for over a week before treatment.

Both the neurology and the ENT academies recommend initial treatment of BPPV with the CRM by all clinicians in all practice settings. Imaging and specialty referral are not indicated for typical BPPV that responds to the CRM. Familiarity with both the Dix-Hallpike maneuver and the CRM are essential for all primary care providers. There are multiple online videos with detailed explanations on how to perform both of these important maneuvers. For patients with recurrent BPPV, there are also patient-directed videos such that they can self-treat for recurrences prior to seeking care.

Characterizing patient preferences surrounding total knee arthroplasty

As part of the Optimal Care model, considerable attention has been given to measuring the quality and efficiency of our specialist colleagues to inform our referral decisions. However, there have been few investigations on which attributes matter most to patients. Investigators from Duke, including Optum Health's Dr. Chad Mather, reported on 174 patients who completed a survey asking them to rank order various attributes surrounding a total knee arthroplasty (TKA) surgery.[28] Patients were recruited when they sought care for chronic knee pain, irrespective of whether they had previously undergone TKA or were considering the procedure. Figure 3 from the paper shows how patients ranked the attributes.



Whole-sample importances. The importance value is written with the standard deviation in parentheses.

It is noteworthy that the top three attributes important to patients all related to the skill and experience of the surgeon. It is also noteworthy that in our healthcare system, these data are often unavailable to patients seeking surgical care. This underscores the importance of the analytical work done by the Optum Health team in helping providers and patients choose specialists based on accurate outcomes data that is important to them. It is also noteworthy that patients were willing to forgo conveniences such as travel distance to the specialist/hospital, waiting time from specialist appointment until surgery to obtain better surgical skill and outcomes. Of only moderate importance to patients were PCP recommendation, out of pocket costs, and post operative rehab options. If as PCPs, we make it clear to patients that our referrals are based on the attributes most important to them, over time they will hopefully place a greater importance on their PCP recommendations.

Nonoperative management of acute Achilles tendon rupture

Acute Achilles tendon rupture is one of the most common orthopedic injuries and may result in severe disability. It is seen more commonly with older age and more active lifestyles. Accumulating data have questioned the benefit of surgical intervention. A recent study from Norway randomized 554 patients into three arms: open surgery, minimally invasive surgery, and nonoperative management. [29]

At 3, 6 and 12 months of follow up, there were no significant between-group changes in the Achilles tendon Total Rupture Score (–17.0 points in the nonoperative group, –16.0 points in the open-repair group, and –14.7 points in the minimally invasive surgery group (P=0.57)). Importantly, there were also no differences in the physical performance and patient reported physical function among the three groups. Although the re-rupture rate was slightly higher in the non-operative group compared to the two surgical groups (6.2% vs 0.6%), over 93% of initial nonoperatively-managed patients avoided subsequent surgeries. The complication rates were significantly higher in both surgical groups compared to the nonoperative group, including nerve injuries (5.2% in the minimally invasive surgery group, 2.8% in the open surgery group, and 0.6% in the nonoperative group). These data are compelling and suggest that the initial management of acute Achilles tendon rupture should be nonoperative.

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Learning objectives	• Discuss multicancer early detection (MCED) testing and the evidence it presents. • Examine two post-hoc analyses of the ASPREE trial around aspirin use and cardiovascular disease, respiratory syncytial virus (RSV) vaccine in older adults and opioid analgesics for low back and neck pain. • Apply medical management in regard to potential harm from oral anticoagulation therapy and the use of shared decision-making in screening and early-stage radiation therapy for breast cancer.

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MCED for cancer detection

Multicancer early detection (MCED) tests measure circulating tumor DNA (ctDNA). This technology has been studied to guide treatment choices, measure response to therapy and for surveillance of established cancers. However, these tests are now being broadly marketed to both physicians and the general population as tests for early cancer detection. The measure of efficacy with these tests is an improvement in cancer survival. However, there are no randomized controlled studies showing an improvement in cancer survival using MCEDs. One company markets directly to consumers and includes a telemedicine consultation with a physician who orders the test.[1] These tests are being recommended yearly by the manufacturers, on top of the current recommendations for other cancer screening tests. Additionally, there is proposed legislation which would, if approved, create mandatory Medicare coverage for these tests. If these were to be implemented at their current cost of $947 per test for the U.S. population aged 50 and older, the yearly cost would be about $100 billion,[1] or ten times the entire budget for the CDC. This does not include the associated costs of PET-CTs and invasive testing that would be needed to evaluate positive test results.

Although it seems attractive to be able to screen for multiple cancers with a single blood test, let's examine the supporting evidence to date. The prevalence of cancer is very low in healthy asymptomatic people in the general population and, therefore, according to Bayes theorem, these MCED tests will often have positive results in persons without detectable cancer, resulting in a low positive predictive value (PPV), which is the most important statistic to consider. Two "demonstration projects" have documented the findings of MCED testing in prospective cohorts totaling ~16,500 subjects, many of whom had prior cancers, tobacco use or hereditary risk factors, and therefore were not representative of the broad population that would use these tests.[2]

The results can be summarized as follows:

- 3.5% (582) of subjects had a positive test.
- 90% of those (521) were false positives and 10% (61) were true positives.
- In the one study that reported the use of PET-CT for a positive screening test, 50% were normal and 50% found suspicious results. 59% of suspicious results were eventually found negative for cancer after additional evaluations, including some with invasive biopsy.
- Many of the diagnosed cancers were of late stage or recurrent cancers, which were not amenable to cure. Of the 582 positive tests, only 2.4% (14) of the subjects had early-stage solid tumors, which might be amenable to cure. This was 0.0008% of the total screened cohort.
- The most frequently found "true" abnormalities were hematologic (19), which would be expected given that hematologic ctDNA would be most easily detected from blood testing. These represented only 0.001% of the screened cohort.

The harms of the frequent false positive findings cannot be overstated. These harms fall into four categories:

- Psychological harms from patients being told that circulating tumor DNA was found in their blood, but a discrete cancer could not be localized.
- Overdiagnosis and subsequent treatment of indolent cancers that would not have progressed in the patient's lifetime.
- Staggering costs associated with the above evaluations.
- Harms from radiation exposure and invasive diagnostic testing and biopsies. About 1% of screened individuals will subsequently undergo full-body PET-CT, which is typically associated with approximately 36 mGy of radiation, the equivalent of 1,800 chest radiographs. At this rate of PET-CT follow-up, 35 women and 25 men would be estimated to develop cancer for each 1 million persons who underwent these screening blood tests at 40 years of age. Thus, paradoxically, many people who undergo MCED blood testing for cancer screening actually will develop cancer because of this testing.[3]

There is currently only one ongoing RCT looking at MCEDs as a cancer screening tool. It has randomized 14,000 patients in the U.K. to MCED screening versus standard of care. The outcome being measured is the detection of late cancers. Results are anticipated in 2026, although cancer survival, the critical determinant of success in screening, is not being measured in this study. The National Cancer Institute recognizes the need to execute the appropriate trials. They have first planned a trial randomizing 24,000 people into a study to evaluate the feasibility of protocol-defined algorithms for diagnostic testing following abnormal screening test results, in preparation for a larger trial. The larger trial will consist of up to three test groups and a control group receiving standard of care screening alone. It is planned to test all-cancer mortality, over a period of seven to eight years, and include up to 300,000 participants, making it the largest cancer screening trial ever performed. It will likely be a decade before results will be available.

So how best to counsel our patients? Unfortunately, a shared decision-making approach won't work here as the fundamental knowledge necessary to inform the patient is not yet available. However, we do know that there are clear harms associated with MCED testing and to date we do not have any evidence of improved cancer survival. We therefore should not order or encourage our patients to have this testing until data from prospective RCTs becomes available. Additionally, pressure needs to be placed on the FDA to mandate the appropriate evidence of benefit prior to test approval or Medicare coverage.

Two post-hoc analyses of the ASPREE trial: Low-dose aspirin use and anemia in the elderly

New studies do not support the use of aspirin for primary prevention of cardiovascular disease (CVD) in elderly patients, resulting in changes to the USPSTF recommendations for aspirin use.[4] The new guideline recommends shared decision-making in adults ages 40–59 given that the net benefit is small. They recommend against initiating aspirin use for primary prevention of CVD in adults 60 years or older. Although the risk of aspirin-induced major bleeding has been well characterized, the incidence of iron deficiency anemia due to low-dose aspirin use is less well studied. Aspirin in Reducing Events in the Elderly (ASPREE) enrolled over 19,000 community residing individuals without prior stroke or CVD or aspirin contraindications, to a primary prevention study of low-dose aspirin versus placebo to assess both the beneficial and harmful effects of aspirin use in this population.[5] The overall trial did not demonstrate any benefit in survival or reduction in the MACE event rate in the aspirin group. A post-hoc analysis of the risk of iron deficiency anemia with aspirin use formed the basis of this report.[6]

The median duration of follow-up in ASPREE was 4.7 years. Hemoglobin was measured annually. Over the duration of the study, the incidence of iron deficiency anemia was 51 per 1,000 patient-years in the aspirin group compared with 43 per 1,000 patient-years in the placebo group, equating to a 19% higher risk with aspirin use. For the entire study population, serum ferritin declined by 16% in the aspirin group compared with 3% in the placebo group. The incidence of major bleeding during the study was 3% in the aspirin group compared with 2.1% in the placebo group, equating to a 43% higher risk with aspirin use. Because hemoglobin levels declined progressively throughout the study in the aspirin group, long-term aspirin therapy would be expected to have even higher rates of iron deficiency anemia. With the appreciation of the risks of chronic iron deficiency anemia with long term aspirin use, this study adds to the evidence showing harm from aspirin use for primary prevention in the elderly.

Two post-hoc analyses of the ASPREE trial: Harms of low-dose aspirin for primary prevention of stroke in healthy elderly

Low-dose aspirin is no longer routinely promoted for primary prevention of ischemic stroke due to the known associated harms, including complications from increased bleeding risk. A recent secondary analysis of the ASPREE trial[7] examined the risk of hemorrhagic stroke and intracerebral bleeding and found a small but statistically significant increase in risk of these events in people on long-term low-dose aspirin, and no difference in ischemic stroke compared to placebo.[8] The study population included over 19,000 adults older than 64, with the majority age 70 and older, who were free of symptomatic cardiovascular disease and were randomized to take daily 100 mg of enteric-coated aspirin or placebo, with a median follow-up period of 4.7 years. As event rates were low, calculations were done based on events per 1,000 person-years. There were 0.5 fewer incidents of ischemic stroke per 1,000 person-years of follow-up in the aspirin group. The hazard ratio for ischemic stroke was not significant at 0.89 (95% CI, 0.71-1.11). The intracranial hemorrhage incidence rate was 0.7 higher. When looking across all types of intracranial bleeding (e.g., epidural, subdural hematomas, subarachnoid hemorrhage, intracerebral bleeding/stroke), hazard ratios were significantly higher for those treated with aspirin (108 individuals [1.1%]) compared with those receiving placebo (79 individuals [0.8%]; HR, 1.38; 95% CI, 1.03-1.84; P = 0.03).

These results show that while event rates are relatively low, there is a small, but important risk of intracranial bleeding in those taking aspirin. Use of aspirin for primary prevention of stroke for this population should not be used routinely.

RSV vaccine in older adults should employ shared decision-making

Based on existing vaccine safety data and available evidence of efficacy in decreasing morbidity from respiratory syncytial virus (RSV) for adults ≥ 60 years old, the Advisory Committee on Immunization Practices (ACIP) (a committee of the Centers for Disease Control and Prevention [CDC]) recently recommended using shared decision-making to decide whether to vaccinate.[9] In May of 2023, two vaccines for adults aged 60 and older were approved for use to mitigate the morbidity and mortality associated with RSV in this age group. ACIP based its guidance on evidence of effectiveness in decreasing RSV-associated lower respiratory tract disease. There was insufficient data to assess efficacy of reducing hospitalization, need for respiratory support or death from RSV. Efficacy data were available for a two-year period. The ACIP recommendation is for a one-time dose. Of note, cost-effectiveness was not taken into consideration for this recommendation. Immunizing against RSV is likely most beneficial for groups that are at highest risk of severe disease. These include patients with frailty, advanced age, significant comorbidities (e.g., COPD, heart failure, DM, CKD, cardiovascular or cerebrovascular disease) or suppressed immune systems, as well as those living in group settings (e.g., long-term care facilities). For otherwise healthy community-dwelling adults, from a health systems perspective, at the current cost of roughly $300 USD per injection, the cost-benefit is not clear.

Opioid analgesics have no role in management of pain in typical musculoskeletal-related acute low back pain and neck pain

A multi-center triple-blinded randomized placebo-controlled trial of 347 adult patients presenting with 12 weeks or less of low back and/or neck pain looked at pain severity over time, and at adverse events.[10] Patients were randomized to receive guideline-recommended care plus opioids or guideline-recommended care plus placebo. Most patients (97%) were recruited from primary care office visits, with the remainder recruited from an emergency room visit. For those in the opioid group, a twice-daily combination of oxycodone/naloxone was prescribed according to protocol and titrated based on regular pain score assessment. Opioids were tapered and stopped when pain score decreased to less than 2 on a 10-point scale or at six weeks of treatment, whichever was sooner. At six weeks, the pain scores did not differ significantly between the two groups (2.78 [SE 0.20]) in the opioid group versus 2.25 (0.19) in the placebo group; adjusted mean difference 0.53, 95% CI −0.00 to 1.07, p=0.051). The rates of reported adverse events was similar between the two groups, although unsurprisingly, the known adverse effects of opioids (e.g., constipation, nausea) was more common in the group taking opioids. In addition to the primary outcome of pain score at 6 weeks, secondary outcomes of pain score at 12 weeks, physical functioning, and other proxy measures of health (e.g., work absenteeism, healthcare utilization, etc.) were similar between groups. More people in the opioid group continued to experience pain at 26 weeks, and this was statistically significant at 52 weeks, favoring the placebo. The placebo group scored better on the mental health subscale of the Short Form 36 (SF-36) at weeks 6 and 12.

In summary, this well-designed trial demonstrated no benefit of opioid analgesia for adult patients with acute low back or neck pain and highlights the potential short- and longer-term harms of using this drug class in these conditions.

Trial of direct-acting oral anticoagulant (DOAC) therapy to reduce stroke and CV events in screen-detected atrial fibrillation shows harm

Oral anticoagulation reduces the risk of ischemic stroke among patients with atrial fibrillation (AF). However, the evidence around the outcomes of anticoagulation in subclinical, screen-detected AF is very different. Implantable loop recorders (ILRs) are increasingly being placed to screen for AF. These devices have a cost of approximately $15,000 per patient and patients receive an additional monthly charge for rhythm monitoring. Clinical trial evidence suggests that screening with ILRs among patients with an increased risks of AF and stroke compared to usual care results in three-fold higher AF detection and subsequent anticoagulant use, but no significant reduction in stroke or overall mortality.[11] These devices are also being placed frequently after a diagnosis of stroke of undetermined etiology, again without strong evidence of clinical benefit using this approach. The 2021 American Heart Association / American Stroke Association clinical practice guideline for secondary prevention of ischemic stroke gives a Class 2a recommendation for long-term rhythm monitoring to detect intermittent AF among patients with cryptogenic stroke. This is a moderate recommendation in which benefits are considered to outweigh risks.[12] However, this guideline recommendation is based on three clinical trials that looked solely at AF detection as the primary endpoint, and not based on improved clinical outcomes including reduction in recurrent stroke.[13,14,15]

Added to this body of literature is a new study which randomized 2,536 patients with subclinical, screen-detected AF to receive either edoxaban or placebo.[16] The mean age of the patients was 78 years. The median duration of the AF was 2.8 hours, and atrial rates were generally greater than 200 beats per minute. The median number of episodes was 2.8 in each patient group. The median CHA_2DS_2 -VASc score was 4. The primary efficacy outcome was a composite of cardiovascular death, stroke or systemic embolism, and the safety outcome was a composite of death from any cause or major bleeding. The trial was stopped at a median follow-up of 21 months, owing to safety concerns and the results of an assessment of futility for the efficacy of edoxaban. There was no significant difference in the primary efficacy outcome of 3.2% per patient-year in the edoxaban group and in 4.0% per patient-year in the placebo group (hazard ratio, 0.81; 95% confidence interval [CI], 0.60 to 1.08; P=0.15). In terms of harm, a safety outcome event occurred in 5.9% per patient-year in the edoxaban group and in 4.5% per patient-year in the placebo group (hazard ratio, 1.31; 95% CI, 1.02 to 1.67; P=0.03), a finding that was statistically significant.

The authors concluded that oral anticoagulation with edoxaban in patients with screen-detected AF did not result in a lower incidence cardiovascular death, stroke or systemic embolism compared to no anticoagulation. However, edoxaban led to a higher incidence of a composite of death from any cause or major bleeding.

To add to the above study results, our data science team at Optum Center for Research and Innovation (OCRI) in conjunction with cardiology researchers at UCSF, used a large deidentified patient data base to identify 48,801 patients with stroke of undetermined etiology who were studied with ILRs versus continuous external monitoring (CEM) lasting between 2 and 30 days.[17] Consistent with the above studies, compared to those with CEM, the ILR group had higher odds of a new diagnosis of AF resulting in initiation of anticoagulants (OR 2.27; [95% CI 2.09, 2.48]), as well as a higher risk of hemorrhagic stroke (OR of 1.60 [95% CI 1.34, 1.93]). There was no difference in mortality. Unadjusted direct medical cost of monitoring was substantially higher in the ILR group ($13,975) compared to CEM ($449). Our conclusion was that although ILRs were associated with more new diagnoses of AF and more initiations of oral anticoagulation compared to long-term continuous external monitors after stroke, there was no reduction in mortality. This finding along with an increased risk of hemorrhagic stroke and higher costs raise the possibility of increased harm caused by the use of ILRs for this indication. In the absence of studies proving clinical benefit, a reconsideration of the use of ILRs after ischemic stroke is warranted. This study was accepted for presentation at the American Heart Association scientific meeting in November 2023 and has been submitted for publication at JAMA Neurology.

Shared decision-making is critical when discussing breast cancer screening both in the elderly and those with limited life expectancy

Breast cancer is the 2nd most common cancer in women in the United States.[18] Breast cancer screening with mammography has been endorsed as an effective public health measure to reduce morbidity and mortality by several professional bodies, including the U.S. Preventive Services Taskforce (USPSTF).[19] The age range and frequency of screening varies among the recommendations, and there is some concern that uniform or blanket recommendations may result in unnecessary screening with resultant, needless over-exposure to radiation and potential overdiagnosis of breast cancer. Similar to overdiagnosis of other conditions such as low-risk prostate cancer, overdiagnosis of breast cancer refers to a diagnosis of an indolent cancer that would not have resulted in symptoms or other impact to the patient had it not been detected in the first place through routine screening of asymptomatic patients. Ongoing trials, such as the WISDOM study,[20] are investigating the efficacy of a more personalized approach to breast cancer risk stratification and screening recommendations using family history and genomic data.

A recent retrospective cohort study of over 54,000 women over age 69 examined the frequency of potential overdiagnosis of breast cancer.[21] Primary findings suggest in women aged 70–74 years, 31% of breast cancer is over-diagnosed through screening. For the age group of 75–84 years, this is 47%, and for those 85 and above that number is 54%. These numbers were even higher when analyzing subgroups with lower life expectancies. As this is a retrospective cohort study and not a prospective randomized controlled trial, the investigators performed additional sensitivity analyses with even more conservative assumptions and the data showed a persistent, albeit lower (15%–44%), rate of overdiagnosis in all age groups.

While the exact rate of overdiagnosis is difficult to pinpoint, the data indicates the risk of diagnosing breast cancer that would not have resulted in overt disease or death increases with increasing age and with decreasing life expectancy. Therefore, a shared decision-making approach is critical when discussing breast cancer screening in asymptomatic individuals, particularly those over age 74. The goal is to thoroughly explore the risks and benefits of screening alongside the risk tolerances and patient preferences of the individual patient. In cases where breast cancer screening results in a breast cancer diagnosis, shared decision-making regarding treatment is also paramount. Active treatment of low-grade cancers (such as ductal carcinoma in situ) in people with limited life-expectancy or frailty may not improve cancer outcomes or comport with patient values.

Omitting radiation therapy in early-stage breast cancer

Most early breast cancers are treated with breast-conserving surgery followed by local radiation therapy (XRT). XRT involves 3–6 weeks of treatment, is associated with significant short- and long-term toxicities, and is costly. Therefore, an effort is underway to identify a population of women with early-stage breast cancer in whom XRT can be omitted.

A recent large prospective trial enrolled 500 patients aged 55 or older with T1N0 tumors that were estrogen and progesterone receptor positive, HERS-2 negative and had a low Ki67 index (a marker of cellular proliferation).[22] Patients with lobular cancer, tumor multifocality, an extensive intraductal component or lymphovascular invasion were excluded due to a higher risk of recurrence. All patients were treated with endocrine therapy (an aromatase inhibitor or tamoxifen) and prospectively followed for five years. The cumulative incidence of local recurrence, at five years was 2.3% (95% CI, 1.2 to 4.1) with the upper boundary of the confidence interval less than the prespecified boundary of 5%. Overall, there were 11 recurrences, 7 contralateral cancers, 23 second primary cancers, and 6 deaths that were reported as first events, for a total of 47 overall and 5-year disease-free survival of 89.9%. A total of 13 deaths occurred (of which only one was related to breast cancer), for a five-year overall survival of 97.2%.

The number of recurrences in the ipsilateral breast was similar to that of new breast cancers observed in the contralateral breast, suggesting that these ipsilateral cancers may in fact have been new breast cancers, also supported by the fact that of the ten cases of ipsilateral breast cancer observed, four occurred away from the site of the original breast cancer. The authors concluded that women 55 years of age or older with T1N0 tumors meeting the above criteria, had a very low risk of local recurrence at five years after breast-conserving surgery when treated with endocrine therapy alone. They noted that the prospective and controlled nature of this study supported their conclusion that such patients are candidates for omission of radiotherapy. Current guidelines recommend against the use of XRT in women aged 70 and older with early-stage hormone receptor positive tumors, so these patients can avoid XRT following breast conserving therapy.[23] Based on this current trial, women meeting the trial criteria should participate in a shared decision-making discussion about whether to forgo XRT following breast-conserving surgery.

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