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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.

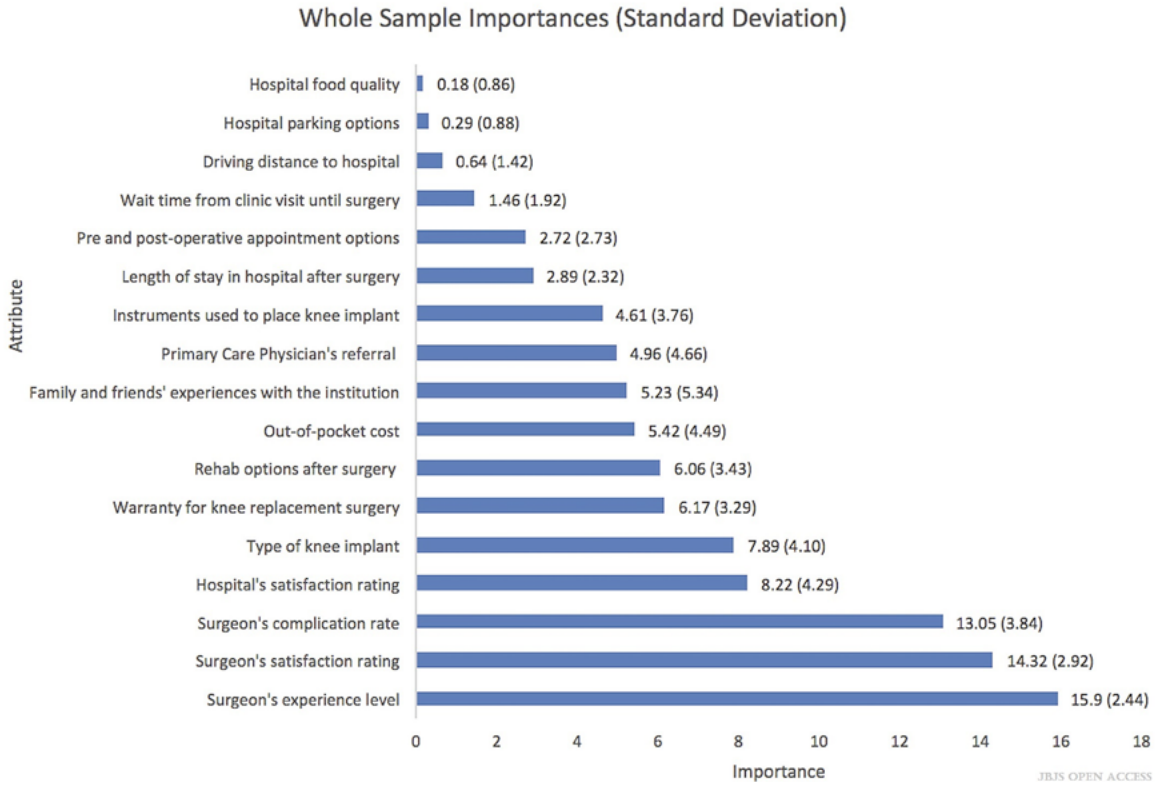
Use of the canalith repositioning maneuver (CRM) for benign paroxysmal positional vertigo (BPPV)

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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Kenneth Roy Cohen, MD, FACP

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

Joshua Jacobs, MD, FAAFP

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

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.

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