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Activity description	Practicing evidence-based medicine (EBM) is important in today's health care environment because this model of care offers clinicians a way to enrich quality, provide patient satisfaction, reduce costs and improve outcomes. A common implementation of EBM involves the use of clinical practice algorithms during medical decision-making to encourage optimal care. This widely recognized practice is designed to address the persistent problem of clinical practice variation with the help of actionable information at the point of care. These e-newsletters will enable health care professionals (HCPs) to put new EBM into practice.
Target audience	This activity is designed to meet the educational needs of physicians, PAs, nurses, nurse practitioners and other HCPs who have an interest in EBM.
Learning objectives	• Understand the risk and assessment of COPD in patients that have never smoked compared to patients who smoke or have been smokers with and without COPD. • Review pharmacological evidence for proton pump inhibitors and gastric cancer risks and selective serotonin reuptake inhibitors (SSRIs) for treating panic disorder. • Discuss medical management studies regarding meniscal tears in younger patients, cognitive behavioral therapy for major depressive disorder, self-administered adult tests for cognitive function and prediction models for pulmonary embolism.

Accreditation statement

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

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

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COPD in never-smokers

COPD has historically been the third leading cause of death both in the U.S. and worldwide, behind cardiovascular disease and cancer. Annually, it causes over 150,000 deaths in the U.S. and over 3 million deaths worldwide. The prevalence of COPD in the U.S. is ~13.5% of the adult population. Unless otherwise referenced, the information in this article is derived from a symposium published in *The Lancet Respiratory Medicine* which included four papers on various aspects of COPD in never-smokers. [1-4]

Most clinicians believe that COPD is almost always associated with longstanding tobacco use, however worldwide this is true in less than 50% of cases. The Social Deprivation Index (SDI) is a composite average of the rankings of the incomes per capita, average educational attainment, and fertility rates of all countries in the Global Burden of Disease study. In countries of middle and lower SDI, air pollution, indoor pollution from poorly ventilated cooking and heating methods, and occupational exposures add up to over 50% of cases, including up to 70% of cases at the low end of the SDI measure.

Even in the U.S., where indoor pollution is less frequent and occupational exposures are regulated more closely than middle and lower SDI countries, over a quarter of COPD cases occur in never-smokers. It is therefore important to have a high index of suspicion and understand the factors that can contribute to COPD in never-smokers. The four major risk factors are asthma, outdoor air pollution, occupational exposures and passive smoking.

The 2022 GOLD Strategy report highlights that asthma "may be a risk factor for the development of chronic airflow limitation and COPD."[5] Asthma may increase the risk for COPD as much as 12-fold compared with those without asthma, after adjusting for smoking. In high SDI countries, asthma is the most common risk factor for COPD in never-smokers, accounting for about 25%-30% of cases in never-smokers. A subset of patients with chronic asthma have persistent airways inflammation rendering them more susceptible to chronic airway remodeling. Potential reasons for COPD developing in an asthmatic include thickening of the basement membrane of the bronchial epithelium, increased airway smooth muscle mass, an increase in mucus-producing cells and subepithelial fibrosis.

Outdoor air pollution contributes to the development of COPD even in high SDI countries. A study from the UK Biobank which controlled for tobacco use in over 300k individuals, showed that about a third of COPD could be attributed to high concentrations of particulate air pollutants.[6] Similar data in the U.S. points to an association of chronic bronchitis in never-smokers and long-term exposure to particulate matter and nitrogen dioxide (NO2).[7] Occupational exposures to vapors, gases, dusts, and fumes is a significant risk factor for COPD in never-smokers. The list of occupational exposures that can lead to COPD is extensive, but the initial screen can be at the level of job "category", with a more extensive occupational history obtained where appropriate. The important job categories that have been linked to occupational asthma and COPD include people working in agriculture, industrial manufacturing and processing, mining, jobs with concentrated exposure to diesel exhaust fumes from machinery and vehicles, and warehouse workers.

Other than the major risk factors noted above, there are accumulating data that at least three other risk factors may contribute to the development of COPD in never-smokers. First, sex may be an important risk factor. Females seem to be at higher risk of COPD than males. High levels of COPD in never-smokers were seen in the third US National Health and Nutrition Examination Survey (NHANES III).[8] Among people with COPD, of the 25% of those with mild-to-moderate COPD who had never smoked, the majority were female (83%). In a study from Rotterdam, the proportion of female participants with COPD who were lifelong never-smokers was 27%, compared with 7% for male never-smokers. One reason could be that females may be more susceptible to COPD due to passive tobacco exposure. Among patients with incident COPD who had never smoked, the proportion of people exposed to passive smoking was 51% and the majority (77%) of those with passive smoke exposure were female.[9] Next, early life exposures may be a significant contributor to COPD in never-smokers. Lung growth continues in the first two decades of life and common conditions that may impair the attainment of maximal lung capacity include premature birth, malnutrition, maternal smoking and severe childhood pneumonia. Because lung function begins to decline in the third decade, nonsmoking individuals with baseline low lung capacity are more at risk for COPD later in life. Lastly, genetics have a significant impact on the future development of COPD. Although alpha one antitrypsin deficiency is widely recognized, it is rare and accounts for only a small fraction of COPD cases. On the other hand, the available data support a model in which the largest contribution to COPD risk arises not from rare variants with large disease impact, but from the combined effect of many common variants with smaller

but combined disease impact. Using a polygenic risk score, those at the highest decile of risk have a 7.5-fold increase risk (European ancestry) or a 4.5 fold increase risk (non-European ancestry) of COPD compared to the lowest decile.[10] Heritability of COPD may be as high as 40%.[11]

So how best can this information be put into clinical practice? Consider the following:

- Counsel patients with a family history of COPD that they may be at increased risk and therefore should avoid not only tobacco use, but also other potential exposures as noted above.
- Clinical presentations of COPD in never-smokers are different than in smokers, with overall milder disease (Table 2). There will often be a younger age at onset, milder airways obstruction, and less exertional dyspnea. Awareness of this different presentation can trigger spirometry assessment in never-smokers who might have COPD presenting with milder symptoms.
- Given the markedly elevated risk of COPD in chronic asthma, persistent asthma should be treated with an inhaled corticosteroid (ICS) as part of the regimen. Additionally, it is prudent to follow patients who have persistent asthma with periodic spirometry to evaluate for subclinical declines in lung function, which could trigger an up-step in therapy. The frequency of spirometry should be guided by the severity of the asthma.
- Never-smokers with COPD may have less severe emphysema, but a higher degree of small airways disease. COPD exacerbations appear to be equally prevalent. They should be treated per the GOLD or COPD Foundation guidelines.
- The risk of lung cancer in never-smokers with COPD is as high as that in smokers who do not have COPD, but somewhat lower than in the population of smokers with COPD. The USPSTF guidelines do not currently recommend CT screening of never-smokers.

	COPD in ever-smokers	COPD in never-smokers
Typical age of onset	>40 years	>30 years
Sex	More males than females affected	Males and females affected equally, or more females than males affected (especially in LMICs)
Symptoms	More cough and dyspnoea (relatively less sputum production)	More cough (relatively less dyspnoea and sputum production)
Respiratory exacerbations	Frequent (and potentially severe)	Frequent (and potentially severe)
Comorbidities	Prevalent	Generally less prevalent
Risk of lung cancer	High	High
Lung physiology	More severe airflow obstruction; greater increase in RV/TLC (hyperinflation); increase in airway resistance; less small airways obstruction; reduced DLCO	Milder airflow obstruction; increase in RV/TLC (hyperinflation); greater increase in airway resistance; more small airways obstruction; normal DLCO
FEV1 decline	Can be rapid	Usually normal
Lung CT imaging	Less air trapping due to small airways obstruction; more emphysema	More air trapping due to small airways obstruction; less emphysema
Sputum inflammatory cells	Greater increase in neutrophils	Increase in neutrophils; relatively greater increase in eosinophils
Pharmacological responses	Long-acting bronchodilators favoured over inhaled corticosteroids in terms of safety and effectiveness, especially among those with predominant emphysema	Not known

COPD=chronic obstructive pulmonary disease. DLCO=diffusing capacity of the lung for carbon monoxide. RV=residual volume. TLC=total lung capacity.

Table 2: Clinical characteristics of COPD in never-smokers compared with ever-smokers[1]

Proton pump inhibitors and risk of gastric cancer

Proton pump inhibitors (PPI) are now commonly used to manage symptoms or treat several gastric conditions. There have been concerns over side effects from PPI agents including infection with resistant pathogens, Clostridium difficile and gastric cancers. Previous studies have suggested an association with gastric cancer but had limitations based on methodologic shortcomings.

Researchers utilized the UK Clinical Practice Research Datalink (CPRD) to look more carefully at the risk of gastric cancer associated with PPI use.[12] The CPRD is a primary care database which contains complete records from 15 million patients. Patients using PPIs were compared with those using histamine-2 receptor antagonists (HR2A) using a new-user active comparator design. Cox proportional hazards models were used to estimate the estimated increased risk for gastric cancer. PPI use was found to have a greater risk of gastric cancer compared to patients using HR2As (see table).

Table: Gastric cancer risk associated with PPI

Agent	New users	Years of follow-up	Gastric cancer cases	Fully adjusted hazard ratio
PPI	973,281	5.1	1,166	1.45
HR2A	198,306	4.2	244	1.0

Kaplan-Meier estimates suggest that the number to harm after five years was 2,121 but only 1,191 after ten years of PPI use. The risk of gastric cancer associated with PPI use is small, but this risk should be considered in evaluating the need for ongoing treatment with PPIs and in creating evidence-based guidelines. Particularly in patients with GERD, PPI's are often continued long term when slow weaning is often
well tolerated

SSRIs likely best for treating panic disorder

A recent systematic review and network meta-analysis suggests several drug classes are more effective than placebo in treating panic disorder with or without agoraphobia.[13] Many of these classes are associated with increased risk of adverse events. The drug class that maximizes efficacy while minimizing risk of adverse events is selective serotonin reuptake inhibitors (SSRIs). The remission risk ratio for this class vs placebo was 1.38 (95% CI 1.26-1.50) while adverse event risk ratio was 1.19 (95% CI 1.01 to 1.41). Specifically, sertraline and escitalopram prescribed at therapeutic doses are the two drugs with the highest remission rate and lowest risk of adverse events in the studies included in
the meta-analysis.

The meta-analysis included 87 studies and over 12,800 participants. However, since the available studies were of moderate to very low certainty level of evidence, the synthesized findings should be interpreted with caution.

Meniscal tears in younger patients: New evidence does not support early surgery

It is critical to understand the benefit of the one million knee arthroscopies performed in the United States each year. Previous studies in patients over 40 years of age have shown there to be no additional clinically meaningful outcomes for patients undergoing surgery for partial meniscectomy compared to exercise therapy. [14,15] Most of the meniscal injuries in this older group of patients are thought to be related to degenerative disease which have not been shown to benefit from meniscectomy.

A recent trial examined the effectiveness of meniscal surgery in patients 18 to 40 years of age.[16] Three quarters of patients had a specific traumatic event. This Danish trial was conducted across seven recruitment sites. Of the 546 patients clinically suspected of having a meniscal tear, 121 had an MRI confirmed meniscal tear and were randomized to surgery or exercise therapy. The type of surgery was determined by the operating surgeon. Surgery was followed by at least a minimal level of postoperative rehabilitation. For patients randomized to exercise, they underwent a specially designed 12-week program with sessions twice a week at one of 19 specific sites. The physical therapists involved in the exercise arm were specially trained and also provided 30-45 minutes of education. Of the 61 patients in the exercise group, 59% completed 18 or more of the possible 24 sessions.

The primary outcome was the between-group difference in change in Knee Injury and Osteoarthritis Outcome Score (KOOS4) from baseline to 12 months. This validated tool has scores that range from 0 to 100 across four domains: pain, symptoms, function in sport and recreation, and quality of life. The minimally clinically significant difference in the KOOS4 is 10 points. Outcomes were collected via online surveys at 3, 6, and 12 months (see table).

Exercise vs surgical outcomes measured by KOOS4

Intervention	# patients	Completed 12 months	Surgery in 12 months	KOOS4 improvement at 12 months		
				Mean	>20%	>50%
Exercise	61	58	16.4 (26%)	16.4	64%	57%
Surgery	60	49	52 (87%)	19.2	76%	38%

In this group of younger patients, 74 % of meniscal injuries were from a specific (traumatic) incident. This trial of exercise vs early surgery for mostly traumatic meniscal tears in younger patients, suggests that a strategy of early surgery was not superior to a strategy of exercise and education with the option of later surgery in improving pain, function, and quality of life at 12 months in young, active adults.

Outcomes do not differ between parathyroidectomy and observation for patients with mild primary hyperparathyroidism

A 2014 guideline recommended surgical parathyroidectomy in eligible patients with primary hyperparathyroidism who meet certain criteria including elevated serum calcium, signs of osteoporosis, or abnormal renal function;[17] although, evidence demonstrating improved clinical outcomes with surgery was lacking.

Given that there are no clear outcome data supporting surgery versus observation in those with mild hyperparathyroidism, authors of a recent study compared surgical parathyroidectomy (n=95 patients) versus observation (n=96 patients) for patients with mild, asymptomatic primary hyperparathyroidism.[18] The primary outcome of the randomized trial was mortality, and various morbidities (cardiovascular events, cerebrovascular events, cancer, bone fractures, and kidney stones) were assessed as secondary outcomes.

After 10 years, outcomes from parathyroidectomy and observation did not differ. A total of 44 deaths and 101 morbidities occurred and were equally distributed between study groups. The authors concluded that parathyroidectomy did not appear to reduce morbidity or mortality.[2] The authors of an editorial about the study wrote that these results provide a strong rationale for the nonoperative management of patients with mild primary parathyroidism.[19]

However, some study limitations deserve mention. Only 68% of randomized patients completed the study. Twenty-three patients in the parathyroidectomy group and 27 in the observation group withdrew. Cross-over also occurred with 18% of the patients randomized to the observation group having surgical treatment during the study period. Lastly, male patients and younger patients were underrepresented, so these results may not be broadly generalizable.

Cognitive behavioral therapy for major depressive disorder is cost-effective in adults

The global burden of disease from major depressive disorder is substantial, causing an estimated 63.2 million disability adjusted life-years lost in 2010 alone.[20] Treatment of this disorder varies, with pharmacotherapy the mainstay in the United States. Cognitive behavioral therapy (CBT) is a form of psychotherapy that focuses on the role of cognitive framing to help influence emotion and behavior to treat major depression. CBT can be delivered in person or via technology (e.g., via the internet) in a guided or unguided manner. It is an attractive adjunct, and a possible first-line alternative for those reticent to being on long-term medication for major depression treatment. A recent systematic review of cost utility analyses for this type of therapy either alone or in combination with usual care suggests this is a cost-effective approach in adults with major depression, when compared to usual care alone.[21] Included studies of adolescent and pediatric populations were inconclusive regarding cost utility.

The authors followed well-established methodologies for selecting studies in both English and Chinese that were published between 2004-2020 for inclusion in their review. Of the 3,306 studies initially identified, 38 qualified for inclusion. The quality of 26 of the studies were characterized as high and 12 as fair. When considering economic evaluations, it is important to state what perspective the cost-benefit is viewed from. In this systematic review, only two of the 38 studies were conducted from the payer perspective, with the remainder from the perspective of society, the health system, or both. Duration of the studies varied, averaging 21 months with a maximum up to five years. Reported costs included both direct costs of major depression care, and indirect costs such as lost productivity, etc. For treatment of major depression in adults, cognitive behavior therapy, either alone or in conjunction with usual care including pharmacotherapy, should be strongly considered.

Can a self-administered test reliably detect changes in cognitive function among adults with cognitive complaints?

Several brief clinical instruments are available for the office-based assessment of cognitive function when adults present with subjective cognitive decline (SCD), mild cognitive impairment (MCI), or dementia. Since approximately two-thirds of patients who present with cognitive symptoms score in the dementia range with office-based testing, it is possible that a self-administered instrument would detect cognitive impairments earlier in the course of disease. As newer treatments become available for Alzheimer's disease and other forms of dementia, earlier detection of cognitive impairment and progression may become relevant for treatment outcomes. In that vein, the Self-Administered Gerocognitive Examination (SAGE) was developed for the patient to self-assess cognitive function.

In a retrospective study, changes in SAGE scores were compared with changes in the office-based Mini-Mental Status Exam (MMSE).[22] Among 424 patients who completed both instruments during the study period, both SAGE and MMSE scores appropriately declined over time when the initial diagnosis was dementia or MCI that later converted to dementia, and the scores appropriately stabilized over time with SCD and MCI without conversion to dementia. A significant decline in SAGE scores occurred at least six months earlier than MMSE scores for MCI converting to Alzheimer's dementia (14.4 versus 20.4 months) and for MCI converting to non-Alzheimer's dementia (14.4 versus 32.9 months). The authors advocated use of the SAGE to detect cognitive decline more rapidly when it occurs.

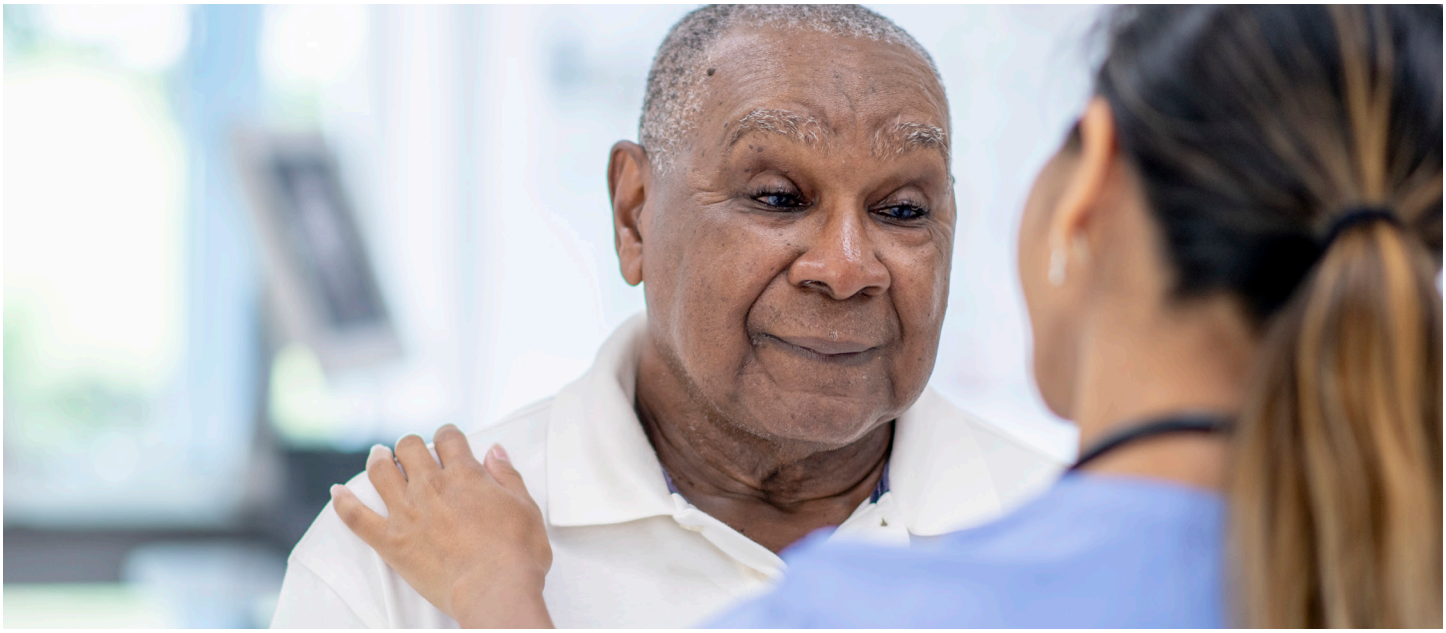
SAGE can be downloaded for free from SAGE - Memory Disorders | Ohio State Medical Center (osu.edu): https://wexnermedical.osu.edu/brain-spine-neuro/memory-disorders/sage#SAGETest.

However, there are study limitations. Most importantly, this was a retrospective study of patients who completed both instruments in the office setting during at least two visits. A psychometrician administered the MMSE and then handed the patient the SAGE to complete on his/her own. The authors noted that patients with vision problems and lower reading levels may not be able to self-administer the instrument. Unfortunately, it is not known if patients can reliably self-administer the instrument from home or when patients with progressive cognitive decline can no longer self-administer the instrument, regardless of office or home environment.

Prediction models for pulmonary embolism

Multiple studies have attempted to identify the ideal combination of clinical decision rules (CDR) (the Wells criteria, Geneva score or YEARS algorithm) and D-dimer testing to aid in the evaluation of suspected pulmonary embolism. In a perfect world the correct combination of a CDR and D-dimer would identify with 100% accuracy those patients that do not have a pulmonary embolism from those that need further testing to aid in the diagnosis.

A recent meta-analysis of 16 studies looked at diagnostic strategies to identify patients with pulmonary embolism.[23] The review included a total of 20,553 patients and evaluated the efficacy defined as the proportion of individuals classified by the strategy as "PE considered excluded" without imaging tests. It also evaluated the safety of the approach, by looking at the diagnostic failure rate. The authors defined this as the predicted 3-month VTE incidence after exclusion of PE without imaging at baseline. Evaluation strategies generally traded off safety vs efficacy, meaning that the strategies with the fewest missed PE's also had the smallest reduction in unneeded imaging. All strategies had acceptable safety levels. Overall, best performing was the Wells rule combined with an age adjusted D-dimer, yielding a low failure rate of 1.1% (CI 0.8% to 1.5%). The efficacy (PE considered excluded) was also high at 47% (CI 42% to 52%) outperforming Geneva and YEARS (although CI for all three overlapped).[24] All of the models are less accurate in ruling out pulmonary embolism in patients over age 80 or with cancer. We continue to advocate for the clinical use of the age adjusted D-dimer combined with Wells criteria for the evaluation of possible PE.



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24. The current OptimalCare algorithm uses the Wells score and age-adjusted D-dimer level.

Kenneth Roy Cohen, MD, FACP

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

John Hitt, MD, MBA

Dr. Hitt 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. Prior to joining Optum, he was Chief Medical Officer at Maricopa Integrated Health System (MIHS) in Phoenix Arizona. Dr. Hitt was a key member of the senior leadership team at MIHS having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and coordinated the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

He served as the Chief Medical Quality Officer for Hennepin Health System. He was a physician leader for VHA (now Vizient), Medical Director at Caremark International and the Vice President of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt graduated from the University of Virginia where he played division one soccer. 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. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

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

Joshua Jacobs, MD, FAAFP

Dr. Jacobs is a Fellow of the American Academy of Family Physicians and an educator with over 20 years of clinical, academic, and leadership experience regionally, nationally, and internationally. He currently serves as National Medical Director for Provider Intelligence within Clinical Performance at Optum Care. In his various roles, he has established new organizational systems to empower clinicians, administrators, researchers, students and staff to thrive and succeed. Examples prior to joining Optum include establishing a new US LCME-accredited medical school; moving the national dialog at the Association of American Medical Colleges (AAMC) medical education services to be more student-centric and evidence-informed using principles of design thinking; helping the country of Singapore transition, accredit and modernize its medical educational model; consulting for the Japanese government on national patient safety initiatives; and creation and oversight of a successful medical device start-up company's research arm culminating in successful FDA clearance. He also has extensive experience in designing and presenting curricula and training sessions, editing, publishing, and grant writing in medical fields.

Dr. Jacobs is a Clinical Professor 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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