OPTUM Care®

Forum for Evidence-Based Medicine

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Activity description	Practicing evidence-based medicine (EBM) is important in today's health care environment because this model of care offers clinicians a way to enrich quality, provide patient satisfaction, reduce costs and improve outcomes. A common implementation of EBM involves the use of clinical practice algorithms during medical decision-making to encourage optimal care. This widely recognized practice is designed to address the persistent problem of clinical practice variation with the help of actionable information at the point of care. These e-newsletters will enable health care professionals (HCPs) to put new EBM into practice.
Target audience	This activity is designed to meet the educational needs of physicians, PAs, nurses, nurse practitioners and other HCPs who have an interest in EBM.
Learning objectives	At the end of this educational activity participants should be able to: • Explore the educational content surrounding resistant hypertension and the high incidence of primary aldosteronism. • Review dapagliflozin for the treatment of chronic kidney disease and its effects. • Apply medical management principles grounded in evidence-based medicine for the surgical treatment of degenerative spondylolisthesis, options for treating frozen shoulder, fecal microbiota transplant and postoperative hernia pain following robotic versus laparoscopic repair.

Accreditation statement

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Credit designation statements

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

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

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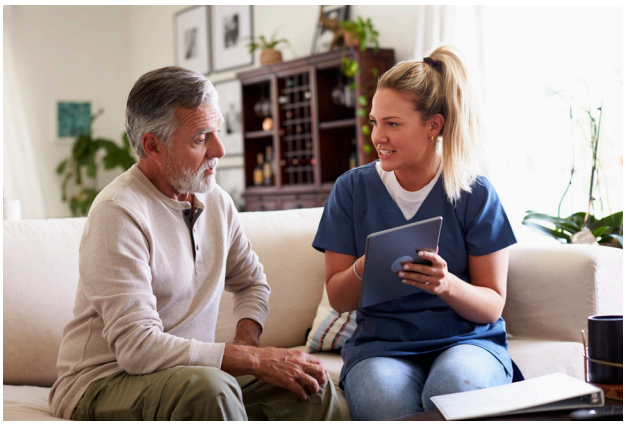
Resistant hypertension and the high incidence of primary aldosteronism

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

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

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



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

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

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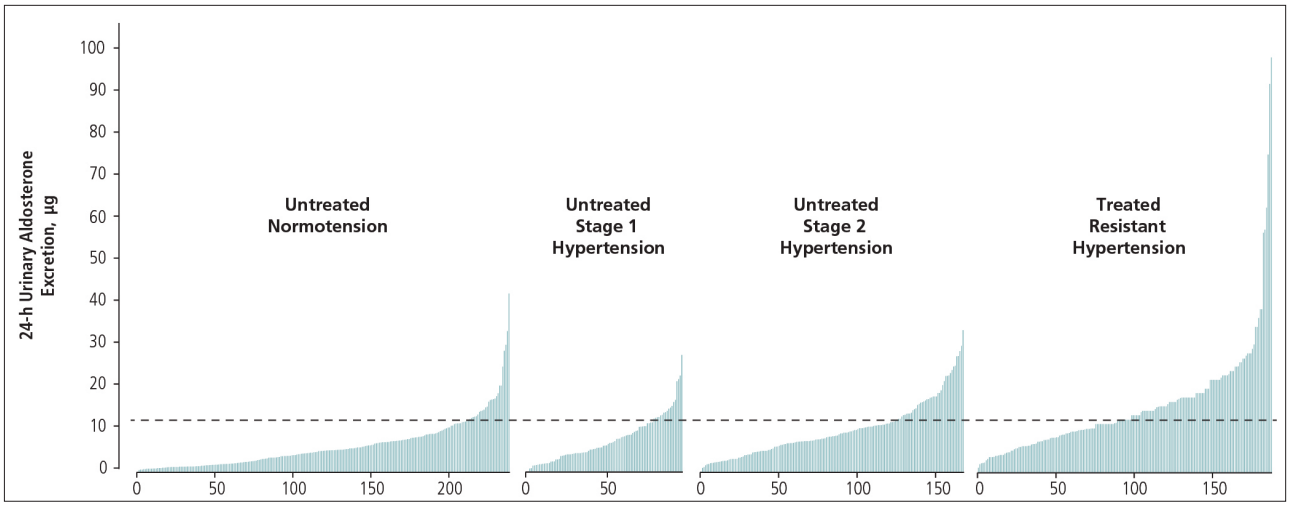

A. The unadjusted urinary aldosterone excretion rate in the context of high sodium balance and renin suppression. Vertical bars represent the unadjusted renin-independent aldosterone excretion rate (y-axis) for each individual participant, ordered from lowest to highest (x-axes). The dashed horizontal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

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

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

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

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

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

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

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

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

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

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

Table 1. Outcomes

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

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

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

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

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

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

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

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

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

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

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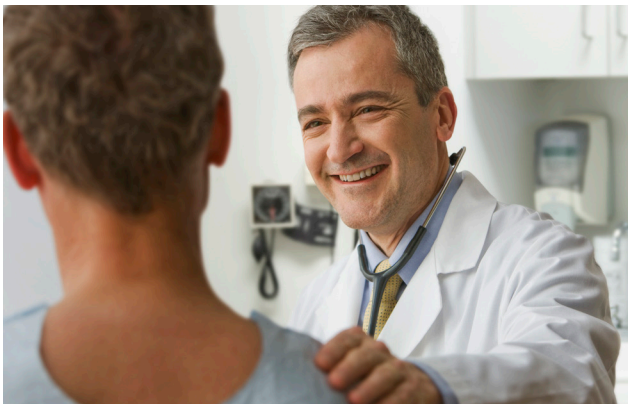
Outcomes at 12 months

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

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

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

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



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

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

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

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

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

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

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

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

Update on the Optum Care shared decision-making tool

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

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

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

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

References:

1. Muntner P, Hardy ST, Fine LJ, et al. Trends on blood pressure control among US adults with hypertension, 1999-2000 to 2017-2018. *JAMA*. 2020;324(12):1190-1200. Doi: 10.1001/jama.2020.14545.
2. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: Follow-up results from the Pressioni Arteriose Monitorate e Loro Associatzioni (PAMELA) study. *Circulation*. 2005;111(14): 1777-1783. Doi: 10.1161/01.CIR.0000160923.04524.5B.
3. Jamerson K, Weber MA, Bakris G, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *New Eng J Med*. 2008;359:2417-2428. Doi: 10.1056/NEJMoa0806182.
4. Raman G, Adam GP, Halladay CW, et al. Comparative effectiveness of management strategies for renal artery stenosis: an updated systematic review. *Ann Intern Med*. 20016; 165(9):635-649. Doi: 10.7326/M16-1053.
5. Baudrand R, Guarda FJ, Fardella C, et al. Continuum of renin-independent aldosteronism in normotension. *Hypertension*. 2017;69(5):950-956. Doi: 10.1161/HYPERTENSIONAHA.116.08952.
6. Kubzansky AD, Adler GK. Aldosterone: A forgotten mediator of the relationship between psychological stress and heart disease. *Neurosci Biobehav Rev.* 2010;34(1):80-86. Doi: 10.1016/j.neubiorev.2009.07.005.
7. Brown J, Siddiqui M, Calhoun DA, et al. The unrecognized prevalence of primary aldosteronism: a cross-sectional study. *Ann Intern Med*. 2020;173:10-20. Doi:10.7326/M20-0065.
8. Funder JW. Primary Aldosteronism: At the tipping point. *Ann Intern Med*. 2020. Published online and accessed on December 1, 2020. Doi.org/10.7326/M20-1758.
9. Williams B, MacDonald TM, Morant SV, et al. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. *Lancet Diabetes Endocrinol*. 2018;6(6):464-475. Doi: 10.1016/S2213-8587(18)30071-8.
10. Williams B, MacDonald TM, Morant SV, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomized, double-blind, crossover trial. *Lancet.* 2015;386(10008:2059-2068. Doi: 10.1016/S014-6736(15)00257-3.
11. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: Case detection, diagnosis, and treatment: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(5):1889-1916. Doi: 10.1210/jc.2015-4061.
12. DeJong C, Mausda C, Chen R, et al. out of pocket costs for novel guideline-directed diabetes therapies under Medicare Part D. *JAMA Intern Med*. 2020;180(12):1696-1699. Doi:10.1001/jamainternmed.2020.2922.
13. Bridwell KH, Sedgewick TA, O'Brien MF, Lenke LG, Baldus C. The role of fusion and instrumentation in the treatment of degenerative spondylolisthesis with spinal stenosis. *J Spinal Disord*.1993;6:461-472. Doi: 10.1097/00002517-199306060-00001.
14. Herkowitz HN, Kurz LT. Degenerative lumbar spondylolisthesis with spinal stenosis. A prospective study comparing decompression with decompression and intertransverse process arthrodesis. *J Bone Joint Surg Am*. 1991;73:802-808. PMID: 2071615.
15. Peul WC, Moojen WA. Fusion for lumbar stenosis-safeguard or superfluous surgical implant? *New Engl J Med*. 2016; 374:1478-1479 DOI: 10.1056/NEJMe1600955.
16. Weiss AJ, Elixhauser A, Andrews RM. Characteristics of operating room procedures in U.S. hospitals, 2011: Statistical Brief #170. 2014 Feb. In: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006 Feb–. PMID: 24716251. hcup-us.ahrq.gov/reports/statbriefs/sb170-Operating-Room-Procedures-United-States-2011.jsp.
17. Austevoll IM, Gjestad R, Solberg T, et al. Comparative effectiveness of microdecompression alone vs decompression plus instrumented fusion in lumbar degenerative spondylolisthesis. *JAMA Netw Open*. 2020;3:e2015015. Doi:10.1001/jamanetworkopen.2020.15015.
18. Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical versus nonsurgical treatment for lumbar degenerative spondylolisthesis. *New Engl J Med*. 2007;356:2257-2270. Doi: 10.1056/NEJMoa070302.
19. Rangan A, Brealey S, Keding A, et al, Management of adults with primary frozen shoulder in secondary care (UK FROST): A multicentre, pragmatic, three-arm, superiority randomised clinical trial. *Lancet.* 2020;396:977–89. Doi: 10.1016/S0140-6736(20)31965-6.
20. Moayyedi P, Yuan Y, Baharith H, Ford AC. Faecal microbiota transplantation for Clostridium difficile-associated diarrhoea: A systematic review of randomised controlled trials. *Med J Aust.* 2017;207:166-172. Doi: 10.5694/mja17.00295.
21. Fischer M, Sipe B, Cheng YW, et al. Fecal microbiota transplant in severe and severe-complicated Clostridium difficile: A promising treatment approach. *Gut Microbes*. 2017;8:289-302. Doi: 10.1080/19490976.2016.1273998.
22. Kelly CR, Yen EF, Grinspan AM, et al. Fecal microbiota transplantation is highly effective in real-world practice: Initial results from the FMT National Registry. *Gastroenterology*. Epub ahead of print. PMID: 33011173. Doi: 10.1053/j.gastro.2020.09.038.
23. Sheetz KH, Claflin J, Dimick JB. Trends in the adoption of robotic surgery for common surgical procedures. *JAMA Netw Open*. 2020;3:e1918911. Doi:10.1001/jamanetworkopen.2019.18911.
24. Petro CC, Zolin S, Krpata D, et al. Patient-reported outcomes of robotic vs. laparoscopic ventral hernia repair with intraperitoneal mesh: The PROVE-IT randomized clinical trial. *JAMA Surg*. 2020:e204569. Doi: 10.1001/jamasurg.2020.4569.

Kenneth Roy Cohen, MD, FACP

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

John Hitt, MD, MBA

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

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

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

Geoffrey Heyer, MD

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

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