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Learning objectives	• Examine the Choosing Wisely® program at 10 years and Optimal Care's progress in eliminating low value care. • Evaluate the cost effectiveness of SGLT-2 inhibitors as first-line pharmacotherapy in adults with Type 2 diabetes mellitus. • Apply pharmacological evidence regarding gabapentin and overdose deaths, hyaluronic acid for osteoarthritis, and recognize when the use of PCSK9 inhibitors or ezetimibebe of value. • Discuss medical management concerning adjuvant chemotherapy, and asymptomatic patients with severe carotid artery stenosis and stroke rate.

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Choosing Wisely® at 10 years and Optimal Care - Are we making progress in eliminating low value care?

This article takes the occasion of the 10th anniversary of the Choosing Wisely® campaign to discuss the program within the context of the Optimal Care model. Choosing Wisely is a partnership between the American Board of Internal Medicine Foundation and the specialty societies. [1] It now comprises 626 measures contributed by 93 specialty societies and has expanded to over 20 countries. [2] It has generated a large volume of literature with 634 articles published last year alone.

Choosing Wisely seeks to minimize patient harm through the use of shared decision-making, discouraging tests and treatments with little benefit, and recognizing the impact of the costs of care on patients and their families. We now understand that this is not simply wasted care, but commonly care that is directly harmful. A recent analysis found that 87.5% of the services the campaign addressed carried a high or moderate risk of direct harm or starting an unnecessary cascade of care. [2] The campaign therefore may have helped keep patients safe. However, critics of the program point to the fact that it has had only a small effect on reducing low value care (LVC).[3] A recent study examining measures of LVC in 556 health systems, encompassing over 11 million Medicare beneficiaries, showed that over a third of patients received LVC tests or procedures.[4] Some of the most highly prevalent LVC medications included opiate use for back pain, antipsychotic use in patients with dementia, and antibiotics for upper respiratory infections. Important invasive LVC procedures included the use of vertebroplasty, epidural steroid injections and coronary artery interventions in asymptomatic individuals.

By allowing the individual societies to establish their own priorities, many of the recommendations largely target services with low impact on cost of care. They also often focus on procedures that are infrequently done and therefore do not have significant impact on the revenue generated by members of the recommending societies. Perhaps most importantly, because Choosing Wisely recommendations must focus on easily definable services, they may miss many tests and procedures that constitute wasteful care and harmful care but cannot be measured with simple claims analyses. For example. over 50% of Choosing Wisely measures are laboratory or imaging tests and only 18% are surgical procedures.

The Optimal Care (OC) model extends the ability to impact LVC beyond that addressed by the Choosing Wisely campaign in several key areas. The OC model is predicated on the fact that up to one third of the health care delivered in the U.S. does not improve health outcomes or quality of life and is therefore either wasted or harmful care. [5,6] It does not require the specialty societies to suggest their recommendations for LVC, but rather examines the clinical outcomes of tests, drugs, and procedures in high-quality evidenced-based literature to determine their effectiveness. As the standard of care has improved for many of the conditions we treat, new drugs, devices, and interventions may show only small increments in effect. Industry sponsors may overemphasize incremental improvements by enrolling large clinical trials where small differences in effect may be statistically significant but may or may not be clinically meaningful. Also, these results are often expressed in relative risk reduction as opposed to absolute risk reduction. To address these trends in clinical trials, OC uses tools such as incremental cost effectiveness, number needed to treat to achieve a given outcome (NNT), number needed to harm with any given intervention (NNH), and comparative effectiveness analyses to examine various treatment options based on metrics and outcomes that are available in the published literature. The goal is to establish the clinically meaningful positive and/or negative effect of any given intervention and deploy this information at the bedside. Finally, the OC team then uses all of the available data to create algorithms that are designed to drive improvements in clinical outcomes while minimizing potential patient harm. Some recent examples of the Optimal Care model that do not exist within the Choosing Wisely framework include:

- Comparative pharmacoeconomic analysis of the two new classes of drugs for chronic migraine showing that the cost to reduce a single monthly migraine day is ~$300 with a CGRP antagonist such as erenumab (Aimovig®), but ~$2,100 with rimegepant (Nurtec®), a “gepant” drug that is being heavily marketed for the treatment of chronic migraine.

- Algorithm development for stable chest pain using the comparative analysis of the new literature comparing the use of coronary artery CTA (with fractional flow reserve) to ischemia testing with nuclear or echo imaging. These studies suggest a 78% reduction in unnecessary heart catheterizations in patients with stable chest pain using the CCTA approach, with improved long-term rates of major adverse cardiovascular events (MACE).[7]
- Analysis of the literature documenting the overtreatment of low-risk prostate cancer and subsequent development of a clinical algorithm and shared decision-making platform (in process) to reduce the unnecessary treatment of many of these patients.[8]
- Analysis of the excess use of non-evidenced drugs and procedures and overuse of lumbar fusion for chronic low back pain (CLBP) to foster the development of a new physiatrist-based model of CLBP to improve outcomes and reduce cost of care for this condition.[9]

Often the available literature is insufficient to determine the efficacy, potential harms, and cost effectiveness of a given treatment or procedure. In these cases, the data science team at the Optum Center for Research and Innovation (OCRI), in collaboration with academic partners, can utilize the extensive data assets within Optum and Optum Care to design "synthetic" randomized controlled trials to test new hypotheses. Results are used to further inform Optimal Care program components to effect change at the bedside to reduce LVC. Studies currently in progress include:

- Comparative analysis of spinal cord stimulator placement and conventional medical management in the treatment of CLBP (submitted for publication).
- Examination of the change in clinical outcomes and cost effectiveness of the placement of implantable loop recorders compared to 30-day event monitoring in patients with cryptogenic stroke.
- Comparative analysis of the efficacy of zoledronic acid and denosumab for the prevention of osteoporotic fracture in women with osteoporosis who have failed oral bisphosphonate therapy.

The ultimate success of the OC model will be measured by documenting not only reductions of LVC and total cost of care, but most importantly, by improvements in patient outcomes. To that end, we have launched our patient reported outcome (PRO) platform and have begun to directly measure the performance of the OC model. It will take several years to scale the PRO initiative and then collect data sufficient for measurement of OC outcomes. These results will then feed back into our shared decision-making modules to inform our patients of the real-world outcomes of their care options. This last important step will ensure that our patients are partnering with their health care team to choose the best care that aligns with their values and preferences.

Preliminary examination of whether using SGLT-2 inhibitors as first-line pharmacotherapy in adults with Type 2 diabetes mellitus is cost effective

A recent large cohort study of adult patients with Type 2 diabetes mellitus (T2DM) who were started on an SGLT-2 inhibitor (SGLT-2i) as first-line pharmacotherapy compared cardiovascular and mortality outcomes in propensity-matched patients to those started on metformin as first-line therapy. [10] Findings demonstrated lower risk in one of the two primary outcome measures in favor of the SGLT-2i group. This was the composite of hospitalization for heart failure (HHF) and all-cause mortality (HHF/mortality). The other primary outcome measure was a composite of hospitalization for acute myocardial infarction (MI), stroke, or all-cause mortality (MI/stroke/mortality). This composite outcome was similar between the two groups. Secondary outcomes measured (HHF alone, all-cause mortality alone) and sub-group analysis showed lower risk of HHF compared with those started on metformin in those patients without previous history of cardiovascular disease (CVD). An additional sub analysis demonstrated those patients with a history of CVD in the SGLT-2i group had a lower risk of MI. The SGLT-2i group had higher rates of genital infections, but other measures of adverse events were similar between groups.

The methodology was robust, but as this is a cohort study, causation cannot be confirmed. That said, based on the data from this study, the number needed to treat (NNT) using SGLT-2 inhibitors instead of metformin as first-line pharmacotherapy for T2DM in patients with no previous history of CVD to prevent hospitalization for heart failure is 37. The NNT for those with a history of CVD to prevent one MI is 11. Using an average annual SGLT-2 inhibitor drug cost of $4,993 per year [11] compared with $156 for metformin, the estimated incremental cost per year to prevent one hospitalization from heart failure using an SGLT-2i as first line pharmacotherapy for T2DM in those without previous CVD is $179,000, which would not be considered cost effective. On the other hand, the cost to prevent one MI in those with previous CVD is $53,200, which may be considered cost effective. Therefore, based on accepted cost effectiveness metrics, the preferred initial therapy for those adults with DM2 but no underlying CVD continues to be metformin. For those patients newly starting drug therapy for DM2 with an existing diagnosis of CVD, SGLT-2 therapy may be considered as initial therapy in those patients where the additional cost is not prohibitive.

There is a higher risk of genital infections using this drug class compared with metformin. Therefore, if an SGLT-2 inhibitor is used, increased surveillance for this treatable complication is indicated.

Gabapentin implicated in overdose deaths

In 2019, the U.S. Food and Drug Administration warned that medicines used to treat nerve pain, gabapentin and pregabalin, can cause serious breathing problems for patients with respiratory disease and those who combine the medicine with opioids. [12] Since gabapentinoids can amplify the effects of illicit opioids, the two drug types are often combined. As a result, gabapentin has been found in nearly 10% of U.S. overdose deaths between 2019 and 2020.[13] Medical examiners have attributed the cause of death to gabapentin in about half of these cases. Data from the State Unintentional Drug Overdose Reporting System suggest that the role of gabapentin in overdose deaths may be growing. [13]

Importantly, care must be taken when prescribing gabapentinoids, particularly since the off-label use of this drug class has dramatically increased, often without an evidence base to support improved outcomes. Patients should be counseled about the added respiratory risks. When patients using prescribed opioids are have known illicit opioid use, gabapentanoid use should be avoided.

Hyaluronic acid for osteoarthritis: Recommendations against its use has not decreased utilization

The use of hyaluronic acid (HA) injections to treat osteoarthritis (OA) has been discouraged as the evidence has not supported benefit over sham injection. In 2013, the American Academy of Orthopedic Surgeons clinical practice guideline recommended against the use of HA. New clinical evidence has not suggested a need to alter this recommendation.

Despite the recommendation against the use of HA, HA utilization has increased from 2012 to 2018. [14] HA use was determined from the Medicare Fee-for-Service Provider Utilization and Payment Public Use Files. HA utilization has increased from 1,090,503 instances in 2012 to 1,209,489 in 2018. This was associated with overall costs for HA use increasing from $290 to

$325 million (2012 and 2018 respectively). The use among orthopedic surgeons remained essentially unchanged over the period. Use among nurse practitioners and physician assistants has increased by 220% and 169% respectively. In contrast, use among rheumatologists has decreased by 26%. Utilization seems to be driven by a desire to avoid or delay total knee arthroplasty, although it is difficult to measure if the revenue associated with its use plays an additional role in utilization. This study demonstrates the difficulty in implementing evidence-based practices or discontinuing practices not supported by evidence when treatment options are limited, clinical trials do not provide compelling evidence of efficacy and recommendations are counter to established norms.

Beyond statins – When may PCSK9 inhibitors or ezetimibe be of value?

Statin therapy is a mainstay in the primary and secondary prevention of cardiovascular disease (CVD), the leading cause of death in the U.S. In some patients, the therapeutic ceiling of statin therapy provides suboptimal risk reduction for adverse cardiovascular outcomes. In other patients, statin therapy is not an option due to intolerance of adverse effects. In these patients, ezetimibe and proprotein convertase subtilisn/kexin type 9 inhibitors (PCSK9i) have been recommended to further reduce LDL-C levels and thereby reduce cardiovascular risk. [15]

A recent systematic review and network meta-analysis of over 83,000 patients by Khan et al. sheds light on the cost-benefit use of these adjunctive medications. [16] The authors quantified the risk reduction of CVD with these agents over a 5-year period for the outcomes of non-fatal myocardial infarction (MI), non-fatal stroke, all-cause mortality, and cardiovascular mortality. The data suggest that when looking at the broad population, adding PCSK9i, ezetimibe or both to those on maximal statin therapy or using them in patients who are statin-intolerant had no significant effect on all-cause or cardiovascular mortality. They then sub-stratified the populations and looked at those with low, moderate, high and very high risk of CVD. Moderate risk was defined as patients with three or four cardiovascular risk factors (median risk of MACE over five years is 7%). High risk was defined as patients with five or more cardiovascular risk factors or a hereditary lipid disorder with no other CV risks (the median risk of major adverse cardiovascular event (MACE) over five years is 18%). Very high risk was defined as patients with established cardiovascular disease or hereditary lipid disorder (median risk of MACE over 5 years is 24%). In the high and very high CV risk populations, there was a small benefit observed in reduction of non-fatal MI and stroke.

From these data we calculated the number needed to treat (NNT) to prevent each outcome in various risk subgroups. Using cost data for these drugs estimated at ~$1,421 per year for ezetimibe and ~$7,056 for PCSK9i;[17] we derived the cost to avoid one event in Table 1.

Table 1. Estimated cost to avoid 1 non-fatal myocardial infarction or non-fatal stroke over 5-year period using PCSK9i and/or ezetimibe in high and very high cardiovascular risk patients.

	NNT adding ezetimibe	Cost to avoid 1 event	NNT adding PCSK9i	Cost to avoid 1 event	NNT adding PCSK9i to those already on ezetimibe	Cost to avoid 1 event	NNT adding ezetimibe to those already on PCSK9i	Cost to avoid 1 event
High risk patients on max statin – non-fatal MI	Did not exceed MID*	N/A	83	$2.93M	Did not exceed MID	N/A	Did not exceed MID	N/A
Very high-risk patients on max statin – non-fatal MI	Did not exceed MID	N/A	63	$2.22M	71	$2.50M	Did not exceed MID	N/A
High risk patients statin intolerant – non-fatal stroke	Did not exceed MID	N/A	63	$2.22M	77	$2.72M	Did not exceed MID	N/A
Very high-risk patients statin intolerant – non-fatal stroke	71	$504,455	48	$1.69M	59	$2.08M	Did not exceed MID	N/A
High risk patients statin-intolerant – non-fatal MI	83	$589,715	59	$2.93M	67	$2.36M	Did not exceed MID	N/A
Very high-risk patients statin- intolerant – non-fatal MI	63	$447,615	43	$1.52M	50	$1.76M	77	$547,085
High risk patients statin-intolerant – non-fatal stroke	77	$547,085	56	$1.98M	67	$2.36M	Did not exceed MID	N/A
Very high-risk patients statin- intolerant – non-fatal stroke	59	$419,195	42	$1.48M	50	$1.76M	77	$547,085

*MID= "minimal important difference" as defined by authors of 12 per 1000 for non-fatal MI, 10 per 1,000 for non-fatal stroke, and 8 per 1,000 for both all-cause and cardiovascular mortality

As can be seen from the results, the costs to prevent one MI or stroke are very high in all situations. For most of the above categories, the reduction in event rates were between 1-2 per 100 patients over five years, hence the high NNT's. Directionally, the results were consistent, small, and only of benefit to patients with high and very high-risk of CV morbidity. Although the absolute reduction in stroke and MI in the high and very high-risk populations was greater with the PCSK9 inhibitors, due to their higher cost, the cost to avoid one event was much higher in this group, far exceeding the Institute for Clinical and Economic Review (ICER) accepted QALY target of $100,000. The cost-benefit ratio for ezetimibe is more favorable though the cost is still above the accepted ICER QALY targets and again, only of benefit for high and very-high risk patients. There was no benefit with either agent in low or moderate risk CVD. These results can help inform our decisions about the costs and benefits of adding PCSK9i's or ezetimibe to maximally tolerated statin doses, and when it may be of benefit to use these drugs in statin intolerant patients.

Adjuvant chemotherapy: Can society afford the cost?

Adjuvant chemotherapy is offered to many patients after chemotherapy treatment. A subset of patients treated with adjuvant chemotherapy benefit, others do not and suffer the adverse consequences of additional chemotherapy. The cost of adjuvant chemotherapy is high and the cost to avert one negative outcome even higher.

To understand the cost of adjuvant chemotherapy, 11 clinical trials reporting outcomes of agents used for adjuvant chemotherapy in the treatment of solid tumors were reviewed over a four-year period.[18] Monthly costs of the agents were obtained from the Micromedex RED BOOK database. Original clinical trial data was reviewed to determine the success of the agent in achieving the primary trial end point. Trials varied in the primary endpoint and included disease progression, relapse-free survival, or the occurrence of a disease related event. From each clinical trial, the number needed to treat to avert one negative outcome was determined. The drug cost per patient was defined as the cost to complete one adjuvant treatment per patient. The overall survival benefit has yet to be shown for any of the agents reviewed.

The total median drug cost of adjuvant chemotherapy was $158,000. The median cost per event averted was $1,610,000.

Improved identification of patients at risk for recurrence is needed to identify the subset of patients most likely to benefit from adjuvant chemotherapy. The current cost to avert a single event is extraordinarily high using current methods to identify patients recommended to receive adjuvant chemotherapy.

Adjuvant chemotherapy for colorectal cancer targeted use

Adjuvant chemotherapy is utilized in many cancers following initial treatment. As noted in the above review, a method to target who might benefit from adjuvant therapy is clearly needed. Ideally, only patients most likely to benefit from adjuvant chemotherapy would be offered this additional treatment. To improve patient selection, the use of adjuvant chemotherapy in patients with stage II colon cancer was directed by the presence or absence of circulating tumor DNA (ctDNA). ctDNA is well known to predict recurrence (>80%) when present after curative-intent therapy.[19] A trial involving 455 patients from 23 Australian centers compared standard management to ctDNA directed therapy.[20] Patients with a performance status of 0-2, without macroscopic evidence of metastatic disease and medically able to receive adjuvant chemotherapy were included. They were randomized 2:1 to the ctDNA group (n=302) and standard therapy (n=153). In the ctDNA group the presence of ctDNA guided recommendation for adjuvant chemotherapy. In the standard therapy group usual criteria to determine high-risk was used. There was no difference in observed survival or recurrence between the groups (see ctDNA table).

Table: ctDNA vs standard therapy outcomes

Parameter	ctDNA guided		Standard therapy		Relative risk (RR)(95% CI)
	ctDNA positive	ctDNA negative	High risk	Not high risk	or hazard ratio (HR)
Received AC	44 of 45	1 of 236	41	182	
% receiving AC	15		28		RR 1.82(1.25-2.65)
2-year RFS	93.5%		92.4 %		RR 1.1% (-4.1-6.2)
3-year RFS	86.4%	92.5	-	-	HR 1.83 (0.79-4.27)
3-year RFS	91.7		92.4		HR 0.96 (0.51-1.82)

AC = adjuvant chemotherapy RFS = recurrence free survival

Importantly, of the 302 patients in the ctDNA randomized group, only 15% required adjuvant therapy, compared with almost twice that number (28%) in the standard therapy group. Importantly, recurrence rates and survival did not differ. This study represents a major step forward in the selection of the subset of patients most likely to benefit from adjuvant chemotherapy. The 13% patients (28% less 15%) who did not receive adjuvant chemotherapy in the ctDNA guided group avoided the complications and side effects accompanying chemotherapy and the added costs of additional therapy without adversely effecting outcomes.

Asymptomatic patients with severe carotid artery stenosis and no surgical intervention had a low annual stroke rate of <1%

As medical and surgical therapies for carotid artery stenosis have evolved, optimal treatment for asymptomatic patients with severe stenosis(es) of 70% to 99% have been questioned. In a recent study, researchers retrospectively evaluated a cohort of community-based patients with severe stenosis of one or both carotid arteries.[21] Between 2008 and 2012, 3,737 study eligible patients were identified from the Kaiser Permanente health system. Of these, 2,314 had not yet had a surgical intervention. The mean duration of follow-up was 4.1 years.

Prior to surgical intervention, there were 133 ipsilateral strokes consistent with a carotid artery distribution, an annual stroke rate estimated at 0.9% per year (95% CI, 0.7%-1.2%). [21] The unadjusted rate of all-cause mortality during the study period was 51.4%. Statin therapy was the most common medical intervention with 74% of patients prescribed a statin at baseline.

The authors list several limitations related to the retrospective nature of the study including the inability to assess aspirin use as it is sold without prescription, the difficulties determining why surgical interventions would be performed in some patients and not others, and the well-published dilemma related to poor documentation of transient ischemic attacks (TIAs). An additional limitation includes the high rate of all-cause deaths and the potential lack of comorbid stroke diagnoses. Overall, in a community-based cohort, there was a relatively low stroke rate among asymptomatic patients with severe carotid artery stenosis(es) and without surgical intervention. Medical therapy is an appropriate option for these patients.

In contrast, a recent systematic review and network meta-analysis examined the results of seven RCT's of surgery compared to stenting for asymptomatic carotid artery stenosis.[22] As has previously been documented, the short-term stroke rate was higher with carotid artery stenting than with surgery. However, relevant to the above results seen with medical management, in those patients who underwent carotid endarterectomy for asymptomatic stenosis in these seven trials, the 30-day combined endpoint of stroke, MI, and death was over 3%. The results of the first contemporary trial of medical management versus surgery for asymptomatic carotid artery stenosis are due at the end of this year and may influence the current recommendation for medical management of asymptomatic carotid artery stenosis.

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

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

Geoffrey Heyer, MD

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine.

He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders. Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons.

Joshua Jacobs, MD, FAAFP

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

Access other Optimal Care evidence-based resources using the links or QR codes below.

Specialty Modules: CME-accredited foundational lectures for primary care that distill key evidence in core specialties that is actionable to promote high-value care and decrease low-value care.

Clinician and Patient Content: A collection of evidence-based clinical algorithms and hand-outs providing actionable decision-support and assistance with shared decision-making.

Grand Rounds: An Optimal Care CME-accredited series of live and on-demand sessions focused on aspects of care important to PCPs and their patients.

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