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Optimal Care Forum for Evidence-Based Medicine

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Learning objectives	• Describe the current practice of screening for prostate cancer with elevated prostate-specific antigen (PSA) levels and recognize the distinction between systematic biopsies versus the MRI-targeted biopsies and the significance to cancer diagnosis outcomes. • Discuss the importance of including a mineralocorticoid receptor antagonist (MRA) in heart failure treatments. • Examine the use of tirzepatide and survodutide for metabolic dysfunction associated steatohepatitis (MASH) and early fibrosis. • Recognize the impact of semaglutide on individuals with myotonic dystrophy type 2 (DM2) and chronic kidney disease (CKD). • Explore the development of a blood test that could aid in the diagnosis of Alzheimer's disease and its diagnostic accuracy. • Analyze the detection rate of colorectal adenomas on colonoscopy when aided by an AI technology.

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MRI-targeted versus systematic biopsy for an elevated prostate-specific antigen (PSA)

When there is a clinical suspicion of prostate cancer based on a PSA elevation, the current practice in most of the U.S. is to perform systematic (12 core) biopsy in all patients. Previous studies have shown that when MRI is done prior to biopsy in this group of patients, many will not have a visible lesion. As summarized in the previous issue of this newsletter, when biopsy is restricted to those patients with a visible lesion on MRI, and targeted to that lesion, both the need for biopsy and the overdiagnosis of insignificant prostate cancers (GG1/Gl 6) are significantly reduced (Forum for Evidence Based Medicine July 2024).[1] The major reason this approach has not been widely adopted in the U.S. is that there are a small number of clinically significant tumors found on systematic biopsy in those individuals without a visible lesion on MRI. Because these cancers can be found and then treated on subsequent screening rounds, the pivotal question is whether delaying the diagnosis in this small number of patients risks the development of incurable prostate cancer between screening rounds.

Against this backdrop is the publication of the updated results of the Swedish GÖTEBORG-2 trial.[2] Men who were 50 to 60 years of age underwent PSA screening. Men with a PSA level of 3 ng per milliliter or higher underwent MRI of the prostate. Men were then randomly assigned to the systematic biopsy group in which they underwent systematic biopsy and, if suspicious lesions were found on MRI-targeted biopsy, versus the MRI-targeted biopsy group which underwent MRI-targeted biopsy only (6,500 men in each group). The results were presented after 4 years and 26,000 rson-years of follow-up.

Through the first 4 rounds of screening, there was a highly significant reduction in the need for biopsy in the MRI-targeted group:

- 7.2% of men in the MRI-targeted group needed biopsy, compared to 24.2% in the systematic biopsy group. This relative reduction in the need for biopsy was 70%.
- The overall rate of cancer diagnosis at 4 years was 2.8% in the MRI-targeted biopsy group versus 4.5% in the systematic biopsy group. With respect to the diagnosis of insignificant (GG1/Gl 6) cancers, there was a 57% reduction in the MRI-targeted biopsy group relative to the systematic biopsy group.
- There was also a 16% reduction in the risk of having clinically significant cancer (GG2-GG5) in the MRI-targeted biopsy group as compared with the systematic biopsy group.

Another way to look at these results is: per 1,000 enrolled men, the MRI-targeted biopsy approach led to 51 fewer men undergoing biopsy and 14 fewer men receiving a diagnosis of insignificant GG1/Gl 6 disease, but it also led to a delay in the diagnosis of GG2 or higher disease in 3 men.

What are the implications for this small group of men with delayed diagnosis of higher-grade disease in the MRI-targeted biopsy group? The authors comment that their data strongly indicate that most prostate cancers become visible on MRI before they become incurable. During approximately 26,000 person-years of follow-up in each group in their analysis, only 5 cases of cancer in the MRI-targeted biopsy group and 7 in the systematic biopsy group were very high risk (either GG 5 or advanced metastatic cancer) detected as an interval cancer. Of the 5 such cancers in the MRI-targeted biopsy group, 4 occurred in men with a PSA level of less than 3 ng per milliliter at the preceding screening visit, so would not have triggered a systematic biopsy using our current U.S. guidelines. This is also consistent with our knowledge of the benefits of cancer screening in general, where it is confined to intermediate growth cancers, with high growth rate cancers not showing improved survival through cancer screening, and low growth rate cancers generally reflecting overdiagnosis. The authors go on to state: "Therefore, diagnosis of a cancer that should be treated is delayed in some instances, but far more often, diagnosis of a cancer that is not likely to ever lead to symptoms, and that otherwise could have led to years of unnecessary active surveillance, the risk of unnecessary treatment, and the stigma of a cancer diagnosis, is prevented. These results should encourage guideline committees to update recommendations around prostate cancer diagnosis and screening."

Use of mineralocorticoid receptor antagonists in heart failure

Two recent publications highlight the importance of including a mineralocorticoid receptor antagonist (MRA) in the treatment of all types of heart failure (HF), not just for heart failure with reduced ejection fraction (HFrEF). The first was a meta-analysis of 4 previous trials including over 13,800 patients and examining the MRAs spironolactone, eplerenone and finerenone.[3] Findings confirmed previous evidence that MRAs used in patients with HFrEF reduced hospitalization (HR 0·63 [95% CI 0·55–0·72] and hospitalization, with or without cardiovascular-related death, and all-cause death (0·72 [0·63–0·82]). Additionally, evidence showed MRAs used in patients with HF with mildly reduced ejection fraction and those with preserved ejection fraction (HFmrEF; HFpEF) also had significant benefit, albeit these effects were more modest. Hospitalization was significantly reduced (0·82 [0·74–0·91]), although mortality was not.

The second publication was of 1 of the 4 studies included in the meta-analysis, above. This study reported on the effects of finerenone in patients with HF with an ejection fraction >40% (HFmrEF and HFpEF) and included about 6,000 patients evenly divided to receive finerenone or placebo.[4] The treatment and placebo groups were roughly equivalent in terms of baseline medication regiment, NYHA HF classification, comorbidities including hypertension, diabetes mellitus and others. Over the course of follow-up (median 32 months), the primary outcome of a composite of worsening HF (that is, first or recurrent unplanned hospitalization or urgent visit for HF) and death from cardiovascular causes was significantly lower in the treatment group (rate ratio, 0.84 [95% CI, 0.74–0.95; P = 0.007). Additionally, the individual outcome of worsening HF was also lower in the treatment group (rate ratio, 0.82; [95% CI, 0.71 to 0.94]; P = 0.006). As with other MRAs, finerenone was associated with increased risk of hyperkalemia. Importantly, comparing these results in the HFmrEF and HFpEF patients to those in the above meta-analysis, the overall improvements with finerenone were similar with respect to hospitalization rates, and once again there was not a significant reduction in mortality rate. Guideline-directed medical therapy for HFrEF typically includes a beta blocker, SGLT2i, ARNI and MRA. Given the high cost of some of these medications, cost-effectiveness should be considered when choosing among a drug class. In the case of MRAs, finerenone typically costs approximately $8,000 per year, whereas the others are available as generics and can cost as little as $60 per year. Use of finerenone combined with a neprilysin inhibitor and an SGLT2i would result in a heart failure drug regimen costing in excess of $20,000 yearly. As the incidence of gynecomastia is markedly increased in men taking spironolactone,[5] eplerenone may be considered for males using MRA therapy. Using MRAs in the treatment of HFrEF, and now HFmrEF and HFpEF, should strongly be considered in all patients.

Tirzepatide and survodutide for metabolic dysfunction associated steatohepatitis and early fibrosis

Metabolic dysfunction associated steatohepatitis (MASH), formerly NASH, is now the second most common cause of cirrhosis and will eclipse alcohol as the most frequent cause by the end of the decade. Metabolic-bariatric surgery has been shown to be highly effective for reversal of MASH and associated hepatic fibrosis, but patient uptake continues to be low. Resmetirom, a selective thyroid hormone receptor beta agonist, was recently approved by the Food and Drug Administration (FDA) as the first pharmacotherapy for MASH with moderate-to-advanced liver fibrosis.[6] The GLP1-RA agents and the related dual receptor agonist compounds (GLP1 receptor agonism combined with GIP or glucagon receptor agonism) have the additional benefits of significant weight reduction, improved glucose tolerance, reduced CV events including CV death, and reduced progression of diabetic nephropathy, among others. If these drugs also have efficacy in reversal of MASH and reduction in progression to cirrhosis, these may be preferred to resmetirom for treatment of MASH as the latter has not been shown to share these important off-target benefits.

Two important phase II randomized controlled trials (RCTs) were published back-to-back in the NEJM in July 2024.[7,8] They evaluated tirzepatide (glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA) and survodutide (glucagon receptor agonist and GLP1-RA) for the treatment of MASH with associated fibrosis. Although these were both placebo-based RCTs and not a direct comparison to resmetirom, it is helpful to review the results of the pivotal phase III trial of this drug in the context of these 2 new trials, as the populations studied in all 3 trials were similar (the tirzepatide study has the additional requirement of a BMI between 27 and 50, with or without diabetes). Alcohol excess was an exclusion in all 3 trials. Evidence of fibrosis was required in all 3 trials, generally in the F2-F3 range.

The tirzepatide trial enrolled 190 patients.

- The percentage of participants who met the criteria for resolution of MASH on liver biopsy without worsening of fibrosis was 10% in the placebo group, 44% in the 5 mg tirzepatide group, 56% in the 10 mg group, and 62% in the 15 mg group.
- The percentage of participants who had an improvement of at least one fibrosis stage without worsening of MASH was 30% in the placebo group, 55% in the 5 mg tirzepatide group, 51% in the 10 mg and 15 mg groups.

The survodutide trial enrolled 293 participants.

- Improvement in MASH with no worsening of fibrosis occurred in 47% of the participants in the survodutide 2.4 mg group, 62% in the 4.8 mg group, and 43% in the 6 mg group, as compared with 14% of those in the placebo group.
- Improvement in fibrosis by at least one stage occurred in 34%, 36%, 34% of the 3-dose ranges, compared with 22% in the placebo group.

Compared to the results seen in the above 2 trials, the resmetirom phase III trial submitted for FDA approval enrolled 966 patients.[9] It showed resolution of MASH with no worsening of fibrosis in 30% of the treated patients compared with 9.7% in the placebo group. Fibrosis improvement by at least one stage without worsening of MASH was seen in 26% of those on the 100 mg dose as compared with 14% in the placebo group.

Once again, these trials were not head-to-head comparisons. However, the improvements in MASH and fibrosis were at least as significant with tirzepatide and survodutide, possibly favoring tirzepatide over the other 2 drugs. In terms of the cost of therapy, the wholesale acquisition (WAC) price of resmetirom is $47,000 yearly. Survodutide has not yet been approved, and the yearly price of tirzepatide is $11,000. Given the multitude of associated benefits of tirzepatide and survodutide — and considering that the most common cause of death in those with obesity or diabetes with MASH remains CVD — if the phase III trials confirm the above benefits, tirzepatide (or metabolic bariatric surgery) should be favored over resmetirom as initial therapy for MASH and early fibrosis.

Effects of semaglutide on CKD in patients with type 2 diabetes

There is now wide recognition of the associated benefits of the SGLT2i and GLP1-RA classes of drugs for type 2 diabetes.[10] Both drug classes have demonstrated reductions in MACE with similar 1%–2% reductions in event rates at 3 years. With respect to the SGLT2is, there have been 2 benefits that have not yet been confirmed with the GLP1-RA class. The most pronounced benefit of the SGLT2is is seen in reduction in hospitalization and improvements in outcomes for patients with HFrEF, and to a much smaller extent, in patients with HFpEF. The second is the improvement in renal outcomes.[11] Although observational data have suggested improvements in renal outcomes with the GLP1-RA class, this has not been demonstrated in placebo based RCTs.

This changed with a study published in the July NEJM, which looked at the impact of semaglutide on those patients with DM2 and associated CKD, defined as eGFR between 50-75 ml/min and uACR >100.[12] Approximately 3,533 patients were randomized to semaglutide 1 mg weekly versus placebo and followed for a median of 3.4 years. Consistent with other studies examining CKD progression, the primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml/min), a 50% reduction in eGFR, or death from renal or CV causes. Primary-outcome events occurred less frequently in the semaglutide group than in the placebo group (5.8 per 100 patient-years of follow-up versus 7.5 per 100 patient-years, for an absolute risk reduction of 1.7%. Lower risk with semaglutide was also observed for a composite of the kidney-specific components of the primary outcome (hazard ratio, 0.79), as well as for death from cardiovascular causes (hazard ratio, 0.71). Secondary outcomes including the rate of eGFR decline, MACE and all cause death also favored semaglutide over placebo.

The number of persons who would need to be treated over 3 years to prevent one primary renal outcome event was 20 (95% CI, 14 to 40). Given the NNT of 20 over 3 years, using the WAC pricing for semaglutide 1 mg of approximately $12,000 yearly, the cost to prevent one primary outcome event per year would be approximately $720,000, which is not considered to be cost effective.

Alzheimer's dementia blood test in the works

The timely diagnosis of Alzheimer's dementia (AD) is helpful in treatment planning including patient and caregiver preparation.[13] As it has been typically a clinical diagnosis that often evolves over time, the introduction of a novel blood test to aid in the diagnosis has the potential to streamline the process. To that end, a recent report described the performance characteristics of a blood test to aid in the diagnosis of AD.[14] The test is used to determine the ratio of plasma phosphorylated tau 217 (p-tau217) to non-p-tau217 alone, and when combined with the amyloid-beta 42 and amyloid-beta 40 plasma ratio, reported as the amyloid probability score 2 (APS2).

In the study, the blood test was compared to AD pathology as determined by abnormal cerebrospinal fluid APS2 and p-tau217 as the primary outcome, and with clinical AD as a secondary outcome. There were 208 patients evaluated from a primary care setting, and 398 from a secondary care (specialist) setting. Half of the patients had pathological findings consistent with AD.

When the plasma samples were analyzed in a single batch in the primary care cohort, the area under the curve (AUC) was 0.97 (95%CI, 0.95-0.99). When the APS2 was used, the positive predictive value (PPV) was 91% (95%CI, 87%-96%), and the negative predictive value (NPV) was 92% (95%CI, 87%-96%). In the secondary cohort, the AUC was 0.96 (95%CI, 0.94-0.98) when the APS2 was used, the PPV was 88% (95%CI, 83%-93%), and the NPV was 87% (95%CI, 82%-93%). When the plasma samples were analyzed prospectively (biweekly) in the primary care cohort, the AUC was 0.96 (95%CI, 0.94-0.98) when the APS2 was used, the PPV was 88%(95%CI, 81%-94%), and the NPV was 90% (95%CI, 84%-96%). In the secondary care cohort, the AUC was 0.97 (95%CI, 0.95-0.98) when the APS2 was used, the PPV was 91% (95%CI, 87%-95%), and the NPV was 91% (95%CI, 87%-95%).

These results are superior to the diagnostic accuracy of the clinical diagnoses by the clinicians in the study. Primary care clinicians had a diagnostic accuracy of 61% (95%CI, 53%-69%) for identifying clinical AD after clinical examination, cognitive testing, and a computed tomographic scan versus 91% (95%CI, 86%-96%) using the APS2. Dementia specialists had a diagnostic accuracy of 73% (95%CI, 68%-79%) versus 91% (95%CI, 88%-95%) using the APS2. Using the percentage of p-tau217 alone demonstrated the same diagnostic accuracy as using the APS2.

Although not yet available widely, the blood test to determine the APS2 or the p-tau217 percentage alone may be useful in confirming a suspected diagnosis of AD. Although the APS2 and p-tau217 had similar diagnostic accuracy, recent trends in AD research studies favor the use of the p-tau217 and this appears to be the clinical assay that will first become available for general use. As a recent published perspective points out, shared decision-making discussions about test interpretation and treatment options are likely to become more complex as the biomarker and monoclonal antibody treatments become more widely available.[15] It is important that these discussions begin before the lab test is drawn. Clinical outcomes and cost-effectiveness studies have yet to be conducted.

AI-enhanced endoscopy and the rising prevalence of small colorectal adenomas

The incidence of colorectal cancer (CRC) in the U.S. has been slowly declining. Currently, the lifetime risk is estimated to be approximately 4%.[16] At the same time, the detection rate of small adenomas on colonoscopy has steadily risen, currently sitting at about 35%–40% of all colonoscopies. Most of these individuals have one to two small adenomas (< 10 mm) and this is a critical point, as there are no data that the presence of these adenomas is associated with an increased risk of CRC.[17] Despite this fact, the recently revised AGA guidelines still endorse a surveillance rate of 7 to 10 years for individuals with one to 2 small adenomas,[17] rather than deferring to the 10-year interval of the average risk general population. Most gastroenterologists continue to surveille these patients at a frequency between 5 to 7 years, with few deferring to the AGA acceptable option of 10 years, and many still using a 5-year interval. This has resulted in an overuse of colonoscopy for surveillance in this average risk population.

Against this backdrop is a new study which examined the detection rate of colorectal adenomas on colonoscopy when aided by an AI technology.[18] The study looked at approximately 2,000 patients with a history of adenomas or family history of CRC (increased risk group), or patients who had a positive FIT test. However, this did not equate to the U.S. average risk screening population and would be expected to have a higher rate of adenomas. They were randomized to standard colonoscopy versus AI-assisted colonoscopy. Adenomas were detected in 57% of the AI-assisted group and 48% of the standard group and the detection rates were similar in both the FIT positive group and the high-risk group. There were no differences in the detection rate of advanced adenomas or CRC. The detection rate of sessile serrated lesions was 3% higher in the AI-assisted group, and 75% of these were in the right colon.

Where CRC screening has had less of an impact on the reduction of CRC mortality is in the detection of flat sessile serrated adenomas in the right colon. These produce less blood than left-sided polyps so are less often detected by FIT, and they are often missed by colonoscopy.[19] As this study demonstrated, detection of advanced adenomas or CRC was no different between the groups, however there was a slight 3% increase in sessile serrated adenoma detection. Interestingly, a study that looked at the detections of right-sided sessile serrated adenomas when the colonoscopist was aware of a positive stool DNA showed a detection rate of 40%, compared to 9% when the stool DNA result was not known.[20]

The question is, would the addition of AI technology simply increase the detection of low-risk adenomas, which do not increase CRC risk, or actually decrease the CRC incidence via detection of more sessile serrated adenomas? Adhering to a 10-year interval in those with one to two small adenomas while at the same time using AI to increase the detection of sessile serrated adenomas, might achieve the best balance of safety, cost and effectiveness.

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Kenneth Roy Cohen, MD, FACP

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

Joshua Jacobs, MD, FAAFP

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

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