GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Multitarget Stool RNA Test: Almost as Good as a Colonoscopy

Multitarget Stool RNA Test: Almost as Good as a Colonoscopy

Multitarget Stool RNA Test for Colorectal Cancer Screening

Barnell EK, Wurtzler EM, La Rocca J, et al. Multitarget Stool RNA Test for Colorectal Cancer Screening [published correction appears in JAMA. 2024 Mar 12;331(10):888]. *JAMA*. 2023;330(18):1760-1768. doi:10.1001/jama.2023.22231

KEY TAKEAWAY: Multitarget stool RNA (mt-sRNA) tests have a 94% sensitivity in the detection of colorectal cancer (CRC) lesions and 46% sensitivity in the detection of advanced adenomas compared to colonoscopy.

STUDY DESIGN: Blinded, prospective, cross-sectional, phase three clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Given low adherence to the gold standard for the detection of colorectal cancer, there is a need for noninvasive, bio-marker-based screening methods with high sensitivity to CRC in average-risk patients who are ≥45 years old. This study aims to establish the overall sensitivity of mt-sRNA in the detection of CRC and high-risk adenomas compared to colonoscopy, the current gold standard.

PATIENTS: Individuals at average risk for colon cancer

INTERVENTION: mt-sRNA

CONTROL: Colonoscopy

PRIMARY OUTCOME: Sensitivity and specificity of mt-sRNA test

Secondary Outcome: Efficacy compared to fecal immunochemical test (FIT)

METHODS (BRIEF DESCRIPTION):

- Patients were invited to participate through social media.
- Interested parties completed an online survey which screened for specific criteria and collected demographic information.
- Patients were excluded from the study if they had a personal known history of CRC, other gastrointestinal (GI) related malignancies, a history of GI conditions that put them at higher risk for CRC, recent history of rectal bleeding within the last month, personal history of colonoscopy within the last nine years or a positive FIT test.
- Before undergoing bowel prep for their respective colonoscopies, patients collected stool samples utilizing a stool collection kit and returned the samples which subsequently underwent mt-sRNA and FIT testing.
- The FIT test consists of an immunochemical fecal occult blood test OC Auto Micro 80 Analyzer (501(k), k041408).
- The mt-sRNA test consists of a nucleic acid extraction instrument (EMAG; bioMerieux) and Bio-Rad's QXDx ddPCR System (510(k), k181661).
- Results of mt-sRNA analysis were compared to both FIT and colonoscopies in the same patient population.
- The sensitivity of mt-sRNA in detecting colorectal neoplasia or advanced adenomas and specificity of detecting no lesions when compared to colonoscopy, the current gold standard, was assessed.

INTERVENTION (# IN THE GROUP): 8,920

COMPARISON (# IN THE GROUP): Same 8,920 patients

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Sensitivity of mt-sRNA test
  - CRC (94%; 95% CI, 81–99)
  - Advanced adenomas (46%; 95% CI, 42–50)
- Specificity of mt-sRNA test
  - Medium-risk adenomas (77%; 95% CI, 74–81)
  - Low-risk adenomas (85%; 95% CI, 83–86)
  - No findings (87%; 95% CI, 86–88)

Secondary Outcome –

- Mt-sRNA was more sensitive in detecting CRC compared to FIT (94% vs 78%; McNemar *P*=.01).
- Mt-sRNA was more sensitive in detecting advanced adenomas compared to FIT (46% vs 29%; McNemar *P*<.001).
- Patient's social backgrounds were found to correlate with sensitivity for advanced adenomas.
  - In patients with low income (<$50,000) in comparison to patients with high income (>$150,000), there was an increased sensitivity in detecting advanced adenomas (55% vs 36%; *P*=.001).

- In patients with public vs private insurance, there was a higher sensitivity rate (56% vs 40%; *P*<.001).

LIMITATIONS:

- Use of decentralized clinical trials for recruitment which introduces variation in colonoscopy procedures and possibly detection depending on physician ability or experience.
- There was also variation in bowel prep, sample collection and pathology analysis and reporting.
- Although the sensitivity was higher in patients with a lower socioeconomic status, it is unclear why this correlation exists.

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Dapagliflozin for Everyone with a Myocardial Infarction and Acute Left Ventricular Dysfunction?

Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure

James S, Erlinge D, Storey RF, et al. Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure. *NEJM Evid*. 2024;3(2):EVIDoa2300286. doi:10.1056/EVIDoa2300286

KEY TAKEAWAY: Dapagliflozin may be beneficial for patients with myocardial infarction (MI) complicated by acute left ventricular dysfunction, but a definite recommendation cannot be made for patients without diabetes or heart failure (HF) due to the low quality of the study.

STUDY DESIGN: Randomized, double-blind, controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to study protocol change of primary outcomes after the study had started and non-preferred statistical methods)

BRIEF BACKGROUND INFORMATION: There is evidence that sodium-glucose cotransporter 2 inhibitors (SGLT-2i) reduce cardiovascular death and hospitalization for heart failure in patients with symptomatic chronic heart failure, regardless of them having diabetes mellitus (DM) as a comorbidity. SGLT-2i's have also been shown to improve cardiometabolic outcomes (weight loss, glycemic control) in patients with DM and established or high risk for atherosclerotic cardiovascular disease. It is not known if this effect is still present in patients without established chronic symptomatic heart failure and/or DM.

PATIENTS: Adults hospitalized with MI complicated by impaired left ventricular systolic function without DM or chronic symptomatic HF

INTERVENTION: Dapagliflozin

CONTROL: Placebo

PRIMARY OUTCOME: Hierarchical composite of death, hospitalization for HF, nonfatal MI, atrial fibrillation/flutter event, a new diagnosis of type 2 diabetes (T2DM), NYHA Functional Classification at the last visit, body weight decrease of ≥5% at last visit
Secondary Outcome: Hierarchical composite of primary outcome without body weight change

METHODS (BRIEF DESCRIPTION):

- Patients: Clinically stable (no episodes of symptomatic hypotension, or arrhythmia with hemodynamic compromise in the last 24 hours), adults ≥18 years old, hospitalized with acute MI (ST and non-ST segment elevation) in Sweden and the UK and impaired left ventricular systolic function (evidenced by imaging or ECG with definite Q waves) without known DM or chronic symptomatic HF.
- Patients were blinded and randomized to one of the following treatments:
  - Dapagliflozin 10 mg once daily
  - Placebo
- This study compared the treatment and placebo groups using a hierarchical composite outcome using the wins ratio.
- With a primary outcome of a hierarchical composite in order of clinical importance of death, hospitalization for HF, nonfatal MI, atrial fibrillation/flutter event, new diagnosis of T2DM, NYHA Functional Classification at the last visit, and body weight decrease of ≥5% at last visit.
- The key secondary outcome excluded the body weight component from statistical analysis. Other secondary outcomes were:
  - Time to the first occurrence of:
    - Cardiovascular death
    - Hospitalization for HF
    - MI (fatal or non-fatal)
    - Major adverse cardiovascular events (MI, stroke, cardiovascular death)
  - Time to new onset of T2DM
  - Change from baseline body weight
  - Time to hospitalization for any cause
  - Time to death of any cause
- In this statistical analysis method, each patient in the treatment and control group are compared to each other and are found to win, lose, or tie.

INTERVENTION (# IN THE GROUP): 2,019

COMPARISON (# IN THE GROUP): 1,998

FOLLOW-UP PERIOD: Median 12 months

RESULTS:

Primary Outcome –

- Dapagliflozin had more wins for the primary hierarchical composite outcome when compared to

placebo (33% vs 25%, respectively; wins ratio 1.3; 95% CI, 1.2–1.5).

Secondary Outcome –

- Dapagliflozin had more wins for the secondary hierarchical composite outcome when compared to placebo (wins ratio 1.2; 95% CI, 1.0–1.4).
- Dapagliflozin reduced body weight from baseline more than placebo (mean difference –1.7 kg; 95% CI, –2.1 to –1.2).
- The rates for the remaining secondary outcomes considered were low and without statistical significance.

LIMITATIONS:

- The original design of the study was modified due to the low number of original primary end-point events (cardiovascular death and hospitalization for HF) collected limiting the power of the study. 772 patients with primary end-point events were needed to give the study a power of 85% to a true hazard ratio of 0.8.
- Results were reported as a win ratio instead of win odds. These results could be misleading in the presence of a large proportion of ties and could misinterpret the similarity between the two interventions.
- Undetermined cause of death was included in cardiovascular death during analysis.
- Power was limited by low rates of initial primary end-point events (cardiovascular death and hospitalization for HF) of other secondary outcomes.
- Patients, regardless of their protocol adherence and continued participation in the trial, were considered for outcomes analysis.
- Funding was received from a pharmaceutical company that manufactures dapagliflozin.

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Unsupervised Online Yoga Program: Effects on Pain and Function in Patients with Knee Osteoarthritis

Effectiveness of an Unsupervised Online Yoga Program on Pain and Function in People with Knee Osteoarthritis: A Randomized Clinical Trial

Bennell KL, Schwartz S, Teo PL, et al. Effectiveness of an Unsupervised Online Yoga Program on Pain and Function in People With Knee Osteoarthritis: A Randomized Clinical Trial. *Ann Intern Med.* 2022;175(10):1345-1355. doi:10.7326/M22-1761

KEY TAKEAWAY: An online unsupervised yoga program improves physical functionality at 12 weeks. However, this improvement was not maintained after 24 weeks.

STUDY DESIGN: Randomized, unblinded, two-group superiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The prevalence of knee osteoarthritis (OA) is high among aging adults. Exercise can improve pain, function, strength, and quality of life in people with osteoarthritis and is universally recommended by clinicians as core treatment. Yoga is becoming a popular form of low-impact exercise. However, yoga can be inaccessible, inconvenient, and cost-prohibitive. This study aims to evaluate the effectiveness of an unsupervised online yoga program on knee pain in individuals with OA.

PATIENTS: Adults with symptomatic knee OA

INTERVENTION: Access to online OA information with an unsupervised online yoga program

CONTROL: Access to online OA information

PRIMARY OUTCOME: Pain during walking and physical function at 12 and 24 weeks

Secondary Outcome: Overall knee pain, stiffness, depression, anxiety, stress, global change, quality of life, self-efficacy, fear of movement, and balance confidence

METHODS (BRIEF DESCRIPTION):

- The trial was coordinated at a single university research center.
- 212 participants from an Australian community were recruited by advertisements, medical practitioners, social media (Facebook), print media, radio media, volunteer database, or recruitment agency.
- Inclusion criteria:
  - >45 years old, activity-related knee pain, and no knee morning stiffness lasting >30 minutes
  - Knee pain on most days of the previous month
  - Knee pain for at least three months
  - Minimum average walking pain score of four (11-point numerical rating scale)
  - Internet access
- Exclusion criteria: Non-English speaking, knee surgery or joint injection in the previous six months, scheduled appointment with orthopedic surgery or planned surgery in the next six months, knee replacement, arthritic condition, regular exercise program in past three months, inability to walk unaided
- An independent biostatistician prepared computer-generated randomization.
- Control participants were granted access to a customized website containing educational material on osteoarthritis, treatment options, exercise, weight loss, pain, sleep, and patient stories.
- Intervention participants were given access to a customized website that contained material identical to the control group but also included a self-directed, unsupervised 12-week progressive yoga program (12 different prerecorded 30-minute Hatha yoga videos to be performed 3 times a week).
  - Each session featured static and dynamic yoga poses intended to activate, strengthen, and stretch core and lower-extremity musculature.
- Outcomes were self-reported using online questionnaires at baseline, 12 weeks, and 24 weeks after randomization.
- Primary outcomes:
  - Knee pain severity during walking: 11 point-NRS scale with scores ranging from 0–10. A score of 0 indicates no pain and a score of 10 indicates the worst pain possible.
  - Difficulty with physical function: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) with scores ranging from 0–68. A score of 0 indicates no dysfunction and a score of 68 indicates maximum dysfunction.

- Self-efficacy was measured on a 10-point pain and other symptoms subscale. Scores range from 1–10 with higher scores indicating greater self-efficacy).
- Comparative analyses were performed using Stata (version 16.1) based on the intention-to-treat principle.

INTERVENTION (# IN THE GROUP): 107

COMPARISON (# IN THE GROUP): 105

FOLLOW-UP PERIOD: 12 and 24 weeks

RESULTS:

Primary Outcome –

- Yoga improved function compared to control at 12 weeks (between-group mean difference –4.0; 95% CI, –6.8 to –1.3).
  - The benefits were not maintained at 24 weeks.
- Yoga did not improve knee pain during walking compared to control at 12 weeks (between-group mean difference –0.6; 95% CI, –1.2 to 0.1).

Secondary Outcome –

- Yoga improved the following compared to control at 12 weeks:
  - Arthritis self-efficacy for pain (mean difference 0.6; 95% CI, 0.1–1.1)
  - Self-efficacy for other symptoms (mean difference 0.6; 95% CI, 0.2–1.0).
- Yoga did not improve the following compared to control: Overall knee pain, stiffness, depression, anxiety, stress, global change, quality of life, fear of movement, and balance confidence.

LIMITATIONS:

- Unblinded study design can lead to inflated treatment effects.
- Unsure if participants were performing yoga correctly because the study was unsupervised.
- Unsure if control participants performed yoga during the study or if intervention participants participated in more intensive non-yoga-related exercise during the study.
- There was a lack of adherence from study participants.
- Not all participants may have had "structural" osteoarthritis, given the study used only clinical diagnostic criteria without radiographs.
- The study required English speakers and access to online resources which may not be generalizable to the rest of the public.

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Is CCBT a Feasible Addition to Depression Management in Low-Income Adult Populations with Limited Access to Resources?

Effect of Computer-Assisted Cognitive Behavior Therapy vs Usual Care on Depression Among Adults in Primary Care: A Randomized Clinical Trial

Wright JH, Owen J, Eells TD, et al. Effect of Computer-Assisted Cognitive Behavior Therapy vs Usual Care on Depression Among Adults in Primary Care: A Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(2):e2146716. Published 2022 Feb 1. doi:10.1001/jamanetworkopen.2021.46716

KEY TAKEAWAY: Computer-assisted cognitive behavioral therapy (CCBT) as an add-on treatment to treatment as usual (TAU), may be feasible and effective at treating depression compared to TAU alone among adults with limited resources.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Depression is a common mood disorder with increasing incidence, as it is the primary diagnosis in 15 million visits per year to the physician's office in the United States. Multiple studies have shown the effectiveness of CCBT in improving access to optimal care and in the treatment of depression. However, few of those studies included patients from low-income groups where decreased internet access, and other social determinants of health may impact the feasibility of CCBT as a treatment option for depression in these populations.

PATIENTS: Low-income adults with depression

INTERVENTION: Computer-assisted cognitive behavioral therapy

CONTROL: Treatment as usual

PRIMARY OUTCOME: Decrease or remission of depression symptoms

Secondary Outcome: Negative self-statements and cognition, anxiety, quality of life, patient satisfaction

METHODS (BRIEF DESCRIPTION):

- Participants were ≥18 years old with a PHQ-9 score of ≥10 and without significant suicidal risk.
  - 75% of participants had less than a college education, and 62% reported an annual income of less than $30,000.
- Participants were randomized into one of the following treatment groups:
  - In addition to TAU, the intervention group received CCBT for 12 weeks using a nine-lesson Good Days Ahead (GDA) computer program, and 12 telephone support sessions, with an average of 20 minutes total support time per week.
  - The TAU-only comparison received standard clinical care which was uncontrolled and included the use of antidepressants and psychotherapy.
- Change in depression symptoms indicated by the PHQ-9 score was measured at baseline, after 12 weeks of intervention; and three and six months post-treatment.
- Response or remission of symptoms was measured using the PHQ-9 score.
  - PHQ-9 scores ranged from 0–27. A score of 1–4 indicated minimal depression, 5–9 indicated mild depression, 10–14 indicated moderate depression, 15–19 indicated moderately severe depression, and 20–27 indicated severe depression.
  - The response was defined by a 50% reduction in baseline scores and remission was defined as a PHQ-9 of <5.
- Anxiety was measured at posttreatment and at the three and six-month follow-up visits using Generalized Anxiety Disorder-7 (GAD-7). Scores ranged from 0–21, with higher scores indicating increasing severity of anxiety.
- Negative cognition was measured using the Automatic Thoughts Questionnaire (ATQ), a 30-item instrument that measures the frequency of automatic negative statements against the self.
  - ATQ Scores ranged from 30–150, with higher scores indicating a higher level of automatic negative self-statements.
- Quality of life was measured using the Satisfaction with Life scale (SWLS), which ranged from 5–35 with higher scores indicating higher life satisfaction.
- Participants' view of the quality of treatment received and patient satisfaction was measured, using the Client Satisfaction Questionnaire-8. Scores

ranged from 8–32, with higher values indicating higher satisfaction.

INTERVENTION (# IN THE GROUP): 95

COMPARISON (# IN THE GROUP): 80

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- CCBT reduced depression symptoms more than TAU alone at post-treatment (mean difference −2.5; 95% CI, −4.5 to −0.9).
- CCBT continued to be more effective than TAU at:
  - Three months (mean difference −2.3; 95% CI, −4.5 to −0.8)
  - Six months (mean difference −3.2; 95% CI, −4.5 to −0.76)
- At post-treatment, the response rate, defined as a 50% reduction in pre-treatment PHQ-9 scores, was 58% (95% CI, 46–70%) in the CCBT group compared with 33% (95% CI, 21–46%) in the TAU group.
- The remission rate, defined as a PHQ-9 score of <5, was 27% (95% CI, 16–38%) in the CCBT group compared with 12% (95% CI, 3.3–21%) in the TAU group.

Secondary Outcome –

- In the CCBT group there were larger differences in all secondary outcomes compared to TAU at post-treatment:
  - Negative cognition (mean difference −14; 95% CI, −20 to −3.1)
  - Anxiety (mean difference −2.8; 95% CI, −3.8 to −0.7)
  - Quality of life (mean difference 3.3; 95% CI, 0.8 to 5.1)
  - Patient satisfaction (effect size 1.19; p<.001)
- All secondary outcomes were significantly improved with CCBT compared to TAU at three and six months, except anxiety at six months.

LIMITATIONS:

- Black and female patients were overrepresented in this study limiting generalizability.
- CCBT was not compared with traditional therapies like standard CBT or TAU with clinician support.
- Participant use of antidepressants and other non-study psychotherapy was uncontrolled, which may impact the accuracy and validity of study findings.
- Both groups had a limited number of treatment sites and a low treatment completion rate.
- 30% of patients had no internet access, therefore the institution provided laptops with internet access. This limits feasibility and ability to implement due to cost and accessibility.
- Potential adverse effects of CCBT were not measured among participants.

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Up in Smoke: Is Vaping a Safe, Viable Option for Cigarette Abstinence?

Cigarette Smoking Abstinence Among Pregnant Individuals Using E-Cigarettes or Nicotine Replacement Therapy

Wen X, Chung MV, Liszewski KA, et al. Cigarette Smoking Abstinence Among Pregnant Individuals Using E-Cigarettes or Nicotine Replacement Therapy [published correction appears in JAMA Netw Open. 2023 Oct 2;6(10):e2338725*]. JAMA Netw Open.* 2023;6(9):e2330249. Published 2023 Sep 5. doi:10.1001/jamanetworkopen.2023.30249

KEY TAKEAWAY: Among pregnant patients who smoked cigarettes before pregnancy, e-cigarette is considered a more successful method of abstaining from cigarette smoking compared to traditional nicotine replacement therapies (NRTs).

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Cigarette smoking is one of the most important modifiable risk factors during pregnancy, with the potential to improve both maternal and neonatal morbidity and mortality outcomes. New methods of NRT, such as e-cigarettes, may provide a solution for reducing risks and harms during pregnancy.

PATIENTS: Pregnant patients

INTERVENTION: E-cigarettes

CONTROL: NRTs (nicotine patches and gum)

PRIMARY OUTCOME: Abstinence rates from cigarette smoking

METHODS (BRIEF DESCRIPTION):

- A secondary data analysis was conducted using the United States Pregnancy Risk Assessment Monitoring System (PRAMS), which employed mail and telephone surveys to assess maternal behaviors and attitudes around pregnancy.
- About 30% of patients were in each age category from 20–24, 25–29, and >30 years old; 79% were non-Hispanic White; 61% had a high school diploma or lower education level; 59% had an annual household income of <$24,000; 44% of patients were primigravida; and the mean pre-pregnancy BMI was 27.
- Pregnant patients in the US who smoked cigarettes before pregnancy and used NRT or e-cigarettes before pregnancy or intrapartum were included in the study.
- Non-users of traditional cigarettes, participants reporting neither NRT nor e-cigarette use to quit smoking and participants who used both e-cigarettes and NRT during pregnancy were excluded from the study.
- Participants were categorized into three groups:
  - NRT during pregnancy (n=372)
  - Existing e-cigarette use during pregnancy (n=890)
  - New e-cigarette users during pregnancy (n=67)
- The primary outcome measure was based upon the response to patients' self-reported number of cigarettes smoked on average per day in the three months before pregnancy and for the last three months of pregnancy.
- Abstinence was defined as self-reported zero cigarettes smoked in the last three months of pregnancy.
- Responses were categorized as: ≥41 cigarettes; 21–40 cigarettes; 11–20 cigarettes; 6–10 cigarettes; 1–5 cigarettes; “I didn’t smoke then” (equivalent to 0 cigarettes)

INTERVENTION (# IN THE GROUP): 957

COMPARISON (# IN THE GROUP): 372

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Smoking abstinence among all (existing and new) e-cigarette users was significantly higher than participants who used NRT during pregnancy (48% vs 18%, respectively; adjusted odds ratio [aOR] 2.5; 95% CI, 1.2–5.2).
- Existing e-cigarette users had a significantly higher rate of smoking abstinence compared to NRT users (50% vs 18%, respectively; aOR 2.6; 95% CI, 1.2–5.5).
- There was no significant difference in smoking abstinence rate between new e-cigarette users and NRT users (15% vs 18%; aOR 1.1; 95% CI, 0.22–5.9).

LIMITATIONS:

- Self-reported data was subject to underreporting, recall bias, and selection bias.
- There was no data on whether e-cigarette use before pregnancy was initiated for cigarette abstinence or whether e-cigarettes were just preferred over combustible cigarettes (interpretation bias).

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