1. **Movement to Reform Pharmacy Benefit Managers Reaches a Boiling Point Nationwide**

A wave of reforms to the $400 billion-a-year industry of pharmacy benefit managers (PBMs) is cresting across the U.S. According to the National Academy for State Health Policy, 101 PBM reform bills are being considered in 41 states this year.

PBMs (such as CVS Caremark, OptumRx, and Express Scripts) contracts typically keep pricing and rebate data secret, leading many to conclude they are partly to blame for the rising price of drugs, which itself is the fastest-rising part of the health-care sector.

As an example, the Ohio Department of Medicaid released its analysis showing that in 2017, CVS Caremark and OptumRx charged taxpayers $224 million more for drugs than they reimbursed pharmacists. That was three to six times the going rate, according to the analyst who did the report, which didn’t look at whether the PBMs were pocketing portions of rebates and other fees they were collecting.

**Tau and Amyloid PET Images in Former National Football League Players**

*Is there in vivo evidence of tau- or amyloid-related changes in former National Football League players?*

Chronic traumatic encephalopathy (CTE) is a tau-related neurodegenerative process with minimal amyloid deposition found in people with repetitive head impacts. Clinically, both cognitive and neuropsychiatric symptoms can occur. To determine whether tau and amyloid deposition can be identified during life in patients diagnosed with CTE, researchers used flortaucipir positron-emission tomography (PET) to identify any tau-related changes and florbetapir PET to identify any amyloid deposition in 26 former National Football League (NFL) players with cognitive and neuropsychiatric symptoms and in 31 controls without histories of traumatic brain injury. In this manufacturer-funded study, participants also underwent screening mental status exam, neuropsychological testing, and neuropsychiatric assessments.

Former players had at least 2 years of NFL experience and 12 years total tackle football experience. The mean age of both groups was about 60 years. More former players than controls were black. The mean screening mental status exam score was lower in the former-player group than in the control group. As a group, former players had higher flortaucipir uptake in the bilateral superior frontal, bilateral medial temporal, and left parietal lobes; correlation coefficients between these brain areas and years of play were about 0.5. Neuropsychological and neuropsychiatric results were not associated with uptake in any of these brain regions. Florbetapir uptake did not differ between the former player and control groups. Only one former player had increased florbetapir uptake.

**COMMENT:** This study provides in vivo evidence of tau-related changes suggestive of CTE in symptomatic former NFL players but a relative absence of amyloid deposition suggestive of Alzheimer disease (AD). Although the tau-affected regions did not correspond to neuropsychological or neuropsychiatric assessments, the sample size was small. Following the path of AD biomarker research, future studies should include asymptomatic participants at increased risk for repetitive head impacts.


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**Lancet 2019 Apr 4**

**Is the Conventional Wisdom on Alcohol and Stroke Wrong?**

*A study in China suggests no causal association between moderate intake and lower stroke risk.*

Several epidemiologic studies have shown that low to moderate alcohol consumption is associated with decreased risk for cardiovascular (CV) disease, including ischemic stroke. However, the nature of these studies makes establishing a causal connection difficult. In an analysis of residents from China who provided blood samples in the China Kadoorie Biobank, more than 500,000 adults (mean age, 52 years) provided blood samples and medical information during the period 2004–2008 and were followed for 10 years. Investigators recorded CV outcomes (including ischemic stroke, brain hemorrhage, and myocardial infarction) using either health registries or electronic records. In addition, the researchers genotyped 161,498 of the participants for variants that affect alcohol metabolism. The authors then evaluated vascular disease outcomes according to self-reported alcohol intake and genotype status.
Rates of regular alcohol consumption were 33% in men and 2% in women. Men who consumed 100 g of alcohol per week (1–2 drinks per day) had a lower risk for all three outcomes than both nondrinkers and heavy drinkers. By contrast, genotype-predicted alcohol intake had a continuous relationship with both intracerebral hemorrhage (relative risk with 280-g intake per week, 1.58) and ischemic stroke (relative risk, 1.27). In the genotype analysis, alcohol intake had a positive association with systolic blood pressure and no association with myocardial infarction. The authors conclude that the apparent protective effect of moderate alcohol on CV disease is not causal.

**COMMENT:** The incorporation of a genetic component in this analysis is interesting. However, the study was done entirely in China, and it is well known that East Asian individuals metabolize alcohol differently. Whether these results apply to Western populations is unclear. Until new studies are done, it is sensible to follow the American Heart Association recommendations on mild to moderate alcohol consumption.


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**Genes Associated with Sleep Are Downregulated in IBD**

*Expression of genes is lower in newly diagnosed cases than in controls.*

Research has shown that disrupting normal sleep patterns and working late-night shifts can lead to increased disease activity. Investigators at a single tertiary-care center prospectively studied 14 patients under age 21 who had a new diagnosis of inflammatory bowel disease (IBD) after colonoscopic exam. Their sleep patterns and expression of six genes associated with the central circadian clock were compared with those in 18 controls who had also undergone diagnostic colonoscopy but with normal findings on biopsy. Expression of the six genes was measured in both intestinal mucosa and serum and was significantly lower (by 3-fold to 66-fold) in both inflamed and noninflamed tissue of patients with IBD compared with controls. Similar disparities were seen in white blood cell assays. There was no difference in weekday daytime sleep or amount of sleep between groups.

**COMMENT:** The pathogenesis of IBD is likely multifactorial. The effect of sleep on the immune system is a new field of investigation that lends biological plausibility to a possible association between sleep disruption and risk for IBD. Moreover, epidemiological trends support a possible association, with the rising incidence of both IBD and poor sleep hygiene.

This study is fascinating as it demonstrates that at the time of diagnosis, patients had downregulation of multiple genes in both serum and intestinal mucosa. For right now, these findings need to be replicated, but perhaps in the future this information could be used as a possible diagnostic marker.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

**Lancet** 2018 Dec 15; 392:2583.

**Aspirin, Omega-3 Fatty Acid, or Both to Prevent Colorectal Cancer**

*Both of these agents were associated with fewer adenomas at 1 year in high-risk patients.*

Several randomized trials have shown that aspirin helps prevent colorectal cancer (CRC), but uncertainties remain about dosing and target populations. Preliminary evidence also suggests that the omega-3 fatty acid eicosapentaenoic acid (EPA) might help prevent CRC. To examine the effects of aspirin and EPA on CRC precursors — colorectal adenomas — U.K. researchers performed this placebo-controlled, randomized trial. About 700 patients (age range, 55–73) at high risk for CRC (i.e., multiple adenomas on baseline standardized screening colonoscopy) received aspirin (300 mg daily), EPA (1 g twice daily), both, or neither for 12 months. Participants underwent repeat colonoscopy at the end of the trial.

The primary outcome, proportion of patients with ≥1 adenoma at 12 months, was similar in all four treatment groups (61%–63%). But mean total adenomas per patient was significantly lower in groups who took aspirin compared with those who did not (1.2 vs. 1.6); this outcome did not differ with EPA. Aspirin (compared with no aspirin) was associated with significantly fewer serrated and right-sided adenomas per patient, whereas EPA (compared with no EPA) was associated with significantly fewer conventional and left-sided adenomas per patient. Few safety concerns emerged in any group.

**COMMENT:** The authors argue that mean number of adenomas per patient predicts future CRC incidence and mortality and that it should be the primary outcome in future CRC chemoprevention trials. The different effects of EPA and aspirin suggest potential individualized prevention strategies based on characteristics of baseline lesions.


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**JAMA** 2019 Apr 9; 321:1361

**Vitamin D Cancer Therapy?**

*Vitamin D₃ supplementation, compared with placebo, did not result in significant improvement in relapse-free or progression-free survival in two new trials.*

Population-based studies and retrospective analyses suggest that higher levels of serum 25-hydroxyvitamin D₃ are associated with lower cancer incidence and cancer mortality and may correlate with improved outcomes in metastatic colorectal cancer (e.g., *J Natl Cancer Inst* 2019; 111:158 and *BMC Cancer* 2010; 10:347)

Now, to examine whether vitamin D₃ supplementation can improve outcomes in patients with cancer, two teams of investigators have conducted prospective randomized trials involving patients with digestive-tract cancers treated curatively and those with metastatic colorectal cancer treated with palliative chemotherapy.

Urashima and colleagues report the results of a multicenter, randomized, controlled, double-blind, phase III trial (AMATERASU) comparing vitamin D₃ supplementation (2000 IU per day) versus placebo in 417 patients (mean age, 66 years) after curative resection of a stage I–III epithelial cancer of the digestive tract. Colorectal cancer was the most common primary (48%–49%) followed by stomach cancer (41%–42%), esophagus cancer (9%–11%), and small bowel
cancer (0.4%–0.6%); nearly half of patients had stage-I disease (40-46%), and about one third (29–31%) had stage-III disease.

At maximum follow-up of 7.4 to 7.6 years, estimated 5-year relapse-free survival (the primary endpoint) was similar with vitamin D₃ supplementation or placebo (77% and 69%, respectively), as was 5-year overall survival (OS; 82% and 81%).

Ng and colleagues report the results of a multicenter, randomized, controlled, double-blind, phase II trial (SUNSHINE) comparing supplementation with high-dose vitamin D₃ (loading dose of 8000 IU/day followed by 4000 IU/day) versus standard-dose vitamin D₃ (400 IU/day) plus placebo in 166 patients (median age, 56 years) with metastatic colorectal cancer treated with FOLFOX and bevacizumab. Most patients had left-sided primary cancers (61%–71%), nearly half had RAS mutation (40%–44%), and a minority had BRAF mutation (7%–13%).

At median follow-up of 22.9 months, progression-free survival (PFS; the primary endpoint) trended superior for high-dose vitamin D₃ supplementation versus standard-dose vitamin D₃ plus placebo (13.0 vs. 11.0 months; \( P=0.07 \); response rate was similar (58%–63%), as was OS (24.3 months). With correction for a between-group discrepancy in performance status, PFS was superior for high-dose supplementation (\( P=0.03 \)). High-dose supplementation achieved desired serum 25-hydroxyvitamin D₃ levels. Diarrhea appeared reduced in the high-dose arm.

**COMMENT:** The results of these two negative trials continue to call into question the value of vitamin D₃ supplementation, either as secondary prevention for cancer recurrence or as palliative chemotherapy in metastatic colorectal cancer. The potential PFS benefit seen with vitamin D₃ supplementation in the SUNSHINE trial, despite absence of any improvement in response rate or OS, will be studied further in an upcoming phase III trial.

**CITATION(S):**
 Ng K et al. Effect of high-dose vs standard-dose vitamin D₃ supplementation on progression-free survival among patients with advanced or metastatic colorectal cancer: The SUNSHINE randomized clinical trial. JAMA2019 Apr 9; 321:1370. (https://doi.org/10.1001/jama.2019.2402)

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**PLoS One** 2019 Apr 17; 14:e0213995

**New Study Links Screen Time to Preschooler Behavior Problems and ADHD Symptoms**

**But the converse is also possible: Behavior dysregulation and short attention span may contribute to media use habits.**

In the age of television and DVDs, several large-scale studies found associations between screen time and child attention and behavior problems (NEJM JW Pediatr Adolesc Med Jan 2008 and Pediatrics 2007; 120:532; NEJM JW Pediatr Adolesc Med Dec 2009 and Acad Pediatr 2009; 9:300). However, current research is limited by two main factors: Few large-scale studies have been conducted since mobile devices were introduced, and most studies don't take into account how preexisting child behavior problems might influence media use.

To address the first factor, researchers analyzed data from a large recent (2009–2012) birth cohort in Canada, focusing on 2427 children whose parents reported daily screen time and behavioral outcomes at age 5 years. Families were primarily white and higher income, and children's rates of behavioral problems were very low (1.2% with externalizing problems).
Compared to children with <30 minutes of screen time per day, those exceeding the Canadian guideline of 2 hours per day (13% of the sample) were 5.0 times more likely to have externalizing problems, 5.9 times more likely to have attention problems, and 7.7 times more likely to show elevated ADHD symptoms — after adjusting for important psychosocial confounders.

**COMMENT:** Although the particulars of the study population may limit applicability, this study demonstrates that correlations between screen time and child behavior problems persist in the age of mobile and interactive media. However, it's highly likely that preexisting child behavior problems contributed to higher media use in this study; in fact, research suggests that parents use media as a calming or behavioral management tool for fussy children, which we often see in clinic. Therefore, to realistically decrease media use by young children, we will need to offer caregivers ideas for alternative activities or soothing strategies.

**CITATION(S):** Tamana SK et al. Screen-time is associated with inattention problems in preschoolers: Results from the CHILD birth cohort study. *PLoS One* 2019 Apr 17; 14:e0213995. (https://doi.org/10.1371/journal.pone.0213995)

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**Measles Reappears in the U.S.**

*Once declared eradicated, measles cases this year reached the highest number since 1994.*

Measles, one of the most readily communicable infectious diseases known, is transmitted by the respiratory route and, after an incubation period of 7 to 21 days, manifests as coryza followed by development of a maculopapular rash. Complications include pneumonia, encephalitis, and death.

The disease was declared to be eliminated from the U.S. in 2000 as a result of a very effective two-dose antimeasles vaccination program. In fact, many young healthcare workers have never seen a case of measles. However, this year, as of April 26, the CDC reported 704 cases of measles in 22 states. Of these cases, 94% were the result of 13 outbreaks, 6 of which were in close-knit, undervaccinated communities, representing 88% of all cases; New York State and City accounted for 67%. Nearly all cases (98%) involved U.S. residents; among the 44 cases imported from other measles-endemic countries, including 34 involving U.S. residents, 91% occurred in unvaccinated persons.

Of note, most patients (71%) were unvaccinated; 11% had received at least one measles-mumps-rubella vaccination, and the vaccination status of the remaining 18% was unknown. No deaths were reported, but 9% of patients required hospitalization. The median age of patients was 5 years; 14% were younger than 1 year, and 4% were younger than 6 months.

**COMMENT:** Despite the tremendous, clearly demonstrated benefits of vaccines, particularly in such viral diseases as measles, mumps, and rubella, a strong antivaccination movement has emerged in the U.S. and worldwide. Rationales for this movement have included religious beliefs and misinformation on the health hazards of vaccination. In the meantime, growing uncertainties about the duration of protection have arisen. Live-virus vaccines were thought to provide life-long protection equivalent to natural infection. However, similar to what has been seen this year with measles, recent mumps outbreaks involved many persons who had been previously immunized against that virus. Studies are needed to reveal whether, in the absence of ongoing natural boosting infections, the immunity conveyed by vaccination (or even by natural infection) with these two viruses may wane with time. Meanwhile, the CDC emphasizes the need to vaccinate travelers to endemic areas unless they can show proof of immunity.


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New Pediatric Hypertension Guidelines Add Value for Predicting Cardiovascular Outcomes

Reclassification of children's blood pressure using 2017 AAP guideline definitions better predicted who would develop left ventricular hypertrophy as adults.

The 2017 American Academy of Pediatrics (AAP) reclassification of hypertension definitions increased the number of children considered hypertensive (NEJM JW Pediatr Adolesc Med Oct 2017 and Pediatrics 2017; 140:e20171904). To determine whether the new definitions add value in predicting adult cardiovascular outcomes, investigators used data from the Bogalusa Heart Study (3940 children followed until age 19–57 years) to compare outcomes in those deemed hypertensive using the 2004 versus the 2017 definitions.

The proportion of children deemed hypertensive increased from 7% using the 2004 definitions to 11% using the 2017 definitions. A total of 329 children were reclassified upward (from normal blood pressure [BP] or prehypertension to elevated BP or hypertension) and 38 children were reclassified downward.

Compared with a propensity score–matched normotensive cohort, the cohort reclassified upward had significantly higher incidence of hypertension, metabolic syndrome, and left ventricular hypertrophy (LVH) in adulthood. When overweight and obese children were excluded, risk for adult hypertension remained elevated in those reclassified upward. No increased risk for adult hypertension, metabolic syndrome, or LVH was observed in the 38 children who were downgraded.

COMMENT: These findings add further support to the 2017 AAP hypertension guidelines. Hypertension in children has adverse consequences for cardiovascular health in adulthood and should be addressed when discovered.


Health Differences Between Transgender and Cisgender Adults

Transgender adults reported poorer mental and physical health than did cisgender adults.

The health status and quality of life of transgender adults has been difficult to study due to a lack of standardized data collection. In 2014, the CDC added an optional sexual orientation and gender identity questionnaire to the national behavioral risk factor surveillance system. The new survey was used in 36 states from 2014 to 2017. Among 730,000 respondents, 0.55% identified as transgender.

Compared with cisgender adults, transgender adults were more likely to smoke cigarettes (19% vs. 16%) and to be physically inactive (35% vs. 26%). Transgender adults were more likely to report fair or poor health status (25% vs. 18%) and to experience severe mental distress (20% vs. 12%); significant differences persisted after adjustment for clinical and demographic factors. Transgender adults also reported 1.2 more days of combined poor physical and mental health in the last 30 days, and 1.3 more days of activity limitations than did cisgender adults.

COMMENT: The authors note that the proportion of respondents identifying as transgender translates to about 1.3 million transgender adults in the U.S. population, meaning that most primary care clinicians likely will care for at least
several transgender patients. The health status of these patients is, in general, worse than that of cisgender patients, with health and lifestyle behaviors worthy of screening and attention.


**JAMA Intern Med** 2019 Mar 18

**Breast Ultrasound as an Adjunct to Screening Mammography?**

*Supplemental ultrasound increased the likelihood of false-positive biopsy recommendations without improving detection of breast cancer.*

Because dense breast tissue can hinder the identification of cancer on screening mammography, breast density notification laws have been enacted along with the suggestion that supplemental imaging such as ultrasound may improve cancer detection. However, the effectiveness of breast ultrasound to supplement screening mammography has not been determined. In a retrospective analysis of Breast Cancer Surveillance Consortium (BCSC) registry data from 2000 through 2013, investigators identified 3386 asymptomatic women who underwent screening breast ultrasound examinations on the same day as screening mammography and matched them 1:5 with >15,000 women who had mammography alone. Women were followed for 12 months after the screening imaging for breast cancer diagnosis or next screening imaging.

Compared with women who had only mammography, those who also received supplemental screening ultrasound were more likely to be white, younger than 50, have dense breasts, and have a first-degree family history of breast cancer. Rates of cancer detection (5.4 and 5.5 per 1000 screens), or interval cancer (1.5 and 1.9 per 1000 screens) were similar between the mammography and ultrasound groups. However, the ultrasound group had a higher false-positive biopsy recommendation rate (52 vs. 22 per 1000), lower positive predictive value of biopsy recommendation (9.5% vs. 21.4%), and more-frequent recommendation for short-interval follow-up (3.9% vs. 1.1%).

**COMMENT:** Although dense breast tissue reduces mammographic sensitivity, the most appropriate and cost-effective supplemental imaging remains to be determined. Such imaging should be inexpensive, specific, and associated with minimal radiation exposure. Although ultrasound is relatively straightforward to perform, the method is not specific enough for asymptomatic screening. One promising option for women with dense breasts is contrast-enhanced digital mammography combined with 3-D tomosynthesis; in small feasibility studies, this approach has been shown to be as accurate as breast MRI, but with lower cost and false-positive rates (*J Comput Assist Tomogr* 2019 Mar/Apr; 43:245).