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Autism Follow-up Screening by PCPs Yields High Accuracy

Tara Haelle

Primary care providers (PCPs) can effectively conduct the follow-up interview after a positive screening on the Modified Checklist for Autism in Toddlers (M-CHAT) without missing cases or flagging too many false-positives, a recent study suggests.

"The online M-CHAT/F [M-CHAT Follow-up Interview] enabled PCPs to clarify positive parent responses to M-CHAT items during well-child visits, rather than requiring another visit or call by a trained interviewer," wrote Raymond Sturner, MD, of Johns Hopkins University, Baltimore, and his colleagues (*Pediatrics*. 2016 Aug 19. doi: 10.1542/peds.2015-3036). "This study found that the performance of the M-CHAT/F by a PCP was equivalent to one administered by trained … staff."

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The authors recruited 47 PCPs at 22 clinics in Maryland to complete an M-CHAT/F during children's 18- and 24-month routine visits if their initial M-CHAT yielded a positive screening. Each family was then contacted again for an M-CHAT/F conducted by a trained research assistant from the Kennedy Krieger Institute Center for Autism and Related Disorders.

The PCPs volunteered for the study and primarily had suburban practices (18% rural and 9% urban). Slightly less than one-third of children at the practices were insured by Medicaid, and the demographic breakdown included 39% white, 33% African-American, 16% Asian, and 8% Hispanic.

Of the 5,071 children screened (mean age, 23 months), 6.7% had a positive screen. Of the 197 M-CHAT/Fs the PCPs completed, 99 children then underwent a full autism spectrum disorder (ASD) diagnostic evaluation, including administration of the Autism Diagnostic Observation Schedule and the Mullen Scales of Early Learning.

PCPs and research assistants agreed 86.6% of the time on the result of the M-CHAT/F screening, with statistically equivalent positive predictive value (PPV), sensitivity, specificity, and overall accuracy. The research assistants' PPV was 0.84, and the PCPs' PPV was 0.88. The PPV for any developmental delay diagnosis was similarly equivalent between the research assistants and PCPs.

Dr. Sturner and his associates noted that the findings confirm "previous studies showing that most children with false-positive screens have developmental difficulties of a degree that would make them eligible for early intervention. Some children with false-positive screens had atypical features not meeting criteria for ASD."

Disclosures: *The National Institutes of Mental Health funded the research. Dr. Sturner is Director of Total Child Health (TCH), a for-profit subsidiary of the Center for Promotion of Child Development through Primary Care, which conducted the study. Barbara Howard, MD, is president of TCH. Tanya Morrel, PhD, is an employee of and stockholder in TCH, and Paul Bergmann has consulted for the company. The remaining authors had no relevant disclosures.*

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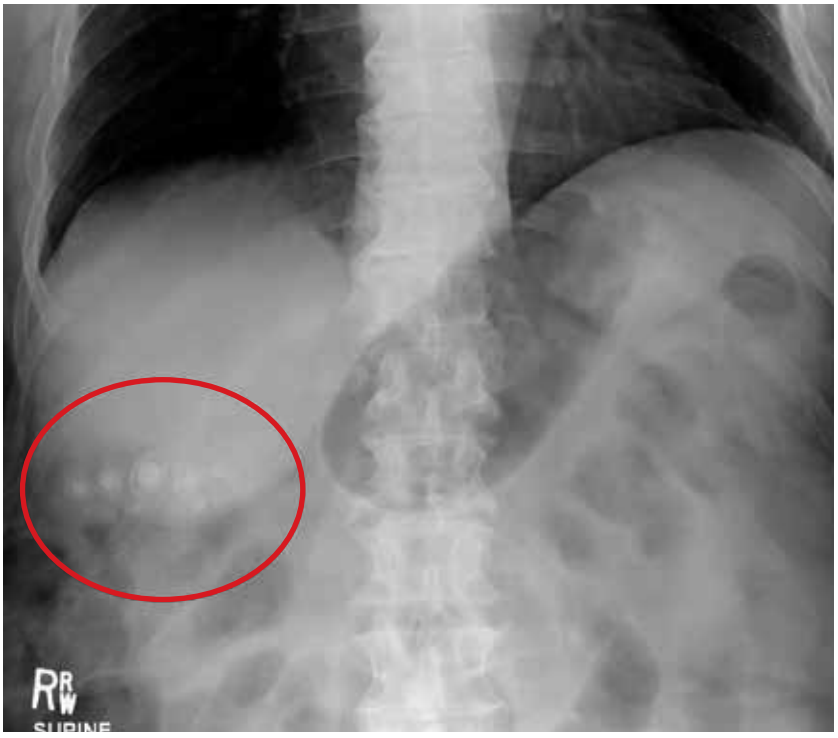
Gallstone Disease Boosts Heart Risk

Deepak Chitnis



Gallstone disease is associated with a 23% higher risk for coronary heart disease (CHD), according to an analysis recently published in *Arteriosclerosis, Thrombosis, and Vascular Biology*.

"Our results suggest that patients with gallstone disease should be monitored closely based on a careful assessment of both gallstone and heart disease risk factors," senior author Lu Qi, MD, PhD, said in a statement.

Dr. Qi, Professor of Epidemiology at Tulane University in New Orleans, and his coinvestigators conducted a meta-analysis of seven distinct studies with a total of 842,553 patients and 51,123 cases of CHD. Patients with CHD were investigated further to determine if there was any history of gallstone disease.

Results showed that there was a 23% higher likelihood of CHD in patients who had gallstone disease, compared with those who did not, with a range of 15% to 33% across the studies; the adjusted hazard ratio (aHR) was 1.23.

A separate prospective analysis of three of the included studies was conducted to determine individual risk factors that may contribute to the association between gallstone disease and CHD. These studies were the Nurses' Health Study (conducted from 1980 to 2010), the Nurses' Health Study II (1989-2011), and the Health Professionals Follow-up Study (1986-2010), involving 112,520 women, 112,919 women, and 43,703 men, respectively.

This analysis revealed a 17% increase in CHD risk (aHR, 1.17). Furthermore, the investigators noted that individuals with a history of gallstone disease who were otherwise healthy—ie, had no history of obesity, high blood pressure, diabetes, or other disorders commonly associated with CHD—still stood a higher chance of developing CHD than individuals with no history of gallstone disease (*Arterioscler Thromb Vasc Biol*. 2016 Aug 18. doi: 10.1161/atvbaha.116.307507).

"Preventing gallstone disease may also benefit heart health," Dr. Qi said. "The potential mechanisms for the association of gallstone diseases with CHD may, at least, include the primary metabolic pathway and the bacterial pathway.... Among patients with gallstones, especially those with cholesterol gallstones, their bile acid and lecithin secretion rates tend to be depressed and cholesterol secretion rates elevated, which could indicate enhanced cholesterol synthesis and therefore increase cardiovascular disease risk."

Disclosures: *This study was supported by funding from the National Institutes of Health, the Boston Nutrition Obesity Research Center, and the United States–Israel Binational Science Foundation. The authors had no relevant financial disclosures.*

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New *HER2*-testing Guidelines Result in More Women Eligible for Directed Treatment

Mary Ann Moon

New guidelines for immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) pathology testing categorize more breast cancers as "equivocal" regarding *HER2* positivity and ultimately lead to identifying more of them as *HER2* positive, investigators reported online in the *Journal of Clinical Oncology*.

The FDA approved the initial set of IHC and FISH guidelines in 1998. The American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) issued their first such guidelines in 2007 and released an update in 2013. "The intent of the 2013 guidelines was to decrease the number of equivocal [cancers]," said Mithun Vinod Shah, MD, PhD, of the Mayo Clinic in Rochester, Minnesota, and his associates.

To assess the impact of implementing the new guidelines, the investigators analyzed 2,851 breast cancer samples sent to their cytogenetics laboratory by 139 medical centers for *HER2* testing during a one-year period. They compared the three sets of testing criteria (FDA, 2007 ASCO/CAP, and 2013 ASCO/CAP).

According to the 2013 guidelines, 69.7% of the tumors were classified as *HER2* negative, 16.1% as *HER2* positive, and 14.2% as equivocal. In contrast, the 2007 guidelines classified 85.1% as negative, 11.0% as positive, and 3.9% as equivocal, while the FDA guidelines (which do not include an "equivocal" category) classified 86.9% as negative and 13.1% as positive. Thus, "by using 2013 guidelines, 358 additional patients were interpreted as positive, compared with the 2007 guidelines, and 298 additional patients were considered positive, compared with the FDA criteria," Dr. Shah and his associates said.

The 2013 guidelines recommend additional chromosome 17 probe testing (among other strategies) to resolve equivocal results. The investigators further analyzed the 405 samples classified as equivocal by the 2013 criteria; 52.3% were reclassified as *HER2* positive, 8.9% were reclassified as *HER2* negative, and 38.8% remained equivocal. Thus, *HER2* positivity in the overall cohort rose significantly, to 23.6%, using the newest guidelines.

These findings demonstrate that using the 2013 guidelines for IHC and FISH pathology testing identifies more women who are eligible for *HER2*-directed therapy, the investigators said (*J Clin Oncol*. 2016 Jul 25. doi: 10.1200/JCO.2015.61.8983).

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Weight Loss Boosts TNFis' Psoriatic Arthritis Efficacy

Mitchel L. Zoler

Weight loss enhances responsiveness of patients with psoriatic arthritis (PsA) to tumor necrosis factor inhibitors (TNFis) and should be part of routine care when using these drugs in this setting, Lianne Gensler, MD, said at an educational symposium organized by the Spondyloarthritis Research and Treatment Network and the Group for the Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).

She cited results from a randomized study of 138 patients conducted in Naples, Italy, which showed that the greater the weight loss of patients with PsA during their first six months of treatment with a TNFi, the greater their rate of achieving minimal disease activity by the end of that time period.

Patients achieving a 5% to 10% weight loss in the first six months on TNFi treatment had a nearly fourfold increased rate of minimally active disease, com-

pared with patients who had less than a 5% weight loss (including those who had no weight change or who gained weight). Those who lost more than 10% of their starting weight had a nearly sevenfold higher rate of achieving minimal disease activity, compared with those who had less than a 5% weight loss (*Ann Rheum Dis*. 2014 June;73[6]:1157-1162).

"I use this result in my routine practice when starting patients on a TNF inhibitor or when patients are not responding to TNF-inhibitor treatment," said Dr. Gensler, Director of the Ankylosing Spondylitis Clinic at the University of California, San Francisco. "It's a patient-centered approach to improving outcomes."

GRAPPA's 2015 guidelines for managing psoriasis and PsA (*Arthritis Rheum*. 2016 May;68[5]:1060-1071) cite the Naples data when recommending that all PsA patients be encouraged to achieve and maintain a healthy body weight, she noted.

The first evidence that weight can affect TNFi response in PsA patients came from a prior report by the same Naples group, which prospectively followed 270 PsA patients—135 obese and 135 at normal weight—starting a TNFi regimen. After 12 months, 36% of patients had minimal disease activity. The obese patients were nearly fivefold more likely not to achieve minimal disease activity, compared with the normal-weight patients (*Arthritis Care Res*. 2013 Jan;65[1]:141-147). Obesity also was linked with a significantly increased risk that patients who achieved minimal disease activity after one year would relapse by the two-year follow-up.

"These studies have provided a new reason for [PsA] patients to lose weight," agreed Atul A. Deodhar, MD, Professor of Medicine and Medical Director of the Rheumatology Clinics at the Oregon Health and Science University in Portland. "Before, we counseled patients to lose weight for other reasons. Now there is a rheumatologic reason."

Smoking cessation is another lifestyle step recently shown to improve TNFi response in PsA patients, Dr. Deodhar added. For example, results from a recent Danish study of 1,388 PsA patients enrolled in the Danish National Registry showed that smokers had significantly worse responses, compared with nonsmokers, during their first six months on a TNF-inhibitor regimen (*Ann Rheum Dis*. 2015 Dec;74[12]:2130-2136).

Both weight loss and smoking cessation "have a powerful effect. I use these results in my practice to counsel [PsA] patients to stop smoking and lose weight," Dr. Deodhar said in an interview.

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Extreme Alcohol Use Worsens HIV Disease

Bruce Jancin

A large, longitudinal study of alcohol consumption patterns among HIV-infected US military veterans indicates that only the highest level of persistent heavy drinking is associated with more advanced HIV disease severity over time. "This suggests that, given the relatively small number of people reporting consistent unhealthy alcohol use, targeted risk reduction and treatment strategies are needed only in those consistent unhealthy drinkers," Brandon D.L. Marshall, PhD, reported at the 21st International AIDS Conference.

The study included 3,539 veterans receiving care for HIV infection at eight VA centers for 15,354 person-years of follow-up. The subjects' median age was 49 years; 98% were men, and 68% were African-American.

Only those scoring in the top 8% on a validated measure of unhealthy drinking showed significant worsening of HIV disease over the eight-year study period. "The relationship between persistent unhealthy alcohol use and greater HIV disease severity is perhaps not as strong as we would have hypothesized," said Dr. Marshall, an epidemiologist at Brown University in Providence, Rhode Island.

Alcohol use patterns were evaluated annually using the Alcohol Use Disorders Identification Test (AUDIT-C), a validated three-question screening tool measuring self-reported frequency, quantity, and binge alcohol use. Alcohol use trajectories were linear and relatively stable over time. Eight percent of subjects were classified as high-risk drinkers (AUDIT-C score of 8 to 12); 24% were deemed at moderate risk (score of 6 or 7); 44% were categorized as lower risk (score of 4 or 5); and 24% of participants

were abstainers. The abstainers were further classified as sick quitters with worsening HIV disease and healthy abstainers.

Of note, this was the first large study to utilize an objective biomarker to validate long-term self-reported alcohol use patterns. Nearly 1,500 subjects had a blood test for phosphatidylethanol, a reliable indicator of exposure to alcohol within the previous 21 days. The biomarker has high specificity for alcohol abstinence and showed good correlation with AUDIT-C results across the board, according to Dr. Marshall.

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Subjects' HIV disease severity trajectory was determined annually using the Veterans Aging Cohort Study (VACS) Index, a weighted score that estimates an individual's risk for all-cause mortality based on age, HIV RNA viral load, CD4 count, and general indicators of organ system injury (eg, hemoglobin, platelets, glomerular filtration rate, and hepatitis C infection). As was the case for AUDIT-C scores, VACS scores remained relatively stable over eight years of follow-up. The HIV disease trajectory was categorized as low risk in 2% of subjects, moderate in 46%, high risk in 36%, and extreme in 16%.

To plot the joint trajectories of alcohol use and HIV disease severity, the investigators employed a statistical technique called *group-based finite mixture modeling* and performed a multivariate logistic regression analysis in which the moderate-risk drinkers and moderate VACS subgroups served as reference standards. Only two significant associations emerged: The highest-risk subgroup of drinkers were at 1.83-fold increased risk for extremely poor VACS trajectory, and the abstainers were at 1.9-fold increased risk for both the most favorable VACS trajectory and an extremely-high-mortality VACS trajectory, reflecting the split in prognosis between the healthy abstainer and sick quitter subgroups. No high-risk drinkers were in the low VACS group.

Unhealthy alcohol use is hypothesized to accelerate HIV disease progression through two mechanisms: Heavy drinkers are less likely to adhere to antiretroviral therapy and remain in care, and the heavy drinking itself has direct negative immunologic effects, Dr. Marshall said.

Disclosures: *Dr. Marshall reported having no financial conflicts of interest regarding his study, funded by the National Institute on Alcohol Abuse and Alcoholism and the National Institute of Allergy and Infectious Diseases.* **CR**

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