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HIV Testing Opportunities Missed For High-Risk Patients

There are many missed opportunities for testing and diagnosis of HIV among high-risk individuals seen in clinical settings, according to a research letter published June 26 in the *Journal of the American Medical Association*.

Nearly half of high-risk individuals, including men who have sex with men (MSM) and persons who inject drugs (PWID), report being seen by a clinician but having not been offered an HIV test.

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Urinary cfDNA Analysis Valuable for Urinary Tract Infections

Sequencing of urinary cell-free DNA (cfDNA) offers a comprehensive examination of bacterial and viral infections of the urinary tract and could be a valuable diagnostic tool for both kidney transplant patients, as well as in the general population, according to a study published June 20 in *Nature Communications*. Analysis of cfDNA improves clinical practice by identifying bacteria and viruses that may be clinically relevant but not routinely detected in current screening protocols.

Urinary tract infections (UTI) are one of the most commonly diagnosed infections and occur at even a higher rate among kidney transplant recipients. UTIs in kidney transplant recipients can lead to serious complications, including graft loss and death. In vitro urine culture is the gold standard for diagnosis of bacterial UTI, but is of limited utility because of the relatively few cultivable organisms.

Isolated cfDNA from 141 urine samples from 82 kidney transplant patients were sequenced. The researchers applied a single-stranded library preparation technique in order to create diverse sequencing libraries that capture short, highly degraded cfDNA. The assay performed well even from just 1 mL of urine supernatant and had a turnaround time of 1 to 2 days.

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HIV Testing Opportunities Missed For High-Risk Patients, *from page 1*

"Eliminating missed opportunities for HIV testing and diagnosis in health care settings may reduce HIV transmission, especially among high-risk groups," write the authors led by Cyprian Wejnert, Ph.D., from the U.S. Centers for Disease Control and Prevention in Atlanta, Ga.

CDC researchers used National HIV Behavioral Surveillance data on adults 18 years or older from 19 U.S. cities. The survey is conducted in rotating annual cycles in cities with high HIV burden. Data from men who had ever had sex with another man (n = 9,105) were collected in 2014, and from men and women injecting drugs (n = 19,357) in the past year in 2012 and 2015. Participants were asked if, during the past year, they had received an HIV test, visited a clinician ("doctor, nurse, or other health care provider"), or been offered an HIV test by a clinician.

The U.S. Centers for Disease Control and Prevention (CDC) recommends at least annual HIV testing for persons at high risk for HIV, such as MSM and PWID.

The researchers found that 22 percent of MSM and 8 percent of PWID tested positive for HIV infection. Of the participants who were HIV-positive, 8 percent of MSM and 12 percent of PWID were unaware of their infection status. Yet, of those who were unaware of their status, 81 percent of MSM and 65 percent of PWID reported having visited a clinician in the past year. Furthermore, only 43 percent of MSM and 24 percent of PWID who visited a clinician in the past year reported being offered an HIV test by their clinician.

The U.S. Centers for Disease Control and Prevention (CDC) recommends at least annual HIV testing for persons at high risk for HIV, such as MSM and PWID. But, 44 percent of MSM and 77 percent of PWID reported not having had an HIV test in the past year. Among those high-risk individuals not tested in the past year, 52 percent and 45 percent of PWID reported visiting a clinician, but not having been offered HIV testing.

At-Home Testing Can Also Up Testing Rates

Recognizing though that some high-risk patients may not be getting tested enough, the U.S. Air Force developed a self-collection blood kit to encourage its active-duty members to be proactive and test for infection more frequently than what's mandated by the military.

Currently, service members are routinely screened every two years, before and after deployments, and when clinically indicated by health care providers, based on symptoms or answers to routine questions about sexual partners and practices.

Service members can call or email to request a kit. The kit includes instructions, supplies to obtain a blood sample via a finger prick, and a prepaid envelope for returning the sample to the HIV Diagnostics and Reference Laboratory at the Walter Reed Army Institute of Research (Silver Spring, Md.).

Takeaway: By capitalizing on clinical visits to expand HIV testing of high-risk individuals, HIV diagnoses can be sped up, increasing awareness of infection status and cutting further transmission.

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Whole-Genome Sequencing Adds Value to Cardiomyopathy Workup

Whole-genome sequencing (WGS) identifies additional genetic causes of hypertrophic cardiomyopathy (HCM) beyond those identified through targeted gene sequencing approaches, according to a study published in the July issue of the *Journal of the American College of Cardiology*. This increased detection of disease-causing variants is mostly a result of screening deep into intronic regions and the identification of intronic variants that impact splicing.

> *"It might be expected that advancing from sequencing 30 genes to 20,000 genes would greatly improve the diagnostic rate, but the gains in this domain appear relatively muted."*
>
> — Euan Ashley, M.B.Ch.B., D.Phil.

Recommendations call for genetic evaluation of all HCM patients and includes sequencing of a panel of about 30 genes, although some expanded panels evaluate hundreds of genes. Given the declining cost of sequencing, some are exploring the utility of replacing panels or reflexing to whole-genome sequencing.

The current study evaluated WGS (mean read depth of 43) on 46 unrelated patients with HCM who had undergone previous genetic testing without a diagnosis (gene-elusive HCM), 14 affected family members, and 12 unaffected members of a severely affected proband. Variants in coding regions of 184 candidate cardiac hypertrophy genes, 58 autosomal dominant genes, 12 X-linked genes, and 114 autosomal recessive genes were examined, in addition to variants in deep intronic regions that alter RNA splicing, large genomic rearrangements, and mitochondrial genome variants.

The researchers found a pathogenic or likely pathogenic variant in 9 of 46 families (20 percent) for which prior genetic testing was inconclusive. Three families had variants in genes not included in prior genetic testing, while one family had a pathogenic variant that was filtered out with prior exome sequencing. Five families had pathogenic variants in noncoding regions—four with deep intronic variants that activate novel splicing and one mitochondrial genome variant.

WGS added incremental value in identifying pathogenic variants in 9 percent of gene-elusive HCM, yielding a molecular diagnosis in an additional 20 percent of patients with prior inconclusive genetic testing. When WGS is used as a first-line test, 42 percent of HCM patients (five of 12 families) received a molecular diagnosis.

"It might be expected that advancing from sequencing 30 genes to 20,000 genes would greatly improve the diagnostic rate, but the gains in this domain appear relatively muted," writes Euan Ashley, M.B.Ch.B., D.Phil., in an accompanying editorial. Given this incremental benefit, the study authors offer the following cautious recommendations.

- First-line genetic testing using a gene panel or exome sequencing–based analysis
  - If testing is inconclusive, no further testing is needed for people with late-onset HCM and a mild phenotype.

- For severe clinical presentation, WGS can be used to look for de novo variants, including consideration of family trio testing.
- For gene-elusive patients with a family history of HCM, WGS-based analysis of intronic regions (MYBPC3) and the mitochondrial genome may improve diagnosis.

One of the study's novel findings is that RNA sequencing or functional assays may be required to prove causality from novel genes variants in deep intronic regions that affect RNA splicing. To date, RNA analysis is typically not currently available in clinical settings.

Takeaway: WGS may potentially provide incremental value as part of genetic testing strategies for patients with HCM.

Next-Gen Sequencing Has Significant Utility for Drug-Resistant Epilepsy

Next-generation sequencing improves definitive diagnoses for children with drug-resistant epilepsy, according to a pilot study published online June 22 in *CNS Neuroscience & Therapeutics*. Furthermore, use of both genetic panels and whole-exome sequencing, can improve treatment efficacy and reduce hospitalizations.

Despite development of new drugs, medications still fail to control seizures in 20 percent to 30 percent of patients. Drug selection remains largely a function of trial and error. Furthermore, drug-resistant epilepsy accounts for the vast majority—estimated to be nearly 80 percent—of the cost of all epilepsy treatment.

"Etiology is a major determinant of treatment, prognosis, and clinical course in epilepsy patients," write the authors led by Jing Peng, from Central South University in China. "During the last few years, accumulated evidence supports the strong role of genetics in unexplained drug-resistant epilepsy patients."

In the current study, 273 pediatric patients (average age 13.2 years) with drug-resistant epilepsy and no obvious cause of acquired epilepsy were evaluated (2012 to 2016), with 74 undergoing whole-exome sequencing (WES), 141 patients an epilepsy-related gene panel testing, and 58 patients clinical whole-exome gene panel testing (clinical WES; 3,994 Mendelian disease-related genes). The researchers developed the first version of the epilepsy-related gene panel in 2012 and included 308 genes. However, as genetic knowledge evolved, so did the panel, which now includes 540 genes. Follow-up assessed patients' seizure and hospitalization frequency.

The researchers found that 86 patients received a genetic diagnosis—a diagnostic yield of 31.5 percent. Clinical WES had the highest detection rate 44.8 percent, followed by the epilepsy-related gene panel) (32.6 percent), and WES (17.3 percent). The tests cost $570 for the gene panel, $720 for clinical WES, and $1,450 for WES, none of which would be covered by insurance in China.

"Considering both cost and detection rate, we believe that a larger gene panel approach, such as clinical WES, can be a comparable alternative to WES analysis in most cases."

— Jing Peng

Diagnoses involved 93 likely disease-causing mutations in 33 genes. Of these, mutations in 20 actionable genes that could direct therapy were identified in 62 patients. More than half of patients with actionable gene mutations (34 of 62) immediately accepted the treatment (12 percent of patients overall). After six months of corrective therapy, 52.9 percent of these patients became seizure-free (6.4 percent of the whole cohort) and 38.2 percent with actionable mutations achieved seizure reduction. Over the follow-up period, patients with either positive or negative genetic results had significantly fewer hospitalization incidents.

"Considering both cost and detection rate, we believe that a larger gene panel approach, such as clinical WES, can be a comparable alternative to WES analysis in most cases," write the authors. "However, reflex testing to WES is an option when a gene panel is negative. It is also important to realize that there is no single best NGS approach."

Takeaway: NGS-based testing can improve diagnostic accuracy, treatment efficiency, and health care utilization among children with drug-resistant epilepsy.

SPECIAL FOCUS: Skin Cancer

General Population Has Interest in Genetic Testing for Skin Cancer Risk

There is moderately high interest and follow through among the general population for genetic testing to determine melanoma skin cancer risk, according to a study published in *JAMA Dermatology*. However, there are difference in uptake based on socioeconomic and demographic factors, with less uptake among less educated individuals and minorities.

The melanocortin-1 receptor gene (MC1R) is known to be associated with melanoma risk, even after adjusting for other factors like hair color and skin type.

There is hope that knowledge of genetic risk may promote skin cancer awareness foster increased prevention-related behaviors (e.g., using sunscreen). Yet, to date, the direct-to-consumer testing model has primarily only reached white, highly educated consumers. Melanoma risk is known to be high among Hispanics, particularly in states with high levels of year-round sun exposure.

The present study assessed prevalence of interest in and uptake of MC1R testing among internal medicine clinic patients in New Mexico. Participants were randomized to either a usual-care condition (a skin cancer pamphlet) or an MC1R test offer. Analysis included the 499 participants (44 percent white; 48 percent Hispanic) randomized to the MC1R test offer. The offer included a login for the

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SPECIAL FOCUS: Skin Cancer

> *"More research is needed to explore barriers to genomic testing among racially and ethnically diverse and less educated patients..."*
>
> — Jennifer Hay, Ph.D.

study website, which required reading three educational modules showing the rationale, benefits, and drawbacks of MC1R testing. Those without Internet access were also offered the opportunity to view the information via paper forms. Uptake was measured for three stages: website log on, saliva test kit request, and return of the saliva test kit.

The researchers found that 46 percent logged onto the website to learn more about MC1R testing (with 18 of the 232 participants using a paper form). Of those who logged on, 88 percent requested a test kit and of those 82 percent returned the kit. The strongest predictors of website log on were race/ethnicity (non-Hispanic whites were more likely to log on) and education (highly educated individuals were more likely versus those not completing high school). However, the strongest predictor of ordering the test was sunburn history.

"More research is needed to explore barriers to genomic testing among racially and ethnically diverse and less educated patients, including lack of knowledge, lower genomic literacy, and lack of confidence in the medical system, to achieve maximum benefits of precision prevention for skin cancer and other chronic diseases in the broad population who stand to benefit from such technologies," write the authors led by Jennifer Hay, Ph.D., from Memorial Sloan Kettering Cancer Center (New York).

Takeaway: There is evidence that genetic risk testing for skin cancer is acceptable to the general population, but efforts are needed to ensure uptake does not further promote health disparities.

Noninvasive Gene Expression Test for Melanoma Cuts Costs

The noninvasive pigmented lesion assay (PLA; DermTech) reduces costs compared to the current standard of care for diagnostic workup of pigmented skin lesions suggestive of melanoma, according to a study published July 11 in *JAMA Dermatology*. The PLA gene expression test cut surgical procedures, missed melanomas, and cost, compared to visual assessment, followed by surgical biopsy and histopathologic assessment (VAH).

"The PLA provides clinical utility in the assessment of pigmented lesions suggestive of melanoma by its ability to transform the current clinical pathway from one that is subjective (hence variable in implementation), invasive, and with a relatively low NPV to one that is objective (hence more predictable), noninvasive, and with a high NPV," writes coauthor John Hornberger, M.D., from Stanford University in California. (Both authors report financial ties to DermTech.)

Current estimates suggest that 3 million surgical biopsies and 780,000 excisions are performed annually in the United States, but these procedures

SPECIAL FOCUS: Skin Cancer

> *"The economic benefits of the PLA are driven by high specificity that substantially reduces the number needed to biopsy to find melanoma by 5-fold (from 15.7 to approximately 2.7)."*
>
> — John Hornberger, M.D.

find approximately 150,000 in situ and invasive melanomas. This low specificity and low negative predictive value suggest the need for more cost-effective tools to improve diagnosis and management of pigmented lesions.

PLA uses an adhesive patch–based sampling to rule out melanoma and the need for surgical biopsy of pigmented lesions suggestive of melanoma. Positive PLA test results are followed up with a surgical biopsy and histopathologic assessment, while negative test results are followed up with surveillance per standard of care. Previous studies have shown reductions in surgical biopsies and subsequent excisions, with a negative predictive value of 99 percent versus 83 percent for VAH. The present study evaluated the cost implications of using PLA versus VAH.

Data input into the economic model were derived from routine use of the test in U.S. dermatology practices and the literature. Participants included patients with primary cutaneous pigmented lesions suggestive of melanoma. Inputs were based on consensus treatment guidelines and Centers for Medicare & Medicaid Services fee schedules. PLA was priced at $500, close to the expected mean selling price.

For the base-case model, researchers assumed the pretest probability of melanoma was 6 percent (range, 2 percent to 10 percent) and that 56 percent of lesions evaluated would be considered clinically suggestive enough to recommend biopsy.

The proportion of patients undergoing initial surgical biopsy was 69.0 percent with the VAH versus 13.3 percent with the PLA. The improved accuracy of the PLA reduced the number of patients undergoing subsequent excision for melanoma from 18.8 percent with the VAH to 7.5 percent with the PLA.

This translated to a relative reduction in surgical procedure costs (biopsy and subsequent excision) was –$395 compared with VAH. Furthermore, the relative reduction in stage-related treatment costs associated with the PLA was –$433 compared with VAH, primarily resulting from avoidance of delays due to false-negative diagnoses. Surveillance costs were reduced by –$119 with the PLA. The increased specificity for PLA relative to VAH and melanoma treatment costs were the most influential variables on cost. The total cost of full diagnostic workup of a lesion suggestive of melanoma by VAH was $947. Subtracting the mean selling price for PLA of $500, the cost savings achieved reached $447 per lesion tested.

"The economic benefits of the PLA are driven by high specificity that substantially reduces the number needed to biopsy to find melanoma by 5-fold (from 15.7 to approximately 2.7)," write the authors.

Takeaway: PLA cuts the number of surgical procedures, missed melanomas, and cost in addition to the invasiveness and subjective nature of diagnostic assessment of pigmented lesions.

Urinary cfDNA Analysis Valuable for Urinary Tract Infections, *from page 1*

Overall, the researchers found that urinary cfDNA sequencing agrees in the vast majority of cases with conventional diagnostic testing, but can uncover bacteria and viruses that remain undetected in conventional diagnostic protocols.

> *"Different layers of clinical information are accessible from a single assay that are either inaccessible using current diagnostic protocols or require parallel implementation of a multitude of different tests."*
>
> — Philip Burnham

Among patients with a diagnosed bacterial UTI, cfDNA fragments accounted for more than one-third of raw sequencing reads. For 41 of the 43 positive urine specimens, sequencing of urinary cfDNA detected the clinically reported organisms to the species level. However, only in 26 of the 43 UTI cases was the organism identified in culture the most prevalent organism detected by cfDNA. Finally, for 42 of the 43 UTI samples, researchers were able to determine the relative abundance of genes conferring antibiotic resistance.

Additionally, nearly half of the samples had detectable levels potentially clinically relevant viruses on cfDNA analysis. Findings support the utility of urinary cfDNA sequencing for the detection of both common and uncommon viral agents, particularly among kidney transplant recipients.

"Different layers of clinical information are accessible from a single assay that are either inaccessible using current diagnostic protocols or require parallel implementation of a multitude of different tests," write the authors led by Philip Burnham, from Cornell University, Ithaca, N.Y. "The assay we present has the potential to become a valuable tool to monitor bacteriuria and viruria in kidney transplant cohorts and to ascertain their potential impact on allograft health."

Takeaway: Urinary cfDNA is a highly versatile analyte to monitor infections of the urinary tract and can reveal the viral or bacterial source of infections that may be undetected with conventional diagnostics. Additionally, urinary cfDNA can predict antimicrobial susceptibility in a timely manner.

Procalcitonin Results Fail to Guide Lower Antibiotic Use

Procalcitonin assays results did not help emergency department and hospital-based clinicians prescribe fewer antibiotics for patients presenting with suspected lower respiratory tract infection, according to a study published July 19 in the *New England Journal of Medicine* to coincide with its presentation at the American Thoracic Society 2018 International Conference in San Diego.

Procalcitonin is a blood-based peptide that correlates with the severity of bacterial infections. European studies have shown that procalcitonin-based guidance reduced the use of antibiotics with no apparent patient harm. However, in the United States there is no consensus among national authorities and medical societies about procalcitonin-guided antibiotic use for suspected lower respiratory tract infection.

The Procalcitonin Antibiotic Consensus Trial included 1,656 patients who presented to the emergency department at 14 U.S. hospitals (primarily ur-

ban, academic medical centers from November 2014 through May 2017) with a suspected lower respiratory tract infection. Treating physicians were uncertain whether antibiotic therapy was indicated. Participants were randomized to either the procalcitonin group (n=826), in which the treating clinicians were provided with real-time initial procalcitonin assay results (bioMérieux), or the usual-care group (n=830).

Participating clinicians retained autonomy over care decisions, but they received training regarding national antibiotic guidelines for lower respiratory tract infection and the procalcitonin antibiotic prescribing guideline. Blood samples were taken for procalcitonin measurement in the emergency department and serially if the patient was hospitalized. In the usual-care group, blood was drawn at enrollment for procalcitonin measurement using the same assay, but the results were clinically unavailable.

The researchers found, overall, 47.2 percent of patients were hospitalized, 36.5 percent received antibiotics in the emergency department, and 59.4 percent received antibiotics within 30 days. In the procalcitonin group, initial procalcitonin assay results were received 95.8 percent of patients with a median time from sample collection to assay result of 77 minutes. Yet, 16 patients left the emergency department before the results could be reported. Just over 2 percent of the patients in the usual-care group received a procalcitonin assay as part of usual care.

There was no significant difference in antibiotic exposure during the first 30 days between the procalcitonin group and the usual-care group (mean antibiotic-days, 4.2 and 4.3 days, respectively). Additionally, there was no significant difference between the groups regarding the percentage of patients receiving any antibiotics within 30 days, the percentage of patients receiving an antibiotic prescription in the emergency department, or the mean hospital antibiotic-days for hospitalized patients. The proportion of patients with adverse outcomes within 30 days was also similar between the groups, with hospital readmission the most common individual adverse outcome.

"It seems likely that physicians already commonly withheld antibiotics based on clinical signs alone, and, therefore, instead of the magic bullet I and many others hoped procalcitonin might be, it offered only limited incremental value over clinical judgment," said lead author David Huang, M.D., from University of Pittsburgh, in a statement.

Takeaway: In this large, U.S. trial, procalcitonin assays did not significantly improve antibiotic stewardship among emergency department physicians and hospital-based clinicians treating patients with suspected lower respiratory tract infections.

Quality Improvement Effort Cuts Peds Inpatient Electrolyte Testing

A multifaceted quality improvement intervention can significantly and rapidly cut electrolyte testing among pediatric inpatients, according to a study published April 4 in *Pediatrics*. Furthermore, the authors show that the reduction in testing yielded financial savings and was not associated with unintended adverse events, suggesting that much of the previous electrolyte testing had been unnecessary.

Cincinnati Children's Hospital aimed to reduce electrolyte testing within the hospital medicine service by at least 25 percent within 6 months. All panels that contained at least one electrolyte test, as well as individual electrolyte tests, were targeted. The group used multiple interventions that included education about the clinical value of electrolyte testing and the costs of testing (session and emails), individual feedback on ordering practices, standardized communication about an electrolyte testing plan, and removal of daily repeating orders in the electronic ordering system. Testing rates and costs for the nine months following the intervention were compared to those at baseline (from Jan. 1, 2015, to Aug. 1, 2016).

> *"Our study's success may in part be traced to the breadth of interventions that encouraged discussions of necessity and value in testing and reduced overuse of testing."*
>
> — Michael J. Tchou, M.D.

The researchers found that at baseline the mean rate of electrolyte testing was 2.0 laboratory draws per 10 patient days. In the two months following the initial education intervention, this rate decreased by 35 percent to 1.3 electrolyte laboratory draws per 10 patient days. Similarly, the number of individual laboratory test results decreased from 18.4 to 13.5 test results per 10 patient days. The number of test results further dropped to 9.5 test results per 10 patient days following the rollout of the cost reference cards, the laboratory plan template in patient notes, and structured rounds discussion. This 48 percent reduction in test results was sustained throughout the rest of the intervention period.

"Our study's success may in part be traced to the breadth of interventions that encouraged discussions of necessity and value in testing and reduced overuse of testing," write the authors led by Michael J. Tchou, M.D., from Cincinnati Children's Hospital Medical Center in Ohio. "Single interventions in isolation, such as a cost display without relevant education about overuse and value, may not lead to the desired behavior change."

Patient charges for electrolyte testing were cut by nearly one-third—from a mean $53.81 per patient day to $38.22, which corresponds to an estimated $292,000 of savings per year. This savings was in part due to the substantial reduction in the use of the hospital's highest-charge electrolyte panel, which decreased from 67 percent to 22 percent of all electrolyte testing. During the intervention, there were no changes in rates of medical emergency team calls or readmissions.

In addition to cost savings, the authors say that by reducing overuse the number of test results that need to be reviewed, this could improve workflow for "frontline" staff, thus creating "time for other value-added work."

Takeaway: Quality improvement efforts can safely cut rates of electrolyte testing in pediatric hospitals without jeopardizing patient safety.

Testing Guidelines *at a Glance*

FDA Recommends Pooled Blood Testing for Zika Virus
The U.S. Food and Drug Administration (FDA) revised recommendations for testing donated blood for Zika virus. The agency will now allow pooled testing of blood donations, rather than universal nucleic acid testing of individual units of blood.

The agency said pooled testing is both more cost effective and "less burdensome" for blood establishments, but that "when certain threshold conditions are present," such as an increased risk of local mosquito-borne transmission of Zika virus in a specific geographic are, a return to individual testing may be triggered.

The final guidance still requires blood establishments to test all donated whole blood and blood components for Zika virus using a nucleic acid test. Since 2016 two assays have been approved under investigational new drug applications—the cobas Zika (Roche Molecular Systems, Inc.) and the Procleix Zika Virus Assay (Grifols Diagnostic Solutions, Inc.). In May of this year, the FDA approved an additional claim for Roche's Cobas Zika test for pooled testing of blood or plasma donations.

U.S. Recommends Expansion of Newborn Screening
Health and Human Services Secretary Alex Azar approved the addition of spinal muscular atrophy to the list of conditions for which the U.S. government recommends newborn screening. Approximately 4 million infants are born and screened annually.

The secretary acknowledged that early screening and treatment can lead to decreased morbidity, including improved achievement of motor milestones. He cautions though, that the addition of spinal muscular atrophy is only a recommendation, not a requirement, and that he would like an update on outcomes, including any harms from screening, within two years.

This recommendation comes about 18 months after the FDA approved the first treatment for spinal muscular atrophy. While the drug is reported to be quite expensive ($750,000 for the first year of treatment and $350,000 after that), the addition of the condition to newborn screening is only expected to cost $1 to $5 per infant tested. Advocates say screening will likely detect 150 cases per year, which would otherwise not be identified until presenting with symptoms, at which point it may be too late to initiate treatment.

Focused Update on Less Common HER2 Testing Scenarios For Breast Cancer
The American Society of Clinical Oncology and the College of American Pathologists released a joint focused update of Human Epidermal Growth Factor Receptor 2 (HER2) clinical practice guidelines. Overall, current HER2 testing algorithms have been confirmed by recent clinical trials showing that for patients whose tumors lack gene amplification and are IHC 1+ or 2+, there is a lack of clinical benefit from adjuvant trastuzumab. This focused update provides additional guidance regarding less common HER2 testing scenarios, including in situ hybridization (ISH) equivocal cases.

The panel examined clinical data for three less common HER2 dual-probe ISH test result groups, assessed the most appropriate testing and interpretation algorithm, and eliminated the ISH equivocal category. The revised diagnostic approach for three less common groups includes more-rigorous interpretation criteria for dual-probe ISH testing and requires concomitant immunohistochemistry (IHC) review to ensure the most accurate HER2 status designation (positive or negative) based on the combined interpretation of the ISH and IHC assays. Additionally, the panel recommends:

- Concomitant review be performed in the same institution to ensure comparable interpretation and assay quality.
- There is insufficient evidence on analytical and clinical validity to endorse the use of multiple alternative chromosome 17 probe testing as the primary strategy to resolve uncommon HER2 test results by ISH.
- Concomitant IHC review should become part of the interpretation of single-probe ISH results to allow the most accurate HER2 designation.

Childhood Cancer Survivors Should Be Screened for Endocrine Disorders
Lifelong surveillance for endocrine disorders is necessary for childhood cancer survivors, according to clinical practice guidelines released by the Endocrine Society. Childhood cancer survivors are at increased risk for endocrine disorders, with up to half of survivors developing an endocrine disorder during their lifetime.

Specific recommendations include lifelong periodic clinical assessment for growth hormone deficiency, life-long annual screening for thyroid-stimulating hormone deficiency, and lifelong annual screening for adrenocorticotropic hormone deficiency for those treated for tumors in the region of the hypothalamic–pituitary axis, especially those who received radiation. Diagnostic testing should use the same tests as used in the noncancer population, the society says.

American Cancer Society Lowers Age for Colon Cancer Screening
The American Cancer Society updated its colon cancer screening guidelines. The organization's most notable change was lowering the recommended age for routine colon cancer screening for patients at average risk from 50 to 45 years, an additional 22 million people. The society says a review of the literature by its experts showed that the rate of new cases of colorectal cancer occurring among younger adults is increasing. Radiation exposure to key endocrine organs (e.g., hypothalamus, pituitary, thyroid, and gonads) places cancer survivors at the highest risk

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Testing Guidelines *at a Glance*

of developing an endocrine abnormality over time, even decades after treatment. The newly released guideline emphasizes individual preference and choice in testing options. Additional recommendations include:

- Age: People who are in good health and with a life expectancy of more than 10 years should continue regular colorectal cancer screening through the age of 75. Screening for people ages 76 through 85 should be based on a person's preferences, life expectancy, overall health, and prior screening history, while people over 85 years of age should no longer get colorectal cancer screening.
- Testing Type: The new guideline does not prioritize among screening test options. Recommended tests include: Annual screening with the fecal immunochemical test or the high sensitivity guaiac-based fecal occult blood test; the multi-target stool DNA test every 3 years; colonography every 5 years; and flexible sigmoidoscopy every 5 years; or colonoscopy every 10 years.
- All positive results on non-colonoscopy screening tests should be followed up with timely colonoscopy.

First-ever Pharmacogenomic Guideline for Guiding Tamoxifen Therapy

There is sufficient evidence to use CYP2D6 genotype to guide decision-making for women who are being considered for tamoxifen treatment for early stage estrogen receptor positive breast cancer. The recommendation provides clinicians with information that will allow the interpretation of clinical CYP2D6 genotype tests, including dosing information and suggestions for use of an alternative hormonal therapy based on CYP2D6 genotype.

Breast Cancer Staging Uses Tumor Biology Markers

The eighth edition of the American Joint Committee on Cancer Breast Cancer Staging System was revised to incorporate tumor biology. It attempts to incorporate the fast-moving field of precision medicine in early breast cancer treatment protocols. Specifically, the staging system incorporates biologic tumor markers—estrogen receptor and human epidermal growth factor 2 status, and the 21-Gene Recurrence Score, that was prospectively validated in the TAILOR-X study. AJCC said that the changes in the staging system acknowledge the value of commercially available, gene-based assays and incorporated prognostic input alongside classification based on traditional anatomic factors.