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Despite 23andMe Authorization, FDA Cautious About PGx Testing

The U.S. Food and Drug Administration (FDA) provided 23andMe (Mountain View, Calif.) authorization for the first direct-to-consumer (DTC) test for detecting genetic variants that may be associated with medication metabolism. However, the very next day, the FDA released a safety communication warning consumers and physicians against making treatment decisions based on genetic tests that claim to predict patients' responses to specific medications.

While the 23andMe authorization included similar cautions in the special controls, the safety communication went further cautioning against claims of tests developed as laboratory-developed tests. Unlike 23andME, other companies that offer PGx tests as a laboratory-developed test—Genomind, Assurex, and Color—require the test to be ordered through a medical provider.

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FDA Enabling New Point-of-Care Tests for Ebola Outbreak, Flu Season

Several recent U.S. Food and Drug Administration (FDA) actions are bringing point-of-care (POC) infectious disease tests closer to patient care. These recent regulatory wins are enabling more rapid diagnosis and clinical decision-making—empowering clinicians to improve antibiotic stewardship and enabling public health authorities to improve outbreak responses.

Rapid, Molecular Flu Testing

The 2017-2018 flu season was severe, with the highest number of cases of influenza-associated illness since the 2009 H1N1 pandemic, when an estimated 60 million people were sick with influenza, according to the U.S. Centers for Disease Control and Prevention.

Earlier this year the FDA's new rapid flu test regulations went into full effect. These efforts were aimed at improving the overall quality of flu testing by improving the test performance of antigen-based rapid influenza diagnostic tests. Despite these improvements, many are moving away from antigen-based testing and towards more ac-

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Despite 23andMe Authorization, FDA Cautious About PGx Testing, *from page 1*

"Tests that make such claims [how a patient will respond to specific medications] that have not been evaluated by the FDA and are not supported by prescribing recommendations in the FDA-approved drug label, may not be supported by scientific and clinical evidence, and may not be accurate," the agency wrote. The agency said it is concerned about health care providers and patients inappropriately selecting or changing drug treatment based on the results from "insufficiently substantiated genetic tests." Specifically, the FDA calls out PGx tests marketed to improve antidepressant prescribing.

Citing warfarin sensitivity as an example, the agency said only FDA-approved labeling for a drug and/or companion genetic test provide health care providers with adequate information on how to use genetic information reported by the genetic test to manage medication treatment using the drug. The FDA further warned that is is looking into certain developers that may be "inappropriately selling genetic tests for the unapproved uses" and will take compliance actions, if necessary.

23andMe's Authorization

The FDA expanded the approved marketing of the 23andMe Personal Genome Service Pharmacogenetic Reports test to include information about 33 genetic variants in eight genes linked with a metabolism of drugs, including 50 commonly prescribed and over the counter medications (CYP2C19, CYP2C9, CYP3A5, UGT1A1, DPYD, TPMT, SLCO1B1, and CYP2D6).

The FDA reviewed data for the test through the de novo premarket review pathway. With the authorization, the FDA is established six special controls, including a labeling requirement with a warning statement noting that the consumer should not use the test results to stop or change any medication. The FDA's review determined the test is accurate (can correctly identify the genetic variants in saliva samples) and that it can provide reproducible results. Additionally, the company submitted consumers understood test instructions and reports.

However, the FDA says the authorization is not intended to provide information on a patient's ability to respond to any specific medication and warns that health care providers should not use the test to make any treatment decisions, without additional clinical testing.

"The authorization allows us to provide customers with information on whether they are predicted to be fast or slow metabolizers based on their genetics, and when supported by appropriate clinical evidence, whether they may experience reduced efficacy or have an increased chance of side effects from certain medications," the company wrote on its blog.

"We've continued to innovate through the FDA and pioneer safe, effective pathways for consumers to directly access genetic health information," said 23andMe cofounder and CEO Anne Wojcicki. "Pharmacogenetic reports are an important category of information for consumers to get access to and I believe this authorization opens the door for consumers to work with their health providers to better manage their medications."

With this authorization, the company has now received FDA authorization or clearance for all categories of its original products.

"This test is a step forward in making information about genetic variants available directly to consumers and better inform their discussions with their health care providers," said Tim Stenzel, director of the FDA's Office of In Vitro Diagnostics and Radiological Health. "This test should be used appropriately because it does not determine whether a medication is appropriate for a patient, does not provide medical advice, and does not diagnose any health conditions."

Takeaway: Despite the new authorization of 23andMe's Personal Genome Service Pharmacogenetic Reports to include PGx information, the FDA is taking a cautious stance on laboratory-developed PGx tests.

At-Home, Smartphone-Based Urine Testing Now a Clinical Reality

In what has been called the "era of the medical selfie," at-home, smartphone-based urine testing is now a reality. In a short timeframe, the U.S. Food and Drug Administration (FDA) cleared two smartphone-based, urine testing platforms for patient use.

> *"This approval opens the door for improved screening for kidney disease, a condition which affects over 10 percent of the population globally."*
>
> — Joe Coresh, Ph.D.

The first to receive 510(k) clearance was Healthy.io (Israel) for its DIP Urine Analysis Test System (Dip.ioH). The company it was the first device the FDA cleared based solely on existing smartphone cameras for Class II clinical claims.

The system received CE mark in 2016 and is commercially available in Europe and Israel, where the company says they will have reached 100,000 users by the end of the year.

The FDA cleared Dip.ioH for testing glucose, specific gravity, blood, pH, protein, and the qualitative detection of nitrite to guide patient management and aid in the diagnosis and monitoring of metabolic or systemic diseases that affect kidney function and endocrine disorders. The agency cleared the system as prescription home-use only, with results provided directly to the physician. The company says the test can aid in the diagnosis of urinary tract infections for people with multiple sclerosis, provide new opportunities in chronic kidney disease prevention, and help pregnant women monitor their health.

While, patients do not have access to test results, the app instructs the patient how to accurately administer the test and the software securely transmits the clinical results directly to the patient's electronic medical records for physician review.

Data submitted to the FDA showed that lay users successfully completed 424 of 429 tests, with results transmitted to the physician. Computer vision algorithms and a unique calibration method produce test results comparable to laboratory urinalysis.

"This approval opens the door for improved screening for kidney disease, a condition which affects over 10 percent of the population globally," said Joe

Smartphone Testing Being Evaluated in Trial of High-Risk Patients

This past spring, the National Kidney Foundation, Geisinger Health System (Danville, Penn.), and Healthy.io launched a novel clinical trial using a smartphone-enabled home urinalysis device to detect chronic kidney disease (CKD) among patients with high blood pressure. One of the best ways to test for CKD and assess kidney damage is a simple urine test, which detects the presence of albumin.

In the trial, 1,000 non-diabetic, primary care patients with hypertension will be randomized to receive either usual care or a mailed Healthy.io urinalysis kit.

Those receiving the kit will receive a letter and phone call educating them on the importance of screening for proteinuria from a team of nurses along with instructions for downloading the smartphone app.

"This new trial using a smartphone app and urinalysis kit will provide important information on how to increase testing for CKD in this high-risk population," said Kerry Willis, Ph.D., chief scientific officer at the Kidney Foundation, in a statement. "Our hope is that a home-based test makes it easier for patients at risk for CKD to comply with regular albuminuria screening, and that this will lead to earlier diagnosis and treatment of CKD, reducing cardiovascular risk and preserving kidney function."

Coresh, Ph.D., a professor at Johns Hopkins University and chair of Healthy.io's medical advisory board, in a statement. "It's exciting to see the FDA applying its rigor and enabling the use of the smartphone for better patient care."

Inui Health (formerly known as Scanadu; Sunnyvale, Calif.) received 510(k) clearance and a Clinical Laboratory Improvements Amendments waiver for its in-home urine analysis platform. The company says its platform enables tests for urinary tract infections, diabetes or pre-gestational diabetes, kidney issues, and preeclampsia.

Specifically, the FDA cleared the device for protein, glucose, leukocyte, nitrite, and ketone testing. The device reports semi-quantitative or qualitative results for each test parameter. The company says a three-pack of test kits is available direct to consumers through the company website for $34.99.

"We see an unprecedented opportunity in bringing powerful diagnostic tests currently only available at labs or clinics to the hands of consumers," said Jaime Tenedorio, CEO of inui Health. "We are enabling individuals to perform these tests anywhere in the world, from Manhattan to Sub-Saharan Africa, empowering individuals to know more and worry less about their health."

Takeaway: Experts expect more smartphone-based diagnostic applications to be cleared with expanded indications for use in the near future, helping to improve access to and ease of ongoing patient monitoring.

Panel Size Affects Accuracy of Tumor Mutational Burden Calculation

Panel size is a critical determinant of test performance and cutoff values for determining the tumor mutational burden (TMB) to guide treatment decisions with immunotherapies, according to a study published Sept. 21 in the *International Journal of Cancer*. Specifically, panels between 1.5 to 3 Mbp are ideal to effectively estimate TMB.

"To provide a wide availability of testing, lab developed tests to determine TMB need to implemented. However, current data that can provide guidance in this context are scarce and preliminary," write the authors led by Ivo Buchhalter, from the University Hospital Heidelberg in Germany.

TMB is increasingly used as a marker for predicting which patients will have a positive response to immunotherapies. Evidence shows a higher mutational burden correlates to improved survival benefits in patients receiving checkpoint inhibitor therapies, as more mutations heighten the chance of immune system activation.

While research studies used whole-exome sequencing (WES) for measuring TMB, WES is not feasible for routine clinical use given cost, computational complexity, and turnaround time. Panels are commercially available, but there has been little evidence suggesting the ideal sizes or methods of calculating TMB.

"Our analyses showed that 'size does matter' with an optimal panel size being reached between 1.5 and 3 Mbp considering the benefit-cost ratio."

— Ivo Buchhalter

This study assessed the performance parameters of two panels from Illumina (San Diego), the TruSight Tumor 170 (TST 170) and TruSight Oncology 500 (TSO 500), a forthcoming panel. The Germna-based reserachers conducted silico analysis (using combinatorial calculations and extensive simulations) using The Cancer Genome Atlas data for 8,371 tumors, across 25 different cancer types, including lung, melanoma, pancreatic, breast, head, and neck, gynecological, and colorectal cancers.

Somatic variants were extracted and annotated using Annovar and Gencode. Only mutations falling into regions included in the Agilent SureSelect V4 enrichment kit were considered. The vendor provided regions covered by the commercial panels. Sequencing panels of sizes 0.5, 1, 1.5, 2, 3, 5 and 10 Mbp were simulated.

The researchers found that the precision of TMB estimation considerably depends on the size of the targeted sequencing panel. Smaller panels result in imprecise measurement of TMB, especially for tumors with low TMB values. Thus, small panels, the authors say are "clinically suboptimal" for patient stratification and response prediction.

"Our analyses showed that 'size does matter' with an optimal panel size being reached between 1.5 and 3 Mbp considering the benefit-cost ratio," write the authors led by Ivo Buchhalter, from the University Hospital Heidelberg in Germany.

The authors add that inclusion of all point mutations (instead of only missense mutations) is both possible and recommended to enhance precision in calculating the TMB.

Since TMB needs to be extrapolated from the number of mutations detected in the sequenced region, for panels smaller than 1 Mbp, the thresholds for the separation of hypermutated from non-hypermutated tumors fall below 10 mutations and will be inaccurate for classification of tumors with TMB close to the threshold, the authors say. In contrast, larger gene panels were associated with higher cutoff values and resultantly, increased robustness and reliability.

"To the best of my knowledge, this is the first publication to use large-scale computational analysis to evaluate how size of the gene panel, and the type of mutations included in the calculations, impacts measurement of TMB," said Phil Febbo, M.D., chief medical officer at Illumina, in a statement. "Of course, algorithms for mutation calling and filters to remove artifacts and germline variants are also components of accurate TMB, but this paper will contribute significantly to ongoing efforts working to standardize TMB as a biomarker."

Takeaway: Panel size is a critical determinant of test performance and cutoff values for determining the TMB.

Sequencing-Based Panel May Improve Evaluation of Thyroid Nodules

A genetic test panel can help patients avoid unnecessary diagnostic thyroid surgeries, according to a study published Nov. 8 in *JAMA Oncology*. More than six in 10 of patients with thyroid nodules of indeterminate cytology could avoid diagnostic surgery with use of ThyroSeq, a multigene genomic classifier testing. The test not only reliably distinguishes between benign and cancerous thyroid nodules, but can also provide a detailed genetic profile of the positive nodules.

"With such a high proportion of preventable surgeries, this test should practically resolve the decades-long struggle and inefficiency of medical care for patients with indeterminate cytology thyroid nodules," said senior author Yuri Nikiforov, M.D., Ph.D., from UPMC, in a statement. "In an era of overdiagnosis and overtreatment, ThyroSeq can improve quality of life for patients by sparing them a lifetime of synthetic thyroid medications and specialist visits, while significantly reducing health care costs."

It is estimated that more than 600,000 thyroid fine needle aspiration biopsies are performed every year in the United States alone, with approximately 20 percent of these having indeterminate cytology results. A large portion of these patients undergoes surgery, but only 10 percent to 30 percent of these thyroid nodules are actually malignant. If a test could reliably diagnose these nodules as benign, diagnostic surgery could be avoided. Additionally, among nodules that are indeterminate, but suspicious for malignancy, a more precise assessment could inform the extent of surgery necessary.

The current study assessed use of the ThryoSeq test in patients from 10 medical centers. Ultimately, 256 patients (79 percent female; n = 286 nodules) with surgical follow-up data were eligible. Pathology review was performed on 274 nodules. Samples from indeterminate nodules (Bethesda III, n= 172; Bethesda IV, n= 101; and Bethesda V, n = 13) were shipped to the University of Pittsburgh Medical Center (UPMC) for ThroSeq testing.

The ThyroSeq Genomic Classifier test is offered in joint partnership between UPMC and CBLPath, a Sonic Healthcare company. The next-generation sequencing-based test assesses alterations (point mutations, gene fusions, and copy number and gene expression

ThyroSeq Demonstrates Cost Effectiveness

A separate, small study published in Endocrine Practice in September showed that ThyroSeq is cost effective compared to diagnostic thyroid surgery for the evaluation of Bethesda categories III and IV nodules.

The Mayo Clinic researchers reviewed cytology and histopathology slides of Bethesda category III and IV. Costs for evaluation of eight Bethesda III nodules and 13 Bethesda IV nodules using ThyroSeq were calculated and compared to the cost of diagnostic thyroidectomy for eight Bethesda III nodules and 11 Bethesda IV nodules.

The researchers found that of those Bethesda III nodules submitted for ThyroSeq, four were positive for mutations and underwent thyroid surgery. For each category III nodule evaluated using ThryoSeq, the average cost was $14,669 versus $23,338 for diagnostic thyroid surgery. For those category III nodules requiring surgery, the cost per thyroid cancer case detected using ThryoSeq was $58,674 versus $62,233 for those detected with diagnostic thyroid surgery.

Of the Bethesda IV nodules submitted for ThyroSeq, six were positive for mutation and underwent thyroid surgery. The average costs per category IV nodule evaluated were $14,641 using ThyroSeq and $24,345 using diagnostic thyroidectomy. The cost per thyroid cancer case detected was $31,721 when using ThyroSeq compared to $53,560 for diagnostic thyroidectomy.

Larger studies of cost savings will be required to further advance coverage decisions for the test. However, the test has already received some positive coverage. In October, ThyroSeq was approved by Medicare Administrative Contractor, Novitas Solutions, for Medicare coverage. Earlier in the year, Aetna issued a positive coverage decision for ThyroSeq.

"Prospective studies will be needed to determine whether patients with the molecular signature of low-risk cancer or NIFTP can have surgery safely delayed or replaced by medical surveillance, as is currently under consideration for small thyroid cancers."

— David L. Steward, M.D.

alterations) in 112 genes linked to thyroid cancer. A genetic classifier score is calculated based on the sum of individual values of all detected alterations. A score of 0 or 1 is deemed a negative test (a score of 1 is commercially reported as currently negative) and scores of 2 and above are considered positive.

The researchers found that based on the 257 nodules with samples adequate for molecular analysis, 59 percent were negative and 41 percent were positive. For all Bethesda III and IV nodules, the ThyroSeq had a sensitivity of 94 percent and 82 percent specificity. With a cancer/noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) prevalence of 28 percent, the negative predictive value (NPV) of ThryoSeq was 97 percent and the positive predictive value (PPV) was 66 percent. The authors say that the 3 percent false-negative rate was similar to that of benign cytology. Further, the missed cancers were all low-risk tumors.

"Prospective studies will be needed to determine whether patients with the molecular signature of low-risk cancer or NIFTP can have surgery safely delayed or replaced by medical surveillance, as is currently under consideration for small thyroid cancers," write the authors led by David L. Steward, M.D., from University of Cincinnati Medical Center in Ohio.

Takeaway: ThyroSeq is showing evidence of being an effective, cost-effective strategy for evaluation of potentially cancerous thyroid nodules with indeterminate cytology.

Ideal Age of Last Cervical Cancer Screening Depends on Test Type

With the adoption of cotesting—human papillomavirus (HPV) plus Pap cytology—cervical cancer screening methodology has focused primarily on the preferred frequency of combined testing.

However, a new study, published Nov. 1 in *The Lancet Oncology*, is re-examining the recommended age of last cervical cancer screening. The Canadian study concludes age at last cervical cancer screening depends on the type of test used. With cytology, lifetime cervical cancer risk reduction might be achieved by screening up to age 75 years, rather than age 65 years as is currently recommended in the United States. However, a single negative exit HPV test at age 55 years provides "strong reassurance" and indicates a very low remaining lifetime risk of cervical cancer.

"The introduction of a test with a higher sensitivity and longer lead time should necessarily drive the establishment of a lower stopping age than for the Pap test," writes Paolo Giorgi Rossi, Ph.D., from the epidemiology unit at Azienda Unità Sanitaria Localein in Italy, in an accompanying editorial.

Cervical cancer incidence and mortality remain high in older, unvaccinated women and may actually be underestimated because women who have had a total hysterectomy are no longer at risk for cervical cancer, but are generally

not from denominators for age-specific cancer incidence. This underestimation of risk may also underestimate the benefits of screening in older women with a cervix.

The Canadian researchers developed a Markov model of cervical cancer screening to estimate the remaining lifetime risk of cervical cancer at different ages and with different exit screening tests. They calibrated and validated the model using Canadian provincial registries and survey data. The model used HPV infection and cancer incidence data from Statistics Canada. The model also reflected typical cervical cancer screening adherence and rate of hysterectomy, with stopping ages varying from age 55 years through age 80 years.

"Our results might not be applicable to future cohorts with high vaccination coverage or who will have been screened for most of their lives with HPV testing."

— Talía Malagón, Ph.D.

The researchers found that cervical cancer incidence excluding women with hysterectomies underestimated the incidence of cervical cancer in women with a cervix by up to 71 percent in women aged 80–84 years. The model predicted that women without HPV vaccination who were never screened have a 1 in 45 lifetime risk of cervical cancer, whereas unvaccinated women with perfect adherence to cytology screening every 3 years between the ages of 25 years and 69 years could reduce the lifetime risk of cervical cancer to 1 in 532 women.

"Our results suggest that most of the prevention of cervical cancer in later life is due to screening before the age of 55 years, " write the authors led by Talía Malagón, Ph.D., from McGill University in Canada.

Assuming no differences in screening practice up to stopping age, the researchers found that increasing the age at which women stopped cytology screening from 55 years to 75 years led to incremental decreases in cancer risk later in life. A woman with a cervix who stopped cytology screening at age 55 years will have twice the 5-year risk of cervical cancer at age 70–85 years versus a woman who continued screening with typical screening adherence.

A woman with a cervix who tested HPV DNA negative to 14 high-risk HPV types and stopped screening at age 55 years will have a remaining lifetime cervical cancer risk of 1 in 1,940), which is lower than the remaining lifetime risk for women who stopped screening at the same age with a final negative cytology test (1 in 440) and is also lower than a woman who ends screening with a negative cytology screening at age 70 years (1 in 1,206).

"Our results might not be applicable to future cohorts with high vaccination coverage or who will have been screened for most of their lives with HPV testing," acknowledge the authors. "However, as it will be many decades before cohorts vaccinated as adolescents reach the age of 50–70 years, our results are likely to be applicable to older cohorts of women for years to come."

Takeaway: The ideal age to stop cervical cancer screening depends upon test type, with a negative high-risk HPV test at age 55 years yielding a lower lifetime risk of cervical cancer than women who continue cytology through age 70 years.

Penicillin Allergy Testing Underused, Could Lead to Cost Savings

Once a patient is labeled as having a penicillin allergy, it is rarely revisited. The label sticks and increases the patient's risk of receiving subsequent suboptimal, alternative antibiotic therapy, even in cases of unconfirmed penicillin allergy.

Yet, in an era of cost cutting and intensified scrutiny on antibiotic stewardship, there is heightened interest in confirmatory allergy testing to "debunk" false penicillin allergies and minimize the use of unnecessary, high-cost, broad-spectrum antibiotics. In 2016, the American Academy of Allergy, Asthma and Immunology (AAAAI) approved a position statement recommending routine penicillin allergy testing in patients with unverified penicillin allergies.

Despite patients' fear of severe reaction from reexposure, penicillin-associated anaphylaxis is extremely rare.

"Penicillin allergy testing is associated with an unrealized potential: this procedure can accurately identify the approximately nine of 10 patients who despite reporting a history of penicillin allergy can receive penicillins safely," the AAAAI said in its position statement. "The AAAAI encourages more widespread and routine performance of penicillin skin testing for patients with a history of allergy to penicillin or another beta lactam (e.g., ampicillin or amoxicillin).... We are confident that more frequent and routine performance of penicillin allergy testing will be associated with reduced costs of care, enhanced patient safety, and improved outcomes of care."

Several recent reports show that penicillin allergy testing remains underused and questions remain about how and where testing should be performed.

Who Should Be Tested and How

All individuals with an unconfirmed penicillin allergy should have their penicillin allergy evaluated and, if appropriate, tested to confirm current hypersensitivity or tolerance, according to a study published in the November issue of the *Annals of Allergy, Asthma & Immunology*. An oral challenge with amoxicillin in patients with low-risk penicillin allergy histories is the optimal method to confirm current tolerance.

Despite patients' fear of severe reaction from reexposure, penicillin-associated anaphylaxis is extremely rare. However, there are known risks that come with the avoidance of penicillin due to unconfirmed allergy, including inappropriate prescribing, inferior clinical outcomes, and higher health care expenditures.

At the Kaiser Permanente Southern California in San Diego, California, from Jan. 1, 2017, to March 30, 2018, 519 children and adults with low-risk penicillin-associated reaction histories had a direct 250-mg oral amoxicillin challenge. One patient had an immediate onset positive result and had a delayed onset positive result. Additionally, 291 adults and children with higher-risk histories had skin testing. Only five patients had positive skin test results and an additional five had a short-term, objective oral challenge reaction after negative skin testing results. There were no delayed-onset oral challenge reactions in the group who underwent skin tests first.

The Kaiser results were similar to six other large studies leading authors Eric Macy, M.D., from the Southern California Permanente Medical Group in San Diego, and David Byles, from the Medical College of Wisconsin in Milwaukee to recommend:

- Low-risk individuals (a history of benign rash, gastrointestinal symptoms, headaches) can safely go to a direct oral amoxicillin challenge with a therapeutic dose to confirm current tolerance. The oral challenge typically involves 250 mg for adults, and one hour of observation to confirm acute tolerance, followed by 5 days of at home follow-up to confirm the absence of clinically significant T-cell–mediated delayed-onset hypersensitivity.
- Skin testing to rule out a high risk of having anaphylaxis during a confirmatory oral amoxicillin challenge in patients with high-risk histories (reaction within the last 12 months or any history of shortness of breath). Puncture and intradermal skin testing should only use penicilloyl-polylysine, with at least 5 mm of wheal and flare greater than the wheal to define a positive test result.

The authors add that individuals seen in all health care settings can be evaluated for current penicillin tolerance, including in the hospital, intensive care units, emergency departments, and outpatient clinics, especially for preoperative workup.

Economic Benefit to Confirmatory Allergy Testing

"Delabeling" children through confirmatory allergy testing for previously unconfirmed penicillin allergies changes subsequent prescription behavior and leads to actual health care savings, according to a study published in May in *Pediatrics*.

Researchers followed up on 100 children with negative results for a penicillin allergy 500-mg oral challenge with amoxicillin given in a pediatric emergency department. One year after the negative test results, primary care providers and/or parents reported 46 antibiotic prescriptions in 36 patients. More than half of these prescriptions (58 percent) were filled with penicillin derivatives. The cost savings of delabeling patients as penicillin allergic was $1,368.13, the cost avoidance was $1,812.00, and the total potential cost savings for the pediatric emergency department within one hospital system population was $192,223, based upon the approximately 6,700 patients per year with a reported penicillin allergy seen in the pediatric emergency department.

Even greater savings and improvements in patient care could have been realized with better communication of label removal and test results to the child's entire care team, but particularly the child's primary care provider.

With the negative test result, the hospital medical record was delabeled. However, families were relied upon to notify the primary care provider about the test results. One year following the negative test result, more than 80 percent of primary care providers were not notified of allergy testing results and over half still had the allergy documented in the chart.

Takeaway: Expanding confirmatory penicillin allergy testing can benefit patient care and generate health system savings.

FDA Enabling New Point-of-Care Tests for Ebola Outbreak, Flu Season, *from page 1*

curate, nucleic acid-based rapid molecular flu tests that can be used at the POC. These Clinical Laboratory Improvement Amendments-waived tests can generate results in less than 30 minutes and can be used in near-patient testing sites, like doctor's offices or walk-in, urgent care clinics.

Just in time for flu season, the FDA granted a CLIA waiver to Abbott for its next-generation Influenza A & B 2 and Strep A 2 molecular assays that are run on the ID NOW platform (formerly Alere i). Results are available in five minutes for influenza and two minutes for Strep A, the company says.

Similarly, Cepheid (Sunnyvale, Calif.) was granted clearance and a waiver for its Xpert Xpress Flu/RSV test back in July. The test can be performed in near-patient settings and provides rapid, accurate molecular detection of influenza A and B viruses, and respiratory syncytial virus RNA from patient specimens in 20 minutes.

"Our first-in class multi-module system deals effectively with the surge of tests demanded by a severe flu season and frees up the laboratory to conduct other more complicated tests," said David Persing, M.D., Ph.D., Cepheid's chief medical and technology officer.

In a recent *CAP Today* webinar on preparing for the upcoming flu season, Gregory Berry, Ph.D., from Northwell Health Laboratories (Lake Success, N.Y.) emphasized that having redundant testing platforms is key to surviving drastic spikes in demand, including supply shortages, such as occurred last flu season. He said last year's severe season led to his laboratory running 600 tests per day. Berry also noted unusually high rates of influenza B and RSV seen during the 2017-2018 season, underscoring the importance of having panels. Additionally, laboratories should be communicating with providers and educating about flu testing algorithms.

Available CLIA-Waived, Nucleic Acid-Based Rapid Flu Tests

- Abbott ID Now Influenza A&B 2 (formerly known as Alere i Influenza A&B 2)
- BioMerieux BioFire FilmArray RP EZ
- Cepheid Xpert Flu + RSV Xpress Assay performed on the GeneXpert Xpress System (GXI)
- Cepheid Xpert Xpress Flu Assay performed on the GeneXpert Xpress System (GXII and GXIV)
- Mesa Biotech. Inc. Accula Flu A/Flu B Test performed on the Accula Dock
- Roche Cobas Liat Influenza A/B Assay (formally known as IQuum Liat Influenza A/B Assay)
- Roche Cobas Liat Influenza A/B+RSV Assay (formally known as IQuum Liat Influenza A/B+RSV Assay)

Ebola Testing for Low-Resource Areas

The FDA announced on Nov. 9 its second emergency use authorization (EUA) for a rapid, fingerstick test for the detection of Ebola virus. The DPP Ebola Antigen System (Chembio Diagnostic Systems; Medford, N.Y.) is notable because it is the first test available under EUA that uses a portable battery-operated reader, which can enable testing in low-resource settings without equipped laboratories.

The latest Ebola outbreak, in the Democrat Republic of the Congo, is proving challenging to control. Unlike previous outbreaks, it is in a densely populated area marked by conflict and regular population movement is complicating identifying and tracking deaths and active chains of transmission. As of Nov. 16, the U.S. Centers for Disease Control and Prevention reports the outbreak has 311 confirmed cases and 171 confirmed deaths.

With this newest EUA, the FDA has now issued a total of 11 Ebola EUAs—nine for nucleic acid tests and two for rapid diagnostic tests.

"Our FDA team of experts in drugs, vaccines and diagnostics continue to collaborate with our federal, international and industry partners to employ our collective expertise, experiences from previous incidents, and resources to assist in the global response to the Ebola outbreak," said FDA Commissioner Scott Gottlieb, M.D., in a statement. "By authorizing the first fingerstick test with a portable reader, we hope to better arm health care providers in the field to more quickly detect the virus in patients and improve patient outcomes."

The DPP Ebola Antigen System is used with blood specimens, including capillary fingerstick whole blood, for individuals with signs and symptoms of Ebola. The test detects viral antigens and provides qualitative results in 15 to 20 minutes with the hand-held, battery-operated DPP Micro Reader. The FDA advises that the DPP Ebola Antigen System should be run in facilities, like treatment centers and public health clinics, where patients are likely to be treated.

"Our patented DPP technology continues to serve as a robust platform for the rapid detection of infectious diseases, and we hope to receive support and funding as we pursue additional regulatory approvals for our rapid Ebola test," said John Sperzel, Chembio's CEO, in a statement.

Takeaway: The FDA's recent actions are enabling expansion of POC infectious disease testing, which ultimately assist in efforts aimed at better antibiotic stewardship and outbreak control.