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Testing Trends: AMP Creates New Quality Guidelines for PGx Laboratory Testing

Pharmacogenetic (PGx) testing has recently come under fire from both the scientific and regulatory community for its lack of self-policing. But the new Association for Molecular Pathology (AMP) position statement outlining best practices for PGx testing may help calm the storm.

Concerns Over PGx Testing

PGx testing provides information to predict the likelihood of medication response and/or risk for adverse medication reactions based on a person's genetic makeup. This information can be useful in guiding medication and dosing decisions. But while PGx testing continues to grow, it remains relatively new and unproven. And as with any new forms of testing, there are concerns about the clinical

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Test Utilization: New Guidelines Recommend Basing Routine Colorectal Cancer Screening on Risk Rather than Age

Even people who are not in diagnostics have probably heard that adults age 50 to 79 should get routine colorectal screening exams. But now that longstanding recommendation has changed. According to new guidelines from an international panel of researchers and experts that were published in *The BMJ* in early October, routine screening recommendations should be limited to individuals with an elevated level of risk rather than the entire age group. This represents a significant departure from current recommendations in most parts of the world.

Colorectal Cancer Screening

One in 20 people in high-income countries get colorectal cancer

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AMP Creates New Quality Guidelines for PGx Laboratory Testing, *from page 1*

validity of particular PGx tests and the quality of PGx laboratory testing. The AMP guidelines are an attempt to allay those concerns by setting out four standards for laboratories providing PGx tests to follow to ensure that testing is carried out in accordance with best practices.

1. PGx Health-Related Claims Must Have Well-Established Clinical Validity

"[PGx] tests that are offered clinically should demonstrate evidence of clinical validity before being offered to patients," the AMP guidelines state. "The drug-gene association must be robust and supported by strong scientific evidence," which may include peer-reviewed literature, FDA drug labels and/or clinical practice guidelines, such as the PGx evidence level standards created by the Clinical Pharmacogenetics Implementation Consortium (CPIC).

2. PGx Test Labs Must Follow CLIA

PGx test providers must comply with the same CLIA standards that are required for all other clinical laboratory tests, the guidelines say, including those requiring that tests be verified under the supervision of, and interpreted and reported by, board-certified molecular laboratory professionals, and that details regarding analytical methodology, validity and quality be readily available to providers upon request.

3. Standards for Test Reporting

The AMP says that laboratories must ensure that the PGx test report can be comprehended by the provider, including those who do not have medical genetics or PGx training. The report should include the interpretation of the findings, the significance of the results and the limitations of the test and list the following information:

- A statement of the metabolizer status determined by the genotype for the genes that affect drug metabolism;
- A list of the drugs for which responsiveness may be affected by the genotype;
- A generalized statement to alert providers when alternate dosage or drug treatment may be considered based on the results;
- A list of resources and references that the provider can utilize to learn more about the genotyping result, the drug-gene association and how to incorporate the result into actionable decisions.

4. Standards for Use of PGx Testing Results

The AMP "strongly recommends" that patients who have direct access

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to their PGx testing results not change their treatment plan on the basis of those results without first talking to their provider. "Any result of a pharmacogenomic test should be discussed with the patient's healthcare provider to determine whether changes to the patient's medication plan are recommended," according to the guidelines.

The Practical Impact of the AMP Guidelines

To appreciate the significance of the AMP guidelines, you need to consider the context and current state of PGx testing. The AMP is hardly alone in harboring concerns about the clinical validity and quality of PGx testing. Regulators feel the same way, including the FDA. Although the FDA has approved the inclusion of PGx information in the labels of hundreds of medications, it has also trained its enforcement sights on test makers for making unproven claims about the capabilities of tests that have not received agency clearance.

Thus, on Nov. 1, 2018, the FDA issued a Safety Communication alerting patients and physicians that claims about the capabilities of unreviewed PGx tests to predict response to specific medications may not be supported by sufficient scientific or clinical evidence. As an example, the Safety Communication cites genetic tests purporting to be capable of predicting whether certain medications used to treat depression may be less effective or have an increased chance of side effects. The relationship between variations and the effectiveness of antidepressant medication has never been established, the Safety Communication states.

The ACLA says the FDA and its constituents would be better served if the agency focused its energies on encouraging "responsible" LDT development by adopting recommendations such as those offered by professional groups. It then cites the AMP guidelines as an example.

Soon after issuing the Safety Communication, the FDA began issuing warning letters to PGx test makers for allegedly making unwarranted claims. At least one recipient of such a letter, Inova Genomics Laboratory, has reportedly stopped offering PGx tests in response.

The laboratory industry has called on the FDA to end the crackdown, which it contends is exercising a chilling effect on PGx and Laboratory Developed Test (LDT) tdevelopment and innovation and compromising medication decisions. In a recent letter, the American Clinical Laboratory Association (ACLA) claimed that the "FDA's actions have the practical effect of taking away valuable tools that physicians rely on for making informed prescribing decisions. . . [and] will result in more patients getting a less effective or the wrong medication, with negative consequences for patient care and health care costs."

The ACLA says the FDA and its constituents would be better served if the agency focused its energies on encouraging "responsible" LDT

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development by adopting recommendations such as those offered by professional groups. It then cites the AMP guidelines as an example.

Takeaway: Nobody disputes the enormous potential value of PGx testing in empowering better medication decisions. But as with just about any other innovative new testing field, PGx science and technology is moving faster than the clinical and government regulators. That puts a burden on PGx test makers and laboratories to police themselves until the regulators catch up. Complying with the new AMP guidelines should serve as a significant step in that direction.

Emerging Tests: FDA Issues New Guidance on Using NGS Data to Secure Antiviral Drug & CDx Test Approval

Next generation sequencing (NGS) data supporting resistance assessments is crucial to developing and gaining FDA clearance for new antiviral drugs and related companion diagnostic tests (CDx). Now the agency has issued a new Technical Specifications document (Tech Doc) telling sponsors they should use that data to support their products.

What the Tech Doc Is All About

Unlike conventional Sanger nucleotide sequence which measures viral resistance by providing an average sequence of the virus population, NGS provides nucleotide sequence information for individual viruses within a viral population, often generating millions or billions of short sequences per sample. The complexity of the data makes it hard for reviewers from the FDA's Division of Antiviral Products to analyze and validate the sequence information. Adding to the challenge is the current lack of a standardized bioinformatics analysis approaches for analyzing such large datasets.

The purpose of the Tech Doc is to explain to sponsors how to compile, analyze and submit NGS resistance assessment data so the Division can review it. The Tech Doc provides crucial guidance on six key issues.

1. Acceptable NGS Platforms

The Tech Doc indicates that the Division will accept nucleotide sequencing data generated from most standard NGS platforms as long as the sponsor submits:

- The appropriate details for the sequencing platform;
- The protocols used for sample preparation;
- The raw NGS data in fastq format; and
- The methods used to analyze the data.

In addition to providing these details to the Division before submitting the sequencing data, sponsors should and submit a mock NGS dataset before any formal submissions to ensure the appropriate data formats and processes are acceptable.

2. Information about NGS Protocol

The Tech Doc calls on sponsors to submit a detailed NGS protocol that includes six design elements:

- A description of the subjects, study time points and sample matrices to be analyzed;
- A description of the NGS platform and all associated performance characteristics;
- Target gene region name(s) and size(s) to be analyzed;
- A description of the general analysis strategy;
- The coverage level to be attempted; and
- A description of the approach used to identify, filter or process sequencing errors.

3. Frequency Tables

Sponsors should provide a frequency table reporting all amino acid substitutions that differ from baseline at frequencies greater than or equal to 1%. The Tech Doc includes the following example:

Frequency Table Example

STUDYID	USUBJID	NGSPL	VISIT	AAPOS	AAREF	AASUB	TCOV	VCOV	AAFREQ
ABC123-999	0123	Illumina	BL	81	R	K	4317	156	0.036
ABC123-999	0123	Illumina	BL	98	K	R	2841	99	0.035
ABC123-999	0123	Illumina	Day 2	98	K	R	9487	366	0.039
ABC123-999	0123	Illumina	Day 3	98	K	R	9474	378	0.040
ABC123-999	0123	Illumina	BL	120	R	Q	4310	200	0.046
ABC123-999	0123	Illumina	Day 2	120	R	Q	12722	470	0.037
ABC123-999	0123	Illumina	Day 3	120	R	Q	12466	489	0.039
ABC123-999	0123	Illumina	BL	147	I	V	3456	742	0.215
ABC123-999	0123	Illumina	Day 2	147	I	V	13456	2709	0.201
ABC123-999	0123	Illumina	Day 3	147	I	V	13297	1934	0.145
ABC123-999	0123	Illumina	BL	150	A	V	3107	43	0.014
ABC123-999	0123	Illumina	Day 2	150	A	T	13116	167	0.013
ABC123-999	0123	Illumina	BL	154	K	R	2987	124	0.042
ABC123-999	0123	Illumina	Day 2	154	K	R	13434	1350	0.101
ABC123-999	0123	Illumina	Day 3	154	K	R	13077	1206	0.092
ABC123-999	0123	Illumina	Day 3	155	R	K	12459	9837	0.781
ABC123-999	0123	Illumina	Day 3	156	P	S	13385	172	0.013
ABC123-999	0123	Illumina	BL	186	V	I	6155	129	0.021
ABC123-999	0123	Illumina	Day 2	186	V	I	17698	269	0.015
ABC123-999	0123	Illumina	Day 3	186	V	I	16474	460	0.028
ABC123-999	0123	Illumina	BL	206	K	H	9698	165	0.017
ABC123-999	0123	Illumina	Day 2	206	K	R	24601	292	0.012
ABC123-999	0123	Illumina	Day 3	210	S	N	23001	255	0.011
ABC123-999	0123	Illumina	Day 3	254	H	R	25145	290	0.012

STUDYID = study protocol number; **USUBJID** = unique subject ID; **NGSPL** = next generation sequencing platform used for sequencing; **VISIT** = study visit that the sample was collected from; **AAPOS** = amino acid position in the target gene; **AAREF** = amino acid present at this position in the reference sequence; **AASUB** = amino acid substitution detected by sequencing; **TCOV** = total coverage at the nucleotide site; **VCOV** = total coverage at the nucleotide position of the variant; **AAFREQ** = frequency of the substitution detected; **BL** = baseline.

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FDA Issues New Guidance on Using NGS Data to Secure Antiviral Drug & CDx Test Approval, *from page 5*

4. Sample Preparation Information

The Tech Doc instructs sponsors to list their methods for:

- Extracting nucleic acids from samples;
- Purifying viral sequences from contaminating background nucleic acids;
- Concentrating viral nucleic acids, including the estimated target copy number input for reverse transcription polymerase chain reaction (RT-PCR) (viral RNA) or PCR (viral DNA) reactions for each sample;
- Denaturing secondary structure;
- Generating double stranded DNA (dsDNA), including a description of the primers;
- Purifying dsDNA for sequencing;
- NGS library preparation; and
- Adding barcodes for multiplexing (if applicable).

5. Information about Data Analysis & Reporting Results

Submissions of sequence data must include a thorough description of the analysis pipeline used to analyze the sequencing dataset and the raw sequence information, including:

- Summary statistics for each sequence run, including total number of reads sequenced per sequence run, quality scores and average length of reads;
- A description of how sequence barcodes were processed;
- Contig and mapping reports—the Tech Doc recommends two data analysis approaches and establishes standards for each: i. mapping of short reads to a reference sequence; or ii. de novo assembly of short reads to assemble contigs.

6. Acceptable Data File Types

The Tech Doc calls on sponsors to provide all raw NGS data from each sequence run in the fastq format. Sponsors can submit an assembled read mapping in .fas, .ace, .sam, or .bam formats, but this is optional.

Takeaway: Although the Tech Doc's recommendations are not technically binding, failing to adhere to them may result in the delay or rejection of the submission. So, antiviral drug and CDx makers need to pay close attention to them.

FDA Watch: Expanded Label Clearance Opens Cologuard to a Younger Market

September was an eventful month for one of the hottest products on the consumer genetic test market, the Cologuard multi-target stool DNA test (mtSDNA) for colorectal cancer screening produced by Exact Sciences. The month started badly with the release of a CMS-sponsored research report finding Cologuard "less effective and considerably more costly" than alternatives. Although Exact Sciences quickly criticized the report and its analytical methodology, its stock took a beating.

But on Sept. 23, less than three weeks later, things turned around when Exact Sciences announced that the FDA had widened its approval for Cologuard to include people age 45 and older, as opposed to the previous approval for people age 50 and older. The clearance, which came a year before the company expected, adds 19 million potential users to Cologuard's target market. It also greatly improves the prospects for a U.S. Preventive Services Task Force (USPSTF) thumbs-up on mtSDNA colorectal cancer screening. The USPSTF decision is expected by the end of the year.

New FDA Approvals

Here's a look at all the important new product approvals announced from late September through early October:

NEW FDA APPROVALS

Manufacturer(s)	Product(s)
Exact Sciences	Expanded clearance for Cologuard DNA-based colorectal cancer screening test in average-risk people age 45 and older (as opposed to previous clearance for people age 50 and over)
Cepheid	Clearance for Xpert BCR-ABL Ultra test for monitoring disease burden in patients with chronic myeloid leukemia
Luminex	510(k) clearance for real-time PCR-based Aries MRSA Assay running on firm's Aries sample-to-answer system
Abbott	Clearance for Architect Stat highly sensitive troponin blood test for more rapid detection of heart attacks
Bühlmann Laboratories	510(k) clearance for Calex Cap fecal extraction device for use with firm's fecal calprotectin test
Qiagen	Clearance for Therascreen PIK3CA RGQ PCR Kit as companion diagnostic to identify advanced breast cancer patients with PIK3CA mutations likely to respond to Novartis' Piqray (alpelisib)
Roche Diagnostics	Clearance for cobas Babesia whole-blood test for screening blood donations
Roche Diagnostics	Clearance for Cobas Pro Integrated Solutions
Roche Diagnostics	Clearance for Elecsys Anti-HAV II test to detect total antibodies (IgG and IgM) to hepatitis A virus
Siemens Healthineers	Clearance for Advia Centaur Testosterone II assay to detect total testosterone run on firm's Advia Centaur XP system

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FDA Watch, *from page 7*

Manufacturer(s)	Product(s)
Siemens Healthineers	Clearance for the Advia Centaur SHBG immunoassay run on Advia Centaur XP system to measure sex hormone-binding globulin (SHBG) used to diagnose androgen disorders
Axis-Shield Diagnostics	Clearance for received clearance for Advia Centaur Erythropoietin assay to diagnose anemias and polycythemias run on Siemens Advia Centaur XP system
Grifols	Clearance for QNext fully automated random-access instrument to perform hemostasis testing by detecting changes in optical density
Fujirebio Diagnostics	Clearance for Lumipulse G Whole PTH chemiluminescent enzyme immunoassay to measure parathyroid hormone levels during differential diagnosis of hypercalcemia and hypocalcemia resulting from disorders of calcium metabolism
Check-Points	Clearance for BD Max Check-Points CPO Assay run on Becton Dickinson BD Max System
Healstone Biotech	Clearance for Accurate Multi Panel Drug Urine Test Cup lateral flow immunochromatographic assay for detecting a combination of two to 15 drugs of abuse
Laboratory for Advanced Medicine	Breakthrough device designation for liquid biopsy blood test to detect liver cancer at Stage I
Prescient Metabiomics	Breakthrough device designation for LifeKit Prevent Colorectal Neoplasia Test for non-invasive detection of precancerous polyps and early-stage carcinomas

Innovation: Breathalyzer May Offer Reliable, Easier Alternative to Blood-Based Opioid Detection

Police officers, law enforcers, employers and drug testing laboratories may soon have a new tool: a breathalyzer test capable of detecting opioid drugs. Engineers and physicians from the University of California, Davis (UC Davis) have developed such a test which would lend itself to use not only for detecting illegal drug use but also monitoring patients being treated with opioids for chronic pain.

Problems with Current Opioid Diagnostic Methods

Current screening methods detect drugs by immunoassays performed on biological samples, such as urine and blood. Results are confirmed by gold-standard methods typically involving separation techniques coupled to mass spectrometry (MS). While the testing techniques provide reliable results, both specimens have sampling limitations. For one thing, drawing the samples is invasive of privacy. Urine, typically used for longer exposures, has a risk of adulteration; blood collection using plasma or serum to detect short-term consumption requires specialized personnel to collect.

The Breathalyzer Alternative

Collection of exhaled breath could be a less privacy-sensitive, non-invasive, painless and relatively easy technique. It would work on breath compounds found in either the exhaled breath aerosol (EBA) gas or exhaled breath condensate (EBC) phase. Drugs are mainly large and low-volatile molecules that can be potentially detected in EBA, e.g., exhaled microcroplets, using filters, and in EBC using a cooling system.

The New Test

The research, which is described in a paper published in the *Journal of Breath Research* published on Oct. 3, was led by a pair of UC Davis professors, **Cristina Davis**, chair of the Department of Mechanical and Aerospace Engineering, and **Michael Schivo** from the UC Davis Medical Center. The test requires subjects to breathe normally into a specialized collection device. Droplets in breath condense and are stored in a freezer for laboratory testing using mass spectrometry to identify compounds in the samples.

The researchers tested their new breathalyzer on chronic pain patients receiving infusions of morphine or hydromorphone or oral doses of oxycodone at the UC Davis Medical Center. They were then able to compare the opioid metabolites collected from the patients' breath with both blood samples and doses given to the patients. "We can see both the original drug and metabolites in exhaled breath," Davis noted.

Test Results

The fact that researchers were able to detect, quantify and identify several opioid metabolites in EBC (and the subsequent ethanol solvent wash of the collection device) confirmed that infused opioid drugs are present in exhaled breath—although in low amounts. Since opioid drugs go through several sites of metabolism before being excreted into the lining fluid detected in exhaled breath, the concentrations of drugs are much lower than in blood for the same opioid metabolites. Even so, the researchers found "promising correlations" between concentrations in blood and breath for some of the main opioids. The implication is that even though they are diluted vis-a-vis, breath concentrations may be a reliable indicator of the presence of opioid metabolites detected by blood testing.

Still Work to Be Done

The initial results were promising. But the researchers will need more data from larger groups of patients before the new test can be fully validated. Davis is hoping to conduct the research in real-time, bedside testing.

At the same time, her laboratory is seeking to extend the test's potential applications for detecting small amounts of chemicals through different

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avenues, e.g., tests diagnosing influenza in people and citrus greening disease in fruit trees.

Takeaway: Blood testing will remain the gold standard in opioid drug detection. But breathalyzer testing has the promise of offering an easier, less invasive and reliable alternative.

Inside the Diagnostics Industry: Quest-hc 1 System Leverages Lab Data to Help Providers Monitor Test Utilization

Getting Medicare and private insurers to pay for lab tests is as challenging as it's ever been. It's not just about reimbursement. Payors have become fanatically dedicated to weeding out lab testing overutilization. While this puts the squeeze on labs, it also creates opportunity to the extent that the source of the most direct and useful data for identifying and preventing lab test overutilization and underutilization are the labs and ordering providers themselves.

The Quest Lab Stewardship Service

The opportunity for labs to leverage their own test data for utilization monitoring has not been lost on Quest Diagnostics, which recently announced that it was partnering with healthcare data analysis firm to offer an innovative new service to help health systems control and track test ordering. Quest Lab Stewardship is designed to integrate with the electronic medical record to guide doctors through the test ordering process so they can be sure they're ordering the right tests and in the right amounts to ensure proper treatment and reimbursement. The system also has the capabilities to create a systemwide set of tests and utilize testing trends across the entire organization.

That's a big deal because health systems typically do a poor job of how much their lab testing varies across the network, explains hc1 CEO **Brad Bostic**. "They usually have a multitude of test compendia in various hospitals that have been acquired and consolidated—getting a standard one is almost impossible." This variation in testing patterns can lead to higher costs and poorer outcomes.

How It Works

On the front end, the Quest Lab Stewardship system displays the tests that a patient most likely needs based on customized parameters which also make lower-value or less-proven tests harder to order. It alerts physicians if tests are ordered twice and directs them to testing results. The system

can also be used to monitor ordering patterns, both organizationally and by individual doctors.

In addition to selling the new service, Quest is using to improve client relations by making it available for free to its reference lab customers. "There are opportunities to drive out overutilization and underutilization, but it's really about driving clinical value," explains **David Freeman**, general manager of information ventures at Quest. "It is about giving clinical lab directors the tools they need to help them figure out where the problems are" and how they can be solved.

New Guidelines Recommend Basing Routine Colorectal Cancer Screening on Risk Rather than Age, *from page 1*

during their lifetime. Actual risk is dependent on personal factors including:

- Age;
- Sex;
- Genetics; and
- Lifestyle factors, such as alcohol consumption, smoking, physical activity and diet.

Because risk increases with age, the global consensus is that people should start getting routine colorectal cancer screening once they reach a certain age. In most countries, the recommended age is 50 but in some countries it is as low as age 45. At age 50, the risk of developing bowel cancer over the next 15 years is typically 1-2%. The most common screening options are:

- Home faecal testing (FIT) every year or every two years;
- Sigmoidoscopy (examination of the lower colon); and/or
- Colonoscopy (examination of the entire colon) done at a clinic or hospital.

The New Approach

But now an international panel of researchers, clinicians and patients has, for the first time, discarded the strictly age-based approach in favor of one based on actual risk. The panel's conclusions are part of The BMJ's 'Rapid Recommendations' initiative to produce rapid and trustworthy guidance based on new evidence to help doctors make better decisions with their patients. The panel made its determination after reviewing the evidence base, including new evidence about the long-term effects of bowel cancer screening, to evaluate the benefit-to-harm balance of screening using a "risk-based approach." The panel took into account an individual's cumulative risk of bowel cancer over the next 15 years, together with risk of harm from the procedure (e.g., bowel perforations or unnecessary treatment), quality of life (e.g., anxiety, burden of procedure), and a person's values, preferences and life expectancy.

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New Guidelines Recommend Basing Routine Colorectal Cancer Screening on Risk Rather than Age, *from page 11*

Overall, the panel wrote, there was "substantial uncertainty" regarding the 15-year benefits, burdens and harms of screening, with the most common screening methods resulting in similar colorectal cancer mortality reductions. "FIT every two years may have little or no effect on cancer incidence over 15 years, while FIT every year, sigmoidoscopy and colonoscopy may reduce cancer incidence, although for FIT the incidence reduction is small compared with sigmoidoscopy and colonoscopy," the panel noted. Serious gastrointestinal and cardiovascular adverse events related to screening, meanwhile, were found to be rare.

The New Colorectal Screening Recommendations

The panel's conclusions:

Routine testing for bowel cancer should not be recommended for healthy individuals age 50 to 79 who have a life expectancy of at least 15 years, because those individuals are at very low risk, meaning the benefits of routine screening are small, uncertain and outweighed by the potential harms;

- Routine screening should be recommended for men and women with a risk of 3% or more in the next 15 years, because this is the point at which the balance of benefits and harms tilts in favor of screening.
- The panel declined to recommend any one test method over another, citing what it called convincing evidence that people's values and preferences on whether to test and which test to undergo vary considerably.

The panel also stressed that there are still many uncertainties in terms of what is the most effective screening test or combination of tests and at what age and interval they should be used, suggesting that these issues should be the focus of future research.