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FDA Authorizes First Direct-to-Consumer Genetic Test for Cancer Risk

The U.S. Food and Drug Administration (FDA) granted marketing authorization to 23andMe (Mountain View, Calif.) for its Personal Genome Service Genetic Health Risk Report for BRCA1/BRCA2—genetic mutations known to be associated with higher risk of breast, ovarian, and prostate cancers. It is the first authorized direct-to-consumer (DTC) genetic test for cancer risk, but the FDA authorization came with special controls that require labeling to indicate the tests' limitations.

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Racial Disparities in Access Reduce Utility of Genetic Testing

Underrepresented minorities (URM) are less likely to receive a diagnosis from genetic testing for cardiomyopathy and are more likely to receive inconclusive testing results, compared to whites undergoing testing, according to a study published Feb. 28 in *JAMA Cardiology*. The authors say that these findings are the result of disparities in access to genetic testing.

"Cardiomyopathy testing has a statistically significant lower detection rate in URM individuals, which is likely because of the reduction of primary data from URM individuals in both the research and clinical testing settings," writes coauthor Latrice Landry, Ph.D., from the U.S. Food and Drug Administration in Silver Spring, Md. Furthermore, the rate of inconclusive test results is also higher in URM individuals, further undermining the utility of genetic testing in these populations and creating additional disparities for these populations beyond the fundamental lack of use of genetic testing already documented for URM individuals.

With a prevalence of 1 in every 500 individuals, cardiomyopathy is one of the most common monogenic cardiac diseases in the US population and genetic testing has become routine for the diagnosis of the condition. In the current study, the researchers analyzed molecular

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FDA Authorizes First Direct-to-Consumer Genetic Test for Cancer Risk, *from page 1*

The test only assesses three of more than 1,000 known BRCA mutations, meaning that a negative test result does not rule out an increased cancer risk. The three mutations examined in the DTC test are most common in people of European Jewish descent; yet only represent a very small minority (2 percent) of hereditary cancer mutations even in this population. According to a National Cancer Institute study, these mutations rarely occur (0 percent to 0.1 percent) in other ethnic populations.

In a blog post 23andMe CEO and cofounder Anne Wojcicki says that insurance coverage criteria limit BRCA testing opportunities. She calls this authorization "a major milestone for 23andMe, but more importantly, a significant step forward for consumers who want direct and affordable access to their health information."

The authorization marks the third received by the company in the past three years using the de novo premarket review pathway and marks a dramatic reversal by the FDA, which forced 23andMe to withdraw its DTC Personal Genome Service (PGS) from the market back in 2013. PGS provided health reports on 254 diseases and conditions, including for categories such as carrier status, health risks, and drug response, which according to the FDA had been marketed as a medical device without proper authorization.

A Summary of 23andMe's Authorizations

February 2015: Authorization enabled the company to launch 40+ carrier status reports directly to customers.

April 2017: Granted the first authorization by the FDA to enable DTC genetic health risk reports. To date the company has launched nine reports conditions, including late-onset Alzheimer's disease, Parkinson's disease, celiac disease, and hereditary thrombophilia.

April 2018: Authorization marks the first DTC genetic test for cancer risk—three BRCA-related mutations.

The FDA said 23andMe provided "sufficient data" to show that the test is accurate (i.e., can correctly identify the three genetic variants in saliva samples with greater than 99 percent concordance to Sanger sequencing, according to the company) and can provide reproducible results (also greater than 99 percent, according to 23andMe). Additionally, the company submitted data on user comprehension studies, showing that instructions and results reports were generally easy to follow and understood by a consumer.

"This test provides information to certain individuals who may be at increased breast, ovarian, or prostate cancer risk and who might not otherwise get genetic screening, and is a step forward in the availability of DTC genetic tests. But it has a lot of caveats," said Donald St. Pierre, acting director of the FDA's Office of In Vitro Diagnostics and Radiological Health, in a statement. "While the detection of a BRCA mutation on this test does indicate an increased risk, only a small percentage of Americans carry one of these three mutations and most BRCA mutations that increase an individual's risk are not detected by this test."

Despite the FDA's special controls, critics in the genetics and oncology communities spoke out.

The FDA further cautioned that consumers and health care professionals should not use 23andMe's test results for treatment decisions without "confirmatory testing and genetic counseling."

Despite the FDA's special controls, critics in the genetics and oncology communities spoke out. Calling the test "incomplete" the American College of Medical Genetics and Genomics issued a statement saying it "believes that a test result has maximal value when the information it provides is interpreted in the context of a particular individual as well as our current knowledge and understanding of the test's limitations." The National Society of Genetic Counselors also issued a statement critical of the authorization saying results "may be confusing or misleading without appropriate education" and highlighted the important role medical professionals play in personalizing testing strategies.

23and Me says that new and existing 23andMe Health + Ancestry Service customers that were already genotyped on the company's most recent platforms will have access to the BRCA report in the coming weeks. However, customers must specifically choose if and when they want to receive this information, the company said in a statement.

Takeaway: The FDA's recent authorization of 23andMe's DTC genetic test for cancer risk based on three BRCA-related mutations is controversial. It is being hailed as an expansion of access to DTC genetic testing by supporters and is being lamented by critics as "incomplete" and potentially confusing to consumers.

Evidence for Liquid Biopsy Lacking, Expert Panel Finds

There is not enough evidence, currently, to support the routine adoption of liquid biopsy tests for any of its promising clinical uses, according to a joint review published March 1 in both the Archives of Pathology & Laboratory Medicine and the Journal of Clinical Oncology. The joint panel said it did not find evidence to support liquid biopsy testing for screening, diagnosing early-stage cancer, making treatment decisions, or patient monitoring, outside of clinical trials.

"Like all new things in medicine, the use of circulating tumor DNA [ctDNA] assays in routine cancer care requires evidence of clinical utility," said Daniel Hayes, M.D., a member of the expert panel, in a statement. "At present, there is insufficient evidence of clinical validity and utility for the majority of ctDNA assays in advanced cancer, including those that interrogate a panel of genes."

The authors acknowledge that despite that fact that the U.S. Food and Drug Administration has only approved a single liquid biopsy test—the COBAS assay for EGFR mutations in non-small-cell lung cancer—the tests are being used in clinical practice.

"This is an area of great interest to both pathologists and oncologists. It's also an area where we see a lot of commercial advertisement, and a lot of enthu-

siasm from the public," said Jason D. Merker, M.D., Ph.D., expert panel co-chair, said in a statement. "We thought it was a good time to look at the literature and take an evidence-based approach to various uses for ctDNA assays."

Given the interest in the technology, an expert panel, convened by American Society of Clinical Oncology and College of American Pathologists, conducted a literature review on the use of ctDNA assays for solid tumors, including assessment of preanalytical variables, analytical validity, interpretation and reporting, and clinical validity and utility. Ultimately 77 identified articles were included. The experts key findings, included:

Preanalytical findings

- Plasma is the optimal specimen type
- Collection should occur in cell stabilization or EDTA tubes, with processing within 6 hours of collection

Analytical validity

- Examination of analytical validity should include evaluation of both the wet laboratory and bioinformatics portions of an assay
- Evidence has not established optimal lower limits of detection for various types of somatic variants
- Future studies should focus on cross-assay comparisons, assay robustness, and the development of proficiency testing mechanisms

Interpretation and reporting

- Variant allele fractions from ctDNA assays need further study
- Reporting of somatic variant should conveys the potential for discordance with tumor tissue testing
- Discussion of potential actionability should be limited to general associations between a variant and therapy options that have established clinical utility in the same primary tumor site

Clinical validity and utility

- Most assays have insufficient evidence to demonstrate clinical validity, and most have no evidence of clinical utility
- Evidence shows discordance between ctDNA assay results and genotyping tumor specimens, suggesting tissue genotyping should confirm lack of detection from ctDNA tests

Takeaway: While the expert panel currently did not find sufficient evidence to support the clinical use of liquid biopsies, they suggest that the rapid pace of research requires reevaluation of the literature soon.

Uses of Liquid Biopsy

- Assessment of disease risk
- Screen unaffected patients for the disease
- Differential diagnosis of a proven malignancy
- Prognosis
- Assessment of treatment effectiveness
- Monitoring disease activity (for recurrence or progression)

Advantages of Liquid Biopsy vs. Traditional Biopsy

- More convenient
- Noninvasive and less risky
- Less expensive collection
- Can be performed serially
- More comprehensive assessment of the tumor burden (no spatial sampling limitations)

Researchers Develop First Multiplex Test for Tick-Borne Disease Detection

Researchers have developed the first multiplex array for diagnosis of tick-borne diseases, according to a study published online Feb. 16 in *Nature Scientific Reports*. The TBD-Serochip can differentially diagnose eight tick-borne infections, including Lyme disease.

It has been estimated that approximately 3 million clinical specimens are tested for tick-borne diseases each year, with serology being the primary method of diagnosis Testing includes use of enzyme-linked immunosorbent assay, indirect immunofluorescent assay, and western blot assays. But, experts say, diagnosis is hampered by varying degrees of test accuracy in the early phase of disease, the need for specialized laboratories, lack of testing standardization, and cross-reactivity between infectious agents.

"The reported incidence of tick-borne disease has risen continuously over the past three decades," write the authors led by Rafal Tokarz, from Columbia University in New York. "Nonetheless, the true incidence of tick-borne diseases is likely greatly underestimated, as patients with presumed tick-borne diseases are rarely tested for the full range of tick-borne agents, and only a fraction of positive cases are properly reported. New diagnostic assays that can detect infections with the full range of TBD agents are urgently needed."

In the February report, researchers from Columbia University unveiled the TBD-Serochip, which consists of 12 subarrays, each able to simultaneously test for the presence of antibodies in blood using more than 170,000 protein fragments.

The authors say the multiplex assay offers many benefits over current serial testing, including:

- Screening for multiple agents simultaneously
- Enhancing the likelihood of antibody detection in early disease states
- Detecting and confirming infection simultaneously

"Because peptides are programmed for synthesis in situ, the array composition can be continuously and inexpensively modified based on performance or the need to address new immunological targets," writes Tokarz and colleagues.

Takeaway: Progress is being made in the detection of tick-borne disease both in clinical patient samples and in the U.S. blood supply.

FDA Approves 1st Test to Screen Blood For Tick-Borne Babesia Disease

In early March, the U.S. Food and Drug Administration approved two donor screening tests to detect Babesia, the tick-borne parasite responsible for babesiosis infections. The tests—Imugen Babesia microti Arrayed Fluorescent Immunoassay, for the detection of antibodies to Babesia microti (B. microti) in human plasma samples, and the Imugen Babesia microti Nucleic Acid Test, for the detection of B. microti DNA in human whole blood samples—are "in-house tests" performed by Oxford Immunotec (Norwood, Mass.).

Experts estimate that there are up to 2,000 cases of babesiosis reported in the U.S. each year, with the majority transmitted from deer ticks in states in the Northeast and upper Midwest. However, babesia can also be transmitted by transfusion of blood or blood components from an infected donor and is a "concern." It is the most frequently reported transfusion-transmitted parasitic infection in the United States, according to the U.S. Centers for Disease Control and Prevention.

The FDA said that investigational use of Babesia donor testing has been in place since August 2012 under investigational new drug applications and has resulted in the removal of "a significant number of infected units" from the blood supply. However, the two tests were granted priority review. The FDA is expected to soon release a draft guidance for testing donor samples for Babesia.

SIDs Results From Genetic Heart Disease Less Than Previously Thought

The vast majority of sudden infant death syndrome (SIDS) cases are not the result of genetic heart diseases (GHDs) or a single genetic cause, according to a study published March 12 in the *Journal of the American Academy of Cardiology*. The researchers found that less than 5 percent of infants who died from SIDS possess genetic variants that are immediately actionable for other family members or would lead to cascade testing.

> *"Unfortunately, despite their rarity, most of these ultra-rare variants still remain variants of uncertain significance stuck in genetic purgatory."*
>
> — David Tester

Despite the fact that up to 80 percent of all sudden unexpected infant deaths are attributed to SIDS, pathogenic understanding of SIDS remains elusive.

In the current study, researchers conducted a whole exome molecular autopsy and targeted analysis of 90 GHD-susceptibility genes in 419 unrelated SIDS cases (257 male; average age 2.7 months) from both the United Kingdom and the United States. Additionally, case-control analysis included 973 control exomes (509 female, 464 male) from the ICR1000 U.K. exome study and the 1958 Birth Cohort study.

The 90 GHD genes included those known to be associated with susceptibility to cardiac channelopathy and cardiomyopathy. "Potentially informative" variants were defined as ultra-rare (minor allele frequency <0.00005) and located in GHD genes.

Overall, 53 of 419 SIDS cases (12.6 percent) had at least one "potentially informative," GHD-associated variant. Less than 1 percent of cases (n = 4) had two "potentially informative" variants. According to the American College of Medical Genetics guidelines, only 4.1 percent of SIDs cases (n = 17) possessed a "pathogenic" or "likely pathogenic" variant. Additionally,

- there was no significant difference in yield between cases and controls for any specific gene.
- infants older than 4 months (past the peak age of SIDs) were more likely to host a "potentially informative" GHD-associated variant.
- there no significant associations between yield of "potentially informative" GHD gene variants and sex, sleep position, or bed sharing habits.

The researchers also compared the previously detected ultra-rare, "pathogenic" or "likely pathogenic" variants seen within sudden death–susceptibility genes among a different cohort of 302 autopsy-negative cases of sudden arrhythmic death syndrome in persons who died at an age greater than 1 year (median age 24 years) to the variants detected in this cohort. The yield was significantly lower in the SIDs cohort compared to the older sudden death cohort (4.3 percent versus 13.0 percent), leading the researchers to conclude most SIDS cases are "largely different genetically and mechanistically" from sudden death occurring after 1 year of age.

"Unfortunately, despite their rarity, most of these ultra-rare variants still remain variants of uncertain significance stuck in genetic purgatory," write

the authors led by David Tester, from the Mayo Clinic in Rochester, Minn. "Importantly, not all of these variants have been characterized functionally, and great caution must still be exercised, even when interpreting ultra-rare variants residing within the major channelopathy genes... Overattribution of SIDS deaths to GHDs has significant implications for the immediate family, and we urge extreme caution in variant interpretation."

Takeaway: Previous research may have overly attributed GHD-related variants as a causative factor in SIDS pathology.

Procalcitonin Testing Improves Antibiotic Stewardship

Using procalcitonin testing results to guide antibiotic decisionmaking is associated with lower rates of antibiotic use, fewer antibiotic-related adverse effects, and improved overall survival, according to a clinical evidence synopsis published March 6 in the *Journal of the American Medical Association.*

Procalcitonin is expressed in response to bacterial infections and can be used as a marker of bacterial infection. February 2017, the U.S. Food and Drug Administration (FDA) approved procalcitonin to guide antibiotic decisionmaking for patients with respiratory tract infections who were either hospitalized or treated in the emergency department.

> *"Currently, the procalcitonin test is only approved by the FDA for use in the hospital or emergency department and further research is needed in primary care using rapid turnaround point-of-care procalcitonin tests."*
>
> — Philipp Schuetz, M.D.

The study included a total of 26 randomized clinical trials published between 2004 and 2016. The studies represented 6,708 patients (men, 57 percent) internationally with acute infections of the upper or lower respiratory tract, including community-acquired pneumonia, exacerbation of chronic obstructive pulmonary disease due to infections, bronchitis, ventilator-associated pneumonia, hospital-acquired pneumonia, and upper respiratory infection.

The researchers found that procalcitonin testing was associated with a shorter duration of antibiotic exposure (-2 days), mean shorter duration of infection (-2.4 days), a 25 percent reduction in antibiotic-related adverse effects, and 17 percent lower 30-day mortality. These results were similar across types of respiratory infections and across clinical settings (e.g., emergency department, medical ward, or intensive care).

"Currently, the procalcitonin test is only approved by the FDA for use in the hospital or emergency department and further research is needed in primary care using rapid turnaround point-of-care procalcitonin tests," write the authors led by Philipp Schuetz, M.D., from University of Basel in Switzerland.

Takeaway: Procalcitonin testing is effective in guiding antibiotic stewardship and improving outcomes among patients with respiratory tract infections. Further research is needed to assess whether rapid procalcitonin tests are as effective in outpatient settings.

Racial Disparities in Access Reduce Utility of Genetic Testing, *from page 1*

diagnostic testing data from 5,729 probands (male, 61.1 percent) referred for testing due to a suspected diagnosis or family history of cardiomyopathy over a 15-year period from October 2003 to December 2017.

The Laboratory for Molecular Medicine at the Partners Healthcare Personalized Medicine launched its first clinical genetic test for hypertrophic cardiomyopathy in 2003 and expanded testing to now encompass 62 genes.

The study defined URM collectively as including individuals identifying as black, Hispanic, Native American, Alaska Native, Hawaiian, and other South Pacific Islander. Those identifying as mixed race were excluded from analysis. Detection of cardiomyopathy was defined as the percentage of probands with a positive report due to identification of one or more pathogenic or likely pathogenic variants. Inconclusive findings were defined as presence of one or more variants of uncertain significance in the absence of a pathogenic or likely pathogenic variant.

The researchers found that of those tested, 79.2 percent were white, 6.1 percent were Asian individuals, and 14.7 percent were URM individuals. Positive detection occurred in significantly more white individuals versus in URM (29 percent versus 18.4 percent, respectively and 25 percent in Asian individuals). However, URM had significantly more nonconclusive test results, compared to white individuals (39.8 percent versus 24.6 percent, respectively and 39.2 percent in Asian individuals). Overall, there was a statistically significant reduction in detection rate of cardiomyopathy for URM, compared with white individuals.

"Racial/ethnic disparities in research study enrollment and the delivery of health care, favoring white individuals and racial/ethnic minorities of higher socioeconomic status, have led to differences in the development and application of the evidence base that underlies the usefulness of genetic testing," writes Landry. "This suggests greater clinical usefulness of genetic testing for cardiomyopathy in white persons in comparison with people of other racial/ethnic groups. This clear disparity warrants further study to understand the gaps in usefulness, which may derive from a lack of clinical testing and research in underrepresented minority populations, in the hopes of improving genetic testing outcomes for cardiomyopathy in nonwhite groups."

Experts widely acknowledge that in the United States, African American individuals and most Latino/Hispanic groups are not adequately represented in genetic databases. However, there is widespread hope that ongoing efforts like the National Heart, Lung, and Blood Institute's Trans-Omics for Precision Medicine, the National Institutes of Health's All of Us Research Program, and the U.S. Veterans Administration's Million Veteran Project should enable better representation of the U.S. population. There is also hope that wider reimbursement will lessen disparities in access to clinical testing.

"The obvious remedy for this dearth of data is to sequence large numbers of well-phenotyped cases and controls from economically, ethnically, and racially diverse populations," writes Glenn Gerhard, M.D., in an accompa-

nying viewpoint. "The ability of those with limited financial means to obtain fully reimbursed genetic testing for hypertrophic cardiomyopathy should significantly expand testing. Should such expansion occur, the database of genetic variants for hypertrophic cardiomyopathy and other genetic disorders in underserved populations should begin to accrue."

Takeaway: Racial disparities in access to clinical testing and participation in research have contributed to a dearth of genetic information from URM in genetic databases. Research now shows that this disparity is affecting the ability of clinical genetic testing to detect disease in URM, compared to white individuals.

Even a Single PSA Screening Test Does Not Cut Mortality

Findings from the latest large randomized controlled study do not support use of even a single prostate-specific antigen (PSA) test for prostate cancer screening. The U.K. study, published March 6 in the *Journal of the American Medical Association* showed that while the single test screening intervention does detect more prostate cancer cases compared to no screening, testing had no significant effect on prostate cancer mortality after a median follow-up of 10 years.

Shared Decision Making Not Taking Hold for PSA Testing

Researchers from the American Cancer Society (Atlanta, Ga.) retrospectively analyzed data from 9,598 men aged 50 years and older participating in the 2010 and 2015 National Health Interview Survey in order to assess changes in shared decision making for PSA testing.

In 2017, the U.S. Preventive Service Task Force released updated recommendations, stating that clinicians should inform men (aged 55 to 69 years) about the potential benefits and harms of PSA testing, so that the decision to undergo testing is an individual one.

The researchers found that a similar proportion (about 60 percent) of men with recent PSA testing reported at least one shared decision-making element in 2010 and 2015. However, over the study period, there was a slight shift away from a discussion of only the advantages towards fully shared decision making (discussion of advantages, disadvantages, and uncertainties).

The so-called CAP trial (Cluster Randomized Trial of PSA Testing for Prostate Cancer) is the largest, randomized trial of PSA screening strategies to date and sought to test "a low-intensity strategy" to reduce overdetection of low-risk prostate cancer cases. However, the study did not appear to improve upon previously examined more intense screening strategies tested in the European Randomized Study of Screening for Prostate Cancer and the U.S. Prostate, Lung, Colorectal, and Ovarian Cancer Screening trials.

"The results highlight the multitude of issues the PSA test raises - causing unnecessary anxiety and treatment by diagnosing prostate cancer in men who would never have been affected by it and failing to detect dangerous prostate cancers," said lead author Richard Martin, Ph.D., from University of Bristol (United Kingdom), in a statement.

CAP included 419,582 men aged 50 to 69 years treated at 573 primary care practices across the United Kingdom. Randomization of the practices occurred between 2001 and 2009, with patients followed until March 31, 2016. Practices were randomized to grant men a one-time invitation for PSA testing or not. Men with PSA levels of 3 ng/mL or greater were given a standardized 10-core transrectal ultrasound–guided biopsy.

The researchers found that the proportion of men diagnosed with prostate cancer was higher in the intervention group (4.3 percent) than in the control group (3.6 percent). However, there was no significant difference in prostate cancer mortality between the groups (0.30 per 1000 person-years for the intervention group versus 0.31 for the control group) after a median follow-up of 10 years. Significantly more low-grade prostate cancer tumors (a Gleason grade of 6 or lower) were identified in the intervention group versus the control group (1.7 percent versus 1.1 percent). Furthermore, as a proportion of detected cancers, the prostate cancer tumors in the screening group were significantly less likely to be high grade.

"A key question is whether the findings from the CAP trial should swing the pendulum further in the direction of not offering screening PSA tests," writes Michael Barry, M.D., Massachusetts General Hospital in an accompanying editorial. "Based on the CAP results, an offer of a single PSA screen in a population of men aged 50 to 59 years is ineffective, and given the higher risk of a prostate cancer diagnosis this approach engenders, likely does more harm than good."

Takeaway: Even low-intensity prostate cancer screening with a single PSA test does not cut prostate cancer-related mortality. Additionally, this low-intensity strategy still appears to overdetect low-grade disease.

Mass. Settlement Could Speed HCV Testing For Prisoners Nationally

In early March, the Massachusetts Department of Correction reached a settlement with prisoners' rights groups over its medical treatment of prison inmates infected with hepatitis C virus (HCV).

The settlement requires testing every prisoner for HCV and treating all who have the disease. While the Federal Bureau of Prisons recommended opt-out hepatitis C testing for all inmates during the prevention baseline visit, few state prison systems have implemented universal testing. The Massachusetts settlement may speed action in other states.

The National Lawyers Guild and Prisoners' Legal Services filed a class action lawsuit in U.S. District Court in Boston in 2015 on behalf of Massachusetts prisoners who had hepatitis C claiming that the state had reduced the number of patients treated for hepatitis C and delayed evaluating prisoners in order to avoid being responsible for the new, costly treatments.

While the Massachusetts chapter of the National Lawyers Guild says this is believed to be the first settlement of its kind, there are increasingly calls for universal HCV screening of prisoners. Inmates in Indiana, Pennsylvania, Missouri, Minnesota and Tennessee have filed similar lawsuits, according to the Wall St. Journal reports. Public health experts are also calling for increased testing and treatment of incarcerated populations, as they represent a "missed opportunity" for intervention.

The prevalence of HCV is known to be substantially higher in incarcerated populations, compared with the general population (up to 35 percent chron-

ic infection in the correctional population versus 1 percent in the general U.S. population). These numbers may actually underestimate the true disease burden among prisoners due to low HCV screening rates in correctional settings.

According to a 2015 study in the American Journal of Public Health, state corrections system directors reported that only 17 states had at least one state-prison facility offering routine opt-out HCV screening, with eight states having no screening program in place.

HCV screening programs can fall into two main categories: opt-in or voluntary or opt-out or universal. Opt-in policies offer HCV testing only to individuals who specifically ask or who self-disclose as being a member of a risk-based group (e.g. individuals who disclose a history of injecting drugs). Opt-out or universal testing policies test everyone and individuals may choose whether to participate. Previous studies have shows that opt-out HIV testing is popular among both prisoners and staff, with a large majority of prisoners accepting opt-out testing.

"Given the number of people infected with HCV and the length of sentence stay (median stay in the USA was 65 months in 2009), correctional facilities offer a unique opportunity for HCV screening to ensure more people know their status and earlier detection," writes Meghan Morris, from University of California, San Francisco, in a September 2017 article in the *International Journal of Prisoner Health*. "Early detection and engagement in care can prevent prisoners from unwittingly transmitting HCV to others after re-entering the general community. Universal opt-out HCV screening at entry into prison may result in a dramatic reduction in the number of new HCV infections over the next 30 years, benefits able to extend beyond the prison environment to the general community."

Takeaway: The Massachusetts HCV settlement may accelerate universal, opt-out testing among incarcerated populations, particularly in states with pending litigation regarding HCV treatment for prisoners.

Guidelines at a Glance

New Recommendations Simplify Testing for Chronic Kidney Disease

In late February, The National Kidney Foundation, the American Society for Clinical Pathology, and leading laboratories and clinical laboratory societies announced a new collaboration to improve testing for chronic kidney disease (CKD). Hypertension and diabetes put 75 million Americans at risk for CKD, but only one in three are aware they have the condition.

The collaborative effort will improve screening, standardize the tests used to detect CKD, thus, increasing the comparability of test results between laboratories, and increase awareness and education around the condition to increase early recognition of the disease.

The new CKD Kidney Profile relies on evidence-based clinical practice guidelines to simplify ordering of the tests needed to detect and diagnose CKD by uniting them together under one heading on the laboratory requisition form or electronic health record order. It is hoped that streamlining of CKD test ordering for estimated glomerular filtration rate testing (serum creatinine with eGFR) and urine albumin-creatinine ratio (albumin, urine [e.g., microalbumin], quantitative).

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Additionally, the organizations recommend that

- Standardize albumin-creatinine ratio reporting using milligrams per gram to make comparison of results received from different laboratories easier.
- Laboratories use the same equation to estimate GFR
- Rename the microalbumin test to one that more accurately reflects what it is measuring—albumin-creatinine ratio, urine.

Recommendations Guide Allele Selection for CYP2C19 Assays

The Association for Molecular Pathology (AMP) released consensus, evidence-based guidelines to aid clinical in the design of pharmacogenomic (PGx) assays. The recommendations are in response to recent studies that compared assays and found that no two assays examine the same alleles. AMP feels the need to standardize PGx allele function and phenotype nomenclature so that variations in test design do not negatively impact test interpretation or patient care.

The recommendations define the key attributes of PGx alleles recommended for clinical testing and identify a minimum set of variants (Tier 1) that should be included in clinical PGx genotyping assays. They also identify an extended panel of variant alleles (Tier 2).

Three Tier 1 CYP2C19 variant alleles were defined as those that are well-characterized and have been shown to have an effect on drug response. They have an appreciable minor allele frequency in a patient population, and have available reference materials. Nine Tier 2 variant CYP2C19 alleles are identified. These alleles meet at least one Tier 1 criteria, but not all criteria. They should be considered optional for inclusion in expanded clinical genotyping panels, as they are low frequency alleles, and do not currently have reference material available.

The organization said the CYP2C19 genotyping recommendations are the first of a series of recommendations for guiding pharmacogenomic testing.