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DIAGNOSTIC TESTING & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

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Designing, Implementing & Managing a High-Profit Lab Outreach Program
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Trump Budget Proposes Steep NIH Cuts, Hike to FDA User Fees

The headlines are harsh. "Terrible," devastating," and "crippling," are words the biomedical industry is using to describe President Trump's proposed cuts to science and medical research in his 2018 budget. Public health interests do, however, see some new resources.

While only Congress has the authority to make budget and appropriation decisions, the administration's budget is considered a "blueprint" of the president's spending priorities. Experts say based on the deep cuts in the 2018 budget proposal to the U.S. Department of Health and Human Services (HHS), including the National Institutes of Health (NIH), biomedical funding is clearly not a priority for President Trump.

"The Trump administration's proposed budget would cripple the science and technology enterprise through short-sighted cuts to discovery science programs and critical mission agencies alike," said Rush Holt, CEO of the American Association for the Advancement of Science in a statement. "Investments in federal research and development make significant contributions to economic growth and public well-being. The administration's proposed cuts would threaten our nation's ability to advance cures for disease, maintain our technolog-

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Blood Test Plus Clinical Characteristics May Improve CAD Diagnosis

A simple blood test can accurately, noninvasively, and quickly diagnose heart disease, according to a study published in the *Journal of the American College of Cardiology*. The soon-to-be commercialized test uses clinical and multi-protein blood test to predict the presence of anatomically significant coronary artery disease (CAD).

CAD is the most common form of heart disease, killing more than 370,000 people in the United States annually, according to the American Heart Association. The current diagnostic methods—CT angiography and stress testing—have drawbacks, including the need for ionizing radiation and high cost.

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Trump Budget Proposes Steep NIH Cuts, Hike to FDA User Fees, *from page 1*

ical leadership, ensure a more prosperous energy future, and train the next generation of scientists and innovators." In his introductory message to the budget proposal President Trump explained that "defense and public safety" budget increases would be offset by "finding greater savings and efficiencies across the Federal Government. ... We are going to do more with less, and make the Government lean and accountable to the people."

The diagnostics industry would be impacted by both the proposed cuts to the NIH, as well as the increase in U.S. Food and Drug Administration (FDA) user fees proposed in the budget.

NIH Budget Cuts

In the proposal, $69 billion is requested for HHS, a $15.1 billion decrease (or 17.9 percent) from the current level. The NIH stands to lose $5.8 billion (an almost 20 percent reduction), bringing its funding to $25.9 billion, which is below 2003 levels. By comparison, 2013 sequestration cuts reduced the NIH budget by 5 percent, a fraction of what's being proposed by the Trump administration. Even still, sequestration, the institute said, led to 700 fewer competitive research grants in fiscal year 2013.

"In the last 15 years, NIH-funded research has built the foundation for many of America's biotechnologies, such as developments in cancer treatments, genomics, and medical diagnostics," said Darrell Kirch, M.D., president of the Association of American Medical Colleges, in a statement. "Medical research takes years to translate from the bench to the bedside and cannot be turned on and off like a faucet. The proposed cuts would set back progress toward critical advancements that could take decades to regain, prevent new ideas from being explored, and have a chilling effect on those who would potentially enter the biomedical research workforce."

The Trump administration says the budget proposal would "reduce [ ] administrative costs and rebalance Federal contributions to research funding." While details are scarce in the two pages dedicated to HHS, the budget proposal also mentions "a major reorganization of NIH's Institutes and Centers."

Advocates for science and medical research remain hopeful that Congress will maintain its bipartisan history of "protecting" research investments, as Congressional members from both parties have expressed public concern over the proposed NIH cuts.

FDA User Fees

In addition to the proposed cuts to NIH funding levels, the administration's proposal looks to "recalibrate" medical product user fees, which could double what pharmaceutical companies and medical device manufacturers (including diagnostics companies) would pay in review costs. The FDA had decreased user fees in 2017 to what the Regulatory Affairs Professionals Society says are the lowest fees since 2013. The White House says the proposed increase in fees is "designed to achieve regulatory efficiency and speed." However, given the current shortage of FDA reviewers and the federal hiring freeze, experts are skeptical, the increase in fees would achieve its stated goal.

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Public Health Emergency Funding

The proposed Budget also "[r]eforms key public health, emergency preparedness, and prevention programs"—such as changing preparedness grants to "reduce overlap," save expense and channel funding to states most in need. Additionally, the budget calls for a new Federal Emergency Response Fund to address public health crises such as the Zika Virus outbreak. Finally, the Centers for Disease Control and Prevention would get a $500 million block grant designed to provide more flexibility and address state-specific needs.

Takeaway: If enacted, the Trump administration cuts to the NIH could have profound negative effects on biomedical research and would increase FDA user fees. While Congress will ultimately decide the budget, the White House proposal would be detrimental to the biomedical industry, including the diagnostics sector.

ACA Credited With Increasing Screening Test Use

There was an uptick in preventive screening resulting from Affordable Care Act (ACA), yet cancer-screening rates in the United States remain below Healthy People 2020 goals. More people received screenings to prevent cancer and heart disease in 2015 than in 2012, according to a March 2017 data brief from the National Center for Health Statistics (NCHS), although the growth in screening was not consistent.

The ACA was intended to improve access to health care through both greater numbers of insured and coverage of "essential health benefits" (certain clinical preventive services) without copayments.

Two studies led by researchers at the U.S. Centers for Disease Control and Prevention (CDC) used 2015 National Health Interview Survey to assess utilization of screening services in a nationally representative adult civilian population. Actual screening rates were compared to the estimated number who should be screened based upon recommendations from the U.S. Preventive Services Task Force or national targets from Healthy People 2020.

- **Colonoscopy:** In 2015, just under two-thirds of insured adults aged 50 to 75 years were screened for colorectal cancer within the recommended intervals. This is up substantially from the colonoscopy rate of 49.1 percent the CDC reported in 2010.

  In the second study, published March 3 in *Morbidity and Mortality Weekly Report (MMWR)*, the authors note the rate of colorectal cancer screening of 62.4 percent in 2015 is below the Healthy People 2020 target of 70.5 percent. Despite progress in increasing screening in many groups, low screening use was reported by persons without a usual source of health care (26.3 percent) and the uninsured (25.1 percent).

- **Pap Testing:** In 2015, more than 8 out of 10 insured women aged 21 to 65 years were screened for cervical cancer (83 percent) in accordance with recommendations. Cervical cancer screening test use was lowest (63.8 percent) among uninsured women.

The screening rate for cervical cancer actually decreased slightly between 2000 and 2015 and remains below the target of 93.0 percent by 2020. However, the *MMWR* authors note that cervical cancer screening recommendations changed in 2012. The new extended screening intervals may have contributed to the slight decline in cervical cancer screening. (See page 5 for further discussion of cervical cancer screening).

- **Glucose Testing:** In 2015, roughly two out of three overweight and obese insured adults aged 40 to 70 years had a fasting blood test for high blood sugar or diabetes in the past 12 months.

"The Affordable Care Act has helped to reduce such barriers by expanding insurance coverage and eliminating cost sharing, in most insurance plans, for preventive services," write the *MMWR* authors, led by Arica White, Ph.D., from the CDC's Division of Cancer Prevention and Control. "Persons without a usual source of health care and the uninsured had the lowest test use, with the overwhelming majority of the uninsured not up to date with breast and colorectal cancer screening."

Takeaway: The ACA is credited with increasing rates of some preventive health screening, although screening rates remain below Healthy People 2020 targets.

Testing Guidelines *at a Glance*

Expanded Carrier Screening for All Women

All women, regardless of ethnic background, should be offered expanded carrier screening prior to pregnancy, according to new recommendations published by the American College of Obstetricians and Gynecologists' Committee on Genetics. Ethnic-specific screening, pan-ethnic screening, and expanded carrier screening are all "acceptable" strategies that can be used to identify the risk of genetic disorders in potential offspring. Additionally, the committee's recommendations say

- Providers should establish "a standard approach that is consistently offered," although the ultimate screening approach for an individual should also be guided by the patient's family history and personal values.
- Expanded carrier screening panels should include conditions that have a carrier frequency of 1 in 100 or greater, a well-defined phenotype, a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life.
- Regardless of ethnicity, screening strategy, or history, all patients should receive carrier screening for the following conditions: cystic fibrosis, spinal muscular atrophy, and thalassemias and hemoglobinopathies (plus a complete blood count).

First Diagnostic Criteria Established for Castleman Disease

Castleman Disease is a rare, complex disease that often looks similar to a lymphoma, but can present like an autoimmune or infectious disorder. Diagnosis is complicated by a lack of a biomarker, leading to a recent push to establish diagnostic criteria (evidence-based consensus), which were recently published in *Blood*. The criteria require multicentric lymphadenopathy with defined histopathology, two or more clinical/laboratory changes (elevated CRP or ESR, anemia, thrombocytopenia, hypoalbuminemia, renal dysfunction, and/or polyclonal hypergammaglobulinemia), and exclusion of mimic conditions (infectious, autoimmune, or malignant).

Many Women Still Leery of 2012 Cervical Cancer Screening Guidelines

The majority of women are willing to undergo less frequent cervical cancer screening, consistent with screening guidelines, if it was recommended by their health care provider, according to a study published in the February special issue of *Preventive Medicine*, dedicated to analyzing the shift from cytology to human papillomavirus (HPV) testing for cervical cancer screening. However, a sizeable minority expresses resistance to longer screening intervals and/or new detection methods, including HPV testing, instead of the traditional Papanicolaou (Pap) test.

In 2012, multiple professional organizations, including the American Cancer Society, the U.S. Preventive Services Task Force, and the American College of Obstetricians and Gynecologists, published updated guidelines for cervical cancer screening that discourage annual testing and screening of low-risk populations (e.g., women below age 21 or above age 65). Cytology is now recommended every three years for women aged 21 to 29 years and cytology every 3 years or HPV co-testing every five years is recommended for women aged 30 to 65 years. However, the authors of the *Preventive Medicine* study say that patients' comfort with the guidelines could affect successful adoption.

The researchers conducted an online survey using a national sample of 376 U.S. women aged 21 to 65 years. The survey assessed sociodemographic characteristics, cervical cancer knowledge, health history (including sexual history), and views on the 2012 cervical cancer screening guidelines following a brief educational summary of the screening recommendations.

More than half of those surveyed (57 percent) report having their last Pap test within the past year and almost 30 percent reported having an abnormal Pap test. Nearly three-quarters of respondents (73 percent) were not aware of the change in cervical cancer screening guidelines. Yet, over two thirds (n = 239) were willing to have a Pap test at longer intervals (every three to five years), if it was recommended by their health care provider. One in five, though, said they would not agree to less frequent screening, even if recommended by their provider. Uncertainty about the longer screening interval appears to stem from concern about developing cancer between screenings, the authors say. Additionally, 45 percent of respondents either opposed or were unsure if they would be comfortable replacing Pap testing with primary HPV testing.

"It is possible that healthcare providers are contributing to patients' hesitancy around less frequent screening," write the authors led by Mary Gerend, Ph.D., from Northwestern University in Chicago. "Recent data indicate that many providers continue to conduct Pap tests annually and only about half initiate and discontinue screening at guideline-appropriate ages."

The authors say their findings can help inform methods to educate patients, and possibly providers, on the screening guidelines and may ultimately cut overscreening and improve guideline adherence.

Takeaway: A substantial portion of women remain hesitant to follow 2012 cervical cancer guidelines, which lengthen screening intervals away from annual screening.

SPECIAL FOCUS: PSA

New Biomarkers May Enable Personalized Prostate Cancer Screening

Early diagnosis of prostate cancer (PCa) is marred by a lack of consensus on the best screening strategy. Prostate specific antigen (PSA) had been in widespread use for routine PCa screening, until the U.S. Preventive Services Task Force (USPSTF) recommended against routine PSA screening in 2012. The USPSTF recommendation has cut screening rates, experts say, but its recommendation is not universally accepted and screening recommendations vary substantially among major medical societies in the United States.

> *"That there is still no clarity about the usefulness and desirability of routine PSA-based screening after 25 years and two large trials suggests that its net benefit is unlikely to be more than marginal, whereas the harms are proven and substantial."*
>
> — Paul F. Pinsky, Ph.D.

A benefit of PSA screening is a reduction in prostate-specific mortality. According to a review published March 30 in the *New England Journal of Medicine (NEJM)* such mortality is estimated based on a "reasonable summary of the evidence" to be approximately one prostate cancer death averted per 1,000 men screened several times each and followed for 10 to 15 years. Yet, common harms associated with PSA-based diagnosis and the treatment of PCa include: anxiety, urinary incontinence, and erectile dysfunction.

Benefits of early detection are thought to be far off, while harms occur nearly immediately with biopsy, radical prostatectomy, or radiation therapy. The main problem with PSA testing is its lack of specificity, which has been shown to lead to unnecessary, and often repeat biopsies and the overdiagnosis and overtreatment of nonaggressive disease.

"That there is still no clarity about the usefulness and desirability of routine PSA-based screening after 25 years and two large trials suggests that its net benefit is unlikely to be more than marginal, whereas the harms are proven and substantial," write the authors led by Paul F. Pinsky, Ph.D., from the National Institutes of Health in Bethesda, Md., in the *NEJM*. "Under the 'first do no harm' principle, it seems reasonable to forgo mass screening as a public health policy at this point but to continue to perform research on how to reduce the harms of PSA screening."

Some screening strategies suggested by Pinsky, include less frequent screening intervals and discontinuing screening for men with very low PSA values. Additionally, though, there is great interest in identifying new biomarkers for diagnosing, staging, and risk-stratifying PCa to inform treatment decisions.

New markers would ideally be collected noninvasively; low enough in processing costs that they could be implemented in widespread screening programs; and differentiate clinically significant cancer from nonaggressive disease.

"Although many studies have shown that novel biomarkers outperform PSA, they are not yet part of daily clinical practice and guidelines," writes co-author R.J. Hendriks, from Radboud University Medical Center in the Netherlands, in a

SPECIAL FOCUS: PSA

Markers Beyond PSA for Early Diagnosis

While interest in new promising biomarkers is high, to date, only a few have reached clinical practice. Below is a sampling of PCa markers of high interest.

Commercially Available

- Prostate cancer antigen 3 (PCA3) - PCA3, a prostate-specific noncoding messenger RNA, which is overexpressed in PCa tissue is available commercially as the U.S. Food and Drug Administration- (FDA-) approved Progensa PCA3 test (Hologic). The test, covered by insurance, costs approximately $385.
- Prostate Health Index - This test, by Beckman Coulter, combines PSA, free PSA and p2PSA using an algorithm to predict the likelihood of finding prostate cancer on a repeat biopsy. The test, covered by insurance, costs less than $100.
- Four-kallikrein panel - The combination of a four-kallikrein panel (4K; total PSA, freePSA, intact PSA, and human kallikrein-related peptidase) can predict biopsy outcome, potentially cutting back the number of men undergoing biopsy. It is available as the 4K laboratory-developed test (OPKO Health).
- Mi-Prostate score - This test from University of Michigan MLabs combines PCA3 and TMPRSS2-ERG with serum PSA levels to predict biopsy outcome.
- SelectMDx - A two-gene (HOXC6 and DLX1), urine-based panel can predict high-grade PCa. The risk score, SelectMDx (MDxHealth) can also potentially reduce the number of unnecessary biopsies.

Noncommercially Available

- Transmembrane protease serine 2-ERG (TMPRSS2-ERG) gene fusion - Gene fusions, often caused by genomic chromosomal rearrangements may initiate the oncogenic process. TMPRSS2-ERG gene fusion may be specific for PCa, but are not yet approved as predictive of prostate biopsy outcome or aggressiveness of disease.
- Exosome-based scoring - Scoring is derived from exosomal RNA (specifically the sum of normalized PCA3 and ERG exosomal RNA) and is associated with high-grade PCa. Two different scoring methods have been developed.

Adapted from: Hendriks RJ, van Oort IM, Schalken JA. Blood-based and urinary prostate cancer biomarkers: a review and comparison of novel biomarkers for detection and treatment decisions. *Prostate Cancer and Prostatic Diseases*. 2017; 20:12–19.

Narayan VM, Konety BR, Warlick C. Novel biomarkers for prostate cancer: An evidence-based review for use in clinical practice. *International Journal of Urology*. March 27, 2017 Accessed from http://onlinelibrary.wiley.com/doi/10.1111/iju.13326/full.

review published in the March issue of *Prostate Cancer and Prostatic Diseases*. "We would recommend that before using new biomarkers as tools for risk stratification, biopsy decisions, and treatment selection in patients with PCa, the biomarkers should be validated and prospectively compared with each other. ... Longitudinal studies are required following men from initial investigation through to diagnosis and treatment of PCa to determine clinical effectiveness and cost-effectiveness to guide doctor and patient in decision-making regarding PCa diagnostics and treatment selection."

Much Interest in Genomic Markers

Better understanding the genetics behind PSA levels may be an important step in personalizing screening, according to a genome-wide association study published Jan. 31 in *Nature Communications*.

The California-based researchers used a discovery cohort (N=28,503) to search for genome-wide variants associated with PSA levels among non-Hispanic, white individuals who had not been diagnosed with PCa. Findings were validated in 11,825 additional men in the Kaiser Permanente cohort (non-cases of other race or ethnicity groups and PCa cases using their PSA levels at least two years before cancer diagnosis) and 5,603 external replication non-cases.

The researchers identified 40 genome-wide significant single-nucleotide polymorphisms (SNPs), of

SPECIAL FOCUS: PSA

> *"Determining the genetic basis of PSA levels, unrelated to cancer, may help increase both the sensitivity and specificity of screening for PCa by adjusting PSA levels for constitutive germline genetics."*
>
> — Thomas J. Hoffmann

which 19 were novel, 15 were previously identified for PSA (14 of which were also PCa-associated), and six previously identified for PCa only. When incorporating PCa cases, analysis suggested that at least half of the 40 SNPs are PSA-associated independent of PCa. The authors note that existence of SNPs that influence PSA levels, but not PCa, and other SNPs that influence both highlights the difficulty of using conventional PSA levels as a screening tool.

"Determining the genetic basis of PSA levels, unrelated to cancer, may help increase both the sensitivity and specificity of screening for PCa by adjusting PSA levels for constitutive germline genetics," write the authors led by Thomas J. Hoffmann, from University of California San Francisco. "Clinicians could more accurately decide who should have a prostate biopsy, thereby reducing unnecessary procedures and their associated morbidities, as well as decreasing overdiagnosis."

NorthShore University Health System in Illinois is one of the first health systems to begin to personalize PCa screening. Last summer, the health system began estimating inherited risk of prostate, breast and colorectal cancer using genetics and providing modified screening schedules for patients based on their results.

Takeaway: While consensus regarding ideal PCa screening remains elusive, research continues to identify new markers or combinations of markers that can improve screening performance and ultimately better differentiate clinically relevant PCa from nonaggressive disease.

Survey Finds Soft Skills Sought in Hiring New Pathologists

It is no secret that new graduates may not be fully equipped with the necessary skills for their first job. Even among new pathologists, on-the-job training is necessary to fulfill both the technical and the "soft" skills needed in actual practice. According to a study published in the February issue of the *Archives of Pathology & Laboratory Medicine*, it is these nonpathology-based soft skills—such as flexibility, leadership, and relationship-building skills—that have emerged as important areas of emphasis for prospective employers.

"Regardless of practice setting, employers place a great deal of importance on interpersonal and communication skills and professionalism, two core residency training competencies that both applicants and residency training programs may prioritize less than those related to medical knowledge and patient care," write the authors led by Miriam Post, M.D., from the University of Colorado, Denver.

Members of the College of American Pathologists (CAP) Graduate Medical Education Committee conducted a survey of CAP fellows who had been in

The most critically important skills and attributes, regardless of practice setting, were:

- ethics/integrity (76 percent),
- work ethic (66 percent),
- professionalism (61 percent),
- diagnostic skills (58 percent),
- emotional stability (55 percent),
- team attitude (54 percent), and
- communication skills (53 percent).

U.S. practice for five or more years and were responsible for hiring a new-in-practice pathologist (NIP; defined as in the workforce for three years or less). The survey addressed 18 skills and attributes employers consider when hiring. The skills and attributes were grouped into the categories of interpersonal style, work style, career motivation and job search, and technical proficiency and rated on a five-point scale.

Responses from 630 pathologists show the majority (71 percent) has had some degree of difficulty hiring entry-level pathologists across practice settings (not-for profit hospital, academic center or hospital, and pathologist-owned laboratory). Reasons cited for this hiring difficulty included inadequate training during residency and applicants having unrealistic expectations regarding work load/hours. The other common reasons for disqualification include poor interpersonal skills, poor communication skills (including difficulty with the English language), poor technical proficiency, and poor references.

The most critically important skills and attributes, regardless of practice setting, were ethics/integrity (76 percent), work ethic (66 percent), and professionalism (61 percent), followed by diagnostic skills (58 percent), emotional stability (55 percent), team attitude (54 percent), and communication skills (53 percent).

While most respondents said they would hire a candidate that did not have an existing relationship with a laboratory staff member, getting in the door might prove difficult. Respondents note that up to 70 percent of jobs are not publicly posted and 83 percent identified "networking/word of mouth" as the most common recruiting method, highlighting the need for applicants to hone their networking skills, the authors say.

Respondents' free-text advice to pathology trainees were thematically categorized into three key themes:

- Capitalize on opportunities during training to enhance leadership skills.
- Develop interpersonal and communication skills.
- Be flexible and know your preferred job characteristics.

Trainees should heed the advice, as the need to hire is expected to continue, with 85 percent of respondents anticipating hiring at least one NIP pathologist in the next 5 years. Hiring in academic settings is expected to be even more robust, with 92 percent reporting anticipated hiring within the next five years and 21 percent of those practicing in an academic setting expecting to hire four or more NIP pathologists over that time frame.

Takeaway: While the fact that NIP pathologists may lack some necessary skills for effective practice on day one is not surprising, trainees should be aware of the growing importance being placed on soft skills that may not be the primary focus of residency and fellowship training.

Blood Test Plus Clinical Characteristics May Improve CAD Diagnosis, *from page 1*

"CAD is a public health concern, and an efficient manner for its noninvasive detection could potentially result in reduction of morbidity, mortality, and cost of this disease," writes lead author Nasrien Ibrahim, M.D., from Massachusetts General Hospital (Boston).

"Advantages of such a reliable clinical and biomarker score include the fact such a technology can be widely disseminated in a cost-effective manner, is easily interpreted, and might be associated with a well-defined sequence of therapeutic steps to reduce risk for CAD-related complications, such as antiplatelet or lipid-lowering therapy."

— Nasrien Ibrahim, M.D.

The researchers used data from 1,251 patients enrolled in the CASABLANCA (Catheter Sampled Blood Archive in Cardiovascular Diseases) study who were referred for coronary angiography (2008 through 2011). A panel of 109 biomarkers was evaluated from blood samples collected immediately before and after the angiographic procedure using the Luminex xMAP multiplex technology platform (Luminex Corporation; Austin, Texas). Candidate proteins and clinical features were selected using least angle regression, in which factors are selected one at a time and evaluated for predictive performance and goodness of fit. Variables are added if they improve the score.

In the training cohort, independent predictors of CAD (70 percent or more) in any one vessel included clinical variables (male sex and previous percutaneous coronary intervention) and four biomarkers (midkine, adiponectin, apolipoprotein C-I [apo C-I], and kidney injury molecule–1 [KIM-1]), which the authors say represent "a unique pathophysiological mix." The combined score "strongly" predicted severe CAD in all subjects in the training cohort. Across scores, the CAD algorithm had 77 percent sensitivity, 84 percent specificity, 90 percent positive predictive value, and 67 percent negative predictive value for severe CAD at the optimal score cutpoint in the validation set. An elevated score also significantly predicted incident acute myocardial infarction during 3.6 years of follow up.

"Advantages of such a reliable clinical and biomarker score include the fact such a technology can be widely disseminated in a cost-effective manner, is easily interpreted, and might be associated with a well-defined sequence of therapeutic steps to reduce risk for CAD-related complications, such as antiplatelet or lipid-lowering therapy," writes Ibrahim.

The test is being commercialized as HART CAD by Prevencio (Kirkland, Wash.). The company says it takes two hours for results and is cheaper than the current diagnostic standards (CT angiogram $2,000 on average and a cardiac catheterization $47,000 on average). Prevencio says it plans to conduct trials for U.S. Food and Drug Administration approval in 2018 and hopes the test would be commercially available by 2019.

Several authors report financial ties to the diagnostic firm Prevencio (Kirkland, Wash.), which funded this study.

Takeaway: A blood test, in combination with clinical features, produces a score that can efficiently and effectively gauge risk of CAD. Such a test could improve diagnosis and early treatment, while decreasing health care costs and deaths.

Genomics May Predict Cancer Treatment Side Effects

While much attention is focused on using genomic markers to target the effectiveness of treatments, simultaneous research is exploring use of genomic markers to identify patients at higher risk of therapy-induced side effects.

Two recent studies highlight the use of genomic markers to identify anthracycline-induced congestive heart failure (CHF) and guide radiotherapy dose to decrease complication risk.

Chemotherapy-Induced Heart Failure

A single nucleotide polymorphism (SNP) identifies patients at high risk for chemotherapy-induced CHF, according to a study published in the January issue of *Clinical Cancer Research*.

Anthracyclines are a widely used class of chemotherapy known to have "dose-limiting side effects," including CHF. Previous research showed that patients that received an anthracycline were five times more likely to develop cardiac symptoms. While the total rate of CHF in patients receiving anthracyclines is low (estimated at approximately 2 percent), the ability to predict which patients might be at increased risk prior to exposure, would be valuable information to optimally counsel patients, clinicians say.

"Many patients still benefit from anthracyclines based on risk or underlying biology of the tumor, [but] the severity of the side effect necessitates a means to identify high-risk patients," write the authors led by Bryan Schneider, M.D., from Indiana University in Indianapolis.

The researchers conducted a genome-wide association study for biomarker discovery and validated findings in two additional cohorts. The discovery cohort included participants in a randomized phase III adjuvant breast cancer trial, while validation occurred in two independent phase III adjuvant breast cancer trials. In total, the three trials enrolled more than 12,500 patients.

The international group of researchers discovered that rs28714259 is associated with nearly a two-time increased risk of anthracycline-induced CHF.

Personalizing Radiotherapy Dose

Current one-size-fits-all radiotherapy dosing protocols can be optimized for effectiveness and toxicity using tumor-specific genomic data, according to a study published in the February issue of *The Lancet Oncology*.

Unlike progress in targeted chemotherapy, radiotherapy, the most commonly used oncological therapeutic agent, has not yet entered the realm of personalized medicine and its dosing is not adjusted based on tumor biology. Current clinical practice uses uniform protocols, despite the possibility that not every patient will derive similar benefit from radiotherapy.

The Moffitt Cancer Center researchers previously developed a gene-expression based radiosensitivity index (RSI) that predicts tumor sensitivity to radiation therapy based on the expression of 10 specific genes. In the present study, the researchers used the RSI to develop a genomics model called the genomic-adjusted radiation dose (GARD).

> *"We emphasize that GARD is not a predictive assay or biomarker for clinical outcome, but rather a model to adapt the prescribed radiation dose to match individual tumour radiosensitivity."*
>
> — Jacob Scott, M.D.

Initially, the researchers analyzed tumors from 8,271 adult patients enrolled in the Total Cancer Care (TCC) protocol using an Affymetrix assay. GARD was calculated for primary tumors from 20 disease sites. GARD was independently evaluated to test associations with clinical outcome in five separate clinical cohorts.

The researchers found a wide range of GARD values across the TCC cohort (range, 1.66 to 172.4) and within tumor type groups. Higher GARD values predicted a higher therapeutic effect from radiotherapy, the authors say, and independently predicted radiotherapy-specific outcome.

"We emphasize that GARD is not a predictive assay or biomarker for clinical outcome, but rather a model to adapt the prescribed radiation dose to match individual tumour radiosensitivity," write the authors led by Jacob Scott, M.D., from the Moffitt Cancer Center in Tampa, Fla. "GARD could provide a scientific framework to adjust radiotherapy doses that have already shown to be safe, both in terms of increasing tumor control (increasing dose to more resistant tumors) and decreasing complication risks (lowering the dose to more sensitive tumors).

Takeaway: Genomic information may provide valuable information to guide treatment decisions and personalize therapy by identifying which patients might be at higher risk for this serious treatment-related toxicity.