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Point of Care: Handheld Device Shows Promise in Detecting Concussion from Blood Samples

A handheld portable device could be more effective than a CT scan in detecting mild traumatic brain injuries (TBI), according to a new study published in *The Lancet Neurology*. Because it is capable of detecting brain injuries within 15 minutes, as well as injuries that CT scans miss, this new technology may help fill a gap in emergency rooms, sporting events and the battlefield—by identifying patients who might otherwise have gone undiagnosed.

The TBI Diagnostic Challenge

More than 4.8 million people in the U.S. visit emergency rooms each year to be evaluated for brain injury. To detect brain injuries, doctors

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Genetic Testing: Multigene Panel Testing Detects Hereditary Risk Variants in Metastatic Breast Cancer Patients

The clinical value of performing multigene panel for inherited cancer in patients with metastatic breast cancer has been the subject of considerable debate. Those who believe in the value of such testing can now point to a new report by researchers from Johns Hopkins University School of Medicine and the Vanderbilt Ingram Cancer Center as evidence that such testing may be beneficial for guiding treatment decisions in some metastatic breast cancer patients, particularly individuals carrying risky mutations in BRCA1 or BRCA2 who might be eligible to receive PARP inhibitor treatment. Here is an overview of the new study, which was reported in the Aug. 29, 2019 edition of *JAMA Oncology*.

What Is At Stake

Multigene panel testing for inherited cancer in patients with breast

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Handheld Device Shows Promise in Detecting Concussion from Blood Samples, *from page 1*

currently utilize physical examinations, CT scans and screening questions for cognitive and neurological symptoms. MRIs are more precise and can pick up injuries that physical exams and CT scans miss. Thus, some 30% of patients who had a normal CT scan were found to have signs of TBI when they were tested via MRI. But while MRIs are more accurate, they are not available at all hospitals. They are also relatively slow and considerably more expensive than CT scans and blood tests.

Because of the limitations of current tools for detecting brain injuries, it is estimated that half of concussions go undetected and undiagnosed. And missing or even waiting days for a diagnosis could have significant consequences for brain injury patients.

The New Device

When TBI occurs, damaged cells release glial fibrillary acidic proteins (GFAPs) that leak out of the brain and into the bloodstream. Thus, detecting elevated levels of GFAP biomarkers in a patient's blood sample could be an effective way to diagnose TBI.

With this in mind, Abbott has manufactured a handheld, portable blood analyzer that produces test results within minutes right by a person's side. Abbott's i-STAT Alinity system measures GFAP proteins from the brain that are released into the blood after a brain injury—serving as a warning signal that further evaluation is needed. The i-STAT Alinity device is not yet commercially available in the U.S. but is commercially available in other markets. Meanwhile, Abbott has more than 120 scientists and engineers researching and developing its concussion assessment test.

The New Study

The new study comes from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI study), a collaborative research effort involving observational and interventional studies funded by the National Institute of Neurological Disorders and Stroke, the U.S. Department of Defense through U.S. Army Medical Research and Development Command and U.S. Army Medical Materiel Development Activity, with support from private and philanthropic partners.

TRACK-TBI researchers evaluated 450 patients admitted to the emergency department of 18 U.S. Level 1 trauma centers with a suspected TBI, and who also received a negative CT scan, to determine if the brain-specific GFAP protein could be a biomarker for detecting TBI. The study used Abbott's i-STAT Alinity device and blood test under development to measure a patient's GFAP protein level and then reviewed MRI scans taken later to confirm the TBI. Researchers found that among the 450 patients studied:

- GFAP levels were significantly higher in patients who had a positive

DTET

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MRI but a negative CT scan, compared to people with both negative CT and MRI scans;

- GFAP levels potentially could be used to predict the type of damage as well as the extent of injury;
- GFAP levels were not significantly elevated in the control groups of healthy individuals nor in those who had only orthopedic injuries.

The study also looked at three additional brain biomarkers to assess any association between elevated levels of those proteins and brain injury:

- S100 calcium-binding protein B (S100B);
- Ubiquitin C-terminal hydrolase L1 (UCH-L1); and
- Neuron-specific enolase (NSE) protein.

The researchers found that elevated GFAP levels were more sensitive for detecting brain injury in patients with a negative CT scan than were elevated levels of UCH-L1, S100B or NSE.

Takeaway: "Blood-based biomarkers are emerging as an important tool to detect TBI, and this research opens up the next chapter for how the condition is evaluated," said ***Geoffrey T. Manley****, M.D., Ph.D., principal investigator of TRACK-TBI, neurosurgeon and professor of neurosurgery, University of California, San Francisco. "Having these sensitive tools could provide physicians more real-time, objective information and improve the accuracy of detecting TBI. This research shows that blood tests have the potential to help physicians triage patients suspected of brain injury quickly and accurately."*

Testing Trends: Study Finds Liquid Biopsies More Effective than Traditional Biopsies in Detecting Cancer Drug Resistance

Liquid biopsies based on blood samples do a better job than traditional biopsies in analyzing both the genetic diversity of the patient's cancer and how tumors evolve drug resistance at the molecular level. That is the finding of a new study from a group of researchers from, among other institutions, Harvard, the Broad Institute of MIT and Massachusetts General Hospital (MGH).

What's At Stake

Like other organisms, tumors evolve to survive adverse environmental changes. A tumor that shrinks in response to one drug may undergo evolutionary change enabling it to fend off the cancer drug and reemerge. Being able to rapidly detect cancer drug resistance and evolutionary patterns is thus crucial to finding a new drug that the tumor will still respond to.

Cancer diagnosis has traditionally relied on tissue biopsies as the principal source of this information. But in addition to being invasive, tissue biopsies provide a glimpse of only one location in a single tumor, which limits their effectiveness to the extent tumor cells may be genetically distinct from one another. Liquid biopsies, by contrast, are performed on patient blood samples containing DNA from tumors, i.e., circulating tumor DNA or ctDNA, which can be isolated and analyzed. But in spite of the advantages of liquid biopsies, tissue biopsy remains the mainstay of cancer diagnosis.

The Study

Are doubts about the effectiveness of liquid biopsy vis-à-vis traditional tissue biopsy warranted? Previous case reports and small case series suggest that liquid biopsy (specifically, cell-free DNA (cfDNA)) may better capture the heterogeneity of acquired resistance. However, the effectiveness of cfDNA versus standard single-lesion tumor biopsies has not been directly compared in larger-scale prospective cohorts of patients following progression on targeted therapy.

The new study, published online in the Sept. 9, 2019 issue of *Nature Medicine*, is the largest to date to directly compare liquid biopsy to tumor biopsy in the setting of cancer resistance. The researchers studied 42 patients with different molecular forms of gastrointestinal cancer who were undergoing treatment with targeted drugs and developed drug resistance. When the patients showed signs of drug resistance, the researchers analyzed their tumors using both liquid and tissue biopsies. Utilizing PhylogicNDT computational tools developed at the Broad Institute, they analyzed the tumor DNA and their resistance mutations.

The head-to-head comparison of liquid and tissue biopsies revealed that in 78% of cases, the liquid biopsies unearthed clinically relevant genetic

alterations linked to drug resistance that were not identified through standard tissue biopsies. Whole-exome sequencing of serial cfDNA, tumor biopsies and rapid autopsy specimens elucidated substantial geographic and evolutionary differences across lesions. "Our findings suggest that liquid biopsy may be the preferred clinical modality for assessing how patients' tumors have evolved after they've become resistant to therapy," notes co-senior author **Ryan Corcoran**, an investigator at MGH and Harvard Medical School.

The Implications

Validation of liquid biopsies, however, may not be the most significant finding from the study.

"Remarkably, we found that nearly every patient we analyzed had developed not just one, but multiple drug resistance mechanisms simultaneously, and this may be more common than we previously thought," said **Gad Getz**, co-senior author of the study, director of the Cancer Genome Computational Analysis Group at the Broad and the Paul C. Zamecnik Chair in Oncology at the MGH Cancer Center. The authors characterize this as "a real paradigm shift that and will force us to rethink" the potential advantages of liquid biopsies over tissue biopsies in treating cancer drug resistance.

Takeaway: Although this is exciting stuff, popping champagne corks would be premature. "To really map out the full landscape of cancer resistance mechanisms, we need much larger studies that span a variety of drugs and cancer types," notes Getz.

LDTs: FDA Cracks Down on Marketing of Non-Approved PGx Medication Response Tests

Laboratory Developed Tests (LDTs) are back in the FDA's enforcement crosshairs. This time the target is marketing claims related to the medication predictive qualities of pharmacogenetics (PGx) tests that have not received premarket clearance or approval.

The FDA's PGx Concerns

PGx tests can be used to detect genetic variants associated with responses to specific medications, e.g., genes that code for drug-metabolizing enzymes or drug targets, explains **Steven Tjoe**, an attorney with Goodwin Procter LLP in Washington, D.C., and former regulatory counsel in FDA's Center for Devices and Radiological Health. PGx test results can inform medication decisions such as drug effectiveness and dosage amounts.

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FDA Cracks Down on Marketing of Non-Approved PGx Medication Response Tests, *from page 5*

The FDA's beef, Tjoe explains, is with claims about the capabilities of unreviewed PGx tests to predict response to specific medications. Thus, on Nov. 1, 2018, the FDA issued a Safety Communication to alert patients and physicians that such claims may not be supported by sufficient scientific or clinical evidence. The FDA 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. So, changing drug treatment based on the results from such tests could result in inappropriate and harmful treatment decisions.

The Follow-Up Enforcement

As the Safety Communication warns, the FDA has backed up its clinical warning with enforcement scrutiny. Thus, in April 2019, the FDA issued a warning letter to Inova Genomics Laboratory for marketing genetic tests that claim to predict patients' responses to specific medications without FDA clearance or approval (See *Lab Industry Report, (LIR), April 29, 2019*). In response, Inova reportedly stopped offering its PGx tests. And Inova is not alone. Tjoe says the agency has also contacted several other laboratories making similar marketing claims about their own PGx tests.

Impact on Laboratories

This new FDA enforcement focus has had a chilling effect on just about all laboratories that provide PGx tests for medication response, including those that have not received a warning letter. According to Tjoe, some laboratories have stopped reporting drug information and no longer mention specific drugs on their websites and marketing materials. Others are reviewing their LDT marketing materials, test menus, test reports and other labeling in response to the FDA actions.

Perspective: Recognize that the FDA's current enforcement activities against clinical laboratories offering PGx tests as LDTs are part of the larger discussion among the agency, Congress, regulators and laboratories about whether and how to regulate LDTs. Laboratories need to pay close attention to these conversations, not only for clues as to FDA's enforcement priorities but also to see what the FDA, Congress and other regulators will actually do about LDTs regulation.

FDA WATCH: New DX Product Approvals

Manufacturer(s)	Product(s)
Zeus Scientific	Clearance for four EIA-based Lyme disease tests: *ZEUS ELISA Borrelia VlsE1/pepC10 IgG/IgM Test System *ZEUS ELISA Borrelia burgdorferi IgG/IgM Test System *ZEUS ELISA Borrelia burgdorferi IgM Test System *ZEUS ELISA Borrelia burgdorferi IgG Test System
Healthy.io	Clearance for smartphone-based albumin-to-creatinine ratio (ACR) test to diagnose chronic kidney disease
BioMérieux	Clearance for ETest Imipenem/Relebactam test to determine minimum inhibitory concentration of Imipenem/Relebactam, a carbapenem-8-lactamase inhibitor combination, against Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae and Pseudomonas aeruginosa
BioMérieux	Clearance for Vitek 2 AST-Gram Negative Eravacycline assay for antimicrobial susceptibility testing of Gram-negative bacilli, running on the firm's Vitek 2 and Vitek 2 Compact systems
Siemens Healthineers	Clearance for Atellica CH Amylase 2 assay running on firm's Atellica CH Analyzer to measure amylase activity in serum, plasma and urine and diagnose acute pancreatitis
Siemens Healthineers	Clearance for Advia Centaur Zika test to detect immunoglobulin M antibodies to Zika virus in serum and plasma specimens using the Siemens Advia Centaur XP + Advia Centaur XPT systems
Agilent Technologies	Expanded clearance for use of its Dako PD-L1 IHC 22C3 pharmDx assay as companion diagnostic test for Merck's anti-PDL-1 immunotherapy pembrolizumab (Keytruda) for esophageal squamous cell carcinoma (ESCC)
Becton Dickinson	Clearance for BD Phoenix Automated Microbiology System – GN Ceftaroline (0.0156-4 µg/mL)
Drawbridge Health	510(k) clearance for OneDraw A1C Test System, which includes a blood collection device and HbA1c test
Hycor Biomedical	Clearance for Noveos Specific IgE Assay, Capture Reagent House Dust Mite D002, Dermatophagoides Farina
Abbott	510(k) clearance for software modification to the ID Now Influenza A & B 2 test (previously called the Alere i), rapid multiplex nucleic acid assay for detection and differentiation of influenza A and influenza B in patients with respiratory infection symptoms
Roche Diagnostics	510(k) clearance for software modification to its Cobas Influenza A/B test running on Cobas Liat point-of-care system
Healthy.io	Clearance for its ACR LAB Urine Analysis Test System consisting of a smartphone app, color board + ACR reagent strips
iCubate	Breakthrough Device designation for its iC-Myco Assay for detection and identification of potentially pathogenic non-tuberculosis Mycobacterium (NTM)

Inside the Industry: Government Report Casts Doubt on Cost-Effectiveness of Leading Genetic Colorectal Cancer Screening Test

Few of the newfangled consumer genetic testing products have had greater commercial success and visibility than Exact Science's Cologuard colorectal cancer screening test. But a troubling new government report casting doubt on the product's effectiveness might have burst the Cologuard bubble, at least for now.

The Growth of Cologuard

Launched in 2014, Cologuard is the first stool multi-target stool DNA test (mtSDNA) for colorectal cancer screening. It has been ordered by nearly174,000, including 142,000 primary care physicians, with 900 new doctors joining the list of orderers each week. According to Madison, Wisconsin-based Exact Science's figures, Cologuard rakes in average revenues of $479 per test at an average cost of $123. The test, which is covered by Medicare, now commands 6% of the total U.S. colorectal cancer testing market.

Adding to the buzz is the recent announcement of Exact's impending $2.8 billion acquisition of Genomic Health, producer of the equally dynamic Oncotype DX consumer genetic screening tests for breast and prostate cancer. Collectively, Cologuard and the two Oncotype DX products represent approximately 40% of all solid tumor incidence. Exact's Chairman and CEO **Kevin Conroy** touted the Genomic Health acquisition as "a pivotal step toward building the leading cancer diagnostics company in the world." And he may not be exaggerating. If the deal gets regulatory approval and closes by the end of the year as expected, the combined company is forecasted to generate $1.6 billion in 2020 pro forma revenue.

New CMS Report Casts Doubt on Cologuard

But those projections were made before the new research report finding that Cologuard is "less effective and considerably more costly" than alternatives. "At its current reimbursement rate, triennial mtSDNA testing also has higher costs than all other strategies, making it an inefficient screening option," according to the paper published in the Sept. 4, 2019, issue of *PLOS ONE*.

One research report is one research report. But this research just so happened to be sponsored by the Centers for Medicare and Medicaid Services (CMS) for the express purposes of analyzing the use of mtSDNA testing for cancer screening of Medicare patients. CMS essentially asked MITRE Corporation to determine whether Medicare has been getting its money worth in shelling out an average $500 per test to cover Cologuard. MITRE commissioned investigators at the Cancer Intervention and Surveillance Modeling Network (CISNET), a consortium of investigators that use academic modeling to study the cost-effectiveness of cancer prevention, screening, and treatment methods, to carry out the research into the cost-effectiveness of Cologuard.

For Exact, the timing could not be any worse. In addition to completing

the Genomic Health acquisition, Exact is awaiting a crucial determination from the U.S. Preventive Services Task Force (USPSTF) which is currently reviewing its position on whether to recommend mtSDNA colorectal cancer screening. The fear, of course, is that the new report will influence the USPSTF's position. raising the prospect of the research paper influencing its position.

Exact wasted no time refuting the report, issuing a company release the very next day claiming that the CISNET analysis and models "understate Cologuard's value proposition, by employing unrealistic assumptions, such as adherence rates (i.e., 100% adherence, or relative adherence over a fairly narrow range) for screening, follow-up and surveillance procedures." The Exact press release criticizes "this academic approach [as] not reflective of clinical practice" and calls on researchers to ditch CISNET models in favor of "analysis that incorporates more accurate real-world data regarding adherence rates."

Takeaway: While it remains to be seen what, if anything, the long-term impact will be, the immediate effect was to spook investors. The day the report came out, Exact's shares fell 10%.

Emerging Tests: FDA Breaks New Ground by Clearing EIA Technology-Based Lyme Assays

Laboratory diagnosis of Lyme disease is based on detecting the presence of antibodies against Borrelia burgdorferi, the bacteria that causes the disease, in a patient's blood. Traditional testing uses a two-tier approach in which a pair of enzyme immunoassays (EIA) are performed followed by a separate protein test called a Western blot to confirm a Lyme disease diagnosis. But on July 29, 2019, the FDA broke new ground by clearing for the first time ever tests that follow a different model relying only on EIA technology-based tests which can be run concurrently or sequentially. Developed by Branchburg, NJ-based Zeus Scientific, the products were all approved via the FDA 510(k) pathway, including:

- The ZEUS ELISA Borrelia VlsE1/pepC10 IgG/IgM Test System;
- The ZEUS ELISA Borrelia burgdorferi IgG/IgM Test System;
- The ZEUS ELISA Borrelia burgdorferi IgM Test System; and
- The ZEUS ELISA Borrelia burgdorferi IgG Test System

In granting 510(k) clearance, the FDA relied on data from clinical studies demonstrating that the alternative modified two-tier test approach is just as accurate as current methods for detecting antibodies for assessing exposure to Borrelia burgdorferi. The FDA also reiterated in announcing the clearance that CDC recommendations should be followed for the diagnosis of Lyme disease and for determining when laboratory tests are appropriate.

Inside the Industry: New Government BRCA Test Guidelines Are a Mixed Bag for Genetic Testing Labs

The US Preventive Services Task Force (USPSTF) issued updated recommendations for BRCA-related cancer risk assessment, genetic counseling and testing in the Aug. 20 issue of the Journal of the American Medical Association (JAMA). The key takeaways: While the USPSTF has expanded the scope of at-risk patients it thinks should receive BRCA testing, it is standing by its previous position of recommending against routine testing of patients without a personal or family history of BRCA-related cancer.

Background

The USPSTF is an independent panel of experts appointed by the US Department of Health and Human Services' Agency for Healthcare Research and Quality charged with making evidence-based recommendations about clinical preventive services, including cancer prevention.

Previous Recommendations

In 2013, the USPSTF recommended that a primary care provider screen women who have family members with breast, ovarian, tubal or peritoneal cancer using assays and tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in the BRCA1/2 breast cancer susceptibility genes. It also recommended that women with positive screening results receive genetic counseling and, if indicated after counseling, BRCA testing.

The USPSTF recommended against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the BRCA1/2 genes.

New Recommendations

The USPSTF has broadened the group recommended for testing to include two new groups:

Women with personal histories of breast, ovarian, tubal or peritoneal cancer, including women successfully treated for these cancers in the past (italicized language is new); and

Women "who have an ancestry associated with BRCA1/2 gene mutations," such as women of Ashkenazi Jewish descent.

What hasn't changed is the recommendation against broad BRCA1/2 screening for women with no personal or family history of breast, ovarian, tubal or peritoneal cancer and no high-risk ancestry.

Impact on the Lab Industry

As consumer genetic testing firms struggle with a soft market, US government-sanctioned recommendations that more women get BRCA testing is certainly welcome news. However, the positivity is tempered by

the USPSTF's refusal to budge on testing for women without personal or family histories of cancer.

Moreover, companies like Myriad Genetics and Invitae are already looking past two-gene BRCA1 and BRCA2 tests to multigene panels for hereditary cancer risk assessment. However, the USPSTF declined to add these panels to its list of recommended tests. "The clinical significance of identifying pathogenic variants in multigene panels requires further investigation," according to the USPSTF's guidelines. "The evidence is currently limited on other moderate penetrance genes, given their relatively low incidence in the population."

Also disappointing to consumer testing firms is the USPSTF's refusal to address two other key issues:

- BRCA-related cancer risk assessment for biological males; and
- BRCA testing for other types of cancer associated with BRCA1/2 such as pancreatic cancer, prostate cancer and melanoma.

Multigene Panel Testing Detects Hereditary Risk Variants in Metastatic Breast Cancer Patients, *from page 1*

cancer is based on the prevalence of pathogenic/likely pathogenic (P/LP) variants. Recent studies show that the prevalence of P/LP variants is similar in patients with breast cancer regardless of whether they the National Comprehensive Cancer Network (NCCN) guidelines criteria for testing. However, most of the participants in these studies were patients with early stage breast cancer and many low-risk variants were identified, raising the question of clinical actionability.

The recent FDA approval of polyadenosine diphosphate–ribose polymerase (PARP) inhibitors for patients with metastatic human epidermal growth factor receptor 2 (HER2/ERBB2)-negative breast cancer with germline BRCA1 and BRCA2 (BRCA) pathogenic variants suggests germline testing of patients with metastatic breast cancer could have therapeutic implications. Exhibit A: A recent study finding that 11.8% of otherwise unselected patients with metastatic prostate cancer harbored a P/LP germline variant, which led the NCCN to change its guidelines recommend germline testing for all patients with metastatic prostate cancer. However, the researchers were aware of no analogous studies to quantify the prevalence of P/LP variants among patients with metastatic breast cancer.

The Study

With that in mind, the research team used a multigene germline panel test from Silicon Valley-based Color (formerly known as Color Genomics) to prospectively search for pathogenic or likely pathogenic variants in 30 genes in 100 individuals with metastatic breast cancer, regardless of whether those

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Multigene Panel Testing Detects Hereditary Risk Variants in Metastatic Breast Cancer Patients, *from page 11*

individuals currently met the NCCN testing criteria. Along with information for family members, the researchers hypothesized that such testing might be beneficial for guiding treatment decisions in some metastatic breast cancer patients, particularly individuals carrying risky mutations in BRCA1 or BRCA2 who might be eligible to receive PARP inhibitor treatment. The findings:

- Of the 100 individuals, 14 were found to have pathogenic or likely pathogenic variants;
- Six of those 14 individuals did not meet NCCN testing guidelines; and
- Conversely, two of the six metastatic breast cancer patients had not been tested in the past even though they carried risky BRCA1/2 mutations and met NCCN testing criteria.

In addition to the pathogenic and likely pathogenic changes found in cancer-related genes such as ATM, BRIP1, or CHEK2, the researchers found another 21 metastatic breast cancer patients who had variants of uncertain significance in one or more of the genes on the panel.

"[G]iven that many of the genes included on the multigene panel are involved in DNA repair," the authors noted, "there is scientific rationale that some of these [pathogenic or likely pathogenic] variants (ATM, BRIP1, CHEK2) may also be predictive for response to PARP inhibitors, a hypothesis currently being tested in clinical trials."

Takeaway: "[O]ur results provide evidence to support genetic testing for inherited cancer predisposition among all patients with metastatic breast cancer, because this group represents a population with a high prevalence of [pathogenic or likely pathogenic] variants that could have therapeutic implications," wrote corresponding author ***Ben Ho Park****, a hematology researcher at Vanderbilt, and his colleagues in the JAMA Oncology research letter.*