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Next-Gen Sequencing, AI Driving Investor Interest in Diagnostics Sector

There is "intense" investor interest and "substantial" investment occurring in the next generation of diagnostics and tools companies (Dx/Tools), according to a year-end report published by Silicon Valley Bank (SVB). Driven by interest in the use of big data and artificial intelligence (AI) to inform care, big-name technology firms are now leading investment in the diagnostics sector.

"Generalist investor and tech corporate investment activity in Dx/Tools has surged," write the authors, led by Jonathan Norris, managing director at SVB. "We expect today's top tech companies to also become the next generation of top Dx/Tools companies. With dedicated Dx/Tools teams, these tech giants could drive sector growth for the next decade."

The report, *Technology Advancements Redefine Promise of Dx/Tools*, defines Dx/Tools as including proprietary tests, actionable data analytics to determine or direct necessary treatment, and research equipment and services.

Who is Receiving Funding?

In total, eight rounds of financing in the Dx/Tools sector have exceeded $100 million since 2015. Dx/Tools fundraising increased 40 percent in 2017, reaching $2.8 billion. However, 60 percent of this

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Molecular Testing Increasingly Adopted for Skin Cancer Diagnosis

Dermatopathologists are increasingly using molecular testing for diagnosis of skin cancer samples. Yet, this adoption remains more concentrated in academic medical centers and high-volume clinical practices, according to a study published in the *Journal of Clinical Pathology*. Additionally, the study found that expanded adoption is stymied by test costs, a deficiency in physician training, and a lack of evidence-based clinical practice guidelines.

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total—or $1.6 billion—came from "mega" investments in liquid biopsy companies Guardant Health (Redwood City, Calif.) and GRAIL (Menlo, Park, Calif.), an Illumina spin off.

"Like any other diagnostic technology, liquid biopsy will require insurance coverage," explains Norris. "Widespread insurance adoption will require multiyear cost-benefit analyses. Early-stage cancer diagnoses reduce personal and financial burden, and we predict that the majority of insurers will cover these tests within the next five years."

- Other testing companies, including point-of-care test companies saw increased investment, particularly for infectious disease tests, albeit at smaller denominations, SVB says.
- Commercial-stage Dx analytics companies received early rounds of funding, reflecting the decreased risk associated with analytics, which don't require the same regulatory approval as testing companies.
- Investment in R&D tools companies was primarily reserved for commercial-stage companies, which have secured revenue-generating partnerships with large pharmaceutical or tools companies.

Who is Investing in Dx/Tools?

Generalist investors, in contrast to health care-focused investors, have quickly become the most active players since their emergence into the sector in 2015. This trend parallels the adoption of artificial intelligence technology. The top three generalist investors in the Dx/Tools sector include Data Collective (13 deals since 2015), khosla ventures (10 deals), and AME Cloud Ventures (nine deals).

SVB notes one challenge for companies attracting generalist investors is that they are accustomed to tech startups that have shorter development and commercialization timelines, compared to Dx/Tools companies. Interestingly, though, these investors appear to be more "risk-tolerant" than top health care investors, SVB says, investing in early-stage companies that still face regulatory and reimbursement hurdles.

Tech giants Amazon and Google have invested in the Dx/Tools sector and are trying to figure out how to integrate and leverage their computational resources in the health care industry.

"This is just the beginning, and we expect these giants to drive sector growth for the next decade," writes Norris. "They see the promise of an emerging ecosystem of companies that are focused on leveraging AI with genomic data to drive new diagnostic and treatment options. … Collaboration among tech and healthcare investors seems natural: It would create an enhanced team to take advantage of technical expertise and experience in health care market approval and adoption."

Despite the enthusiasm, Norris issues one cautionary note, writing, "The next few years will prove out the actual value of these technologies, as determined by key health care stakeholders (i.e., payers)."

DTET

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Generating Returns for Investors

Driven by heightened investment, valuations are also increasing in the sector.

- Dx/Tools now includes three unicorns, or companies valued at more than $1 billion — Human Longevity (San Diego), 23andMe (Mountain View, Calif.), and Illumina-spin out, Grail (Menlo, Park, Calif.).
- Four companies are categorized as "breakouts" with valuations between $500 million and $1 billion (e.g., Gingko Bioworks, Guardant Health, Natera, and Pathway Genomics). Interestingly, unicorns' investments are dominated by health care investors (67 percent), while breakout companies are dominated by generalist investors (66 percent).
- Standout companies, those valued between $250 million and $500 million, including 10x Genomics, AssureX Health, Color, Quanterix, Twist, and Zymergen, are even further dominated by generalist investors (76 percent) and is the only of the three categories to include R&D tools companies.

However, these "lofty" valuations are making it difficult for Dx/Tools companies to generate high-multiple returns for investors. Unlike years 2013 to 2016 when there were 42 exits in the sector (26 mergers and acquisitions [M&A] and 16 initial public offerings), there were no "big exits," valued at $50 million or more, occurring in the Dx/Tools sector in 2017, according to SVB. Historically, Norris writes, Dx/Tools M&A activity occurred in the range of $100 million to $200 million. But, he says, based on current valuations, "robust exit multiples will be difficult to achieve."

Nonetheless, Norris is optimistic.

"We think this investment activity may be a precursor to acquisitions and lead to a land grab that could provide significant exit upsides and end the current Dx/Tools exit drought," he writes.

Takeaway: Investor interest in the Dx/Tools sector is surging, driven by general investors' enthusiasm for next-generation sequencing, liquid biopsy, and AI.

Dermatology Conference Highlights Gene Expression Tests for Skin Cancer

Several companies presented findings at the American Academy of Dermatology's annual meeting (Feb. 16-18, San Diego) indicating that gene expression profiling is making inroads in clinical dermatology practice for informing diagnosis and biopsy decisions for melanoma.

Adhesive Patch Enables Skin Cancer Gene Expression Profiling

DermTech (San Diego) markets a noninvasive dermatology gene expression platform that uses adhesive patches to collect epidermal skin samples, rather than a traditional scalpel-based biopsy. The samples are shipped overnight without the need for special storage or handling. DermTech has shown that RNA suitable for analysis can be extracted from the patches for up to 8 days after sample collection with storage at ambient conditions. The shelf life of the biopsy kits is 3 years.

The company's Pigmented Lesion Assay (PLA) assesses gene expression consistent with melanoma, with results able to inform a clinician's decision to biopsy the suspicious lesion. The PLA assay is intended for use on pigmented lesions that meet at least one of the ABCDE melanoma classification criteria. The PLA assay detects the presence or absence of expression for two oncogenic genes, PRAME and LINC00518, which are both known to be elevated in melanoma.

At the American Academy of Dermatology's annual meeting DermTech presented several studies demonstrating the ability of noninvasive gene expression testing to differentiate melanoma from benign lesions. When assessing 103 histopathologically confirmed melanoma samples, PLA showed good accuracy with 97 percent reported as either PLA positive or mutation positive. Additionally, the assay was prospectively validated in 523 real-world PLA samples and accurately ruled out melanoma risk in pigmented lesions.

"The diagnosis of early-stage melanoma can be challenging histopathologically and has a discordance rate as high as 27 percent," said DermTech collaborator and study author, Clay Cockerell, M.D., of Cockerell Dermatopathology in Texas, in a statement. "This study demonstrated that gene expression and mutation analyses can provide valuable objective information when assessing difficult pigmented lesions."

Furthermore, DermTech assessed the potential cost savings of the PLA assay. The company said that the higher accuracy of the PLA versus use visual assessment and histopathology resulted in fewer unnecessary procedures and office visits, while "not compromising" melanoma detection.

Gene Expression Assay Informing Clinical Care

The use of a 31-gene expression profile test results in a change in the clinical management of melanoma patients in almost half of cases, according to a study presented at the American Academy of Dermatology's annual meeting. Furthermore, the company reported that the changes in patient management were appropriate and remained within the context of established practice guidelines.

Castle Biosciences (Houston) conducted a multicenter, prospective clinical impact study that included 247 patients from 15 dermatology, medical oncology or surgical oncology centers. Clinical impact of the DecisionDx-Melanoma gene expression test was assessed by examining laboratory tests, imaging, frequency of clinical visits, adjuvant treatment discussion, and plans for referral to surgical or medical oncology before and after test use.

Overall, the company found that nearly three-quarter of the patients had a Class 1 (low-risk) result (73 percent), while just over one-quarter had a Class 2 (high-risk) result (27 percent). In total, 49 percent of patients tested experienced a change in clinical management recommendations following the receipt of the DecisionDx-Melanoma test. However, change in management varied by risk. Class 1 patients showed a 36 percent post-test change in management plans, while 85 percent of Class 2 patients had a change in management following the DecisionDx-Melanoma test.

The company's found that 79 percent of management changes were "in a risk-appropriate direction." For example, 91 percent of decreases in care documented were for low-risk patients, while 72 percent of increases in care were provided for high-risk patients. The most significantly changed management practices were follow-up frequency and imaging.

"Across the different practice settings in this study, the DecisionDx-Melanoma test informed risk-appropriate patient management decisions, consistent with previous publications demonstrating that the test impacts one in two clinical management decisions," said Federico Monzon, M.D., Castle Biosciences' chief medical officer, in a statement. "These findings align with national guidelines, which recommend that a patient's individual risk of recurrence should drive management decisions."

Takeaway: There is mounting evidence that gene expression profiling may be useful for evaluating potentially cancerous skin lesions..

Genotype-Matched Diets Don't Aid Weight Loss

As most people who have ever tried dieting know, there is no single diet strategy that is consistently superior to others for the general population. Some have suggested that genotype or insulin-glucose dynamics may affect diet outcomes.

Despite the hope that genotype-matched diets may make weight loss easier, a new study published Feb. 20 in the *Journal of the American Medical Association* shows that genotype-tailored diets don't impact weight loss.

In the Diet Intervention Examining The Factors Interacting with Treatment Success clinical trial, 609 adults aged 18 to 50 years without diabetes and with a body mass index between 28 and 40, were randomized to either a 12-month HLF (n=305) or HLC diet (n=304). The study also tested whether three single-nucleotide polymorphism multilocus genotype responsiveness patterns or insulin secretion (INS-30; blood concentration of insulin 30 minutes after a glucose challenge) were associated with weight loss.

The researchers found that 40 percent of participants had a low-fat genotype, while 30 percent had a low-carbohydrate genotype. However, weight change at 12 months was −5.3 kg for the HLF diet and −6.0 kg for the HLC diet. Over 12-months of weight loss there were no significant diet-genotype pattern interaction or diet-insulin secretion (INS-30) interaction with 12-month weight loss.

"There is considerable scientific interest in identifying genetic variants that help explain interindividual differences in weight loss success in response to diet interventions, particularly diets with varying macronutrient compositions," write the authors led by Christopher D. Gardner, Ph.D., from Stanford University in California. "In the context of these two common weight loss diet approaches, neither of the two hypothesized predisposing factors was helpful in identifying which diet was better for whom."

Takeaway: Verifying patient-reported penicillin allergies with PST is feasible in routine care and can improve antibiotic stewardship.

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Tests Emerging to Advance Cardiovascular Risk Assessment

While testing for cardiovascular conditions does not garner the headlines that oncology testing does, several recent studies demonstrate how the introduction of genetic testing and other new testing methods can improve cardiovascular risk assessment and diagnoses. *DTET* highlights some recent testing developments in the field of cardiovascular medicine.

Common Variants Contribute to Early-Onset Coronary Artery Disease

Diagnostic workup of early-onset coronary artery disease (EOCAD) should include determination of a polygenic risk score resulting from the cumulative risk posed by a high number of common genetic risk variants, according to a study published Jan. 8 in *Circulation: Genomic and Precision Medicine*. The authors say that the combined effect of these common variants on coronary artery disease risk may be more prevalent than high heritability, monogenic disorders like familial hypercholesterolemia.

The study calculated a genetic risk score for 111,418 British participants from the UK Biobank cohort. The genetic risk score was based on the presence of 182 independent variants associated with coronary artery disease (GRS182). Genotyping used the Affymetrix UK Biobank Lung Exome Variant Evaluation Axiom array or the Affymetrix UK Biobank Axiom Array. Participants with documented obstructive coronary artery disease were identified through codes for coronary artery bypass grafting or coronary angioplasty with or without stenting.

The researchers found that 96 individuals from the large cohort had EOCAD (77 men and 19 women). Participants with a diagnosis of EOCAD had a significantly higher GRS182 compared to those without EOCAD. An increase of one standard deviation in GRS182 corresponded to an 84 percent increased risk or EOCAD. The prevalence of a polygenic contribution that increased EOCAD risk similar to those with familial hypercholesterolemia was estimated at 1 in 53. Individuals with documented obstructive CAD, regardless of age of onset, also had a higher GRS182 versus controls.

"The increase in genetic risk was independent of other known risk factors, suggesting that testing for multiple genetic differences is clinically useful to evaluate risk and guide management," said senior author Guillaume Paré, M.D., from McMaster University in Canada, in a statement. "Combining polygenic screening with current testing for familial hypercholesterolemia could potentially increase five-fold the number of cases for which a genetic explanation can be found."

Adding Genetic Test Helps Pinpoint Cause of Stroke

The vast majority of spontaneous intracerebral hemorrhages have no underlying macrovascular cause. However, certain types of stroke, namely lobar spontaneous intracerebral hemorrhages with cerebral amyloid angiopathy (CAA), are associated with a higher risk of recurrent stroke than those associated with arteriolosclerosis.

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> *"Identifying the cause of a brain hemorrhage is important to planning patient care."*
>
> — Mark A. Rodrigues, M.B.Ch.B.

New research suggests that adding a simple genetic test to a CT scan evaluation improves prediction of CAA-associated lobar intracerebral hemorrhage, which may ultimately impact treatment decisions.

The study included consecutive adult patients with first-ever intracerebral hemorrhage confirmed by CT. Two neuroradiologists independently evaluated reformatted head CT images. APOE genotype analysis was also conducted. CT and genetic features were used to inform development of a model for identifying lobar intracerebral hemorrhage associated with CAA.

The researchers found that participants with lobar intracerebral hemorrhage and moderate or severe CAA were significantly more likely to be APOE ε4 carriers. Additionally, these participants were significantly more likely to have specific CT characteristics, including a strictly lobar intracerebral haemorrhage, subarachnoid haemorrhage, and finger-like projections from the intracerebral hemorrhage than participants with lobar intracerebral hemorrhage and absent or mild CAA.

"Identifying the cause of a brain hemorrhage is important to planning patient care," says Mark A. Rodrigues, M.B.Ch.B., the lead author of the study. "Our findings suggest that the combination of routine CT scanning with APOE gene testing can identify those whose ICH has been caused by CAA, a group who may be more at risk of another ICH or dementia."

Novel, Adaptable Cholesterol Estimation Best in Nonfasting Samples

Novel adaptable low-density lipoprotein cholesterol (LDL-CN) estimation is more accurate in nonfasting patient samples than the classic Friedewald method (LDL-CF), according to a study published Jan. 2 in Circulation. This advantage is particularly noticeable in cases of low LDL-C and high triglycerides.

"In making evidence-based decisions about lipid-lowering therapy, clinicians and patients can place greater confidence in LDL-C results from nonfasting samples that are calculated with the novel method of LDL-C estimation compared with the classic Friedewald equation," write the authors led by Vasanth Sathiyakumar, M.D., from Johns Hopkins University in Baltimore, Md.

The study evaluated samples from 1,545,634 patients (959,153 fasting for 10–12 hours and 586,481 nonfasting) participating in the Very Large Database of Lipids study. Rapid ultracentrifugation was used to directly measure LDL-C content (LDL-CD). Accuracy was defined as the percentage of LDL-CD falling within an estimated LDL-C (LDL-CN or LDL-CF) category. The magnitude of differences between LDL-CD and estimated LDL-C (both methods) were stratified by LDL-C and triglyceride categories.

The researchers found that in both fasting and nonfasting samples, accuracy was significantly higher with the novel method across all clinical LDL-C categories,

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compared with the Friedewald estimation. For samples with LDL-C less than 70 mg/dL, nonfasting LDL-CN accuracy was significantly superior to LDL-CF accuracy (92 versus 71 percent). In this lower LDL-C range, 19 percent of fasting and 30 perecent of nonfasting patients had differences between LDL-CF and LDL-CD that exceeded mg/dL. In comparison, using the novel estimation, only 2 percent and 3 percent of patients, respectively, had similar differences.

Takeaway: Several recent studies demonstrate how the introduction of genetic testing and other new testing methods can improve cardiovascular risk assessment.

Molecular Testing Increasingly Adopted for Skin Cancer Diagnosis, *from page 1*

Researchers used a 15-question online survey in 2017 to assess how dermatopathologists are employing molecular testing and their opinions of the broader role and utility of molecular technologies in clinical practice.

Based on responses from 136 fellows of the American Society of Dermatopathology, the researchers found that the vast majority of respondents (94 percent) reported using one or more of the 10-queried molecular tests. Nearly two-thirds of dermatopathologists order 12 or more molecular tests per year, while 5 percent report ordering two or less assays per year.

The most commonly used molecular tests are T-cell and B-cell clonality studies (92 percent of respondents), BRAF gene mutation testing in melanoma (66 percent), and fluorescence in situ hybridization testing of melanocytic tumors (57 percent). The authors note that responses could not assess whether it was the dermatopathologist or a referring physician that ordered BRAF testing. Next-generation sequencing was amongst the least frequently used tests (16 percent).

The majority of respondents (87 percent) report using the test in order to "obtain a more objective and reproducible diagnosis," while approximately one quarter report malpractice or litigation concerns as a reason for ordering molecular tests.

Just over half of respondents (53 percent) report feeling either extremely or very confident incorporating the results of molecular tests into histopathological assessments. When asked about training in molecular technologies, just under one-third received education in medical school, while approximately two-thirds received instruction during residency and fellowship.

More frequent use of molecular testing was significantly associated with relevant instruction during residency training, primary board certification in pathology, affiliation with an academic medical center, higher volume clinical practice, and presence of on-site clinical molecular pathology/cytogenetics laboratory. Use of molecular testing was significantly lower for dermatopa-

thologists at "in-office" settings, compared to those practicing in a private lab or a department of pathology or dermatology. Interestingly, there was no association between numbers of molecular tests ordered and the provider's age.

Respondents' cited barriers to wider adoption of molecular testing in the practice of dermatopathology include: test costs (86 percent of respondents), physician knowledge and training (76 percent), and a lack of evidence-based clinical practice guidelines (70 percent). Additionally, logistical concerns, such as the amount of paperwork required and test turnaround times, were also reported as challenges.

"Dermatopathologists are ideally suited to play a supportive role in translating molecular and genomic data into clinical care," write the authors led by Kristin Torre, from the University of Connecticut in Farmington. "In order to provide guidance to dermatologists and other clinicians, dermatopathologists must acquire a broad working knowledge of available technologies, including their clinical utility, advantages, limitations, cost-effectiveness, and evolving applications in the management of skin diseases."

For more information on the use of specific gene expression tests for melanoma see p. 3.

Takeaway: Adoption of molecular testing for the diagnosis of skin cancers is more heavily concentrated in academic and high-volume practice settings.

FDA Set Record in 2017 for Targeted Therapy Approvals

For the he fourth consecutive year, targeted therapies accounted for more than 20 percent of all new drug approved by the U.S. Food and Drug Administration (FDA), according to the Personalized Medicine Coalition's (PMC's) recently released its 2017 Progress Report, *Personalized Medicine at the FDA*. In 2017, the FDA approved 16 new molecular entities—34 percent of all new drugs, agents, or therapeutic biologics approved in 2017.

"Even the large number of newly approved therapies classified as personalized medicines in 2017 does not provide the whole picture," writes PMC in the report. "The growing list of personalized medicines available to doctors and their patients also includes many significant new personalized medicine indications for [15] previously approved drugs in 2017."

PMC specifically highlights the importance of the expanded approval of Keytruda (pembrolizumab) for all solid tumor types in advanced cancers with microsatellite instability-high or mismatch repair deficiency (is particularly significant as it marks the first time an oncology drug has been approved based on a biomarker, regardless of where the tumor is located in the body.

As DTET has previously reported, PMC also highlights other "significant" FDA approvals, including the first:

- Authorization for marketing of health-related genetic tests directly to consumers—23andMe's Personal Genome Service Genetic Health Risk tests.

- Approval of personalized medicine biosimilar for Herceptin (trastuzumab), which was first approved for HER2-positive breast cancer in 1998.
- Joint approval and coverage decision with the FDA and the Centers for Medicare and Medicaid Services for Foundation Medicine's FoundationOne CDx test, which uses next-generation sequencing technology.

"While ongoing challenges in the areas of scientific discovery, diagnostic regulatory policy, coverage and reimbursement, and implementation of new technologies into clinical practice are still outstanding," PMC writes, "the science leading health care away from one-size-fits-all, trial-and-error medicine and toward the utilization of molecular information to improve outcomes and make the U.S. health system more efficient is clear."

Takeaway: The FDA's record number of personalized medicine-related approvals in 2017 shows the commitment by the pharmaceutical and diagnostic industries, as well as the FDA, towards advancing targeted treatments.

Speed Record Set for Whole-Genome Sequencing

Stephen Kingsmore, M.D., D.Sc., and his team at Rady Children's Institute for Genomic Medicine (San Diego) were awarded the Guinness World Records title for fastest genetic diagnosis on Feb. 3 with a time of 19.5 hours. Kingsome set the previous record of 26 hours in 2015, while at Children's Mercy (Kansas City, Mo.).

"Our evolving ability to find the answers to medical mysteries through rapid whole genome sequencing is providing hope for babies and children with rare, genetic diseases," said Kingsmore, president and CEO of Rady's, in a statement. "By speeding delivery of genomic insights, we are equipping physicians with the information they need to provide precision care for the youngest and most fragile patients."

Rady's sequencing workflow is engineered to both accelerate and scale up genomic data interpretation—reducing the time and cost of whole genome sequencing. The institute says that up to one-third of babies admitted to a neonatal intensive care unit in the United States have a genetic disease, with treatment currently available for more than 500 of these genetic diseases. Quick initiation of therapy in newborns can help prevent disabilities and life-threatening illnesses associated with 70 of these conditions.

The institute began performing genomic sequencing in July 2016. By the end of January 2018, the team reports having completed testing and interpretation of the genomes of more than 335 children enrolled in its research studies. Additionally, the institute reports that one-third of the patients received a genomic diagnosis with 69 percent of those benefitting from an immediate change in clinical care.

Work is now focused on building a research-to-bedside pipeline extending from Rady's to children's hospitals nationwide. "Our hope is that pediatric

genomic medicine will one day become routine so that ultimately all children who need it can have access to this life-saving technology," says Kingsmore.

The record-setting analysis involved a collaboration between Rady and other technology and data-science companies. Together, the team optimized an "ultra-rapid, accurate, and scalable process" by integrating several time-saving technologies that shaved 6.5 hours off of the previous record. Partners included:

- Illumina (San Diego) - The Rady's team used Illumina's NovaSeq 6000 Sequencing System, a new generation of high-density flow cells that enable reassemblage in digital form, and the Nextera DNA Flex library preparation.
- Clinithink (Alpharetta, Ga.). Clinithink has a natural language processing platform that automatically extracts crucial phenotype information from a patient's electronic medical record.
- Diploid (Belgium) - Diploid's Moon variant interpretation software uses artificial intelligence to spot genetic mutations within sequenced genomic data and make a preliminary diagnosis of rare diseases in about 4 minutes.
- Edico Genome (San Diego) - Edico Genome's DRAGEN (Dynamic Read Analysis for GENomics) platform provides ultra-rapid sequence alignment and variant calling significantly increasing the speed of secondary analysis.
- Alexion (New Haven, Conn) - Alexion provided rare disease and data science expertise that enabled the translation of clinical information into a computable format for guided variant interpretation.
- Fabric Genomics (Oakland, Calif.) - Fabric's clinical decision support software, OPAL, enabled rapid diagnosis by helping to find the correct genetic cause of illnesses.

Takeaway: The increasing speed of whole-genome sequencing is bringing the prospect of its use for rapid clinical diagnostics closer to reality.

Testing Guidelines at a Glance

Updated Testing Guidance for Targeted Tyrosine Kinase Inhibitors

Updated testing guidelines for testing related to targeted tyrosine kinase inhibitor treatment for lung cancer were recently published in the *Archives of Pathology & Laboratory Medicine*. The guidelines were a collaboration of the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology.

The guidelines serve to update 2013 evidence-based guideline was published by the same groups. An expert panel was convened to systematically review the new evidence regarding additional laboratory technologies, targetable genes, patient populations, and tumor types for testing.

The panel wrote that the 2013 guideline was "largely reaffirmed" with updated recommendations to allow testing of cytology samples, require improved assay sensitivity, and recommend against the use of immunohistochemistry for EGFR testing. Eighteen new recommendations include:

- ROS1 testing for all adenocarcinoma patients
- Inclusion of additional genes (ERBB2, MET, BRAF, KRAS, and RET) for laboratories that perform next-generation sequencing panels
- Immunohistochemistry as an alternative to fluorescence in situ hybridization for ALK and/or ROS1 testing
- Use of 5% sensitivity assays for EGFR T790M mutations in patients with secondary resistance to EGFR inhibitors
- Use of cell-free DNA to "rule in" targetable mutations when tissue is limited or hard to obtain.