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New Trends, Applications, and IVD Industry Analysis

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2015 Had Promising Signs Amid Tough Fundraising Climate for Dx Cos

Last year was a "banner" year for investment activity in the health care industry. Overall, in 2015, venture capital (VC) investment in health care hit a 15-year high, reaching roughly $59 billion. The picture was particularly bright for the biopharma sector, which saw record VC investment, even at the earliest of stages, along with increases in mergers and acquisitions (M&A). The diagnostics and tools sectors lagged significantly behind biopharma in both of these measures. Silicon Valley Bank's report, *Trends in Healthcare Investments and Exits 2016*, along with *DTET* interviews with analysts, point to some continuing investor concerns over diagnostics and tools sectors, but with some emerging signs of optimism.

"The two things that are bothering almost everybody are a lack of certainty around reimbursement and the lack of certainty around regulation," says Harry Glorikian, a diagnostics industry consultant and director of the Diagnostics Marketing Association. "If you look at the proposed regulations and you look at your assay, you should have an idea where you fall, and hopefully you are planning ahead. But, ideally the FDA will put a stake in the ground so that investors and companies can understand the rules of engagement. We might not like them, but we will have the marching orders or you may have some companies decide it is so expensive, we can't play this game."

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Testing Trends to Watch for in 2016

The last year saw a continuation of several testing trends including further expansion of molecular testing and reliance on larger panels, rather than single gene testing, in areas like testing for hereditary cancer predisposition. Uptake of next-generation sequencing-based testing also continued in 2015, particularly in the areas of oncology—where more targeted therapeutics were approved—and non-invasive prenatal testing.

Without a doubt, these trends will continue, fostered by completion of more studies generating evidence of clinical utility and cost effectiveness, and greater integration of molecular testing recommendations into professional society's clinical practice guidelines. In addition to technology-driven testing trends, consumer preferences will shape laboratory testing and volumes.

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2015 Had Promising Signs Amid Tough Fundraising Climate for Dx Cos, *Continued from top of p.1*

VC-Early Investment Down, But New Funds Entering

Unlike in biopharma, which saw an increase in early-stage funding (97 deals in total), the diagnostics and tools sectors saw a sharp decline in series A investments from 45 deals in both 2013 and 2014 to only 17 in 2015. On the positive side, some larger venture capital investors, traditionally more active in other sectors, like WuXi Venture Fund and Morningside Group, made some bets in the diagnostics and tools industries. Silicon Valley Bank's Jonathan Norris, lead author of the report, tells *DTET* he anticipates seeing some "stabilization" in early-stage funding of diagnostics and tools companies in the coming year, but points out a third area of concern for investors looking at the space—intellectual property protections.

> *"As an investor it is difficult to look at these three challenges and understand how to get to a return in a reasonable amount of time."*
>
> —Jonathan Norris, Silicon Valley Bank

"As an investor it is difficult to look at these three challenges and understand how to get to a return in a reasonable amount of time," Norris says. "These three inputs lead to question marks and question marks need more time and more money. It is difficult to predict how to get a decent return with these question marks."

Exits Declined for Diagnostics/Tools in 2015

Investors realize their returns when companies are able to "exit" either through M&A or an initial public offering (IPO). Last year both M&As and IPOs declined in the diagnostics and tools sectors, according to Silicon Valley Bank analysis. However, experts predict an uptick in M&A in the diagnostics industry in 2016.

"We are seeing new companies created over the last few years that have a different makeup than those created six, eight, or ten years ago," Norris explains. "Back then there was a lot of promise in the market, but there were some things in the market that needed to develop and these developments took time and cost early entrants. Now companies are more cost effective at developing the technology and with their capital structure and number of employees."

This "capital efficiency" led to a significant decline in time-to-exit in 2015 in the diagnostics/tool sectors. Years to exit reached the lowest since 2010 with a median of 3.5 years.

Sampling of Top $ Diagnostics Acquisitions, 2015

- Danaher bought water filter maker Pall for $13.8 billion
- OPKO Health acquired Bio-Reference Laboratories for $1.47 billion
- Roche purchased molecular microbiology company GeneWEAVE Biosciences for $425 million
- Thermo Fisher Scientific acquired reagent maker Alfa Aesar for $403 million
- Agilent Technologies purchased cell metabolism tool maker Seahorse Bioscience for $235 million in cash

Norris says he expects to continue to see a "barbell" look to acquisitions with activity among these efficient, emerging companies and also among more mature, commercial stage companies that may not have enough revenue to be IPO candidates, but are finally breaking even.

For instance, analysts expect Thermo Fisher to be a big newsmaker this year, even after its January announcement that it purchased Affymetrix for $1.3 billion. Analysts anticipate seeing a continued trend of "tuck-in M&A" in 2016, particularly among smaller, specialty diagnostics companies, which offer the potential for higher-margin, higher-growth testing.

Takeaway: Analysts expect to see an uptick in M&A activity in the diagnostics and tools sectors this year, along with a continuation of tight VC investment capital in early-stage companies.

Testing Trends to Watch for in 2016, *Continued from bottom of p.1*

Consumerization Driving Shift in Testing

With patients now responsible for a larger share of their health care bills, including laboratory charges, they are taking a closer look at their testing needs. Laboratories may, over time, see shifts in volumes away from traditional testing settings towards those that cater to convenience and cost, including those offering testing in retail establishments, direct-to-consumer testing, and expanded over-the-counter, point-of-care testing kits.

The trends of patient empowerment and the consumerization of health care converge in the area of direct-to-consumer laboratory testing. Interest in tests is not limited to the more controversial direct-to-consumer genetic testing (now limited to traits, carrier status, or ancestry, and not pharmacogenomics or disease risk), but there is growing interest in more traditional laboratory tests rooted in wellness and prevention.

In 2016, look for further growth of laboratories like Health Check USA, WellnessFX, and Direct Labs on the traditional testing side. In the direct-to-consumer genetic testing space, 23andMe announced at the January JP Morgan Healthcare Conference (San Francisco; Jan. 11-14) that it will launch additional health reports with U.S. Food and Drug Administration clearance this year. Despite progress from 23andMe, there has not been definitive direction in how the U.S. Food and Drug Administration plans to oversee direct-to-consumer genetic testing. Expect further letters and potential conflict between the agency and some laboratories engaging with consumers without approval (Pathway Genomics, DNA4Life, and DNA-CardioCheck).

Liquid Biopsy

No list of trends to watch for this year would be complete without mention of liquid biopsy testing. While consumer-driven testing may focus on more basic tests, liquid biopsy technology is moving forward toward ever more sensitive detection and towards greater overall growth.

Emerging platforms are enabling capture of rare, circulating cells or cell-free DNA (see *Inside the Diagnostics Industry* in *DTET*'s January 2016 issue). But, 2015 was a breakthrough year in demonstrating the clinical utility of these tests. In 2016, look for movement towards expanding non-invasive prenatal testing to average-risk markets, clinical adoption of liquid biopsy for multiple applications in oncology monitoring by companies like Guardant Health, Exosome Diagnostics, and Trovagene, and further emergence of the technology in post-organ transplantation surveillance. The year also began with a large announcement that Illumina is spinning off and heavily investing in Grail ($100 million raised), which will develop a pan-cancer screening test. In 2016, look for more companies applying liquid biopsy technology towards development of pan-cancer screening, but commercialization is likely several years away. (See *Inside the Diagnostics Industry* in this issue to learn about Chronix Biomedical's One Test). Liquid biopsy for oncology monitoring is a much more "mature" application.

Takeaway: Look for signs of a shift away from traditional testing settings, especially for basic laboratory testing, as well as an increase in patient-directed wellness testing. On the advanced technology side, liquid biopsy technology will continue to permeate clinical care in 2016, particularly for oncology and transplantation monitoring. G2

PCT Effective to ID Invasive Bacterial Infection in Febrile Infants

Aprocalcitonin (PCT) assay has better diagnostic accuracy than C-reactive protein (CRP) concentration, white blood cell (WBC) count, and absolute neutrophil cell (ANC) measurement for detecting invasive bacterial infections (IBIs) in febrile infants less than 3 months of age, according to a study published in the January issue of *JAMA Pediatrics*. Both PCT and CRP perform similarly for identifying severe bacterial infections (SBIs) in these infants, although urinalyses may be adequate to detect urinary tract infections (UTIs), which account for the majority of these SBIs.

"Although it would be unwise to use the PCT assay alone, combined with careful analysis of the case history, physical examination, and appropriate tests, it provides important information for the detection of IBIs in this population," writes lead author Karen Milcent, M.D., from Paris-Saclay University in France.

Given that there are few diagnostically reliable symptoms or clinical signs and these signs are often indistinguishable from viral infection in young infants, a complete sepsis evaluation, empirical antibiotic therapy, and hospital admission are recommended for febrile infants up to one month of age and are common for those between one and two months of age, the authors say. Evaluation of PCT assays have been lacking in infants less than 3 months.

The French researchers prospectively evaluated infants aged 7 to 91 days (n= 2,047) consecutively admitted for fever to 15 French pediatric emergency departments (Oct. 1, 2008 through March 31, 2011). The researchers found that 6.8 percent of infants were diagnosed with SBIs, while one percent had IBIs. Blood cultures identified 11.0 percent and 1.7 percent of those infections, respectively. The most common SBIs were UTIs (115 of 139). Of the IBIs, there were 13 cases of bacteremia and eight cases of bacterial meningitis.

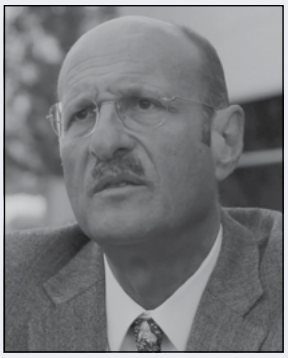
The PCT assay offered an area under the curve (AUC) similar to that for CRP concentration for the detection of SBI (0.81 versus 0.80, respectively). However, the AUC for the detection of IBI for the PCT assay was significantly higher than that for the CRP concentration (AUC, 0.91 versus 0.77, respectively). Using a cutoff value of 0.3 ng/mL for PCT and 20 mg/L for CRP, negative likelihood ratios were 0.3 for identification of SBI and 0.1 and 0.3 for identifying IBI, respectively. Similar results were seen for infants younger than one month of age and for those with recent fever onset (less than 6 hours).

"Our results suggest that it may be possible to improve clinical practice for the treatment of young febrile infants," write the authors "Although our optimal PCT threshold is calculated in isolation and may be different in the multivariable model, one advantage of our results may be the potential to avoid lumbar puncture, particularly in patients older than 1 month with a PCT level less than 0.3 ng/mL."

Takeaway: This study provides evidence that PCT assays have better diagnostic accuracy than CRP for detecting IBI in very young febrile infants. G2

Inside The Diagnostics Industry

Chronix Uses cfDNA to Change Screening for Common Cancers



Howard Urnovitz, Ph.D., CEO, Chronix

Molecular testing firm Chronix Biomedical (Germany and San Jose, Calif.) has set out to change the face of cancer diagnostics on several fronts. Its Second Opinion line of tests is currently available in Europe to improve the accuracy of existing screening methods for prostate cancer and breast cancer. Additionally, the company is currently validating both a pan-cancer screening test, One Test, and an organ transplant rejection test, all based on the principles of utilizing circulating cell-free DNA (cfDNA) as an early sign of changing cellular dynamics in the body.

DTET recently spoke with Howard Urnovitz, Ph.D., the CEO and co-founder of Chronix about the company's plans to commercialize the tests in the United States.

Your Second Opinion cfDNA-based tests initially target two common cancers—breast and prostate. Why target these cancers as an initial strategy?

Chronix Biomedical chose to start with prostate and breast cancer because we saw the trend of negative reports about the current screening tests of PSA and mammograms. These two early screening tests both have low accuracy leading to many misdiagnoses. We believe by adding a blood genetic test to the screening protocol we can increase the accuracy of the current test practices and reverse the trend back to supporting early detection.

Tell us about the role Second Opinion tests can play in routine clinical decision making as supplementary tests.

We built these as laboratory-developed tests (LDTs). Our Second Opinion laboratory report indicates whether a patient's cfDNA matches the cancer fingerprints in our database. One section of the report summarizes the exact regions on the human chromosome where a patient's cfDNA may or may not correlate with the database. In another section, the report gives an overall copy number instability (CNI) score on whether a sample is outside the range of 97 percent of our healthy control database. These additional data points, along with clinical history and other laboratory results, assist physicians in making important medical decisions.

Some physicians are using the Second Opinion test for surveillance of men with elevated PSAs under "wait and watch." Men with elevated PSAs, but no Second Opinion correlation, can be regularly monitored to see if any cancer fingerprints ever appear. Second Opinion can limit the number of cancer-free individuals going for unnecessary tissue biopsies.

The Second Opinion testing also addresses the significant level of overtreatment of prostate cancers that are indolent or slow-growing. Indolent prostate cancer is usually not a threat to a man's lifespan or health. Second Opinion provides a quantitative and qualitative report on whether the amount of cfDNA is increasing in the blood and whether the pattern of the cancer fingerprints is changing, suggesting that the tumor is changing.

Inside The Diagnostics Industry

What is the economic case for using Second Opinion tests?

Approximately one million prostate biopsies in the United States are false positives. If the prostate biopsy costs between $1,500 and $2,000, we are wasting up to $2 billion a year in unnecessary biopsies. The costs are much higher if you add in the ancillary costs of complications from infection, incontinence, or erectile dysfunction as a consequence of unnecessary biopsies. We estimate that our testing protocol will cost less than $2 billion a year and therefore lower the costs to the health care system, while minimizing the anxiety associated with biopsy procedures.

"We don't believe the evidence supports the notion that cancer is a disease defined by single nucleotide polymorphisms. Cancer is a disease of CNIs."

—Howard Urnovitz, Ph.D., CEO, Chronix

Chronix has stated that its cancer biomarkers relate to the "earliest" signs of genomic instability and are present, regardless of the cell of origin. Does this signal the potential for a future pan-cancer screening test using cfDNA?

Chronix Biomedical is currently in multiple discussions to conduct large validation and economic health studies on its One Test. Our design goal is for one blood test for the 17 types of cancer that cause the highest economic burden to the health care system. Currently, we have completed studies on samples from 11 different types of cancer and were successful in detecting cancer cfDNA in all 11 cancer types. We are expanding the test to include 17 cancers in our evaluation study.

We don't believe the evidence supports the notion that cancer is a disease defined by single nucleotide polymorphisms. Cancer is a disease of CNIs. We are the only company we know of that is reporting on CNI scores and genomic positions. Our evaluation study will be testing 500 samples of each cancer plus matching controls for 17 cancers. We are looking at a 17,000-person validation study to generate the data. We anticipate no lower than 90 percent accuracy for most cancers. We will submit the One Test data to the U.S. Food and Drug Administration (FDA) and work as hard and quickly as we can to obtain approval.

You say you will submit the One Test to the FDA for approval. Please explain Chronix's regulatory strategy.

We will have to obtain FDA clearance because the test is informing an individual for the first time they may have a specific cancer. Previously, I successfully completed a 26,000-person FDA clinical study for a urine test for HIV. I know what it takes to undertake big studies that have big implications. For AIDS testing, when you are telling somebody for the first time they have HIV, those are serious medical claims that need to have the support from FDA clinical trials. I believe that informing an individual that they may have a specific life-threating cancer would also require similar FDA clinical trials.

One thing particularly interesting about Chronix is its interest in applying cfDNA-based technology outside of oncology. Can you tell us about the development of the cfDNA test for transplantation rejection?

We continue to conduct validation studies of our organ transplant efficacy tests. We published the first results from our heart and kidney transplant studies. Our multicenter

Inside The Diagnostics Industry

trial in liver transplantation has been completed and the manuscript is in preparation. The performance of a test for the detection cfDNA from cells of a transplanted liver that is being rejected by a patient is highly superior with an area under the curve (AUC) of about 97 percent, compared to conventional liver testing such as aminotransferases, bilirubin and gamma-glutamyl transferase, which showed AUCs between 0.79 and 0.90. Our plan is to finish our validation studies on liver, heart and kidney and seek regulatory approvals.

Early detection of cancer is essential because it is easier to put out a match than a forest fire.

This is a very different technology from our cancer testing next-generation technology. Professors Schütz and Oellerich had been studying transplant biomarkers for two decades, before joining with Chronix Biomedical. Our team came up with a way to combine a panel of primers so that within minutes we can determine which cfDNA biomarkers are organ-specific and which markers are host. It is clearly more powerful than currently used markers. Our test allows a physician to know whether an organ is being rejected at the earliest time point possible, giving the highest probability for success in not losing the transplanted organ. The Chronix test is clearly more effective in treating a patient than currently used markers.

How important are economic trials to driving commercial adoption and reimbursement for liquid biopsy tests? What are your commercialization plans in the United States?

Large prospective studies with key opinion leaders are necessary to show clinical utility with the goal of becoming a standard of care and obtaining reimbursement. Chronix expects to conclude its Second Opinion prostate cancer evaluation study on 1,500 men with elevated PSA in 2016. We will use this data to offer the test as an LDT in the United States from a CLIA-certified lab. The company will work with health care insurers to obtain reimbursement for the test.

After ASCO this year, we will begin validation studies on our One Test for cancer. We are actively raising additional funds for the One Test study, which we estimate, will cost $50 million and take 4 years to complete.

Chronix Biomedical By-the-Numbers

- 2 patents issued, 6 patents pending
- 5 tests in product line
- 9 peer-reviewed publications on cfDNA diagnostics
- 20 employees
- $34 million equity capital raised to date

Chronix is a pioneer in cfDNA diagnostics. We were the first to match cell-free nucleic acids with the human genome in a paper published in 1998. In 2008, we were the first to publish that we could use next-generation sequencing as a liquid biopsy for cfDNA using an animal model. In 2010, we confirmed its utility as a liquid biopsy for breast and prostate cancer cfDNA.

Early detection of cancer is essential because it is easier to put out a match than a forest fire. Cancer diagnostics need to create more early-stage success stories and decrease the cost of continuing care from $120 billion to a more sustainable number. I believe we can reach these objectives with the use of Chronix Biomedical technology.

Paper-Based Test May Increase Male Fertility Self-Testing

A paper-based assay can provide quantitative measurement of live and motile sperm concentrations and motility, in only 10 minutes, according to a study published online Jan. 8 in *Clinical Chemistry*. This approach, the authors say, is as accurate as laboratory-based methods and could promote over-the-counter self-diagnostic testing among men, embarrassed to seek clinical testing.

The authors say that up to half of infertility globally is caused by male factors. They believe this paper-based microfluidic test can improve upon costly and complex conventional testing (counting chambers, computer-assisted sperm analysis [CASA], and vitality assays such as dye exclusion or hypotonic swelling), as well as existing commercially available home microfluidic-based semen analysis tests—which are hampered by prolonged multistep processing, lack of quantification, reliance on the end-user interpretation, and measurement of only one semen parameter.

The authors say the simple design and fabrication make the test low cost, with total material costs of approximately $0.05 per device.

"All these current semen analysis techniques suffer from limitations that prevent their widespread application: testing procedures are long and complex and require expensive equipment, and the results are subjective, varying from clinician to clinician. … A low-cost and rapid test for semen analysis, suitable for both clinical and self-diagnosis, would have substantial implications for patient care, write the authors led by Reza Nosrati, from University of Toronto in Canada. "Our paper-based technology is an attractive alternative to conventional laboratory testing, with additional potential for self-screening of male fertility potential."

This paper-based device (multilayer porous composite) measures the diaphorase flavoprotein enzyme (present in metabolically active human sperm) through colorimetric change of yellow tetrazolium dye to purple formazan to quantify live and motile sperm concentration. A detectable color change on the readout indicates sufficient fertility potential. Optimal operating parameters include 4-mm diameter reaction spots, 3-µL sample volume, and 10-minute reaction time.

Fresh human semen samples from five patients and 12 healthy donors were analyzed using the paper-based assay as well as a conventional CASA system for concentration and motility, and a dye exclusion assay for sperm vitality.

The researchers found the paper-based assay had detection limits of 8.46 and 15.18 million/mL for live and motile sperm concentrations, respectively. The live and motile sperm concentrations and motility values correlated 100 percent with those of the standard clinical approaches. Additionally, the device was determined to be so robust and could tolerate conditions of high absolute humidity (22.8 g/m^3) for up to 16 weeks when packaged with desiccant.

The authors say the simple design and fabrication make the test low cost, with total material costs of approximately $0.05 per device. Sinton tells *DTET* that his group is conducting further validation in partnership with a leading urology lab and fertility clinic. He is aiming for either direct commercialization and/or licensing that will make products available in the next few years.

Takeaway: A paper-based assay capable of measuring three common sperm parameters in a self-test format could substantially impact care for male fertility.

Mass Spec Use Expanding Throughout Clinical Laboratory Medicine

Mass spectrometry (MS) is rapidly transitioning from specialized clinical testing—drugs of abuse confirmations, newborn screening, and steroid analysis—to being broadly applied throughout clinical laboratory medicine. A special January issue of *Clinical Chemistry* was dedicated to exploring current uses of MS in clinical laboratories, challenges to employing the technology, and emerging areas of potential advancement.

Interest in MS is driven by its analytical specificity and sensitivity. In clinical laboratories, MS is being used for detection of small molecules (biogenic amines, amino acids, and organic acids) and larger compounds (proteins and ribosomal RNA). Its use has penetrated most areas of laboratory medicine including microbiology, anatomic pathology, genetic disorders and pharmacogenetics, immunology, endocrinology, and toxicology.

Despite the widening adoption of clinical MS, real challenges remain to expanded application. Among the areas experts say that improvements can be made are: increasing ease of use, including, cutting sample prep and better connectivity to automation and laboratory information systems/laboratory information management systems; bringing down the high capital cost of equipment ($200,000 to $500,000); addressing lack of automation which necessitates a skilled labor force (especially for design and validation of laboratory-developed tests); and resolving regulatory uncertainty. In addition to the general regulatory uncertainty around laboratory-developed tests, MS experts say that there is a lack of U.S. Food and Drug Administration- (FDA-) approved methods leading to differences in MS methods between laboratories affecting reproducibility, as well as existing variance in data libraries.

"Until MS becomes 'just another detector' on an automated FDA-approved platform, the full benefit of the technology will not be realized," write Paul J. Jannetto, Ph.D., from the Mayo Clinic, Rochester, Minn. and Robert L. Fitzgerald, Ph.D., from University of California, San Diego, in a review in the Clinical Chemistry special issue.

While some of these issues are being addressed, manufacturers and researchers are exploring new areas of opportunity for MS to expand, including direct tissue analysis, point-of-care feasibility, and application to proteomics and genomics.

Takeaway: MS has made huge strides in the clinical laboratory in the past several years and further applications are expected, particularly as MS equipment advances to include simpler sample prep, better ease of use, and a smaller footprint.

Cost Effectiveness of Nail Fungus Confirmatory Test Treatment-Specific

Recommendations for universal confirmatory testing of toe nail fungus before systemic therapy should be replaced with therapy-specific recommendations, according to a study published Dec. 23, 2015 in *JAMA Dermatology*. The cost effectiveness of testing, the authors say, should be reconsidered in light of new drug pricing.

The new study found that empirical treatment with terbinafine for all patients with suspected onychomycosis is more cost-effective than confirmatory testing across all prevalence of disease, with "minimal" effect on patient safety. However, confir-

matory testing before treatment with the new drug efinaconazole, is associated with cost savings, given the drug's high price tag.

Standard confirmatory testing was established in international guidelines based on cost-effectiveness studies from the 1990s. But since that time, the cost of treatment has changed dramatically. A full 12-week course of terbinafine dropped in cost from $547 in 1999 to $10 today, the authors say, while the novel topical solution efinaconazole, 10%, costs $2,307 for full treatment of one nail.

"Confirmatory testing for onychomycosis still has a place in clinical care. The emergence of efinaconazole, 10%, as a novel and expensive agent for the treatment of onychomycosis reinforces the value of confirmatory testing in an era of cost-containment."

—Anar Mikailov, M.D.

The researchers evaluated three approaches to onychomycosis evaluation before treatment with oral terbinafine or efinaconazole, 10%: empirical therapy without confirmatory testing; pretreatment confirmatory testing with potassium hydroxide (KOH) stain followed by periodic acid–Schiff (PAS) evaluation if KOH testing is negative; and pretreatment testing with PAS. Cost analyses were modeled for prevalences of 30 percent, 60 percent, 75 percent, and 90 percent. National reimbursement values were used to establish costs for KOH stain prep in the office ($6), PAS test ($148), and liver enzyme monitoring (aspartate aminotransferase, $21 and alanine aminotransferase, $22).

The study found that the cost for immediate treatment with terbinafine was lower than the cost for either of the testing strategies across all disease prevalences. At a disease prevalence of 75%, per-patient cost savings of empirical terbinafine therapy without confirmatory testing was $47, compared with the KOH screening model and $135 compared with PAS testing. In contrast, testing before treatment with efinaconazole, 10%, was associated with cost savings across all disease prevalence, with higher savings at a lower prevalence. At a disease prevalence of 75 percent, the savings of testing versus empirical therapy was $272 per nail with the KOH screening algorithm and $406 of savings per nail treated with the PAS algorithm.

"Although adverse events from inappropriate treatment with terbinafine for patients without onychomycosis is a concern, our analysis demonstrates that current testing paradigms create a substantial cost burden and require between $9.62 million and $233.89 million in testing costs to avoid one case of clinically apparent liver injury," write the authors led by Anar Mikailov, M.D., from Brigham and Women's Hospital in Boston, Mass. "Confirmatory testing for onychomycosis still has a place in clinical care. The emergence of efinaconazole, 10%, as a novel and expensive agent for the treatment of onychomycosis reinforces the value of confirmatory testing in an era of cost-containment."

Takeaway: The cost-effectiveness of confirmatory testing before initiation of treatment for onychomycosis is largely driven by drug costs and treatment-specific recommendations should be followed for confirmatory testing. G2

Labs Must Weigh Economics of ALK Mutation Testing Strategies

Antibodies for immunohistochemistry (IHC), fluorescent in situ hybridization (FISH) probes and labor drive the cost of testing for anaplastic lymphoma kinase (ALK) mutations in lung cancer patients. Given the increasing availability of molecularly targeted therapies and the accompanying reliance on genetic mutational analysis, laboratories need to identify the most cost-effective testing approach for their setting, say the authors of a study published Jan. 6 in *Diagnostics*.

Professional society guidelines support testing for ALK mutations. Many studies have evaluated the inter-test concordance between FISH, the standard method to directly detect ALK rearrangements, and IHC, which detects aberrant proteins resulting from rearrangements. But, little attention has been given to comparing the testing strategies in terms of cost and workflow for laboratories.

"We recognize that there are differences in the choice of antibodies, probes, platforms, level of automation, and involvement of laboratory staff, all of which would have an impact on the cost of different ALK testing strategies."

—Shivang Doshi, Boston Healthcare Associates

The researchers developed a cost-impact model that compared four alternative testing strategies—IHC only, FISH only, IHC pre-screen followed by FISH confirmation, and parallel testing with both IHC and FISH. Key model inputs were derived from a review of the literature and interviews. U.S. IHC and FISH reimbursement rates were based on the Medicare physician fee schedule. Given variance in European markets, the average payment on a per test basis was determined from laboratory interviews.

Ten laboratories were interviewed (three in the United States, three in Germany, two in Spain, one in France, and one in the United Kingdom). Their annual lung cancer-specific ALK testing volume ranged from 150 to 1,500 in the United States and from 200 to 3,600 among European laboratories. Interviews captured information on ALK testing techniques and materials, test volumes, batch size, test configuration (platforms, kits, etc.), average turn-around times, assay workflow, and use of resources/supplies—reagents (anti-ALK antibodies for IHC and probes for FISH), consumables, equipment (light or fluorescent microscopes, automated processors), and personnel (technicians and pathologists).

The researchers found that the IHC alone was the least expensive approach, overall (average cost per sample of $90.07 in the United States and $68.69 in Europe). The IHC FISH parallel strategy (both methods on all patients) is the most expensive (average cost of $441.85 in the United States and $279.46 in Europe). In both locations, the IHC reflex FISH strategy, in which FISH is performed only on patients who test positive by IHC, is only slightly more expensive than the IHC only strategy. IHC and FISH protocols overlap in some aspects of workflow, such as slide sectioning, processing, incubation (with either anti-ALK antibody or FISH probe), and visualization under light (IHC) or fluorescent (FISH) microscope, however, the researchers found that in practice, turnaround time for ALK analysis varies widely.

"We recognize that there are differences in the choice of antibodies, probes, platforms, level of automation, and involvement of laboratory staff, all of which would have an impact on the cost of different ALK testing strategies," write the authors led by Shivang Doshi, from Boston Healthcare Associates (Massachusetts). "Hence, the total cost of the different ALK strategies will change depending on factors listed above, though it is unlikely to have an impact on the directionality of our findings from the model."

Takeaway: Given the differences in testing costs, turnaround time, and reimbursement, laboratories need to assess the overall costs—of testing and associated treatment decisions—and clinical benefits associated with different ALK testing strategies.

Key Model Parameters

	Cost per Sample
U.S. IHC	$89.00
E.U. IHC	$67.88
U.S. FISH	$330.00
E.U. FISH	$197.72
	Time to Result (working days)
IHC only	1 to 2 days
FISH only	2 to 5 days
IHC reflex FISH	3 to 7 days, if IHC (+)
IHC FISH parallel	2 to 5 days

*The overall turnaround time for ALK testing may require up to three weeks, if test requisition, sample collection and transport are included, the authors say.

G2 INSIDER

Daily INR Measurement for Inpatients Could Improve Safety

More frequent international normalized ratio (INR) monitoring of hospitalized patients taking the anticoagulant warfarin could increase patient safety, according to a study published online Dec. 14, 2015 in the *Journal of Hospital Medicine*. Specifically, the authors say, daily INR measurement and recognition of a rapidly rising INR could decrease the frequency of warfarin-associated adverse events.

Warfarin is one of the most common causes of adverse drug events, yet there is limited evidence to guide appropriate warfarin monitoring frequency for hospitalized patients. In 2015, the Joint Commission (JC) reissued its anticoagulant-focused National Patient Safety Goal, which mandates the assessment of baseline coagulation status before starting warfarin, and calls for warfarin dosing based on a "current" INR, although current is not defined. In the present study, the researchers retrospectively analyzed Medicare Patient Safety Monitoring System data to identify patients hospitalized from 2009 to 2013 for pneumonia, acute cardiac disease (myocardial infarction or heart failure), or surgery, who received warfarin. If a patient's INR level never reached above 1.5, they were excluded from analysis.

The researchers identified 14,217 patients, of whom 1,055 (7.4 percent) developed a warfarin-associated adverse event. Warfarin treatment was started on the first day of hospitalization for 6,825 patients (48.0 percent). Among these patients, the vast majority (95.8 percent) had an INR measured within one day. The authors say this showed a high level of adherence to this JC safety standard.

However, among the 8,529 patients who received warfarin for three or more days, INR was not measured on two or more days for 18.2 percent of patients. Patients who had two or more days on which the INR was not measured had higher rates of INR at 6.0 or above, compared to patients for whom the INR was measured daily. Overall, patients with no INR measurement for two or more days had 48 percent higher chance of having a warfarin-associated adverse event, compared to patients with daily INR measurement. The odds were even higher (73 percent) for cardiac and surgical patients, but with no odds difference for pneumonia patients. Furthermore, a 1-day increase in the INR of 0.9 or higher occurred in 12.5 percent of patients and predicted a subsequent INR of more than 6.0.

"Because our results suggest that lapses in INR measurement lead to over-anticoagulation and warfarin-related adverse events, it may be appropriate to measure INRs daily in most hospitalized patients receiving warfarin," write the authors led by Mark Metersky, M.D., from University of Connecticut in Farmington. "Our results suggest that use of a warfarin dosing protocol that considers both the absolute value of the INR and the rate of rise could reduce warfarin-related adverse events. … These results provide actionable opportunities to improve safety in some hospitalized patients receiving warfarin." G2

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