Rapid biomarker testing for NSCLC

Streamlining GI testing with MDx
The human side of lab automation
Reducing lab errors

EXECUTIVE SNAPSHOT
Hanjoon Ryu
CEO
MedTest Dx
SYNDROMIC TESTING FROM BIOFIRE:

Improve Laboratory Efficiency.

BioFire’s syndromic testing allows you to quickly identify infectious agents that produce similar symptoms in patients. BioFire’s innovative PCR technology provides hospitals, clinics, physicians and patients with the results they need in just one hour using any of the FilmArray® Panels: respiratory, blood culture identification, gastrointestinal and meningitis/encephalitis.

- **Fast.** Quick turnaround times and fast answers make your lab an invaluable partner to clinicians.
- **Easy.** With just two minutes of hands-on time, the FilmArray® System is easily used by any tech, on any shift and at any size institution.
- **Comprehensive.** The FilmArray® Panels test for a comprehensive grouping of viruses, bacteria, parasites, yeast and antimicrobial resistance genes associated with a particular syndrome.

To learn how syndromic testing from BioFire can help make YOUR lab more efficient, visit biofiredx.com

Data on file at BioFire Diagnostics.

**Syndromic Testing: The Right Test, The First Time.**
Respiratory - Blood Culture Identification - Gastrointestinal - Meningitis/Encephalitis
Sysmex has a decades-long legacy of developing better analyzers. Today, we’ve moved well beyond “building better boxes” into four key areas to create a more holistic, intuitive ecosystem that improves lab operations, promotes better care and enhances patient management practices.

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- NEXT GENERATION DIAGNOSTICS – continuing to pioneer the future of diagnostic performance
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- HARMONIZED SUPPORT – combining truly personalized service with a revolutionary technology platform

Go Beyond a Better Box™ at WWW.SYSMEX.COM/BEYOND_MLO to see how Sysmex improves hematology and your entire lab.
CONTINUING EDUCATION

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By Edward H. Kaplan, MD

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Hanjoon Ryu
CEO
MedTest Dx
HOW CAN YOU ACHIEVE MAX IMPACT?

WITH THE NEW BD MAX™ VAGINAL PANEL

Traditional diagnostics leave up to 40% of women with vaginal infections undiagnosed after an initial clinical visit.¹ The BD MAX Vaginal Panel provides more complete, accurate detection,² to help more patients.

➤ The first microbiome-based, polymerase chain reaction (PCR) assay that directly detects pathogens causing bacterial vaginosis, vulvovaginal candidiasis, and Trichomonas vaginalis²

➤ Maximize efficiency with 1 collection, 1 test for the 3 most common causes of vaginitis

➤ Supports antimicrobial resistance initiatives by reporting Candida krusei and C. glabrata

START MAXIMIZING YOUR IMPACT

VISIT BD.COM/DS
New man to head the FDA
What will Dr. Scott Gottlieb mean for labs?

On May 9, the U.S. Senate voted on President Trump’s nomination of Scott Gottlieb, MD, to be the new commissioner of the U.S. Food and Drug Administration (FDA). By a vote of 57 to 42, Dr. Gottlieb was confirmed. The vote was, as news reports say “largely” along party lines. But it was not as much so as some of the president’s other nominees, who had virtually no support from Senate Democrats. Five Democrats joined with the Senate’s 52 Republicans to confirm Gottlieb.

What will Scott Gottlieb as FDA commissioner mean for the clinical lab? Will approval of new diagnostics be accelerated or delayed? Will there be more stringent oversight of laboratory-developed tests (LDTs)?

To answer that, it’s useful to look at the new commissioner’s professional history. He is 44 years old, and he is a physician. (He is also a cancer survivor.) Unlike many of President Trump’s nominees for government posts, he is something of a “Washington insider”: He served in George W. Bush’s second administration as an FDA deputy commissioner, spent a year as a senior adviser to the administrator at the Centers for Medicare and Medicaid Services, and has been serving on the federal Health IT Policy Committee.

In the private sphere, he has been a fellow in the conservative American Enterprise Institute think tank. He has had success as a venture capitalist. He has had financial relationships with large pharmaceutical companies—a point that worried some senators who voted “no” on his confirmation. Reportedly, he has served on the boards of directors for American Pathology Partners, MedAvante, Glytec, Daiichi Sankyo, Aptiv Solutions, Graladis, Toler Pharmaceuticals, Molecular Insight Pharmaceuticals, and Bravo Health. Dr. Gottlieb promised senators that he would sever his ties to Big Pharma and the biotech industry, and divest himself from healthcare companies.

There is no question that as FDA head he will work toward creating a faster-track for drug approval, perhaps particularly for cancer drugs and “orphan” drugs for rare diseases. He wrote in 2012: “In so heavily prioritizing one of its obligations—the protection of consumers—the FDA has sometimes subordinated and neglected its other key obligation, which is to guide new medical innovations to market. Ultimately, the only way to change the threshold for approval of these sorts of drugs is to change the FDA review culture itself.”

That tells you what he thinks and what he plans to do. He affirms that part of the FDA’s mission is to protect consumers. But he thinks that the other part is to help bring new products to the market, and he believes that has gotten short shrift, so he will restore the balance by making changes in the FDA review process. That is, the fast-track.

In the public mind, the FDA is mostly associated with drug approval. Of course, we know that it also approves medical devices and, most important I assume to the readers of MLO, diagnostics. So back to my original question: what does this mean for the clinical lab? Well, apart from the issue of company diagnostics, it probably means that diagnostic assays will also be on a faster track, and that should be, in a broad sense, good for business. It may mean that the controversial topic of proposed tighter regulation of LDTs, which has been discussed in these pages and many other places for years now (e.g., my “From the Editor” in the January and March 2017 issues), will recede as the FDA backs further away from changing the status quo. That could be good for labs too—as long as sufficient (not duplicative) regulation remains in place to protect the public.

Everyone loses if that first “obligation” is lost. But if Dr. Gottlieb can thread the needle between public safety and industrial development, maybe everyone wins.
ADD SOME SUNSHINE TO YOUR WORKFLOW.  
Make the BioPlex 2200 Vitamin D part of your routine.

Consolidating your Vitamin D testing with a unique menu of autoimmune and infectious disease assays is a bright idea available only on the BioPlex 2200 system.

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Patients testing positive for the EGFR T790M mutation may be eligible for TAGRISSO

- Nearly 2 out of 3 cases (98/155) of progression with first-generation EGFR TKIs are related to the acquired EGFR T790M mutation
- The cobas® EGFR Mutation Test v2 can identify the EGFR T790M mutation via tissue or plasma testing
- In a Phase III, randomized, open-label, head-to-head clinical trial of 419 patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease had progressed on or after EGFR TKI therapy, TAGRISSO outperformed doublet chemotherapy (pemetrexed plus carboplatin or cisplatin)

Median progression-free survival was more than twice as long with TAGRISSO than with doublet chemotherapy**

**As determined by investigator assessment (IA).
Testing for the presence of the EGFR T790M mutation in plasma specimens is recommended only in patients where tumor tissue is not available.

IMPORTANT SAFETY INFORMATION

- There are no contraindications for TAGRISSO.
- Interstitial Lung Disease (ILD)/Pneumonitis occurred in 3.5% and was fatal in 0.6% of 833 TAGRISSO-treated patients. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms indicative of ILD (e.g., dyspnea, cough, and fever). Permanently discontinue TAGRISSO if ILD is confirmed.
- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 833 TAGRISSO-treated patients, 0.7% of patients were found to have a QTc > 500 msec, and 2.9% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia.
- Cardiomyopathy occurred in 1.9% and was fatal in 0.1% of 833 TAGRISSO-treated patients. Left Ventricular Ejection Fraction (LVEF) decline ≥ 10% and a drop to < 50% occurred in 4% of 655 TAGRISSO-treated patients. Conduct cardiac monitoring, including an assessment of LVEF at baseline and during treatment in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue TAGRISSO.
- Keratitis was reported in 0.7% of 833 TAGRISSO-treated patients in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye) to an ophthalmologist.
- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during TAGRISSO treatment and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose.
- The most common adverse reactions (≥20%) in patients treated with TAGRISSO were diarrhea (41%), rash (34%), dry skin (23%), nail toxicity (22%), and fatigue (22%).

INDICATION

TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor therapy.

Please see Brief Summary of complete Prescribing Information on adjacent pages.

References:

For more information about testing to identify patients eligible for TAGRISSO, visit TAGRISSOhcp.com

AstraZeneca

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COBAS is a registered trademark of Roche.

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INDICATIONS AND USAGE
TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

Dosage and Administration
Compliance with the use of a nasogastric tube is required. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions and immediately drink.

Dosage in Patients Who Have Difficulty Swallowing Solids
Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonic during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces of) water and immediately drink.

If administration via nasogastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions and appropriate water flushes (approximately 30 mL).

Dosage Modification

Adverse Reactions

Table 1. Recommended Dose Modifications for TAGRISSO

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Adverse Reaction</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Intestinal lung disease (ILD)/Pneumonitis</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
<tr>
<td></td>
<td>QTc interval greater than 500 msec or at least 2 separate ECGs†</td>
<td>Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at 40 mg dose.</td>
</tr>
<tr>
<td></td>
<td>Symptomatic congestive heart failure or asymptomatic left ventricular dysfunction that persists ≥ 4 weeks</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
<tr>
<td></td>
<td>Adverse reaction of Grade 3 or greater severity</td>
<td>Withhold TAGRISSO for up to 3 weeks.</td>
</tr>
<tr>
<td>Other</td>
<td>If improvement to Grade 0-2 within 4 weeks</td>
<td>Resume at 80 mg or 40 mg daily.</td>
</tr>
<tr>
<td></td>
<td>If no improvement within 3 weeks</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
</tbody>
</table>

† QTc = QT interval corrected for heart rate

Drug Interactions

Strong CYP3A4 Inducers
If concurrent use is unavoidable, increase TAGRISSO dosage to 80 mg daily when coadministering with a strong CYP3A4 inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer [see Drug Interactions (7), and Clinical Pharmacology (12.3) in full Prescribing Information].

Contraindications
None.

WARNINGS AND PRECAUTIONS
The following information is for ILD Pneumonitis, QTc Interval Prolongation, Cardiomyopathy and Keratitis reflects exposure to TAGRISSO in 833 patients with EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) who received TAGRISSO at the recommended dose of 80 mg once daily in AURA3 (n=279), AURA Extension (n=201), and AURA2 (n=210), and an expansion cohort in the first-in-human trial of osimertinib (AURA1, n=143).

Interstitial Lung Disease/Pneumonitis
Intestinal lung disease (ILD)/pneumonitis occurred in 3.5% (n=29) of TAGRISSO-treated patients (0.3% of cases were fatal). Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed [see Dosage and Administration (2.4) and Adverse Reactions (6) in full Prescribing Information].

QTc Interval Prolongation
Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 833 patients treated with TAGRISSO in clinical trials, 0.7% (n=6) were found to have a QTc greater than 500 msec, and 2.9% of patients (n=24) had an increase from baseline QTc greater than 480 msec [see Clinical Pharmacology (12.2) in full Prescribing Information]. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of greater than 470 msec. Conduct periodic monitoring with ECGs and electrolys in patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QT interval prolongation with signs/symptoms of life-threatening arrhythmia [see Dosage and Administration (2.4) in full Prescribing Information].

Cardiomyopathy
Across clinical trials, cardiomyopathy (defined as cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 1.9% (n=16) of 833 TAGRISSO-treated patients: 0.1% (n=1) of cases were fatal.

Left Ventricular Ejection Fraction (LVEF) decline greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients who had baseline and at least one follow-up LVEF assessment.

Conduct cardiac monitoring, including an assessment of LVEF at baseline and during treatment in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue TAGRISSO [see Dosage and Administration (2.4) in full Prescribing Information].

Keratitis
Keratitis was reported in 0.7% (n=6) of 833 patients treated with TAGRISSO in clinical trials. Proptosis refers patients with signs and symptoms suggestive of keratitis (including injection, lacrimation, sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

Embryo-Fetal Toxicity
Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

pregnant females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5-times those observed in patients at the 80 mg dose level.

Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose [see Use in Specific Populations (8.1), (8.3) and Clinical Pharmacology (12.3) in full Prescribing Information].

ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling: Intestinal Lung Disease/Pneumonitis [see Warnings and Precautions (5.1) in full Prescribing Information].

QTc Interval Prolongation [see Warnings and Precautions (5.2) in full Prescribing Information].

Cardiomyopathy [see Warnings and Precautions (5.3) in full Prescribing Information].

Keratitis [see Warnings and Precautions (5.4) in full Prescribing Information].

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to TAGRISSO (80 mg daily) in patients with EGFR T790M mutation-positive metastatic NSCLC in an open-label, randomized, active-controlled trial (AURA3, n=279) and in two single arm trials, AURA Extension (n=201) and AURA2 (n=210). Patients with a history of interstitial lung disease or radiation pneumonitis who required: steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from trial enrollment.

Clinical Trial
The safety of TAGRISSO was evaluated in AURA3, a multicenter international open label randomized (2:1) controlled trial conducted in 419 patients with unresectable or metastatic EGFR T790M mutation-positive NSCLC who had progressive disease following first line EGFR TKI treatment. A total of 278 patients received TAGRISSO 80 mg orally once daily until intolerance to therapy, disease progression, or investigator determination that the patient was no longer benefiting from treatment. A total of 136 patients received pemetrexed plus either carboplatin or cisplatin every three weeks for up to 6 cycles; patients without disease progression after 4 cycles of chemotherapy could continue maintenance pemetrexed until disease progression, unacceptable toxicity, or investigator determination that the patient was no longer benefiting from treatment.

Clinical Trials of AURA3, AURA Extension, AURA2
In the clinical trials of AURA3, AURA Extension, AURA2, and the patients with a history of interstitial lung disease or radiation pneumonitis who required: steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from trial enrollment.

Clinical Trial
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Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in AURA3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>41</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Skin disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Dry skin</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Nail toxicity†</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>28</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 3. Common Laboratory Abnormalities (>29% for all NCI CTCAE Grades) in AURA3

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy (Pemetrexed/Carboplatin or Pemetrexed/Carboplatin) (N=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>61</td>
<td>11</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>83</td>
<td>81</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>46</td>
<td>49</td>
</tr>
</tbody>
</table>

* Based on the number of patients with available follow-up laboratory data

TAGRISSO® (osimertinib) tablets, for oral use

Effect of Osimertinib on Other Drugs

Coadministering TAGRISSO with a BCRP substrate increased the exposure of the BCRP substrate compared to administering the BCRP substrate alone [see Clinical Pharmacology (12.3) in full Prescribing Information]. Increased BCRP substrate exposure may increase the risk of exposure-related toxicity.

USE IN SPECIFIC POPULATIONS

Use in Pregnancy

Tagrisso® does not adversely affect fertility.

Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in AURA3

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<tr>
<td>Fatigue</td>
<td>28</td>
<td>5</td>
</tr>
</tbody>
</table>

* Based on the number of patients with available follow-up laboratory data

AURA Extension and AURA2 Trials

The safety of TAGRISSO was evaluated in two single arm trials, AURA Extension (n=201) and AURA2 (n=210). A total of 411 patients with EGFR T790M mutation-positive NSCLC who received one or more prior EGFR therapies including an EGFR TKI were treated with TAGRISSO (80 mg daily). The majority of patients were heavily pre-treated. Enrolment involved 66% of patients that had received at least 2 prior treatment regimens, 46% had received 3 or more prior lines of therapy, and 63% had received prior platinum-based chemotherapy.

Median duration of exposure to TAGRISSO was 7.7 months (range: 0.5 to 11.6 months). The toxicity profile of TAGRISSO observed in the AURA Extension and AURA2 trials was generally consistent with the toxicity profile observed in the AURA3 trial. Four patients (1%) treated with TAGRISSO developed fatal adverse reactions of ILD/pneumonitis. Discontinuation of therapy due to adverse reactions occurred in 5.6% of patients treated with TAGRISSO. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis.

DRUG INTERACTIONS

Effect of Other Drugs on Osimertinib

Strong CYP3A Inducers

Coadministering TAGRISSO with a strong CYP3A inducer decreased the exposure of osimertinib compared to administering osimertinib alone [see Clinical Pharmacology (12.3) in full Prescribing Information]. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid coadministering TAGRISSO with a strong CYP3A inducer (e.g., phenytoin, rifampin, carbamazepine, St. John’s Wort) [note: effect of St. John’s Wort varies widely and is preparation-dependent]. Increase the TAGRISSO dosage when coadministering with a strong CYP3A inducer if concurrent use is unavoidable [see Use in Specific Populations (8.1) in full Prescribing Information]. No dose adjustments are required when TAGRISSO is used with moderate or weak CYP3A inducers.

TAGRISSO® (osimertinib) tablets, for oral use

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AstraZeneca 2017

Iss. 03/17 3380004 4/17

MLO201705_AD AstraZeneca-20752.indd 9 5/12/2017 2:46:06 PM
Lung cancer in America

158,080
Is the approximate number of Americans who died from lung cancer in 2016.

27 percent
Is the proportion of all cancer deaths attributed to lung cancer in the U.S. in 2016.

51.7
Per 100,000 is the age-adjusted death rate from lung cancer for American men.

34.7
Per 100,000 is the age-adjusted death rate from lung cancer for American women.

415,000
Is the approximate number of Americans living today who have been diagnosed with lung cancer at some point in their life.

83 percent
Is the proportion of Americans living with lung cancer who are age 60 or older (2013 figures).

17.7 percent
Is the five-year survival rate for lung cancer overall.

55 percent
Is the five-year survival rate for lung cancer that is diagnosed when it is still localized.

>50%
Is the proportion of lung cancer patients who die within one year of diagnosis.

~80%
Is the proportion of small cell and non-small cell lung cancer in women in which smoking is a contributing factor.

~90%
Is the proportion of small cell and non-small cell lung cancer in men in which smoking is a contributing factor.


Zika Virus

Researchers identify potential ZIKV target. New research provides insights into why infection with ZIKV after birth generally causes only mild symptoms, whereas devastating fetal malformations can develop when infection occurs during pregnancy.

Healthy people are protected by antiviral factors of the innate immune system. Investigators have now shown that reducing levels of one antiviral factor called interferon-induced transmembrane protein 3 (IFITM3) makes cultured cells highly sensitive to ZIKV infection.

The research team found that IFITM3 normally stops multiplication of the virus in human cells at an early step, preventing the infected cells from "implosive" cell death. Therefore, drugs that block this cell death pathway might be helpful for preventing the effects of ZIKV infection during pregnancy.

“We describe a striking succession of events that may lead to the death of cells infected with ZIKV virus. Hopefully, the cells are equipped with antiviral gatekeepers that allow the host to control the infection,” says Dr. Olivier Schwartz of Institut Pasteur, senior author of The EMBO Journal study.

A speedy, sensitive, and low-cost detection test for ZIKV. A fast, highly sensitive, and inexpensive new test not only detects ZIKV in mosquitoes and human bodily fluids, but can also distinguish between African and Asian strains. That could improve efforts to more effectively track the virus’s spread.

Colorado State University researcher Nunoya Chotian and colleagues devised an assay to directly detect ZIKV from mosquitoes and several different types of unprocessed clinical samples (including human blood, saliva, and semen). They amplified ZIKV genomes using a molecular technique called loop-mediated isothermal amplification (LAMP), an approach that proved comparably sensitive to the current gold-standard detection method, qRT-PCR. Unlike qRT-PCR, however, LAMP does not require costly reagents. Importantly, LAMP did not yield false-positives for closely related pathogens such as dengue virus and chikungunya virus.

The researchers validated the LAMP test using virus artificially spiked into materials obtained from healthy individuals, and also in clinical specimens collected from confirmed cases of ZIKV infection. LAMP was also sufficiently sensitive to identify one single infected mosquito from a collection pool of 50 uninfected insects. The authors say that LAMP’s minimal processing requirements and accelerated turnaround time will be valuable for ZIKV surveillance and control.

New Studies

Displaying EHR lab test costs doesn’t deter doctors from ordering them. Patients are stuck for a blood draw almost every day they are admitted to a hospital. Lab tests are one of the most common orders placed by doctors, but research indicates that nearly one-third of those tests are not needed.

Hospitals nationwide are seeking ways to use price transparency—displaying the price of lab tests at the time when doctors are placing the order—to nudge doctors to consider whether the benefits are worth the cost. Results of a new study, however, show that simply displaying the Medicare allowable fees did not have an overall impact on how clinicians ordered the tests.

In the new study, researchers randomly assigned 60 groups of inpatient laboratory tests to either display Medicare allowable fees in the patient’s EHR (intervention arm), or not (control arm). The randomized clinical trial was conducted at three hospitals within the University of Pennsylvania Health System over a one-year period and compared changes in the number of tests ordered per patient per day, and associated fees, for more than 98,000 patients (totaling over 142,000 admissions).

Results of the study showed that in the year prior to the study, when cost information was not displayed, the average number of tests and associated fees ordered per patient per day was 2.31 tests totaling $27.77 in the control group, and 3.93 tests totaling $37.84 in the intervention group. After the intervention, when cost information was displayed for the intervention group, researchers noted the average number of tests and associated fees ordered per patient per day did not change significantly: they were 2.34 tests totaling $27.59 in the control group, and 3.93 tests totaling $37.84 in the intervention group. After the intervention, when cost information was displayed for the intervention group, researchers noted the average number of tests and associated fees ordered per patient per day did not change significantly: they were 2.34 tests totaling $27.59 in the control group, and 3.93 tests totaling $37.84 in the intervention group.

Though the study found no overall effect, the authors noted important findings in specific patient groups that have implications for how to improve price transparency in the future. For example, there was a slight decrease in test ordering for patients admitted to the ICU—an environment in which doctors are making rapid decisions and may be more exposed to the price transparency intervention. The authors also found that the most expensive tests were ordered...
less and the cheaper tests were ordered more, suggesting that future interventions might be more successful if they are better designed to framed relative pricing.

Saliva test predicts prolonged concussion symptoms in children. Although most of the three million concussions diagnosed in the U.S. each year occur in children, the bulk of clinical guidelines are based on adults. Because of this, pediatricians are limited in how long a child may suffer symptoms such as headaches, fatigue, and trouble concentrating that can interfere with school and other activities.

New research presented at the 2017 Pediatric Academic Societies Meeting, which was published early online last month, however, suggests a simple saliva test may yield more answers. Investigators from Penn State College of Medicine presented an abstract of the study. “Peripheral microRNA patterns predict prolonged concussion symptoms in pediatric patients” at the conference.

Micro ribonucleic acids (miRNAs) are genetic molecules, chiefly found within cells, that help regulate protein production. Previous studies have found altered miRNA levels in the saliva of children with mild concussions. This mirrored similar miRNA changes in cerebrospinal fluid of patients with severe brain injury.

The researchers studied 50 children between the ages of 7 and 18 years with mild traumatic brain injury. Spit samples were collected and tested for miRNA levels. In addition, concussion symptoms were evaluated through parent and child Sports Concussion Assessment Tool (SCAT-3) surveys, a standardized tool commonly used to evaluate injured children for concussion and to guide clinical decision-making. The surveys were taken within 14 days of injury and again four weeks post-concussion. The 29 children with prolonged concussion symptoms had higher scores for headaches, fatigue, and difficulties concentrating.

Steven Hicks, MD, PhD, FAAP, lead study author, says the salivary miRNA levels were significantly more effective than evaluations using SCAT-3 survey in children who had mild concussions. “Although young children may continue to experience headaches, fatigue, concentration difficulties, and other concussion symptoms that lasted longer than four weeks. Results showed the standard survey to be less than 70 percent accurate in identifying children who would have prolonged concussion symptoms, he says. In comparison, he reports, miRNA in saliva correctly predicted whether concussion symptoms would remain present for at least a month nearly 90 percent of the time.

“We believe that saliva-based RNA testing holds great promise as an accurate and non-invasive method for evaluating pediatric concussions and giving patients and families a more accurate prognosis,” Dr. Hicks says.

Cancer

Women should continue cervical cancer screening until age 65. Cervical cancer is often thought of as a disease that primarily affects young women. Because of this, many older women fail to keep up with appropriate screening as they age. While current guidelines indicate that screening can be stopped for average-risk patients after age 65, many women lack the appropriate amount of screening history to accurately assess their risk.

A new study in the American Journal of Preventive Medicine found that incidence rates of cervical cancer do not begin to decline until age 65 in women without a hysterectomy and that women over 65 who have not been recently screened may benefit from continued surveillance.

“An older woman who has not had her cervix surgically removed has the same or even higher risk of developing cervical cancer as a younger woman,” says lead investigator Mary C. White, ScD, Chief of the Epidemiology and Applied Research Branch, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention (CDC).

“Women who have not had a hysterectomy need to continue to be screened until age 65, and possibly later if they have not been screened for many years or are at special risk, consistent with current U.S. Preventive Services Task Force recommendations.”

In 2013, one-fifth of cervical cancer cases and one-third of cervical cancer deaths occurred among women 65 years of age and older. Current recommendations say that screening can be stopped at age 65 if an adequate testing history indicates consistently negative results. Three consecutive negative cytology results or two consecutive negative co-test results within the last 10 years, with the most recent test within the last five years, are considered sufficient reason to stop screening average-risk women after age 65.

Using data from the 2013 and 2015 National Health Interview Survey, investigators looked at the use of screening tests and rates of cervical cancer for women 65 and older. The data revealed that many women approaching the “stopping” age of 65 were not getting sufficient screening. Researchers established that the proportion of women not recently screened increases with age. While only 12 percent of women in their 40s had no recent screening history, that number progressively increased for women in their 50s and 60s. Nearly 850,000 women aged 61 to 65 years had not been screened within the last five years.

Higher prostate cancer risks for black men may warrant new approach to screening. A new study indicates that higher prostate cancer death rates among black men in the United States may be due to a higher risk of developing preclinical prostate cancer as well as a higher risk of that cancer progressing more quickly to advanced stages. Published or more online in CANCER, the study suggests that screening policies may need to be tailored to the higher-risk status of this population.

Among black men in the U.S., the incidence of prostate cancer is 60 percent higher than that of white men, and their mortality rate from prostate cancer is more than twice as high. To understand why, researchers used three models of prostate cancer incidence and prostate specific antigen (PSA) screening in the U.S. to estimate disease onset and progression based on prostate cancer data from 1975 to 2000 reported by the Surveillance, Epidemiology, and End Results program of the National Cancer Institute.

The investigators estimated that 30 percent to 43 percent of black men develop preclinical prostate cancer by age 85, a risk that is 28 percent to 56 percent higher than that of white men.

Among men with preclinical disease, black men have a similar risk of being diagnosed (35 percent to 49 percent) compared with the general population (32 percent to 44 percent) in the absence of screening. Their risk of progression to advanced disease by the time they’re diagnosed is 44 percent to 75 percent higher than in the general population, however (a 12 to 13 percent risk in black men versus a seven to nine percent risk in the general population).

“We found that the interval from getting preclinical cancer to being diagnosed is longer—10 years or more on average—and is similar in black and white men. But during that interval, cancers in black men tend to progress faster,” says Ruth Etzioni, PhD, a senior study author. “What this means is that in developing screening policies for black men, it will be important to consider beginning screening them at an earlier age and potentially screening them more frequently than would be recommended by general population guidelines.”

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Rapid biomarker testing for improved clinical decision-making in non-small cell lung cancer

By Edward H. Kaplan, MD

One devastating aspect of lung cancer is that it can develop slowly and remain undetected for years before becoming symptomatic. By the time lung cancers are discovered and diagnosed, a high proportion (>66 percent) of them have reached an advanced, malignant, and aggressively metastatic stage that is not amenable to surgical intervention. Many patients with newly diagnosed lung cancer face a poor prognosis and a five-year survival rate of approximately 16 percent, according to the American Cancer Society (2012), despite the increasing range of systemic and targeted therapies that have become available.

The demand from clinicians and patients for clinically relevant real-time biomarkers that guide treatment decisions and prognosticate and monitor for response to therapy and/or disease progression, therefore, is high. The objective of this article is to review the newest developments in the field of biomarker testing for non-small cell lung cancer (NSCLC), and to demonstrate its emerging role as a standard of care in clinical management.

Biomarker testing in diagnosis and treatment

The mainstays of treatment for advanced NSCLC include generalized therapies (platinum-based or single-agent chemotherapy and radiation), immunotherapies (checkpoint inhibitors), second line without biomarker, Keytruda (checkpoint inhibitor) in frontline patients with high PD-L1 staining, and targeted tyrosine kinase inhibitor (TKI) drugs, which are directed at specific mutations in the epidermal growth-factor receptor (EGFR). However, several new developments are shaping changes in the NSCLC treatment landscape. For one, the number and breadth of targeted therapies for NSCLC continue to grow as new drugs are being brought to market. At the same time, it has become well understood that the presence of certain tumor biomarkers is highly predictive of an individual's response to both generalized and targeted treatments, and this understanding is supported by new diagnostic tools capable of providing actionable information with which to make critical decisions about clinical management.

The profiles now provided by some commercially available biomarker tests can give physicians the opportunity to improve patient quality of life by reducing ineffective treatment. Such information can be used to customize the treatment plan, helping to avoid wasting precious time, causing debilitating therapeutic side effects, and dedicating financial resources to therapies that are not likely to work. Additionally, this information may suggest a benefit in pursuing subsequent broad molecular profiling which can identify rare mutations that might present options for therapeutic alternatives or clinical trials. Biomarker testing may help enable physicians to provide their patients with an objective, realistic assessment of prognosis and life expectancy to facilitate planning together for appropriate palliative care and end-of-life decisions.

Basic research efforts into gene-expression profiling and genome-wide association studies continue to uncover potential correlations between the presence of genetic mutations and the aggressiveness of NSCLC and other cancers. A handful of these genetic aberrations—including point mutations, deletions, and fusions—have been proven to have direct predictive value with respect to treatment efficacy and prognosis in NSCLC. These so-called “driver” mutations sometimes perform a direct, mechanistic role in driving malignant transformation and cancer progression, and are often targets for current drug therapies. Some of these mutations include:

- EGFR sensitizing mutations (delE746-A750); L858R): Mutations in the EGFR gene that render NSCLC cells sensitive to first- and second-generation EGFR-TKIs. Patients may benefit from treatment with afatinib, erlotinib, or gefitinib.
- EGFR resistance-conferring mutations (T790M): A second-site mutation associated with acquired resistance to gefitinib and erlotinib. Patients with this mutation may benefit from treatment with third-generation EGFR-TKIs osimertinib.
- ALK fusion variants (EML4 (E6:A20, E13-A20, E20-A20)): A translocation mutation that results in overexpression of the ALK kinase gene, resulting in dysregulation of critical downstream signaling pathways. Patients may benefit from treatment with crizotinib, ceritinib, or alectinib, depending on previous therapies.
- ROS1 fusion variants CD74 (C6:R34, C6:R32); SDC4 (S2:R32, S2:R34); SLC34A2 (S13del2046:R32, S13del2046:R34); EZR (E10:R34); TPM3 (T8:R35): Another genetic translocation that results in aberrant receptor tyrosine kinase activity. Patients may benefit from treatment with crizotinib, ceritinib, or alectinib, depending on previous therapies.
- RET fusion variants KIF5B (K15:R12, K16:R12, K22:R12, K23:R12, K24:R11, K24:R8); CCDC6 (C1:R12); TRIM33 (T14:R12): Patients with mutations in this oncogene may benefit from treatment with cabozantinib or vandetanib.
• KRAS mutations (G12C, G12D, G12V): Mutations in this critical oncogene lead to constitutive activation of intracellular signaling cascades that normally regulate cell growth and differentiation. Prognosis is generally poorer in patients with these mutations.

• BRAF mutant V600E: Mutations in this serine/threonine-protein kinase adversely affect cell division and differentiation. Patients may benefit from vemurafenib, dabrafenib, or dabrafenib+trametinib.

Genetic and/or genomic testing panels that include these mutations (Table 1, pg. 14) are those that are most likely to provide actionable information to guide treatment strategies.

Turnaround time in biomarker testing
The clinical course of newly diagnosed, advanced NSCLC can be rapid, with prognoses typically measured in months. Early intervention with appropriately targeted therapies can increase the overall chance of survival, and therefore speed is critical when obtaining biomarker information that might influence the design and initiation of a therapeutic strategy. However, the results from tumor biopsies generally take three weeks or more, and inadequate sampling at the initial biopsy can lead to even longer wait times. According to a recent study, nearly 80 percent of patients diagnosed with NSCLC did not receive the results of biomarker testing in time for the initial consultation with their oncologist, and the median time to receive those results was 21 days after the initial consultation. When biomarker profiles were available at the initial consultation, patients experienced markedly shorter median times from consultation to decision (0 vs. 22 days, p = 0.0008), and to initiation of treatment (16 vs. 29 days, p = 0.004), compared to patients whose biomarker data were not yet available.

Timely availability of biomarker profiles is likely to improve due to the recent advent of so-called liquid biopsy for use in NSCLC biomarker testing. Liquid biopsy exploits the presence, in blood or other body fluids, of intact circulating tumor cells (CTCs) or cell-free, circulating tumor DNA (ctDNA) that is shed when tumor cells undergo apoptosis or necrosis. These cells and nucleic acids represent a readily available, easily accessible, and virtually limitless source of analytical material compared to tissue biopsy. In the last five years or so, the testing platforms that have been developed to analyze them have improved in sensitivity, speed, and cost to the point where they can achieve results much faster than techniques that begin with tissue as a starting material. With this technology, blood samples can be acquired on the same day as a tissue biopsy to yield rapid biomarker genotyping results.

Liquid biopsy is unlikely to replace the need for tissue biopsy in the near-term because information from tissue histology remains essential to diagnosing and subtyping the cancer. Liquid biopsy technologies are also limited in their ability to detect small, early-stage tumors that are not actively shedding material. However, due to its rapid time to results, biomarker testing of liquid biopsies represents such a powerful companion technique that the Cleveland Clinic included in its list of top ten medical innovations projected to impact patient care in 2017.

Figure 1. The “reflex strategy” for NSCLC diagnostics.

*For patients previously treated with EGFR-TKI

continued on page 14
Newer detection platforms
Liquid biopsy and other improvements in biomarker testing for NSCLC have been enabled by new diagnostic platforms that are faster and more sensitive than traditional immunohistochemistry, fluorescence in situ hybridization (FISH), and traditional rtPCR.

Droplet digital PCR (ddPCR) is a newly developed technique that uses water-oil emulsion droplet technology for highly sensitive, quantitative, reproducible detection of rare target mutations in ctDNA as well as cDNA copied from ctRNA.9–12 With this technique, processed nucleic acids from blood samples are diluted and partitioned into thousands of tiny droplets, each of which acts as an independent PCR amplification chamber. The results of amplification and detection yield absolute information regarding the quantity of mutations in the sample, independent of the amplification reference curves required for quantitative rtPCR experiments. Biomarker test platforms using ddPCR technology are very fast and highly sensitive (Table 1); median turnaround time for ddPCR testing in advanced stage NSCLC is three days, compared to 12 to 27 days for tissue genotyping assays.4 A recent study assessing performance of a ddPCR-based biomarker-testing platform demonstrated a sensitivity of 88 percent, specificity of 99 percent, and overall concordance with tissue biopsy of 96 percent. Thus, ddPCR is well suited for the sensitive analysis of small, defined panels of validated target biomarkers that yield clinically actionable information.

Next-generation sequencing (NGS) is a general term encompassing a variety of high-throughput, highly parallel DNA sequencing technologies that have replaced simple dye terminator sequencing methods.13 NGS enables relatively rapid, massively parallel analysis of large DNA segments or complex samples, including entire genomes. Originally developed to reduce the time and costs of genome sequencing, NGS technologies can analyze broad panels of genes for multiple mutations, all at the same time. In biomarker testing, NGS is well suited for liquid biopsy analysis and faster than more traditional methods, and it generally allows for analysis of larger gene panels than can be conducted with ddPCR (Table 1). However, much of the additional information currently yielded by NGS-based genomic panels is not actionable for NSCLC. Large panels have the potential to confuse clinical decision-making, because many of the genes and mutations are less well characterized, have not yet been validated, and are not yet part of recommended diagnostic guidelines.

Proteomic biomarkers provide complementary information
Another promising new direction for NSCLC biomarker testing is the availability of clinically validated tests that measure a patient’s response to a growing tumor using blood-derived proteomic information. Such tests take advantage of the complex biological interactions that occur as tumor cells begin to break free of normal growth control pathways, and the

<table>
<thead>
<tr>
<th>Source</th>
<th>Mutations/Fusions</th>
<th>Platform</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Turnaround Time</th>
<th>Medicare Reimbursed</th>
<th>Source material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company 1</td>
<td>*EGFR, *T790M, *ALK, ROS1, RET, *KRAS, BRAF</td>
<td>ddPCR</td>
<td>91%</td>
<td>100%</td>
<td>72 hours</td>
<td>Yes</td>
<td>Blood (ctRNA)</td>
</tr>
<tr>
<td>Company 2</td>
<td>ALK, hENT1, MET, PD-L1, PTEN, ROS1, TOP1, TP, TRKpan, TUBB3</td>
<td>NGS, IHC</td>
<td>N/A</td>
<td>N/A</td>
<td>4-5 days</td>
<td>Yes</td>
<td>Tissue</td>
</tr>
<tr>
<td>Company 3</td>
<td>*EGFR, *T790M, *ALK</td>
<td>rtPCR w/ NGS</td>
<td>EGFR: 88%</td>
<td>97%</td>
<td>5 days</td>
<td>Yes</td>
<td>Blood</td>
</tr>
<tr>
<td>Company 4</td>
<td>*EGFR, T790M, ALK, ROS1, RET, MET, MET, HER2</td>
<td>rtPCR</td>
<td>90%</td>
<td>100%</td>
<td>5-7 days</td>
<td>Yes</td>
<td>Blood (CTDs)</td>
</tr>
<tr>
<td>Company 5</td>
<td>EGFR1, EGFR T790M, ALK1, ROS11, KRAS1, PD-L1</td>
<td>ddPCR</td>
<td>N/A</td>
<td>N/A</td>
<td>5-9 days</td>
<td>Yes</td>
<td>Not specified</td>
</tr>
<tr>
<td>Company 6</td>
<td>*EGFR, *T790M, KRAS, BRAF</td>
<td>ddPCR w/ NGS</td>
<td>URINE: EGFR Exon 19: 67%</td>
<td>EGFR L858R: 75%</td>
<td>2 weeks</td>
<td>Yes</td>
<td>Blood or urine</td>
</tr>
</tbody>
</table>

Abbreviations: ddPCR, droplet digital PCR; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation (high-throughput) DNA sequencing; rtPCR, reverse transcriptase PCR. Refer to text for detailed description of biomarkers.

*Clinical validation data available. N/A indicates no validation data was found online.
2. No published data could be located.

Table 1. Currently available genetic biomarker testing for NSCLC.
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patient’s immune system responds with attempts to regulate and shut down this uncontrolled growth. This biological interplay between tumor and host releases a variety of acute-phase reactant proteins into the bloodstream. These can be detected and quantified, yielding important insights into the aggressiveness of the cancer and its susceptibility to available treatments.

So far, there is just one proteomic test that is commercially available for NSCLC. This proprietary test uses an advanced form of mass spectrometry, called matrix-assisted laser desorption/ionization-time of flight (MALDI-ToF), to detect and measure the chronic expression proteins associated with patient responses to aggressive cancer. The information yielded by this test can identify which patients are likely to benefit from first-line, standard-of-care platinum doublet therapy, and it is also predictive of therapeutic benefit from EGFR-TKIs. The results of the test have also been shown to be highly predictive of overall prognosis.

Putting it all together: the reflex strategy

Tissue histology, genetic/genomic tests, and proteomic tests yield complementary information. Combining their results using what is termed a “reflex strategy” can be a powerful tool to help guide clinical management.

For example, a patient presenting with newly diagnosed NSCLC can undergo tissue and blood biopsy on the same day. Tissue histology confirms the diagnosis and aids in sub-typing the disease. Meanwhile, in as few as 72 hours after the blood draw, rapid genetic profiling from the liquid biopsy provides information regarding sensitizing EGFR mutations, as well as the presence of EML4-ALK, ROS1, or RET positive results, which indicate candidates for specific EGFR-TKIs and other targeted therapies.

For patients treated with EGFR-TKI therapy whose disease subsequently progresses, genetic profile testing can be performed again, without need for additional tissue biopsy, to detect EGFR mutations that confer resistance to EGFR-TKI, and to predict whether or not the tumor may be susceptible to third-generation EGFR-TKI inhibitors.

Patients whose initial genetic profile indicates the presence of wild-type EGFR, or whose EGFR status is unknown, can be reflexed to proteomic profiling to determine how aggressively their tumor is growing. A predicted prognosis of “good” indicates that a patient’s tumor is likely to respond to platinum-based therapy, single-agent chemotherapy, or EGFR-TKI-based therapies. A “poor” prognosis identifies aggressive cancer that is unlikely to respond to EGFR-TKI therapies and may also not respond to standard of care.

Availability of this information has been shown to change patient and physician decisions about treatment and supportive care in positive ways. They can preserve valuable time by shifting their focus from ineffective therapies to investigating broad genetic profiling, clinical trial options, or alternative treatments, thereby avoiding overtreatment that negatively impacts quality of life in terminally ill patients.

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In conclusion, the adoption curve for biomarker testing for NSCLC is accelerating, driven by rapid improvements in analytical technologies, drug development, and evidence-based translational research. For clinicians, understanding the relevance and utility of the current state of biomarker testing is essential for optimizing outcomes and providing quality patient care. Laboratorians play a vital role in performing such testing and disseminating its results to oncologists.

REFERENCES
RAPID BIOMARKER TESTING FOR IMPROVED CLINICAL DECISION-MAKING IN NON-SMALL CELL LUNG CANCER

June 2017 (This form may be photocopied. It is no longer valid for CEUs after December 31, 2018.)

TEST QUESTIONS

Circles must be filled in, or test will not be graded. Shade circles like this: ● Not like this: X

1. What proportion of lung cancers have reached a metastatic stage by the time they are discovered and diagnosed?
   a. >98 percent
   b. >78 percent
   c. >88 percent
   d. >96 percent

2. According to the American Cancer Society (2012), the five-year survival rate of lung cancer patients is
   a. 5 percent.
   b. 16 percent.
   c. 46 percent.
   d. 66 percent.

3. Traditional therapies for the treatment of advanced non-small cell lung cancer (NSCLC) include generalized therapies, immunotherapies, second line without biomarker, Keytruda, and targeted tyrosine inhibitor drugs.
   a. True
   b. False

4. New biomarker tests are showing promise in treating NSCLC because the presence of the biomarker is predictive of the patient’s response to
   a. generalized treatments.
   b. targeted treatments.
   c. both a and b.
   d. neither a nor b.

5. Profiles of biomarker tests can be used by physicians to customize a treatment plan, which helps to
   a. avoid wasted treatment time.
   b. avoid causing debilitating side effects.
   c. avoid the spending of financial resources on therapies that aren’t likely to work.
   d. all of the above

6. The gene mutations noted in the article that have been found to have a direct role in treatment efficacy and prognosis in NSCLC are
   a. EGFR, ALK, ROS1, RET, KRAS, and BRAF.
   b. EGFR, ALK, and BRAF.
   c. ASK, ROS1, KRAS, and BRAF.
   d. ALK, ROS1, RET, KRAS, and BRAF.

7. Obtaining timely results in biomarker and biopsy information is crucial to the overall chance of survival.
   a. True
   b. False

8. Typical results from tumor biopsies generally take
   a. 1 week or more.
   b. 3 weeks or more.
   c. 4 weeks or more.
   d. 8 weeks or more.

9. According to the article, a recent study showed that the percentage of patients who did not have biomarker results by the time of their initial consultation was
   a. 55 percent.
   b. 70 percent.
   c. 80 percent.
   d. 95 percent.

10. This type of biopsy exploits the presence of cells or DNA in blood or other body fluids that can be measured in a testing system.
    a. tissue
    b. droplet
    c. liquid
    d. none of the above

11. Liquid biopsy shows promise to replace the need for tissue biopsy because it can also subtype the cancer.
    a. True
    b. False

12. Which type of technology uses a water-oil emulsion that is very fast and highly sensitive?
    a. ddPCR
    b. rtPCR
    c. FISH
    d. MALDI-ToF

13. The median turnaround time for ddPCR technology in advanced stage NSCLC is
    a. 1 day.
    b. 3 days.
    c. 5 days.
    d. 7 days.

14. This type of technology has the capability to analyze broad panels of genes for multiple mutations.
    a. PCT
    b. PCR
    c. NF5
    d. NGS

15. Proteomic tests measure the chronic inflammatory proteins associated with patient responses to aggressive cancer and are highly predictive of overall prognosis.
    a. True
    b. False

16. The one proteomic test that is commercially available for NSCLC uses which type of methodology?
    a. nPCR
    b. ddPCR
    c. MALDI-ToF
    d. NGS

17. The term “reflex strategy” refers to a powerful tool that helps guide clinical management of NSCLC and uses which combination of tests?
    a. tissue histology and proteomic tests
    b. tissue histology and genetic/genomic tests
    c. proteomic tests and genetic/genomic tests
    d. tissue histology, proteomic tests, and genetic/genomic tests

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P = Poor; E = Excellent

1. To what extent did the article focus on or clarify the objectives?
   P O O O O E

2. To what extent was the article well-organized and readable?
   P O O O O E

3. How will you use the CE units?
   state license
   employment
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Clinical labs streamline GI testing with MDx

By Sherry Dunbar, PhD

The standard approach for determining the cause of diarrheal disease in a patient is tedious and time-consuming. The series of tests required for each case—representing a range of different assay types, each of which can take days to generate results—doesn’t serve the best interests of patients, physicians, or clinical labs, largely because they do not generate results quickly. The traditional approach was shaped by decades of adding tests for different bacteria, parasites, or other causes as the community’s understanding of these diseases expanded.

Surely if we could invent a new protocol from scratch, knowing everything we now know about these diseases and their causes, it would look nothing like the piecemeal, step-by-laborious-step approach currently used in labs. Today, with the rise of outcomes-based medicine, we have a rare opportunity to do exactly that: rethink how we manage testing for diarrheal diseases. Any effort to rein in costs while improving patient care must involve generating answers more promptly, subjecting patients to fewer tests, and accelerating decisions about treatment.

Molecular testing offers the streamlined process that could meet all of those requirements. There are several options available now, from panel tests that cover the vast majority of infectious causes of diarrheal diseases to “pick-and-choose” assays that allow physicians and lab experts to select the most likely agents. These diagnostics produce results rapidly, with higher accuracy and less hands-on time than conventional tests. They are cost-effective and, most importantly, they get actionable information into the hands of physicians so patients can be treated (or deliberately not treated) sooner.

Diagnostic complexity
Diarrheal disease occurs frequently and has a remarkably high burden, leading to approximately 760,000 deaths in children under the age of five each year worldwide. Globally, there are an estimated 1.7 billion cases annually.

What makes these illnesses so difficult to diagnose is the vast array of potential causes and the tremendous overlap in symptoms. Diarrheal disease can be brought on by viruses, bacteria, and parasites, often through foodborne illness or unsanitary water. But there are also many non-infectious causes of diarrheal disease, such as medications, food allergies, and inflammatory bowel disease. Physicians trying to determine the cause of a patient’s diarrhea must become detectives, hunting for clues to help track down the culprit.

The process begins with a complicated flow chart, which recommends certain tests based on symptoms, travel history, duration of illness, and other pertinent factors. Those tests are run in various clinical labs; microbiology, virology, and molecular testing facilities are each responsible for certain assays. Tests that involve culturing are particularly time-intensive, requiring many different steps and a significant amount of hands-on time. Parasite tests require daily stool collection for three days followed by microscopy, which suffers low sensitivity because it is easy to miss the parasite by choosing the wrong bit of sample to examine.

Usually, these tests are run one at a time; with each negative result, the physician chooses another potential cause to test. Definitive results can take a week or more to generate, during which time the patient is likely either going without needed treatment or being given treatment that is not relevant to his or her specific condition.

Molecular testing
In recent years, new molecular tests have become available for various causes of diarrheal disease. These assays cover potentially responsible infectious agents—viral, bacterial, and parasitic—with some methods including more than 90 percent of potential culprit sites in a single panel. Other types of molecular tests allow users to select the most likely causes and test only for them, but if subsequent rounds of testing are needed, the existing sample can be used; it is not necessary to return to the patient to start the process all over again. Labs that have adopted molecular testing for diarrheal disease can eliminate the vast majority of culturing, enabling their staff to run tests for more patients in less time.

Some payers have expressed concern that panel-based molecular approaches constitute unnecessary testing because they assay for such a broad range of possible causes. The reality is that these tests dramatically improve patient care while reducing the time and costs associated with multiple rounds of conventional testing. Unlike the standard techniques, they produce useful diagnostic results for the vast majority of cases. For most patients, these tests replace a tedious, frustrating process with a “one and done” approach, in many cases getting them on the road to recovery faster. Molecular tests can simplify the diagnostic path for patients, physicians, and clinical labs teams alike.

Numerous studies of molecular tests for diarrheal disease have been conducted in patient populations around the world.
Results from studies in Asia, Africa, the United States, and elsewhere consistently show that these assays are highly accurate, in some cases detecting pathogens missed by conventional tests that have long been considered the standard. 4-7 They also detect cases of coinfection that would likely go undetected with a serial testing strategy. With such strong clinical utility, molecular testing offers the chance to streamline the diagnostic process for diarrheal disease, potentially reducing the morbidity and mortality burden associated with these illnesses.

Moving forward
As more clinical labs adopt molecular assays as the primary test for cases of diarrheal disease, we can expect definitive diagnoses for more patients, as well as shorter hospital stays. A significant reduction in the use of laborious conventional tests will also ease the burden on clinical labs, making it possible to generate answers for more patients in less time.

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How MALDI-TOF MS has changed the microbiology lab

By Mary Valdez, MS, MT

Four years ago in this space, my colleague Anne Beall wrote about the introduction of mass spectrometry into the microbiology laboratory. Her column was forward-looking, because it came just two months after the U.S. Food and Drug Administration (FDA) granted 510(k) de novo clearance to the first matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometer for clinical use in the identification of disease-causing bacteria and yeast. The enthusiasm about this approval was the first fundamentally new technology introduced to clinical microbiology labs in many years. The Cleveland Clinic named MALDI-TOF MS as one of the “Top Ten Breakthrough Medical Technologies of 2013.”

At the time of the FDA clearance of this technology, I was working for a large, full-service provider for clinical laboratory and anatomic pathology services in southern Florida. We served as the core lab for 13 hospitals, providing all routine microbiology testing for them as well as specialty testing for hospitals throughout Florida.

Our lab director was quick to acquire MALDI-TOF MS because we were eager to adopt technology that would reduce the turnaround-time of our results. We immediately realized several key benefits from MALDI-TOF MS. While mass spec-based methods for pathogen identification still require culture, MALDI-TOF can effectively identify a pathogen from significantly less culture growth compared to standard biochemical methods, which require clearly developed and well distinguished colony development. MALDI-TOF MS can often make an accurate identification based on the first signs of growth. This is vitally important and a key benefit of MALDI-TOF that leads to multiple other advantages. Most bacterial organisms begin to grow at 18 to 24 hours, but it can be another day, if not 48 hours or more, before sufficient isolated growth is seen to perform biochemical identification. Because of this, we immediately cut our identification times by six hours to several days. At the first signs of culture growth, we would run the isolate on MALDI-TOF MS, and we had a positive identification within minutes.

The benefits of rapid infection identification are well documented. When clinicians can intervene quickly with optimal antimicrobial therapy, patients recover faster and have reduced length of hospital stay, and hospitals can save dramatically on pharmacy expenditures. Our clinicians noticed this almost immediately after adopting MALDI-TOF MS.

Of course, positive identification is just one part of the puzzle. Rapid identification also provides very useful information regarding pathogens with intrinsic resistance. Anaerobic organisms provide an excellent example of this benefit. Anaerobes are high-maintenance pathogens that require a much more manual and time-intensive process to get a positive identification. They must be protected from oxygen exposure and typically need at least 48 hours of oxygen-free incubation to see visible growth. However, because of poor methodology during specimen collection, transportation, and preparation for anaerobic culture, delayed identification of anaerobes and the need for a second sample collection and repeated culture are not uncommon. The delays prolong proper treatment and can contribute to the deterioration of a patient’s condition.

One example is Bacteroides, an anaerobic gram-negative bacilli. Bacteroides species are a common cause of infections that can develop in all body sites including the central nervous system, head, neck, and abdomen, as well as skin and soft tissue infections. They are often difficult to isolate and identify, and even a small coat of contaminant can lead to slow growth of the organism and the increasing resistance to antimicrobial agents.

One member of the Bacteroides family, B. fragilis group, includes several species including B. fragilis, which is the cause of many clinical infections. The bacteria in this group are resistant to penicillins, usually through the production of beta lactamase.

When an organism such as Bacteroides can be rapidly identified, this provides physicians with information they can use—along with antibiogram data and patient assessment—to make treatment decisions. We found that for certain organisms, especially anaerobes, we could provide physicians with useable data before the susceptibility results were available.

Of course, having a positive identification is critical to selecting the right susceptibility test. So by generating results quickly from colony growth, MALDI-TOF MS also helps in speeding the process of antimicrobial susceptibility testing by guiding the laboratory to choose the correct susceptibility testing to perform.

Another benefit was that with only two reagents, a pipette tip and a MS slide, MALDI-TOF MS significantly reduces the use of the reagents required and waste generated compared to routine biochemical identification.

For the core lab I worked at, MALDI-TOF MS was an ideal tool that provided many benefits, improved our workflow, and provided clinicians with faster results. For this reason, a growing number of labs are investing in this technology.

Microbiology is never black and white, but when you can provide positive pathogen identifications after only 18 to 24 hours—even if the culture is mixed—the benefits to the lab, clinicians and patients are significant.

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Mary Valdez, MS, MT, serves as product manager of ID/AST Systems at bioMerieux, Inc. She joined the company in early 2016 after spending 16 years as a Section Coordinator in the Microbiology Lab at Integrated Regional Laboratories in Fort Lauderdale, FL.
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Emerging strategies for optimizing clinical chemistry performance

Performance partnerships are playing an increasingly important role

By Jeffrey Hill, MLS(ASCP), MS, LSSBB(ASQ), PPM

In the realm of diagnostics, clinical chemistry has been at the forefront of the technological revolution to create automated environments that enable fast, cost-efficient, high-quality testing. In 1978, the industry was changed with the introduction of an automated system that allowed a number of critical routine chemistry tests to be performed using one consolidated unit.1 This initial system made it possible to complete these tests, commonly ordered as a STAT, in less than one minute using a single laboratory sample. This technology became a foundation for the future of automated chemistry testing.

While great strides have been made in chemistry testing technology, today’s clinical laboratories continue to face emerging complexities, owing largely to industry growth, an ever-changing healthcare landscape, and network consolidations. Effective and advancing rapidly, innovation has succeeded in bringing significant relief to over-burdened laboratories carrying the weight of increasing test volumes, stricter cost controls, labor shortages, and multifaceted network operations. In the fast-paced laboratory environment, however, the benefits of technology are not always fully realized. For this reason, many laboratory professionals are looking beyond technology for solutions that will help them achieve their efficiency, cost, and care goals.

Industry advancements have enabled most manufacturers to produce high-quality products with Six-Sigma assay performance. But the availability of these products may be only part of the equation. For laboratories seeking to improve turnaround times (TATs), lower cost of ownership, and address the need for standardization throughout the organization, the other part of the equation may be to optimize available technology by building robust business systems.

Performance partnerships as a total solution

Since the 1980s, industrial companies, faced with the competitive pressures of globalization, have embraced Lean principles, Six Sigma techniques, and continuous process improvement practices to create business systems that offer a sustained competitive advantage.2 Many laboratories have sought similar solutions that would help them achieve performance goals unattainable via technology alone. This has led corporations with successful business systems to partner with their lab customers to help them apply proven continuous improvement methodologies to healthcare. These partnerships are strategic alliances formed for the purpose of elevating a laboratory’s ability to meet increasing industry demands and achieve care and efficiency goals. An established performance partner addresses laboratory operations beyond chemistry instrumentation, considering the strategic use of these instruments, workflow, resource management, and the day-to-day execution of tasks by personnel.

Improving TATs

One of the roles of a strategic partner is to help laboratories optimize operations to improve TATs. This involves designing a laboratory with Lean concepts, measuring performance, and using problem-solving techniques that drive continuous improvement. Many times, lab leaders discover that the lab was not designed in a truly strategic manner. Instead, instrumentation has been acquired somewhat haphazardly, in response to specific needs at specific times. This ad-hoc approach to purchasing instruments can create redundancies in equipment and wasteful workflow. It also puts a strain on already-stretched resources, as each system has its own training protocol, reagent requirements, maintenance schedule, troubleshooting steps, and service contract.

An instrument vendor that understands Lean processes can help identify waste in laboratory personnel about areas where their current workflow is fragmented and inefficient, and enables them to implement process improvements.3

Once equipment and workflow are optimized, vendors may help laboratories build a culture that supports regular measurement of key performance indicators (KPIs) and the use of tools that guide laboratory team members to action. Problem-solving processes are an important part of continuous process improvement. They help teams identify the root causes of problems and then implement meaningful and actionable countermeasures. This step involves full-team engagement, cross-functionality, action-driven response, and the input of a knowledgeable partner who can help to problem-solve areas that need attention.

Lowering cost of ownership

Cost containment is presently a major concern in all areas of healthcare, including clinical chemistry. Lowering testing-related costs involves a clear understanding of a laboratory’s current operational practices around expenditures and revenue. Looking merely at costs per test gives only a portion of the profitability picture. Finding and reducing hidden costs is important to maintaining a laboratory’s economic health.

One area in which hidden costs often lurk is the execution of routine tasks. These include system calibration and quality control functions, both of which are vital for ensuring that equipment performs as intended. Simplifying these activities through automation can promote testing accuracy, reduce workload, and decrease those hidden costs.

Reagent management is also time-consuming. Storing, replacing, and thawing reagents slows down the workflow by requiring staff time and attention. Selecting concentrated reagents allows for fewer replacements, saving on both costs and time. Their smaller packages are also more easily stored. Refrigerated storage space is surprisingly expensive, and it is often not considered when evaluating new instrumentation. Thus improving reagent management can contribute greatly to a laboratory’s overall savings.

To lessen system maintenance burden, requiring precious staff-hours, many laboratories choose instruments with simpler designs that require less cleaning and troubleshooting. Reducing consumables is another way to save on overall costs. This includes using permanent glass cuvettes to minimize resources allocated for their replacements, biohazardous waste disposal, and maintenance of plastic cuvettes.

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System uptime is vitally important to laboratory performance. While costs are surely impacted by a lag in uptime, there also are far-reaching consequences. Emergency rooms and operating rooms may become impacted with patients waiting for test results. Physicians may be unable to provide patients with information in a timely manner, which could affect patient care and compromise the doctor-patient relationship. Finding systems and services designed to maximize uptime is crucial when considering costs and performance.

**Standardizing operations**

As it is in many industries, consolidation is a prominent theme in healthcare. Network consolidations often introduce new challenges, however, including duplication of efforts, multiplication of systems, and non-standardization of processes. Standardizing laboratory operations across a network can improve quality, reduce costs, and maximize labor resources. Standardizing consumables simplifies inventory management tasks and allows kits to be shared across the network, saving costs, creating process efficiencies, and reducing needed storage space. Standardizing workflow means that in all areas of the network, there is consistency in systems and processes. Because of this, laboratory personnel can be cross-trained to work in multiple areas. That is a factor that may be increasingly important as laboratories are faced with continuing labor shortages.

Beyond laboratory optimization, standardization plays an important role in patient care. With standardized processes, tests are processed the same way across a network. Result ranges are the same, so interpretation of results is consistent, not only for the laboratorians but also for the physicians. This can greatly improve laboratory performance and reduce variables that can cause error.

Despite technological advancements, today’s laboratories continue to feel the pressure to deliver accurate and timely results, manage costs, and address the challenges of network consolidations. While high-quality products can greatly improve the efficiency and effectiveness of laboratory operations, these systems can be further optimized through superior business systems. The value of a knowledgeable partner with the ability to implement efficiencies through laboratory design, process mapping, KPI measurement, and problem-solving processes will enable laboratories to enhance the quality of patient care through improved TATs, reduced cost of ownership, and standardization of systems and processes.

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Jeffrey Hill, MLS(ASCP), MS, LSSBB(ASQ), PPM, has more than 20 years' experience in laboratory science within the clinical, research, and academic spheres. He has served as a Lean consultant in a variety of fields including clinical/research laboratory, allied health services, manufacturing, customer service, and logistics. He has earned the level of Master Black Belt within the Danaher Business System and master facilitator in Lean, Leadership and Growth.

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Many infectious agents of clinical significance infect the central nervous system (CNS) and are thus of interest to the diagnostic laboratory. Examples can be found from every imaginable pathogen type; some of the better known suspects include viruses such as herpesviruses, various enteroviruses, and JC virus; bacteria such as *C. pneumonia*, *N. meningitidis*, *T. pallidum*, and *H. influenzae*; yeast and fungi including *C. neoformans* and *Candida* spp.; and parasites like *Acanthamoeba* spp., *Balamuthia* spp., and *T. gondii*.

Many tests for infectious agents can make use of relatively easily obtained sample types, from direct swabs of accessible surfaces to expelled samples (urine, stool, sputum) to peripheral blood samples. Access to the CNS compartment is significantly more challenging, as direct tissue biopsy isn’t a simple option, and the presence of the blood-brain barrier negates any possible use of peripheral blood as a reliable sample type. The best option left is cerebrospinal fluid (CSF), a protein-rich liquid which serves functions including cushioning of the brain, nutrient diffusion, and maintenance of intracranial pressure. An average adult CNS total volume is estimated at approximately 150 ml; however, only relatively small volumes (1-2 ml) are generally available for safe collection via lumbar puncture. CSF is an intrinsically sterile sample type, meaning that almost any pathogen detection is both pathogenic and significant, although exceptions can occur due to contamination during sample collection or may result in context of a systemic, non-CNS infection if there are transient breakdowns in the blood-brain barrier.

**Challenges of CSF**

Two challenges are common in the use of CSF as a diagnostic sample. The first is that titers of organisms may be quite low, which is one of the reasons why highly sensitive molecular methods may be the test modality of choice in this sample type. (By comparison, one study of CSF viral culture for HSV showed only a four percent positive detection rate in biopsy proven cases of HSV encephalitis.) Unfortunately, the second problem is that CSF may often contain numerous substances inhibitory to nucleic acid amplification tests (NAATs) such as polymerase chain reaction (PCR) and in particular is rich in RNases, which can be problematic for efficient recovery of RNA targets such as enteroviruses. Optimal use of CSF as an MDx diagnostic specimen type thus requires both efficient recovery of low titer nucleic acids present and effective removal of a range of possible inhibitors, possibly along with RNase inactivation.

While rapid, crude sample preparation methods can work well for providing PCR template in some settings, this does not appear to hold true when the specimen is CSF. One representative study of this by Alfonso and coworkers reported on the relative efficacy of four CSF sample preparation methods in context of recovery of *T. gondii* DNA. In this example, all four approaches began by obtaining a cell pellet from the CSF by a brief low speed centrifugation. The least effective method was to digest this pellet with proteinase K followed by phenol-chloroform extraction, alcohol precipitation, and resuspension; the authors report a limit of detection (LOD) of 117 tachyzoites. Direct boiling of the cell pellet in sterile water was a better approach, with an estimated LOD of 16 tachyzoites. This was still significantly improved upon by an approach of proteinase K digestion in a cell lysis buffer followed by centrifugation to remove debris and testing of supernatant, with a reported LOD of two tachyzoites. Finally (and reassuringly, if your lab has invested in commercial nucleic acid extraction systems), a commercial extraction method based on the now common chaotropic lysis/silica adsorption/wash/elute approach was the clear winner, with a reported LOD of a single tachyzoite.

Two further observations might be made with regard to these results. First, it’s sometimes suggested that PCR inhibition observed with CSF samples is likely due to high protein content. That the poorest results of this study were obtained with phenol-chloroform extraction (a potent protein removal approach) casts some doubt onto this claim and suggests that CSF inhibition likely arises from non-protein constituents, at least in the context studied here. A second indirect observation is that three of the sample preparation approaches described here would likely have little effect on inactivating endogenous RNases; they are notoriously robust against proteinase digestion and extended boiling. Only the fourth (commercial) method, with use of a chaotropic lysis agent, would have much effectiveness at inactivating RNases. Thus, if the assay target were an RNA species such as an enterovirus, an even bigger bias in favor of the fourth method would likely have been observed. In fact, it’s notable that one of the early references for the use of guanidine thiocyanate (chaotrope)-based extraction methods was expressly in the context of CSF samples.

**Two takeaways**

A takeaway from this, then, is that CSF extraction is probably best done by commercially available, chaotropic lysis-based methods (which include most of the common paramagnetic particle-based methods and common spin-column methods). As another takeaway, recall that we observed above that target organism titers can be low in CSF. This suggests

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that inclusion of a carrier or coprecipitant molecule such as tRNA during the extraction process is also likely a wise choice. (Briefly, these act as a sacrificial material to intrinsic losses in the process; that is, if X ng of nucleic acid is normally lost in the protocol through adherence to plasticware, escape in aqueous waste phase, and other reasons, and all your input is meaningful target nucleic acid but on the order of X ng, you may lose all of it. If, however, you add in 9X ng of a carrier at the start for a total of 10X ng input, now the X ng lost consists of 0.9X ng carrier and 0.1X ng target material, meaning you still have 0.9X ng target material coming out, or 90 percent of your input.) This second point—frequently low target content—is also why functional removal of NAAT inhibitors by simple dilution of extracts may not be a viable option for CSF-derived samples, even though it often works with other, more target-rich specimen types.

As with most other MDx specimen types, fresh samples are ideal; however, freshly frozen CSF samples have been successfully extracted with recovery of at least some intact nucleic acids following prolonged storage. DNA targets are generally more stable than RNA ones for recovery after frozen storage, and in either case use of a sample which has been through multiple freeze-thaw cycles is highly undesirable. Post extraction, the eluted nucleic acids can be stored equivalently to any other MDx extracts (i.e., -20 °C for DNA, or RNA short term; -80 °C recommended for RNA longer term).

While the invasive collection nature of CSF can be outweighed by its ability to sample the otherwise hidden CNS compartment, this value proposition in its collection only holds true when it can be extracted and analyzed in a manner that maximizes its diagnostic utility. Less than ideal laboratory practices that may allow acceptable diagnostic accuracy on less demanding sample types cannot always be expected to perform well when CSF is being examined. Starting with the largest possible input volume of fresh sample and using best practices in extraction methods are crucial in making the most of this sample type.

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Protein biomarker discovery
Researchers are bridging the gap between discovery and validation for clinical use

By Scott Peterman, PhD, and Lisa Thomas, BS, MBA

Diagnostic testing plays a vital role in modern medicine, helping clinicians make informed decisions regarding disease identification and treatment. The majority of routine chemistry tests are currently based on spectrophotometric or immunologic analysis. There has been a growing realization, however, that even advanced diagnostic assays will require screening for multiple (rather than individual) markers using in vitro diagnostic multivariate index assays (IVDMIAs) and the inherent ability of mass spectrometry (MS) to multiplex analytes efficiently and precisely. This has put MS-based protein biomarker discovery at the forefront of molecular diagnostics research.

And much progress has been made over the past two decades. The latest advances in proteomics technologies, from advances in MS technology and tandem mass tag reagents to the creation of powerful bioinformatics software, spectral libraries, and peptide databases, are creating new opportunities for the development of protein biomarkers for disease diagnosis, prognosis, and prediction of response to therapeutic treatment.

However, despite the large number of candidate protein biomarkers reported, there is a well-documented shortfall between the number of candidate biomarkers identified and those cleared or approved by the FDA for clinical use. Here, we consider whether the use of robust quality control (QC) measures and robust experimental design can help bridge this gap and accelerate the translation of biomarkers from bench to bedside.

Protein biomarkers
Proteins are particularly useful molecules to use as biomarkers as they are often the effectors of diseases and the targets of therapeutic treatments. Using panels of protein biomarkers, healthcare experts can perform accurate disease diagnosis through convenient non-invasive testing. Such screening enables early disease diagnosis in donor samples from individuals who otherwise present no unusual symptoms.

But protein biomarkers offer more than just early disease diagnosis; they also present significant opportunities in terms of personalized medicine. In the treatment of cancer, for instance, protein biomarkers are now being used to guide treatment choices. The detection of proteins associated with tumor drug resistance or sensitivity toward chemotherapy, hormone therapy, or immunotherapy is already being used to predict the type of treatment that may be most effective. Used in combination with genome and transcriptome sequencing, targeted proteomics can help healthcare experts deliver more effective treatment tailored to an individual’s condition.

Bridging the gap
The past two decades have witnessed significant advances in the proteomics technologies used to identify new protein biomarkers. Research has resulted in the identification of many thousands of candidate protein biomarkers. However, relatively few of these candidates have successfully translated into FDA-approved clinical diagnostic tests. Too often, biomarkers identified in initial discovery studies have not shown reproducible activity during subsequent validation.

A key consideration when developing clinical diagnostics is defining the clinical intended use. For example, when developing cancer protein biomarkers, it is important to establish whether they will be used for screening, diagnosis, or prognosis. The intended use will determine the target population used to progress the biomarkers from the discovery stage to approval, and will have a significant impact on the overall clinical performance of the diagnostic test.

Careful study design is also essential to reduce the potential for systematic bias and ensure that conclusions are meaningful. Some of the most common sources of bias involve systematic differences in subject selection or specimen collection between donors and control subjects. This bias can be minimized by adopting uniform collection and freezing protocols with accurate knowledge of donor history and, for example, ensuring that not all disease samples are from one institution while healthy samples are from another.

It is also important to ensure that proteomics experiments at the discovery stage are designed appropriately to reduce analytical variability, which can increase the likelihood of false positives when identifying biomarkers. Factors associated with poor sample handling, such as storage duration and temperature, can impact reproducibility in proteomics investigations.

Challenges associated with proteomics
One way to improve confidence in the clinical viability of candidate biomarkers and increase statistical significance is the use of larger population sizes. And, thanks to advances in the analytical performance of mass spectrometry (MS) instrumentation and ultra-high performance liquid chromatography (UHPLC) technologies, as well as rapid improvements in the capability of bioinformatics software, proteomics investigations can now be performed on an unprecedented scale, with exceptional analytical precision and workflow robustness.

Though the ability to study thousands of donor samples in a single proteomics study offers significant advantages in terms of investigational capability, it also presents a number of challenges around the design of analytical workflows. While the acquisition time required for initial discovery stage proteomics investigations may be a matter of days, for large-scale studies involving several hundred or thousands of donor samples this can be several weeks. With a longer analytical run comes the greater likelihood of workflow disruption; this is a factor that is often underestimated and even overlooked completely.

Understanding how factors such as the gradual decline in chromatographic performance caused by the impurities present in biological samples, and the need to recalibrate MS instruments mid-investigation, affect the reliability of experimental data over the duration of an analytical investigation is therefore of increased importance for large-scale studies. Even using the most rugged and robust MS and UHPLC technologies, analytical workflows will need to be interrupted for recalibration and closely monitored for performance issues.

To draw meaningful conclusions from large-scale proteomics studies, it is therefore essential to deploy robust QC and system suitability strategies to separate biological differences from analytical variance.

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Analytical vs. biological variance
Establishing statistical significance in proteomics studies requires hard metrics based on robust analytical controls. There are two approaches that are often adopted for the assessment of analytical variance in these types of studies.

The first approach involves spiking donor samples with one or more non-human proteins that act as internal controls. Proteins such as alcohol dehydrogenase from yeast or beta-galactosidase from *E. coli* are often used for this purpose, although a wide variety of others are also available. To ensure that these controls are representative of the entire sample preparation and analysis workflow, these control proteins should undergo the same protocols that donor samples are subjected to, including sample handling, digestion, and recovery. Proteins should also be chosen to avoid overlap with endogenous peptides where possible.

A parallel approach involves creation of a pooled sample containing all of the donor samples, analyzed at regular intervals throughout the analytical run. This global QC sample would be injected every five to ten injections, thus providing a real-time system suitability check for the full set of donor samples. Using the same sample with exactly the same molecular complexity, and analyzed via the same method, this replicate can be used to determine the statistical variance of the method.

While the QC protein provides system suitability for each individual donor sample, the pooled sample provides a global QC metric at well-defined time points to assess the statistical significance of the overall acquisition workflow. Used in combination, these QC measures enable an assessment of statistical significance of results to be made, and therefore the contribution of analytical variance to experimental variance.

Many software packages exist that can help automate this process and simplify the statistical analysis required. And as the use of certain controls become established, it is likely that software packages will incorporate these more commonly used protocols as default options, further simplifying analysis.

The broader use of biomarker panels in clinical diagnostics promises more personalization and effective treatment of diseases. However, the translational gap that exists between proteomic biomarker discovery and validation is a significant one that must be closed if we are to accelerate the progression of sensitive and selective biomarkers from the research laboratory into the clinic.

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Keeping clinical lab errors to a minimum

By Jeff Osborne

Today’s healthcare climate challenges the clinical laboratory to offer improved patient care while reducing costs and increasing efficiencies. There is no room for error, however small. Seventy percent of all medical decisions are made based on high-volume laboratory testing and the corresponding results.1 Critical information in the clinical laboratory directly impacts patient care and must be delivered with excellence. Performance improvement initiatives to optimize the lab are integral to achieve key quality benchmarks. Methodologies must be put in place that safeguard against lab errors at all stages, and a culture must be developed in which staff will not hesitate to report deficiencies. Leadership also must be engaged and provide oversight at all levels within the health system to be effective. While the frequency of errors in the clinical lab is generally lower than other departments across a health system, any error that impacts quality patient care is too many.

The impact of error

Errors are a lab’s worst enemy because they increase waste—wasted time, resources, and supplies. These wastes cost the lab money, decrease its efficiency, and ultimately pose increased risks for the patient.

Clinical labs perform billions of tests each year. The results represent the bulk of a patient’s electronic medical record, and they are a key driver of medical decisions. Given the volume of tests performed, even if only a small fraction have errors, large numbers of patients can be affected. While the impact on patient care is not something we can easily apply a value or a dollar amount to, the bottom line is that every test matters, and labs need to consistently deliver the right results for the right patient at the right time.

Phase by phase

Testing presents challenges across the phases—pre-analytical, analytical, and post-analytical—all of which should be reviewed and addressed.

The majority, probably the large majority, of errors are associated with the pre-analytical phase. Mislabeled specimens are the most costly. Whether specimens are collected by phlebotomists or nurses, the laboratory has a major role in identifying, tracking, and correcting errors. Larger hospitals and health systems have accelerated their use of positive patient ID barcoding and handheld printers to print patient labels at the bedside as one method of addressing the problem. In facilities where this has been implemented, a drop to almost zero patient ID errors during patient specimen collection has been observed.

To further tighten up the patient identification process, the next step in achieving quality excellence is to track “near misses.” Under-reporting can be an issue in this context. To empower staff to report near misses, there often needs to be a culture shift in which all staff are de-personalized and the entire organization looks at the process that resulted in the error. Health systems that have a strong Lean program or have adopted the practice of “Just Cause” typically approach errors in a manner that empowers staff to speak up about potential errors.

For the analytical phase, emergency department (ED) test turnaround time (TAT) is one of the most common metrics. Labs use this metric to evaluate how well they perform some of their most critical tests. Delays in delivering the test results can lead to delayed patient care and extend length of stay in the ED. When evaluating how a lab is performing on ED TAT, multisite hospital laboratories often have the added challenge of disparate criteria for evaluating what constitutes good performance. To address this, all stakeholders should be involved to define TAT acceptance criteria and measure their performance against internal and external benchmarks. Being able to identify where there are gaps in performance and making them visible allow the laboratory team to take steps to close those gaps.

As the quality process matures, the lab can move from measuring the outcomes metrics (ED TAT) to focusing on the leading indicators that drive the TAT (for example, non-barcoded, QNS samples). Implementation of quality-leading indicator metrics and a robust program to review and act quickly on the results are staples of laboratories that successfully eliminate errors at this stage.

The post-analytical process is the final step. The sample was successfully collected, and the lab has completed the ordered tests. Now all that is left is to tell the physician. Errors at this stage in the process range from sending results to the wrong physician, to having to resend the results because they didn’t arrive, to failing to call physicians with critical value results in a timely manner.

Technology can play an important role in reducing errors in this stage. In the outreach environment, non-affiliated physician groups can be connected directly to their laboratory results through a portal, so the right physician receives his or her patients’ results (usually the same day). This saves significant non-value added time for laboratory staff, who no longer need to manually mail/call results to physicians—a process that is in itself susceptible to errors. Being able to reduce the number of errors and improve the consistency of result delivery helps a lab demonstrate an improved quality maturity level. This in turn leads to increased physician satisfaction and the lab becoming the physician’s “lab of choice.”

Maintaining improvements

Once a process change has been put into place, the only way to maintain that change is through ongoing, proper monitoring of the process. This requires regularly tracking and displaying the performance of the leading indicators and differentiating between normal and special cause variation in results (control charts are especially helpful with this). Successfully sustaining a positive process change also requires a culture where staff work together to identify problems. When the entire team takes ownership of its performance and is supported in its goal to achieve zero defects, the impossible goal of “perfect” quality becomes approachable.

The next 20 years will see advanced clinical labs taking on a more significant role in healthcare delivery. Using advances in technology and analytics and developing a culture of excellence will allow laboratories to improve their quality and service and mature into powerhouses for positive patient care. The success of the lab of the future depends on the work we do today to increase efficiency, utilization, and quality.

REFERENCE

Jeff Osborne is the Chief Executive Officer and President of Accumen, Inc. (and its subsidiary, Chi Solutions, Inc.), which provides clinical laboratory consulting, outreach, comprehensive patient blood management (pBHM), and laboratory excellence solutions for hospitals and health systems.
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The human side of lab automation

Here are some best practices to break down the “silos”

By Sophie Dochez Belin

Breaking down silos in your organization is the first step to a smooth automation transition, and it should happen before equipment installation even begins. If thinking about how to do this makes you feel uneasy or confused, you are not alone. But it can be done, with advanced planning, and maybe a little help from a friend.

The human side of the automation process often is overlooked, but it is as important as addressing the physical and technical aspects of the transition. The most successful lab transformations occur as a result of staff input, alignment and adaptability—all of which require communication.

The more a laboratory automation solution project is fully integrated, through IT and multi-disciplinary analyzers, the more complex the change is for an organization that, like most do, had been operating in silos. This is because traditional processes and muscle memory are interrupted when an automation project is underway, but the workload does not stop. Strong collaboration among laboratory staff and stakeholders, however, preserves productivity during the temporary disruption.

While every project is unique, deploying the following best practices throughout implementation will improve alignment among colleagues and positively affect the outcome.

Identifying stakeholders

Upon deciding to initiate an automation project, identify each stakeholder who will support or feel the effect of the project. This is an opportunity both to gain crucial buy-in through staff involvement and to excite staff by demonstrating how their input will make their roles and the laboratory’s offerings better. Stakeholders range from lab directors and purchasing decision makers to vendor project managers and many others—such as IT specialists, quality managers, lab technicians, disciplines managers, and others who can offer insight into the hospital or health system’s protocols for upgrades or modifications. This is an opportunity both to gain crucial buy-in through staff involvement and to excite staff by demonstrating how their input will make their roles and the laboratory’s offerings better. Each stakeholder will bring to the table different experiences, backgrounds, and skill sets as part of the planning process.

Give them a voice

Once you have identified stakeholders, meet with them to develop a list of needs and desirable outcomes, and to discuss their anticipated roles and responsibilities during planning and execution. Discuss all possible goals versus what is feasible against the project budget, to ensure that everyone is aligned on the outcomes. Goals should be specific, measurable, and, most important of all, achievable. Expand thinking beyond one or two years ahead to consider expansions and updates that may happen five or 10 years from now. All of these variables will contribute to developing the most effective project plan. Discussion points should include:

• internal and external factors, opportunities, and risks that may influence the outcome of the project
• the budget
• specific objectives and project scope (and importantly, what may be considered outside the scope)
• a realistic and achievable timeline with specific milestones
• defined return on investment so stakeholders can easily recognize the value
• frequency and forms of communication to keep stakeholders apprised.

Consider outside help

How to navigate these decisions—or where to begin—may seem overwhelming. Consider enlisting the aid of a workflow consultant and a project manager.

A workflow consultant is an expert trained to methodically analyze a laboratory’s productivity objectively and offer solutions for improvement. He or she adds value to the project team by conveying to decision makers cost justifications for modifications based on process improvement methodologies and offering case studies from other projects with similar goals. The early planning stage is the optimal time to add a workflow consultant to the project team.

A project manager is an expert certified to coordinate the technical and physical aspects of implementation, resources management, and third-party management. The project manager works hand-in-hand with the workflow consultant and is responsible for validating project milestones and timing, and for adhering to budget compliance.

Maintain stakeholder involvement

Deliver regular progress updates. Use the predetermined channels to communicate to all stakeholders. There is no such thing as over-communication. Take advantage of the opportunities to celebrate milestones and to highlight the success criteria established during the planning phase. When the project is complete, showcase the ROI the laboratory is contributing to the greater hospital or health system.

In closing, automation success hinges on detailed planning and cross-collaboration, which requires input from and communication with stakeholders from the beginning. Communication and involvement throughout every implementation phase will avoid common obstacles resulting from miscommunication or ambiguity.

Sophie Dochez Belin serves as Global Marketing Manager for Services for Siemens Healthineers Laboratory Diagnostics. In her role, Sophie is responsible for identifying new service offerings to enhance customer satisfaction, from lab design services to performance management services.

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North Memorial Health Care

An example of the value that a workflow consultant and project manager can bring to an automation project is provided by the experience of the North Memorial Health Care (NMHC) reference laboratory in Minnesota.1 NMHC serves the Twin Cities metropolitan area with a Level I trauma center, community-based primary and urgent care, and a 24/7 reference laboratory that provides vital services to area physician offices, clinics, nursing homes, and other organizations. Its reference laboratory was among the first in the area to implement automation, but as the system aged and healthcare reform challenged the NMHC to run lean, the laboratory could no longer meet goals to improve quality, efficiency, and productivity while reducing costs. Too many processes remained manual and therefore prone to error, leading to workflow inefficiency and inconsistent turnaround times, which in turn forced some testing to be sent offsite.

NMHC aimed to generate revenue by expanding its reference laboratory but was constrained by a system that could accommodate neither growing demand nor changing test menus. Defining its upgrade requirements, NMHC wanted total automation, from pre-analytic to post-analytic processes, with the ability to prioritize STAT testing on the track. It sought a consolidated solution that would enable the lab to cross-train staff to work where they were most needed. A smaller-footprint solution would occupy less space and also take less time for people and tubes to traverse.

The consultation team performed a workflow analysis that identified opportunities to optimize track design, menu balance, and load balance. For example, to streamline workflows, the laboratory deployed automation modules for tube input/output, centrifugation, decapping, sealing, desealing, and refrigerated storage and retrieval. With guidance, NMHC designed its track with a “T” at one end to accommodate more instruments for a seamless transition when the lab integrates additional test disciplines in the future.

At pre-implementation meetings, the workflow consultant and project manager set expectations, answered questions, and provided a timeline. Further, they project-managed the installation to ensure everything was in place to support smooth implementation and trained NMHC staff on the new system.

The NMHC laboratory automation example demonstrates the advantages of deploying a strategic vendor relationship to help navigate the process. NMHC now has increased capacity, faster and more-consistent turnaround times, and staffing efficiencies. After implementing automation, the laboratory was able to increase its annual reference lab sample volumes 12 percent. Additionally, the lab was able to decrease turnaround times for BNP and troponin tests to benefit trauma, stroke, and cardiac patients. BNP turnaround times were reduced by 19 percent and troponin turnaround times were reduced by 17 percent.1 These improvements were critical in extending NMHC’s leadership as both a community care provider and a revenue-producing reference lab.

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Humanitarian endeavor brings rapid cancer diagnostics to sub-Saharan Africa and Haiti

By Dan A. Milner, Jr., MD, MSc(Epi), FASCP

More than 18 months ago, the American Society for Clinical Pathology (ASCP) set out to design a humanitarian program of major proportion. At the time, ASCP CEO E. Blair Holladay, PhD, SCT(ASCP)CM, called it “herculean.” The endeavor was to bring rapid cancer diagnostics to severely resource-limited countries in sub-Saharan Africa and the Caribbean nation of Haiti.

Approximately 650,000 people in Africa develop cancer annually, and about 510,000 cancer deaths occur annually due to limited treatment. More than one-third of the cancer deaths in Africa are from cancers that are easily preventable and/or treatable, if detected early. Histotechnology laboratories are a major gap in many African countries, which prevents many people from getting the diagnosis and treatment they need.

Since it was announced in October 2015 by the administration of former President Obama, Partners for Cancer Diagnosis and Treatment in Africa has achieved several major milestones. Last fall, it introduced advanced histotechnology and telepathology to the Butaro District Hospital, in Butaro, Rwanda. The telepathology connection is enhanced by the simultaneous installation of a fully automated tissue processing system, which has transformed the capacity of the laboratory toward 1,000 blocks per day and allows for same day turnaround on biopsies. The Partners Initiative has also entered into an agreement with Rwanda’s Minister of Health to move forward with augmenting a second laboratory site and providing cancer diagnosis and treatment education to clinicians in 47 different hospitals.

Partnership with Mutombo

In December 2016, ASCP announced a partnership with NBA Hall of Famer and philanthropist Dikembe Mutombo to provide patients in his homeland, the Democratic Republic of Congo (DRC), access to rapid cancer diagnostics and appropriate care and treatment. Plans call for building a new histopathology lab, which will be used by Biamba Marie Mutombo Hospital in Kinshasa, DRC, and will add to the existing histopathology laboratory capacity in the DRC.

In March 2017, ASCP leaders visited Kenya, Uganda, Tanzania, Rwanda, and the DRC to meet with the stakeholders and conduct assessments to determine country readiness to open more telepathology laboratories. As a result:

- ASCP has completed planning for telepathology services at the Rwanda Military Hospital (RMH) to serve RMH, Kigali Central Teaching Hospital, and King Faisal Hospital in Rwanda. Deployment began in May 2017.
- The Uganda Cancer Institute (UCI) is planning implementation for telepathology with ASCP in Kampala to serve UCI, Mulago Hospital, and Makerere University in Uganda, with deployment scheduled for August 2017.
- The Kenyan National Public Health Laboratories is installing a national anatomic pathology reference lab in Nairobi, which will serve all patients in Kenya through referral networks and hubs and which ASCP plans to support with telepathology.
- The Kilimanjaro Christian Medical Center is planning implementation for telepathology with ASCP in Moshi, Tanzania, to serve the 15 million-plus catchment area of patients for diagnostics of cancer.

The rapid pace at which the Partners Initiative has been moving forward would not have been possible without three key elements: partnerships, country assessments, and funding. The process itself began by connecting with partner countries to understand the perceived needs, assessing the situation on the ground to determine the actual needs and what is most feasible and plausible within that location, and then creating an implementation plan.

In-country assessments

ASCP hopes that observers do not look at the second element of the Initiative, the country assessment, and consider it to be patronizing—affluent folks in the United States responding in a condescending way to people in “underprivileged” countries. That’s not what ASCP and its partners are doing, and to say otherwise would be a bad rap. The fact is, it is common for people of any nation who ask for help in pathology not to—well, not to be pathologists. Therefore, some mutual discussion and education about pathology is often required to get a team all on the same page.
challenges then comes in the implementation that follows. This is where partners come in—so challenges can be met and unforeseen issues can be dealt with.

It’s important to keep in mind that ASCP can’t do it alone, and it’s critical to have buy-in from the country partners, including the Minister of Health, the pathologists, the hospitals/health centers, and the financial backers for the effort. Each country is unique regarding who these partners are.

The Partners for Cancer Diagnostics and Treatment in Africa Initiative includes a medical education steering committee as well as partners who have education as their mission. Part of the process includes an assessment of a country’s current and future needs. Initiative leaders work with in-country schools and partners to ensure that there is a plan in motion to create the sustained workforce needed to do the work going forward.

Meeting financial challenges

Then there is the issue of funding, the third element in the Initiative. Whether through donations of equipment or money, there must be fiscal support for a project because pathology is expensive in terms of personnel, reagents, equipment, and time. The Initiative has reached out to establish critical industry partnerships, as well as with leaders in several countries in sub-Saharan Africa and in Haiti. Sakura Finetek provided histopathology instruments to the laboratory for preparing biopsies. Pfizer provided funding support. Global health expert Paul Farmer, MD, and his team from Partners in Health (PIH) make care and treatment available for patients post-diagnosis. Other prestigious partners include Roche Diagnostics, GE Healthcare, the National Cancer Institute, and the Union for International Cancer Control (UICC). The Partners Initiative is also supported by more than 600 ASCP members who have volunteered their time to review slides and make diagnoses, via cloud technology. A team of ASCP volunteer pathologists in the U.S. will use the telepathology equipment to perform rapid diagnostics and review patient specimens for therapy in conjunction with the one pathologist stationed in Butaro. The system has multiple uses, including primary diagnostics (when pathologist is absent), secondary consultation, clinical correlation conference, and teaching Rwandan pathology residents.

Recruiting new partners

All the solutions for cancer in Africa exist. We just have to get them to Africa in an efficient and timely manner to start seeing impact. We need everything for standard pathology including grossing hoods, tissue processors, embedding stations, microtomes, slide stainers, and coverslippers. We need microscopes. We need storage equipment for blocks and slides. We need computers and software to manage the laboratory. We need reporting systems to get the diagnoses back to the patients and care givers.

We have identified partners who are helping or can help us with these items, but no single partner can provide sufficient numbers of any one item to meet all of the needs. We need clinicians in-country to be trained to identify cancer; surgeons to be able to biopsy/remove lesions; oncologists to be able to act on our diagnoses; and a cadre of ancillary health workers to support and care for our patients. Again, we have identified partners, but do not have enough to cover what we could do. So, our major challenge is to either recruit duplicate partners to expand what we can do or publish what we are doing in a “how to” manner so that others can create and execute similar approaches. This is not a competition and not a process to seek glory. This is providing care for people who need it—a moral obligation in a time when cancer does not have to be a death sentence.

Dan A. Milner, Jr., MD, MSc(Epi), FASCP, is chief medical officer of the American Society for Clinical Pathology (ASCP) and oversees the Society’s global healthcare initiatives. He came to ASCP in September 2016 from Harvard Medical School, Boston, where he held the positions of Associate Professor of Pathology and Associate Professor in the Department of Immunology and Infectious Disease at the Harvard T. H. Chan School of Public Health.
Testing for vaginitis and group A strep

This month, we introduce our newest “Tips” expert: Nicholas M. Moore, MS, MLS(ASCP). Mr. Moore serves as Assistant Director of Clinical Microbiology and Assistant Professor at Rush University Medical Center in Chicago. He is responsible for the education of medical students, pathology residents, and infectious disease fellows related to clinical microbiology. He is actively engaged in clinical research funded through the Centers for Disease Control and Prevention (CDC) related to the rapid identification of multidrug resistant organisms and controlling the spread of these organisms in healthcare settings.

I have just moved to a new hospital. On the vaginal wet prep, we have only three reportable parameters: yeast cells, clue cells, and trichomonas vaginalis—but not white blood cells (WBCs). Do you think that in not reporting WBCs we are leaving out an important parameter for diagnosing vaginitis?

Vaginitis is a general term that refers to a myriad of disorders of the vagina that may be due to infection, inflammation, or other causes that lead to changes of the vaginal microbiota. The most common symptoms include a malodorous discharge, itching, changes in urinary frequency, and general discomfort. Commonly, vaginitis is due to infection with Candida spp. or Trichomonas vaginalis, which when combined account for more than 90 percent of cases.

Because these symptoms are non-specific, women who develop these symptoms should be evaluated by a clinician. The evaluation should include a pelvic examination and some limited diagnostic studies to determine the cause. Saline wet mounts are often used in approaches to provide diagnostic evidence for vaginitis in symptomatic women. A sample of vaginal discharge is collected with a vaginal/cervical scraper or a cotton-tipped swab. The sample is mixed with a few drops of 0.9 percent saline on a slide, coverslipped and examined using light microscopy. Normal vaginal discharge should reveal a predominance of squamous epithelial cells, rare polymorphonuclear leukocytes (PMNs), and Lactobacillus spp. The laboratorian is checking for the appearance of budding Candida spp. hyphae, T. vaginalis, clue cells, or increased PMNs, as these are characteristics of bacterial vaginosis (BV).

In my laboratory, we report the Nugent score, which takes into account the average number of morphotypes of bacteria, including Lactobacillus, Gardnerella/Bacteroides, and curved Gram-negative bacilli. We report and semiquantitatively the presence of PMNs, yeast, and clue cells as rare, few, moderate, or many. We perform a separate Trichomonas antigen test; for the majority of our patients both tests are ordered.

I think the presence of WBC may be helpful, but if your laboratory is using only the Amsel criteria, reporting WBC is not one of the parameters. The Amsel criteria includes production of a grey-white discharge, increased vaginal pH >4.5, positive whiff-amine test, and/or >20 percent of observed epithelial cells seen are clue cells.2 In one study of 640 women evaluated for BV, observation of clue cells was the most reliable diagnostic finding to predict BV.

A month ago, we heard that group A strep should be tested with reagents to group and report other non-haemolytic streptococci. Why is this necessary?

Because of the high specificity of most commercial latex kits, I don’t think it is necessary to confirm PYR on a beta hemolytic strep isolate. I do think it is important, though, that other beta hemolytic strep colonies that grow but test negative for group A be tested with reagents to groups C and G, as these should be reported to cause pharyngitis. Depending on the local epidemiology or in certain scenarios, the presence of other organisms could be responsible for a patient’s condition and should not be ignored.

Our doctors request strep group A culture on throat specimens which are negative for rapid strep group A testing. On culture workup, if we have beta hemolytic strep, we perform latex grouping only for GAS and report negative for GAS if latex is negative and positive if latex is positive. I think we should confirm all GAS with PYR, and also should group and report other non-GAS. What is your take on this?

Throat culture continues to be the recommended standard to diagnose exudative pharyngitis caused by group A strep (Streptococcus pyogenes).1 Throat cultures have a reported sensitivity between 90 percent and 95 percent.2 However, most labs first rely on a rapid test directly from a throat swab. Many commercial rapid antigen tests have specificities ≥95 percent, but sensitivities can vary from 65 percent to 90 percent.2,3 Because of this decreased sensitivity, it is recommended and best.

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Table 1. Differential diagnosis of organisms that can cause an exudative pharyngitis.

Table 1. Differential diagnosis of organisms that can cause an exudative pharyngitis.
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**Automated ESR analyzer**

The iSED is a fully-automated ESR analyzer that is capable of analyzing samples in 20 seconds, using just 100μl of blood directly from the primary EDTA collection tube. The 20-position iSED has a continuous, random access feed and is also compatible with BD Microtainer MAP Microtubes without any additional sample manipulation, making it effective for pediatric testing and avoiding QNS issues. No batching, pipetting, sample splitting, or duplicate primary tubes are necessary. The analyzer interfaces with any LIS, measures 14.3 x 10.5 x 13.4 inches, and is manufactured in the United States.

ALCOR, www.rsleads.com/706ml-151

**Clinical chemistry system**

The ACE Axcel Clinical Chemistry System offers advances that enhance in-office laboratory testing. Its comprehensive menu of routine and specialized assays provides an effective tool in the diagnosis and management of diabetes, heart disease, metabolic syndrome, and anemia, as well as other diseases. Processing up to 285 tests/hour, the ACE Axcel offers touch screen functionality, an intuitive user interface, and Internet connectivity, with no external water or waste supply required.

Alfa Wassermann, www.rsleads.com/706ml-152

**Simplified urinalysis testing**

The AU-4050 is a fully automated and integrated urine analyzer that consolidates two technologies to perform urine chemistry and sediment analysis. The compact analyzer measures 31.5 inches wide. This provides the ability to standardize technology throughout a healthcare network. The hybrid analyzer employs flow cytometry technology to reduce subjective sediment interpretations.

**Helicobacter pylori test**

AutoGenomics Inc. has developed a test to detect *Helicobacter pylori* and mutations at 2142G and 2143G on the 23S Ribosomal RNA. Several publications indicate that these mutations are responsible for causing resistance to clarithromycin, the first line drug prescribed for eradicating *H. pylori*. The INFINITI H. pylori QUAD Assay can be performed on AutoGenomics’ INFINITI Plus and INFINITI High Throughput System (HTS), which utilize a proprietary multiplexing microarray technology. The INFINITI H. pylori Assay is for Research Use Only and not for use in diagnostic procedures. AutoGenomics is currently conducting clinical studies for 510K submission for this assay to the FDA.

AutoGenomics, www.rsleads.com/706ml-154

**Multiplex testing includes QC**

The BioPlex 2200 System combines proprietary random access multiplex testing with innovative software and QC features to maximize workflow and ensure result accuracy. Fully automated, it eliminates batch testing, providing reproducible results with fast turnaround times. This System supports a variety of autoimmune, infectious disease, and specialty assays, such as the fifth-generation HIV Ag-Ab assay and the Vitamin D assay. Processing up to 285 tests/hour, the ACE Axcel delivers consistent technology. This unique and user-friendly system includes features to simplify workflow with continuous access loading and unloading of samples. Other features include disposable tips to eliminate contamination and sample carry over, a unitized test cartridge to reduce waste of reagent and eliminate cross contamination, 120 tests/hour, 30 minute time to result for all assays, stand alone.

BioPlex 2200 can process a minimum of 150 individual bead results per assay.


**Immunoassay instrument based on CLEIA**

The LUMIPULSE G1200 is a robust, mid-sized, fully automated immunoassay instrument based on CLEIA (chemiluminescent enzyme immunoassay) technology. The unique and user-friendly system includes features to simplify workflow with continuous access loading and unloading of samples. Other features include disposable tips to eliminate contamination and sample carry over, a unitized test cartridge to reduce waste of reagent and eliminate cross contamination, 120 tests/hour, 30 minute time to result for all assays, stand alone.

**continued on page 48**
Optilite® is a special protein analyzer designed to bring simplicity to complex analytical processes.

**Key features include**

- Automatic re-dilution to end result
- Continuous loading and unloading of samples, reagents and cuvettes
- Three methods of antigen excess protection
- Optimized assay protocols for Freelite®, subclasses, and many other special protein assays with wide measuring ranges and large dilution steps

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Visit us at AACC 2017 **Booth 1629**

The Specialist Protein Company

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Binding Site Inc.
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info@thebindingsite.com
www.bindingsite.com
or capable of connecting to track systems, and faster calibration using less reagent (most assays use 2-3 point calibration).

Fujirebio, www.rsleads.com/706ml-156

Blood lead analyzer

These FDA-approved blood lead analyzers use electrochemistry to provide quantitative results in three minutes, using just 50 μL of blood. LeadCare Ultra offers throughput and convenience for high-volume clinical labs, while LeadCare Plus makes it cost-effective for labs to bring lead testing in house at virtually any volume. These compact systems feature electronic calibration, require no set-up or routine maintenance, and don’t need highly trained staff to operate them. LeadCare II is a CLIA-waived blood lead analyzer for use at the point of care.


800 photometric tests per hour

The BA-800M Chemistry Analyzer was launched in early 2017. The analyzer offers a throughput of 800 photometric test results per hour and an overall throughput of 1,200 tests per hour with ISE. The Sample Delivery Module offers 440 sample positions, providing large volume laboratories hours of unmanned operational time. The design of this analyzer minimizes reagent usage per test, ensuring that the laboratory is recognizing the lowest operating cost per test. The BA-800M can be twinned to increase the capacity for labs with expanding test volumes. The advanced features of the BA-800M Analyzer provide the laboratory with smooth and enhanced operational and workflow efficiencies.

MedTest, www.rsleads.com/706ml-158

Cardiac biomarker analyzer

This cardiac biomarker analyzer is available in the U.S. with a 5.1 percent CV for Troponin I at the 99th percentile cutoff. With the flexibility to run whole blood or plasma samples, PATHFAST allows for up to six simultaneous tests in under 17 minutes. The test menu includes Troponin I, CK-MB, NTproBNP, D-Dimer, hsCRP, and Myoglobin. With measurement unaffected by hemolysis (up to 1000 mg/dL), results can be obtained quickly and with accuracy and precision.

PATHFAST, www.rsleads.com/706ml-159

Chemiluminescence-based immunoassay

The FastPack IP is a chemiluminescence-based immunoassay analyzer that is designed for the physician’s office laboratory. With its simple three-step operation (pipette sample, load the pack, press RUN) and its rapid turnaround time (7-12 minutes depending on assay), the FastPack IP will fit into any workflow. The system’s menu consists of Vitamin D, Testosterone, PSA, TSH, T4, and hCG. The FastPack IP minimizes the need for callback of patients as it allows diagnosis and treatment in a single visit.


POC PT/INR coagulation analyzer

The Xprecia Stride Coagulation Analyzer is a POC PT/INR device cleared by FDA based on the new rules published in March 2016. It delivers fast, reliable Prothrombin Time/International Normalized Ratio (PT/INR) testing for POC monitoring and management of oral anticoagulation therapy with warfarin, a vitamin K antagonist. No bigger than a smartphone and weighing just 10.5 oz., the Xprecia Stride Coagulation Analyzer can be brought directly to the patient’s finger for efficient and comfortable blood sample application. The analyzer uses fresh capillary whole blood, and results are expressed as INR. It utilizes the same Dade Innovin reagent used by Siemens Healthineers central lab analyzers to minimize any potential for variability. Studies have shown the performance to be equivalent to a reference laboratory hemostasis system, with results available within minutes.

Siemens Healthineers, www.rsleads.com/706ml-161

Compact chemistry analyzers

The Indiko series, Indiko and Indiko Plus, are fully automated random access bench-top analyzers. Analyzer, system reagents and consumables form a fully supported system for therapeutic drug monitoring and drugs of abuse testing. The user menu is intuitive, and the continuous way of working, adding samples, reagents, and cuvettes without interrupting the ongoing analysis, gives walk-away freedom. The low-volume cuvette design enables small sample and reagent volumes and minimal water consumption. On-board sample capacity is up to 108, and any mix of sample cups or tubes can be used.

Tissue cassette printer
The Signature Cassette Printer is designed for use in pathology and histology labs to print high-resolution text, graphics and bar codes directly onto tissue cassettes. The increasing use of 2D bar codes for accurate specimen identification also requires the use of a latest-generation direct-to-cassette printer. The Signature Cassette Printer utilizes thermal transfer ink ribbons. Advantages include: 1) virtual silence while printing; 2) no smell or smoke; 3) does not require proprietary cassettes and no fume removal system is required; 4) no ink tanks or print heads that dry out, need maintenance, and have short expiration dates; 5) crisp, clear text, graphics, and bar codes that won’t smear or rub off during or after processing; and 6) the ability to print color on white cassettes, eliminating the need for colored cassettes. An exclusive feature of the Signature Cassette Printer is that a smaller lab can start with the manual-feed SCP-M. When processing volumes increase, it can add the robotics module later. The same SCP-M printer is simply configured for robotics and lab automation enclosures
HEMCO enclosures are designed to enclose robots and other lab automated processes by providing exhaust air systems or HEPA filtered clean workstations. Robots are beneficial in many applications, and are proven to increase efficiency and productivity. Robots integrated into existing facilities are shown to increase output and improve quality, while providing additional flexibility in the production process. Enclosures are built to protect robotic processes from contamination and personnel from hazardous fumes. Utilizing a flexible, modular design, HEMCO Enclosures are engineered and built to exact customer size and design requirements. HEMCO offers a wide selection of standard sizes in vented or HEPA filtered models.

Get to the next-level of HIV testing
Introducing the BioPlex® 2000 HIV Ag-Ab diagnostic test. The first and only test that simultaneously detects, differentiates, and reports HIV-1 p24 antigen and antibodies to HIV-1 (Groups M and O) and HIV-2.
Bio-Rad Laboratories
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BioFire FilmArray Torch
FilmArray Torch is the latest advancement in molecular infectious disease diagnostics. The high-throughput FilmArray Torch is a fully-integrated, random and continuous access system designed to meet your laboratory’s syndromic infectious disease testing needs.
BioFire Diagnostics
www.rsleads.com/706ml-402

Simplify POCT Administration, Management, & EHR Integration
Orchard® Trellis™ offers POCT management and EHR integration tools to ease the workload of POCT coordinators. Results are captured real-time in your LIS and EHR, and Trellis supports user certification, remote handling of QC for POCT instruments, and automated billing.
Orchard Software
www.rsleads.com/706ml-401

KRONUS® is pleased to offer the first commercially available 3-Screen Islet Cell Autoantibody Test Kit. 3-Screen Islet Cell Autoantibody (GAD1A/2/ZnT8Ab) Test Kit†, provided in a simple, highly-robust and user-friendly ELISA assay format.
†For Research Use Only. Not for Use in Diagnostic Procedures.
KRONUS, Inc.
www.rsleads.com/706ml-403

Forensic grade consumables
A new product line sealed with the new purity grade “Eppendorf Forensic DNA Grade” complies with the stringent requirements of the recently released ISO18385. This standard specifies the demands on manufacturers of products which are used in forensic DNA laboratories to further minimize the risk of contamination. Eppendorf confirms the compliance for every production lot and provides lot-specific certificates. The comprehensive approach of this product line assures an excellent purity and performance level as well as optimised packaging that supports contamination and error-free handling. The Forensic DNA grade products encompass consumables for DNA extraction, sample processing, and PCR setup as well as for sample storage.
Eppendorf
www.rsleads.com/706ml-200

Robotics and lab automation enclosures
SHEMCO enclosures are designed to enclose robots and other lab automated processes by providing exhaust air systems or HEPA filtered clean workstations. Robots are beneficial in many applications, and are proven to increase efficiency and productivity. Robots integrated into existing facilities are shown to increase output and improve quality, while providing additional flexibility in the production process. Enclosures are built to protect robotic processes from contamination and personnel from hazardous fumes. Utilizing a flexible, modular design, SHEMCO Enclosures are engineered and built to exact customer size and design requirements. SHEMCO offers a wide selection of standard sizes in vented or HEPA filtered models.
HEMCO
www.rsleads.com/706ml-202

3-Screen Islet Cell Autoantibody Test Kit
KRONUS® is pleased to offer the first commercially available 3-Screen Islet Cell Autoantibody (GAD1A/2/ZnT8Ab) Test Kit†, provided in a simple, highly-robust and user-friendly ELISA assay format.
†For Research Use Only. Not for Use in Diagnostic Procedures.
KRONUS, Inc.
www.rsleads.com/706ml-403
New automated HDL3-C assay from Randox

Introducing a new automated assay for quantitative determination of HDL3-C in human serum or plasma, which can be applied to most biochemistry analyzers. Randox HDL3-C is for research use only, and not for diagnostic use in USA.

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Randox Laboratories-US, Ltd.
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Optilite® – The Future of Special Protein Testing

Optilite is the perfect solution for your modern protein laboratory. It’s fully optimized to create simplicity from complex analytical processes. The analyzer and assays work together, giving you the freedom to allocate your time more effectively.

Binding Site
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Introducing the BD MAX™ Vaginal Panel

Elevate the standard of care with the first FDA-authorized, microbiome-based assay that detects the 3 most common infectious causes of vaginitis. Consistent, accurate results that surpass traditional methods for vaginitis detection.

BD Diagnostics
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The Next Dimension in Blood Culture

First FDA-cleared system with fully automated load & go, automated blood level detection, & automated unloading.

Biomerieux
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Accelerating Lab Efficiency

Reliable products create efficiency and confidence in your results. From standards to sample prep and separation, MilliporeSigma provides products that are rigorously tested and documented to ensure the highest level of quality in the industry.

Millipore-Sigma
www.rsleads.com/706ml-406

Thermo Scientific™ CEDIA® Buprenorphine II Drugs of Abuse Assay

The new, CEDIA Buprenorphine II Assay is the only one on the market that detects all major metabolites, minimizing potential false-negatives. This next-gen assay also has no significant cross-reactivity to other opioids (including morphine), making it suitable for testing urine samples from patients on slow-release morphine therapy.

Thermo Fisher Scientific
www.rsleads.com/706ml-410

Quick turnaround time for CSF counts

GloCyte delivers highly accurate and precise TNC and RBC counts, with just 30 μL of sample per test, using a novel combination of fluorescence and imaging technology with linearity down to 0 cells/μL.

Advanced Instruments
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Explore how we can take your lab BEYOND A BETTER BOX

Sysmex® XN-Series Hematology Analyzers enable laboratories of any size to implement advanced clinical

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www.rsleads.com/706ml-411
cobas® EGFR Mutation Test v2

Designed to provide clear, actionable results, the cobas® EGFR Mutation Test v2 is a real-time PCR assay approved as an aid in first-line and subsequent therapy decisions for patients with non-small cell lung cancer (NSCLC).

Roche Diagnostics
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cobas Liat PCR System

Whether your flu A/B, RSV or strep A result is positive or negative, you can confidently treat patients at the time of visit without confirmation – when they need it most. CLIA-waived test results in 20 minutes or less.

Roche Diagnostics
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Blood Glucose Linearity and Daily QC

Introducing Linearity DROP LQ Blood Glucose (Item #K736M-5) and Control DROP LQ Blood Glucose (Item #K078M-8). These ready-to-use liquid products are intended to be used with quantitative assays on clinical laboratory analyzers, simulating human patient samples. For more information please visit: www.auditmicro.com

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Deliver definitive CT/NG results

The cobas® CT/NG v2.0 Test is the only third-generation chlamydia/gonorrhea test with dual targets for CT and NG and an internal control, providing high sensitivity and specificity for definitive results.

Roche Diagnostics
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Mercy Medical Center
North Iowa

Medical Technologist: Mercy Medical Center – North Iowa, New Hampton, IA; Bachelor’s Degree in Chemical, Physical, or Biological Science, or Medical Technology as well as Medical Technology certification; MLS/MT (ASCP) registry required.

Mail CV to: Heidi Willrett, Employee Relations Coordinator | HR, Mercy Medical Center – North Iowa, 1000 4th ST SW, Mason City, IA 50401.
Providing innovative solutions to serve the chemistry and toxicology markets

If you were explaining MedTest Dx to someone who is not familiar with the organization, how would you characterize its primary areas of expertise? When it comes to the clinical chemistry and toxicology markets, MedTest is uniquely positioned to deliver cost-effective and comprehensive solutions for laboratories as well as for regional and local IVD companies who have missing pieces in their total solution. In addition, what I really want MedTest to be known for is that we are the “customer excellence freaks.” Customers come first for everyone at MedTest.

What are the major categories of solutions that the company provides for the clinical lab? We have two types of customers: laboratory customers and business customers. The laboratory customers are the ones who are performing the tests. We provide them with reagents, instruments, installation, customer training, technical phone support, and field service when needed. But more importantly, we provide them with full implementation support so that they can get their operation up and running quickly and smoothly.

The business customers are the global IVD companies who put together their solutions for their laboratory customers. They can outsource reagents, instruments, and service from MedTest in any way they need. We are very flexible in customizing the solutions to help them be successful.

How and when did the MedTest Dx brand of products come into being? MedTest has more than 30 years’ history of quality products and services in the industry. Many readers might be familiar with our product brands, such as MedTest DX, Pointe Scientific, Medical Laboratory Solutions (MLS), and Clinitox Diagnostix. Each brand brings its own in-depth expertise and innovative ideas.

• The MedTest DX brand provides the latest technology in chemistry and hematology instrumentation, along with reagents for general chemistry and drugs-of-abuse screening testing.
• The Pointe brand is well known globally for its high-quality reagent development and manufacturing, with more than 75 products approved by the FDA. Pointe’s flagship product, an immunoturbidimetric direct HbA1c reagent, is innovative in measuring HbA1c directly, providing the best sensitivity and specificity results. Many well-known IVD companies use our HbA1c reagents.
• The MLS brand is well known in the United States for its high-quality instrument refurbishment program as well as nationwide field service coverage. This enables MedTest to deliver the “best in class” responsiveness and customer excellence to the laboratory. Many IVD business customers who lack a service infrastructure contract with us to provide service to their customers.
• The Clinitox Diagnostix brand brings innovation to the LCMS testing segment. We work with laboratories and help them implement their customized LCMS testing and maintain the quality of operations by providing them with necessary equipment, reagents, and consumables.

And MedTest brings all four of those brands together? Yes. We can be a “single source supplier” for toxicology laboratories who are performing both drug screening and confirmation testing. We can be a project manager for those who are establishing a new laboratory in chemistry and toxicology, since we provide them with full implementation support above and beyond selling the supplies and equipment. We can be a partner for many IVD companies who need outsourcing options to keep their resource utilization efficient. We can provide them with our reagents, instruments, and service individually or collectively.

People sometimes think there’s “nothing new under the sun” in Chemistry. Why are they wrong? As I think about our health delivery system, disease diagnosis should be accurate and available in a timely manner—that will never change. Many laboratories, outside of the big teaching hospitals and the big commercial laboratories, have been ignored by the big IVD companies. Those laboratories are the ones who are most vulnerable to the consequences of healthcare reform and reimbursement reduction. They need a partner who can bring true cost savings, timely responsiveness, and support. MedTest can be that partner. From that point of view, our strategy and what we are doing is very innovative and new.

As CEO, how do you view the culture and potential of the organization you lead? I am proud of my team and their faith in the company roadmap we’ve created. The roadmap has experienced many turns and changes that have transformed the company into an exciting platform for delivering real value to clinical laboratories worldwide. I have been very fortunate to have met many great minds and hearts who have provided me with the opportunities to experience innovative and strategic development of products, businesses, and customer relationships. Together we have made MedTest a forward-looking company with the vision to become a leading solution company for clinical chemistry and toxicology laboratories.
When was the last time you got this excited about osmometry?

There’s a lot to get excited about with OsmoPRO®, the newest multi-sample osmometer from Advanced Instruments.

With OsmoPro, you can deliver the most accurate test results, streamline your workflow and do it all with the greatest of ease.

Go with the PRO… OsmoPRO.

Intuitive touch screen operation
Integrated 2D barcode scanner
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Small 20μL sample volume
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Address outcomes and cost with MTB/rifampin testing

One or two negative *M tuberculosis*/rifampin resistance assay results support the release of TB patients from airborne infection isolation. Less subjective than the AFB smear and with a 24-hour turnaround time, MTB/RIF is an excellent add-on to an AFB culture for more accurate diagnosis, insight into antibiotic choice, and earlier patient release when appropriate. That’s a win for everyone.

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Test Code</th>
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<tr>
<td><em>M tuberculosis</em> Complex and Rifampin Resistance, Culture and PCR, Sputum</td>
<td>94578(X)</td>
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<tr>
<td><em>M tuberculosis</em> Complex and Rifampin Resistance, PCR, Sputum</td>
<td>94577(X)</td>
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</tbody>
</table>

For more information about MTB/rifampin testing, contact your Quest Diagnostics sales representative.

Reference

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