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MEDICAL LABORATORY OBSERVER

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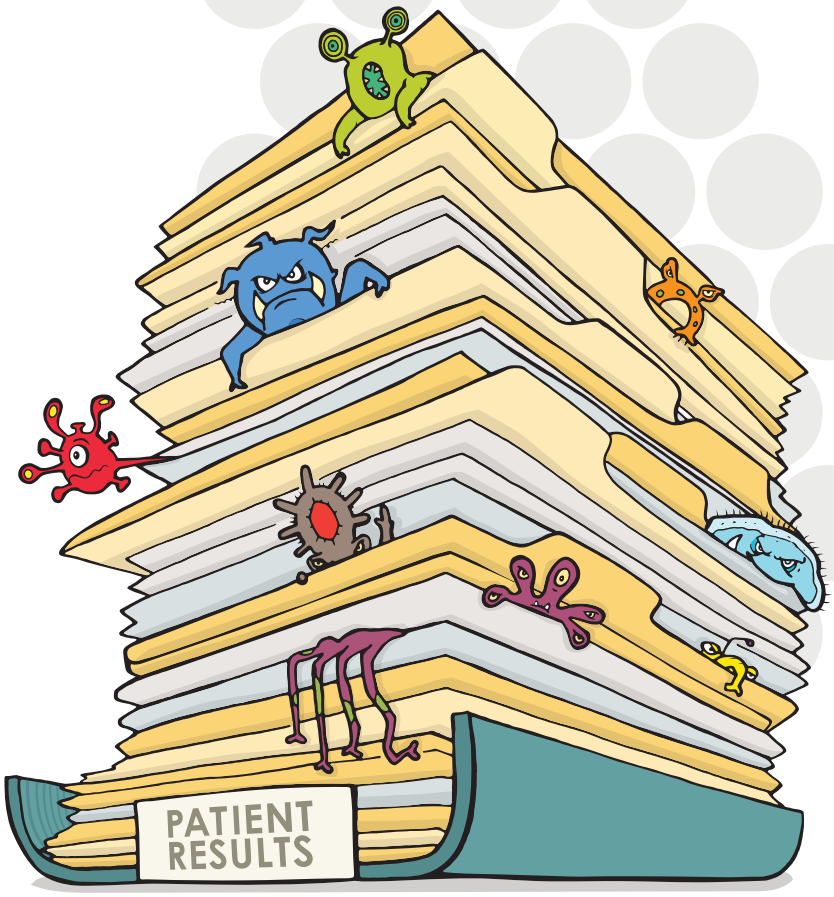

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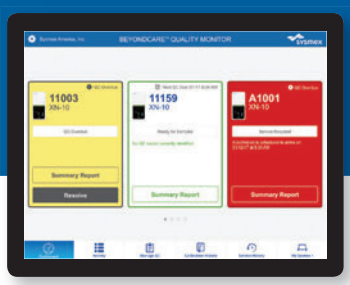

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Congress should take up H.R. 2066

It has now been a year since H.R. 2066—the Promoting Integrity in Medicare Act of 2017 (PIMA)—was introduced in the U.S. House of Representatives by Rep. Jackie Speier (D-CA). On April 6, 2017, Rep. Speier offered the bill, which would end the physician self-referral loophole in the so-called Stark Law ("Ethics in Patient Referrals Act"), which was originally passed in 1989, refined in budget reconciliation laws in the 1990s, and implemented in stages by the Centers for Medicare and Medicaid Services in the first decade of this century.

The Stark Law prohibits physicians from referring Medicare patients to clinical labs in which the physician has a financial interest, but it has a number of exceptions, ostensibly for same-day in-office ancillary services. The exceptions have been stretched to include imaging, physical therapy, radiation treatments for cancer, and anatomic pathology services. That has circumvented the intention of the Law.

The PIMA legislation, sponsored by Rep. Speier and co-sponsored by Reps. Dina Titus (D-NV) and Ro Khanna (D-CA), is formally known as "H.R. 2066: To prevent abusive billing of ancillary services to the Medicare program, and for other purposes." The part of the bill dealing with anatomic pathology refers to the Government Accounting Office's (GAO) finding that "'self-referring providers likely referred over 918,000 more anatomic pathology services' than they would have if they were not self-referring, costing Medicare approximately $69,000,000 more in 2010 than if self-referral was not permitted."

The legislative history of the PIMA Act, which can be reviewed at *https://www.congress.gov/bill/115th-congress/house-bill/2066/all-actions*, does not take long to summarize: On the day of its introduction, the bill was "referred to the Committee on Energy and Commerce, and in addition to the Committee on Ways and Means, for a period to be subsequently determined by the Speaker, in each case for consideration of such provisions as fall within the jurisdiction of the committee concerned." The next day, April 7, 2017, the Committee on Energy and Commerce referred it to the Subcommittee on Health; two weeks later, on April 21, 2017, the Ways and Means Committee did the same.

And there it sits, as of now. This is what we mean when we say that a bill "died in committee."

Not that the bill lacks supporters. Laboratory organizations, as well as some stakeholders related to delivery of the other "ancillary services" affected by the misuse of the exceptions to Stark, have been outspoken in support of PIMA. Strong arguments can be made that H.R. 2066 would retain the in-office ancillary services exception where appropriate but remove inappropriate applications; protect patients from receiving treatment or testing that is not really needed but is recommended based on, shall we say, financial incentives available to ordering physicians; and save billions of dollars for the Medicare program.

The arguments against PIMA are harder to imagine, though I'm sure there are reasonable ones. I will assume that there is a legitimate case that could be made, that opponents are not motivated simply by an ignoble desire to protect unethical physicians. But by bottling up the bill in committee, House leadership is not allowing the issue to be debated by House members. Partisan politics should be put aside and the bill should be given a fair and expeditious hearing.

Paul Ryan, are you not Speaker of the *entire* House? A valid bill is a valid bill no matter which party its sponsors and co-sponsors belong to, and it deserves a hearing and an up-or-down vote.

Alan Lenhoff

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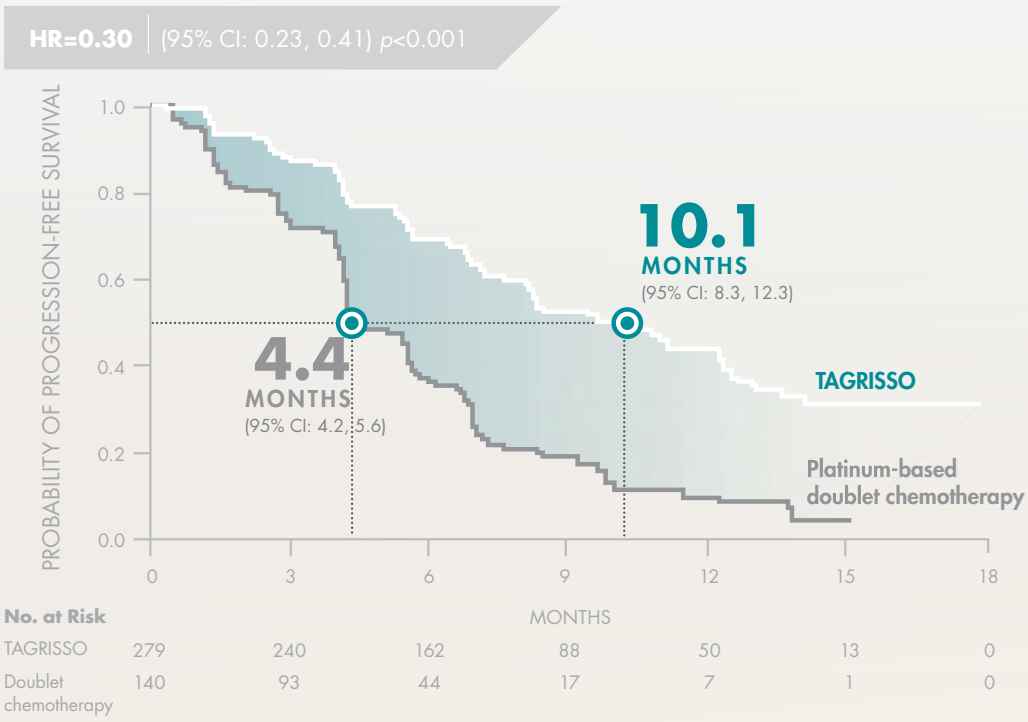
- Nearly 2 out of 3 cases (98/155) of progression with first-generation EGFR TKIs are related to the acquired EGFR T790M mutation[1]
- The **cobas**® EGFR Mutation Test v2 can identify the EGFR T790M mutation via tissue or plasma testing[2]
- In a Phase III, randomized, open-label, head-to-head clinical 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)[3]

Median progression-free survival was more than twice as long with TAGRISSO than with doublet chemotherapy*[3]



*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[3]

TAGRISSO®
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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 (eg, 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: 1. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013;19:2240-2247. **2.** cobas® EGFR Mutation Test v2 [package insert]. Indianapolis, IN: Roche Molecular Systems, Inc.; 2016. **3.** TAGRISSO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.

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

AstraZeneca

TAGRISSO® (osimertinib) tablets, for oral use

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

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

Patient Selection

Confirm the presence of a T790M EGFR mutation in tumor or plasma specimens prior to initiation of treatment with TAGRISSO *[see Indications and Usage (1) and Clinical Studies (14) in full Prescribing Information]*. Testing for the presence of the mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing. Information on FDA-approved tests for the detection of T790M mutations is available at http://www.fda.gov/companiondiagnostics.

Recommended Dosage Regimen

The recommended dose of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

Administration to 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 ultrasonicate 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 with appropriate water flushes (approximately 30 mL).

Dosage Modification

Adverse Reactions

Table 1. Recommended Dose Modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue TAGRISSO.
Cardiac	QTc[†] interval greater than 500 msec on at least 2 separate ECGs[b]	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.
	QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	Permanently discontinue TAGRISSO.
	Symptomatic congestive heart failure or asymptomatic left ventricular dysfunction that persists ≥ 4 weeks	Permanently discontinue TAGRISSO.
Other	Adverse reaction of Grade 3 or greater severity	Withhold TAGRISSO for up to 3 weeks.
	If improvement to Grade 0-2 within 3 weeks	Resume at 80 mg or 40 mg daily.
	If no improvement within 3 weeks	Permanently discontinue TAGRISSO.

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).
[b] ECGs = Electrocardiograms
[†] QTc = QT interval corrected for heart rate

Drug Interactions

Strong CYP3A4 Inducers

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when coadministering with a strong CYP3A 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 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), AURA2 (n=210), and an expansion cohort in the first-in-human trial of osimertinib (AURA1, n=143).

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 3.5% (n=29) of TAGRISSO-treated patients (n=833); 0.6% (n=5) 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 60 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 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 *[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. 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.

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. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended human dose. When males were treated prior to mating with untreated 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:

Interstitial 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, drug induced interstitial disease or radiation pneumonitis that required: steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from trial enrollment.

AURA3 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 279 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. Left Ventricular Ejection Fraction (LVEF) was evaluated at screening and every 12 weeks. The median duration of treatment was 8.1 months for patients treated with TAGRISSO and 4.2 months for chemotherapy-treated patients. The trial population characteristics were: median age 62 years, age less than 65 (58%), female (64%), Asian (65%), never smokers (68%), and ECOG PS 0 or 1 (100%).

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%). Serious adverse reactions were reported in 18% of patients treated with TAGRISSO and 26% in the chemotherapy group. No single serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (ILD/pneumonitis).

Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (1.8%), neutropenia (1.1%), and diarrhea (1.1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3%).

Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in TAGRISSO-treated patients in AURA3. AURA3 was not designed to demonstrate a

statistically significant reduction in adverse reaction rates for TAGRISSO, or for the control arm, for any adverse reaction listed in Tables 2 and 3.

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

Adverse Reaction	TAGRISSO (N=279)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=136)	
	All Grades[a] (%)	Grade 3/4[a] (%)	All Grades[a] (%)	Grade 3/4[a] (%)
Gastrointestinal disorders				
Diarrhea	41	1.1	11	1.5
Nausea	16	0.7	49	3.7
Stomatitis	15	0	15	1.5
Constipation	14	0	35	0
Vomiting	11	0.4	20	2.2
Skin disorders				
Rash[b]	34	0.7	5.9	0
Dry skin[c]	23	0	4.4	0
Nail toxicity[d]	22	0	1.5	0
Pruritus[e]	13	0	5.1	0
Metabolism and Nutrition Disorders				
Decreased appetite	18	1.1	36	2.9
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	14	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	10	0.4	9	0.7
General Disorders and Administration Site Conditions				
Fatigue[f]	22	1.8	40	5.1

* NCI CTCAE v4.0.

[a] No grade 4 events were reported.

[b] Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and acneform dermatitis.

[c] Includes dry skin, eczema, skin fissures, xerosis.

[d] Includes nail disorders, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, nail toxicity, onychoclasis, onycholysis, onychomadesis, paronychia.

[e] Includes pruritus, pruritus generalized, eyelid pruritus.

[f] Includes fatigue, asthenia.

Table 3. Common Laboratory Abnormalities (>20% for all NCI CTCAE Grades) in AURA3

Laboratory Abnormality	TAGRISSO (N=279)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131[a])	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)
Leukopenia	61	1.1	75	5.3
Lymphopenia	63	8.2	61	9.9
Thrombocytopenia	46	0.7	48	7.4
Neutropenia	27	2.2	49	12

[a] 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 790M mutation-positive NSLC 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 pretreated. Prior to enrollment, 68% of patients 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: <0.1 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 CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid coadministering TAGRISSO with strong CYP3A inducers (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 CYP3A4 inducer if concurrent use is unavoidable *[see Dosage and Administration (2.4) in full Prescribing Information]*. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

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.

Monitor for adverse reactions of the BCRP substrate (e.g., rosuvastatin, sulfasalazine, topotecan), unless otherwise instructed in its approved labeling, when coadministered with TAGRISSO.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended human dose *[see Data]*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the closure of the hard palate (gestation days 6 to 16) at doses of 1 mg/kg/day and above (0.1-times the AUC observed in patients at the recommended dose of 80 mg), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

Lactation

Risk Summary

There are no data on the presence of osimertinib in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death *[see Use in Specific Populations (8.1) in full Prescribing Information]*. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise a lactating woman not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose *[see Use in Specific Populations (8.1) in full Prescribing Information]*.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO *[see Nonclinical Toxicology (13.1) in full Prescribing Information]*.

Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male fertility are reversible *[see Nonclinical Toxicology (13.1) in full Prescribing Information]*.

Pediatric Use

The safety and effectiveness of TAGRISSO in pediatric patients have not been established.

Geriatric Use

Three hundred and forty-six (42%) of the 833 patients in AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and an expansion cohort in the first-in-human trial of osimertinib (AURA1, n=143) were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (9.8% versus 6.8%) and more frequent dose modifications for adverse reactions (10.1% versus 6.0%) in patients 65 years or older as compared to those younger than 65 years.

Renal Impairment

No dose adjustment is recommended in patients with mild, [creatinine clearance (CLcr) 60-89 mL/min, as estimated by the Cockcroft Gault method (C-G)] moderate, (CLcr 30-59 mL/min, as estimated by C-G) or severe (CLcr 15-29 mL/min) renal impairment. There is no recommended dose of TAGRISSO for patients with end-stage renal disease *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is recommended in patients with mild hepatic impairment [total bilirubin less than or equal to upper limit of normal (ULN) and AST greater than ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST] or moderate hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with severe hepatic impairment *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

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Autism Awareness

April is Autism Awareness Month. Following are some key statistics about a disorder that the American public has become increasingly aware of—and that medicine is understanding and treating more successfully than ever.

1 in 68
children in the United States have autism.

1 in 42
boys are diagnosed with autism.

1 in 189
girls are diagnosed with autism.

4 years old
is the average age of autism diagnosis.

6 months old
is the earliest that signs of autism in babies can be identified.

3.5 million
is the estimated number of people in the U.S. affected by autism spectrum disorder (ASD).

More than 80%
of people on the autism spectrum are children.

70 million
is the estimated number of people worldwide with ASD.

1%
is the estimated percentage of people in the world with autism.

$60,000 per year
is the average cost for families affected by autism.

$236 to $262 billion
is the annual cost of autism services to Americans.

50%
of children with ASD have average or above-average intelligence.

25%
of people with autism are nonverbal.

30% to 50%
of people with autism also have seizures.

ZERO
Is the known scientific link between vaccines and autism.

• **Source:** h*ttp://kerrymagro.com/68-things-to-know-about-autism-for-autism-awareness-month*

Autoimmune Disease

A weakened gut barrier may contribute to autoimmune disease. When the gut microbe *Enterococcus gallinarum* leaks out of the intestines and sets up camp in other organs such as the liver, it appears to trigger an autoimmune response similar to what's seen in lupus, a new study in mice reveals. In humans, *E. gallinarum* was detected in the livers of lupus patients but not healthy controls, hinting at a potential cause for that autoimmune disease.

While studying mouse models of lupus, Yale University researcher Silvio Manfredo Vieira, PhD, and colleagues found that treatment with an antibiotic reduced mortality and secretion of lupus-related immune system proteins. That suggested that a type of bacteria may be exacerbating the disease. They fluorescently traced bacteria in the mice, detecting the presence of *E. gallinarum* in the lymph nodes, liver, and spleen. Intriguingly, they found that *E. gallinarum* in these organs resulted in increased secretion of immune signals that are associated with autoimmunity in lupus patients, yet the presence of other types of bacteria in these organs did not induce such autoimmunity.

In human liver biopsies, they detected the presence of *E. gallinarum* in samples from lupus patients, but not in healthy controls. In addition, many liver samples from patients with autoimmune hepatitis were found to contain *E. gallinarum*. These results suggest that, if *E. gallinarum* manages to escape from the gut, it has the potential to trigger disease.

In a related Perspective, Sandra Citi, MD, PhD, of the University of Geneva (Switzerland), highlighted this study and a related one, providing more context on the mechanisms behind a leaky gut barrier and potential therapies to improve it. In a different study also evaluating the gut barrier, University of Pennsylvania microbiologist Christoph Thaiss and colleagues found that high blood sugar levels, as seen in diabetes and obesity, are associated with intestinal barrier dysfunction and susceptibility to infection in mice. Preliminary data supports this finding in humans as well. Together, these studies highlight the importance of a healthy gut barrier in preventing disease.

Diabetes

Unique inflammation patterns emerging in patients with type 1 diabetes. Analysis of the inflammation-promoting proteins in the blood of patients with type 1 diabetes and related kidney disease indicates that the promoters of inflammation are diverse even in the same medical condition and that patients probably would benefit from an anti-inflammatory treatment that directly targets theirs, scientists report.

Chronically high levels of glucose in type 1 diabetes appear to get the attention of the immune system, resulting in chronic inflammation that can destroy organs, nerves, and blood vessels. So Medical College of Georgia scientists looked at blood levels of a dozen mediators of inflammation in 89 patients with diabetes-related kidney disease as well as 483 patients without the kidney problems. The mediators' presence in the bloodstream indicates they might be having an impact body-wide. Previous studies in similar patients have assessed one or only a handful of these mediators.

The new, more comprehensive assessment of a dozen mediators found that 10 were elevated in patients who had related kidney damage. But it was proteins in the TNF-alpha family and IL-6 that were significantly elevated in 40 percent of these patients, compared to those with well-functioning kidneys. Another 40 percent of patients had moderately elevated levels of these mediators, indicating that they might not be the strongest treatment target for that second group.

Blood levels of these inflammatory mediators may provide biomarkers for predicting who has or who will likely get diabetes-related kidney disease. They also could help assess the effectiveness of treatment or prevention strategies.

Two classic inflammatory markers regularly measured in hospitals, C-reactive protein and serum amyloid A, did not appear to be significant players in these patients, according to the researchers.

Infectious Diseases

CRISPR/Cas9 technique suppresses malaria infection in mosquitoes. Using the gene editing technique CRISPR/Cas9, scientists have shown that inactivating the gene FREP1 (fibrinogen-related protein 1) reduces mosquitos' susceptibility to infection with *Plasmodium*, a genus of parasites that causes malaria in humans. George Dimopoulos, PhD, and colleagues at Johns Hopkins University recently presented those findings in *PLOS Pathogens*.

Inside an *Anopheles gambiae* mosquito, *Plasmodium* undergoes a series of infection steps before reaching the mosquito's salivary gland, from which it spreads to bitten humans. This infection cycle relies on the activity of several mosquito proteins. Recently developed CRISPR/Cas9 tools offer new opportunities to study these proteins and determine whether they can be targeted to block malaria transmission.

Dimopoulos's team had previously identified and examined several mosquito proteins involved in *Plasmodium* infection, including FREP1. A vaccine candidate based on targeting FREP1 was recently developed, but Dimopoulos' group took a different approach. They used a CRISPR/Cas9 technique to inactivate the FREP1 gene in *A. gambiae* mosquitos and explore the effects on malaria parasite infection.

The team found that FREP1 inactivation via CRISPR/Cas9 significantly suppressed infection of the mosquitos with both human and rodent *Plasmodium* parasites. This supports a potential for CRISPR/Cas9 technology in altering the genomes of wild mosquito populations to prevent the spread of malaria, which kills nearly 500,000 people worldwide every year.

However, the permanent inactivation of FREP1 in all mosquito stages and tissues also resulted in fitness costs for the mosquitos, including reduced blood-feeding ability, lower fertility, a lower egg hatching rate, slowed development, and reduced longevity after feeding on blood. This raises concerns that mosquitos with permanently inactivated FREP1 would not be able to compete with non-mutant mosquitos in the wild effectively enough to block malaria transmission. The investigators are now exploring ways to inactivate FREP1 in the gut of adult female mosquitoes only, with the hope of reducing the fitness cost while retaining resistance to the malaria parasite.

In any case, the findings highlight the potential for CRISPR/Cas9 gene editing techniques to inactivate parasite host factors and improve understanding of malaria. Further research could also explore strategies to enable mosquitos with inactivated FREP1 to successfully compete with non-mutants.

Vitamin D

Vitamin D may help prevent heart failure after heart attack. New research has shown how vitamin D may help protect tissue and prevent heart failure after a heart attack, potentially offering a low-cost addition to existing treatments for heart failure. A team at the Westmead Institute for Medical Research found that vitamin D prevents excessive scarring and thickening of heart tissue following a myocardial infarction.

Researchers used mouse models to investigate the impact of 1,25D, a form of vitamin D that interacts with hormones, on the cells that form scar tissue after a heart attack. These cells are called cardiac colony-forming unit fibroblasts (cCFU-Fs).

Lead researcher James Chong, PhD, says that vitamin D was known to help protect against heart failure, but its interaction with cCFU-Fs was not well established. "We still don't fully understand how mechanistically vitamin D can help with heart disease management," Chong explains. "We wanted to know more about how it protects the heart after a heart attack."

Heart attacks occur when blood supply to the heart is blocked, leading to tissue damage. This triggers an inflammatory response where the cCFU-Fs replace the damaged tissue with collagen-based scar tissue.

"This is a problem because scarring of heart tissue can reduce the heart's ability to pump blood effectively, which can lead to heart failure," Chong says.

"Our research shows that vitamin D actually blocks the cCFU-Fs from forming scar tissue. By blocking cCFU-Fs, vitamin D may play an important role in lowering the risk of heart failure. This study is the first to demonstrate the role of 1,25D in regulating cardiac progenitor cells, and the findings are encouraging."

Antibiotic Resistance

No progress seen in reducing antibiotics among outpatients. Despite aggressive public health campaigns aimed at reducing unnecessary prescriptions for antibiotics, the drugs continue to be prescribed at high rates in outpatient settings such as clinics and physician offices, according to a new study by researchers at Washington University School of Medicine in St. Louis. The study was published March 8 in the journal *Infection Control & Hospital Epidemiology*.

The researchers analyzed de-identified data from Express Scripts Holding Co., which manages drug benefits for employers, and found that 98 million outpatient antibiotic prescriptions were filled by 39 million people during a three-year period from 2013 to 2015. Moreover, the researchers found no decline in the overall antibiotic prescription rate during that time.

"This study suggests that current guidelines on prescribing antibiotics are not being followed," says the study's first author, Michael Durkin, MD. "If they were, we would have seen an overall decrease in antibiotic prescribing rates over time. This is concerning because the overuse of antibiotics is costly and contributes to the rise of drug-resistant superbugs."

The data tracked monthly prescription rates for all antibiotics, including the five that are prescribed most often in outpatient settings: azithromycin, amoxicillin, amoxicillin/clavulanate, ciprofloxacin, and cephalexin.

The average number of antibiotic prescriptions per 1,000 beneficiaries was 826 per year. The researchers noted that there was a slight decrease in such rates in 2014, followed by a slight increase in 2015. Overall, the fluctuations were not statistically significant.

Chemistry analyzers' advancing technology offers increased testing capabilities

By Steve Ishii

Clinical chemistry has been defined as the branch of medicine that is focused on analyzing biological matter or body fluids to deliver timely, relevant, and precise diagnostic information about the clinical condition of the human body.[1] While this merging of chemistry with medicine has been traced back thousands of years, the field of modern clinical chemistry, as it is known today, emerged in the early 1900s.[2] As late as the early 1960s, most laboratories consisted of small enterprises in which technologists performed only a handful of manual tests, including glucose, urea, creatinine, electrolytes, cholesterol, basic enzymes, total protein, and albumin/globulin.[3]

These tests remain as some of the cornerstones of clinical chemistry today; however, the manner in which testing is performed has evolved substantially. Driven by a number of factors—including technological advancements and industry changes—clinical chemistry has grown to include large, integrated, and automated laboratories with sophisticated instrumentation that can perform hundreds to thousands of tests per hour.

History of clinical chemistry

The twentieth century became the age of modern clinical chemistry, with Harvard biochemist Otto Folin (1867-1934) more or less establishing clinical biochemistry in the United States. It was during the first decades of the century that blood and urine were first measured using quantitative analysis and instrumentation, and the results applied to human disease and health.[2] What might be called the Golden Age of Clinical Chemistry began during the years after World War II. Between 1948 and 1960, such products as radioimmunoassay and the autoanalyzer were introduced.[4] The latter ushered in the broad use of batch analyzers. Although many measured only one analyte, they enabled the testing of up to 100 samples at a time in continuous mode.[5]

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LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. Describe the history of clinical chemistry systems upon the emergence of modern clinical chemistry in the 1900s, and list the basic tests.
2. Discuss the rise of automation and what technological advancements brought to that era in clinical chemistry..
3. Explain how trends in healthcare have shaped the functionality and design of analyzers.
4. Discuss what future advancements in chemistry analyzers may achieve.

Photoelectric colorimeters, having been introduced in 1939,[6] also came into widespread use during this time. The standard then was visual colorimetry. It was believed that using photocells to measure light intensity would provide greater reliability than analysis by the human eye.[6] During the 1960s, the combination of the autoanalyzer and photometer eventually replaced the visual colorimeter.[4]

The rise of automation

Several years later, the advent of computer- or microprocessor-based technology and software programming ushered in a new era for diagnostic testing—one that would eventually lead to automated environments that would enable laboratories to perform fast, high-quality testing and gain workflow efficiencies. In the days of early computer development, however, most chemistry tests still involved manual analysis. Many procedures relied on a process in which chemical reagents were mixed together, with the output being measured using a spectrophotometer.

Mid-decade, a number of technological advancements were introduced; these included instruments dedicated to a single or dual test menu, such as the flame photometer, and the chloride/CO_2 and glucose analyzers. In 1978, the ASTRA (automated STAT routine analyzer) was introduced. This analyzer's microprocessor-driven design enabled processing of seven of the most-commonly ordered STAT tests—sodium, potassium, chloride, CO_2, glucose, BUN, and creatinine—in one minute using one consolidated system. Performing these same tests prior to the introduction of this platform normally would have taken 10 to 20 minutes. It also helped to bring to bringing automated pipetting to the industry.[3]

In the succeeding decades, the industry has witnessed a fast-evolving series of technological advancements in clinical chemistry instrumentation. With each new system generation, novel features have been introduced—such as closed tube sampling, automated maintenance processes, streamlined calibration, and internet-based remote diagnostics—all of which are intended to help laboratories better meet the needs of physicians and patients, while creating efficiencies, driving quality, lowering costs and addressing fluctuations in the workforce.

Today's analyzers

Improvements in analyzer design and performance continue to be driven by a number of factors: technological breakthroughs, enhanced manufacturing practices, the integration of software into the lab environment, and medical discovery. In addition, changes in the reimbursement landscape and user needs have spurred the development of systems that feature flexibility and performance that far surpass their predecessors.

Technological breakthroughs. Computer technology has transformed clinical chemistry in two overarching areas: automation and informatics. Automation has touched every facet of clinical laboratory operations, enabling increased throughput to accommodate higher testing

Figure 1. ASTRA 8 (Automated Stat Routine Analyzer) – 1978. Microprocessor controlled chemistry analyzer capable of measuring sodium, potassium, chloride, CO2, glucose, blood urea nitrogen, and creatinine in one minute.

volumes; elevating quality by reducing human error and lessening the risk of sample cross-contamination; enhancing safety by reducing exposure to biohazardous materials; and improving workflow through greater system uptime and walkaway times.

Today, laboratories operate with greater efficiency than ever before. Processes that were, in the past, performed manually, now are performed via instrumentation. Full automation of pre-analytical, analytical, and post-analytical tasks enables laboratories to perform more work using less labor and fewer resources. Similarly, computers and microprocessor technology have enabled the creation of smaller-footprint units that accommodate higher test volumes. Today's consolidated systems typically perform hundreds of tests on one platform, whereas preceding systems required a number of dedicated instruments, each performing only a few selected tests.

Automation combined with cloud-based technology has helped laboratories streamline daily operations and better manage patient information—all of which has become increasingly important due to trends in the workforce that have resulted in personnel shortages. Automating routine responsibilities frees laboratorians to focus more on patient care and functions for which they are specifically educated and trained. A pivotal area in which laboratories have been able to improve uptime and avoid unplanned costs is in automating inventory management. Cloud-based systems can help ensure timely ordering of reagents and consumables across an entire network, helping busy laboratories avoid workflow disruptions due to the potential inefficiencies resulting from manual inventory control processes.

In today's world of Big Data, large amounts of information are available—but that can be more of a hindrance than a help to good practice if lab leaders do not manage the information effectively. Making that data relevant and usable for improving operations is important in helping laboratories achieve their continuous improvement goals. Today, lab directors need to coalesce actionable data into a single repository to drive decisions and provide valuable insights into laboratory performance network-wide. This can be accomplished via cloud-based analytics, and this will be increasingly important as the trend toward network consolidation continues to grow.

Enhanced manufacturing practices. Manufacturing practices have progressed alongside technological development. Throughout the 1800s and 1900s—from Eli Whitney's cotton gin and interchangeable musket parts, to Henry Ford's moving assembly line, to Walter Shewhart's statistical quality control charts, to Motorola's Six Sigma methods[7]—companies have sought to sustain a competitive advantage by improving quality and reducing errors. For the clinical lab, finding solutions to improve performance unachievable with technology alone has been key to attaining these goals. Such solutions include adopting Lean processes, forming strategic partnerships, and taking a "total laboratory" approach to operations. In the past, chemistry analyzers functioned as standalone workstations. Today, however, these systems are integral components of complex multifunctional operations that involve other disciplines, automated platforms, and information management tools.

Integration of software. Quality has long been a driver of design and development. Advancements in software have had a profound influence on processing in the laboratory. Evolutions in software have opened pathways for automation, which heightens consistency and reduces operator error, and for fast and accurate analysis, predictive analytics, and data interpretation, which help to ensure the highest quality of results.

Medical discoveries. Science has enabled an increasingly rich understanding of the human body and the diseases and disorders to which it is subject—and of the biomarkers that offer objective evidence of those diseases and disorders. For clinical chemistry, that means that new and novel assays for use in the diagnosis and management of various disease states are being constantly discovered and developed. As highly specialized assays continue to become a part of the standard of care, analyzer design must keep pace with the accompanying workload demands.

Evolving healthcare landscape. The healthcare industry has changed significantly in the past several decades. In the 1980s, some states introduced the concept of diagnostic related groups (DRGs)—a statistical system of classifying any inpatient stay into a specific group for the purpose of identifying appropriate reimbursement rates. This system would eventually have a significant effect on the clinical chemistry landscape, as physicians began to order only those tests for a specific condition that were approved according to the corresponding DRG.

Figure 2. Creatinine Analyzer 2 – 1979. Single channel benchtop analyzer measuring creatinine levels in serum, plasma, and urine samples using an enzymatic Jaffe reaction.

Figure 3. Glucose Analyzer 2 – 1979. Single channel benchtop analyzer measuring glucose levels in serum, plasma, and urine samples using an glucose oxidase electrode.

In the late 1990s, the Health Care Financing Administration (the forerunner to the Centers for Medicare and Medicaid Services, or CMS, part of the U.S. Department of Health and Human Services) redefined chemistry panels—a group of individual chemistry tests—in terms of eligibility for government reimbursement. Again, this influenced how physicians ordered diagnostic tests. In 2007, CMS began to replace DRGs with "Medicare-severity DRGs" (ms-DRGs), designed to recognize complications and comorbidities.[8]

These and other legislative and regulatory factors—for example, some provisions of the Affordable Care Act, such as the carrot-and-stick of Meaningful Use—have influenced the modern laboratory, which is under increasing pressure to produce fast, accurate results while reducing costs. Most recently, the CMS's controversial re-setting of reimbursement rates based on data collection processes that many laboratory stakeholders consider to be flawed has threatened the financial viability of some labs. In this context, manufacturers continue to work on technology solutions that will meet volume demands, produce precise results, and lower cost of ownership. Many of these solutions now involve creating reliable systems characterized by high throughput, maximized uptime, efficient reagent and energy usage, and simpler—yet sophisticated—mechanisms for easy maintenance.

The future of chemistry analyzers

Chemistry analyzers have come a long way during the last few decades, and the fast pace of technological development will fuel further technological enhancements. The drivers that affect development today will catalyze change in the future, accompanied by new, as yet unforeseen, drivers. It is anticipated that growth will be most robust in the areas of automation and software. Manufacturers will work to meet the laboratory's need to manage increasing workloads with decreasing resources, simplifying labor-intensive tasks that

continued on page 16

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are still performed manually today. Areas targeted for higher levels of automation will include instrument maintenance, system troubleshooting, and consumables management.

Software development initiatives will target workflow inefficiencies and results processing. Cloud-based systems and integrated networks will enable patient histories to be recorded and recalled, regardless of where testing is performed.

In addition to this, designers will continue the trend of downsizing units to reduce footprint, allowing more testing capabilities with smaller-sized machines. This will help laboratories save valuable space while still meeting the demands of physicians and patients. This will also pave the way for new technology in the area of point-of-care devices, reducing, for example, the need for large sample volumes.

Selecting a chemistry analyzer

Given all the benefits of modern instrumentation, the choice of an analyzer is not merely about the capabilities of the system. As with most technology, the choice should be based on user need. Laboratories must consider testing volume/throughput and the types of diagnostic tests that the system will perform. In addition, lab directors should think about the desired level of automation, as well as pre-analytical sample handling and post-analytical data management needs. Beyond instrumentation functionality, the laboratory must also examine space and cost constraints, taking into account footprint and system operating costs.

While choosing the right instrument is important to ensuring successful laboratory operations, it is only part of the equation. Laboratories today are looking for knowledgeable partners to help them apply proven continuous improvement strategies—borrowed from the manufacturing industry—to healthcare. A partner who is able to offer a total laboratory solution beyond instrumentation placement can help the laboratory to achieve its patient care and operational efficiency goals. This includes supporting the use of the instruments, identifying opportunities for automation, detecting workflow gaps, and helping to create efficiencies in managing resources.

Clinical chemistry has evolved greatly over time, driven by numerous factors—not the least being technological advancements in the world at large. Computers, microprocessors, and robotics paved the way for automation and cloud-based technology. With this, laboratories no longer consist of small standalone, manually operated units that performed a handful of tests; instead, they have transformed into bustling hubs featuring large integrated platforms that produced thousands of tests per hour with sophisticated information management systems. Future growth will build on this foundation, providing more capabilities in smaller-sized units. Instrumentation alone is only part of the equation. A strategic partnership can optimize laboratory performance, strengthening system advantages by integrating them into a total lab solution.

Please visit mlo-online.com for references.

Steve Ishii serves as Senior Marketing Manager, Strategic Marketing, Global Chemistry for **Beckman Coulter**. He has worked for that company for 37 years, focused primarily on chemistry products.

TEST QUESTIONS

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

1. **What term is used to describe the merging of chemistry with medicine?**
   - a. biological chemistry
   - b. clinical chemistry
   - c. forensic chemistry
   - d. organic chemistry

2. **In what era did the field of modern clinical chemistry emerge?**
   - a. late 1800s
   - b. early 1900s
   - c. late 1900s
   - d. early 2000s

3. **In the early 1960s most chemistry laboratories performed a limited number of tests, but they were automated.**
   - a. True
   - b. False

4. **Which biochemist established clinical biochemistry in the United States?**
   - a. Otto Folin
   - b. Linus Pauling
   - c. Frederick Sanger
   - d. Isaac Asimov

5. **What chemistry product(s) became available post-World War II?**
   - a. photoelectric colorimeters
   - b. radioimmunoassays
   - c. autoanalyzers
   - d. all of the above

6. **During the days of early computer development in chemistry analyzers, many procedures used a methodology in which the output of the tests were measured by a**
   - a. nephelometer.
   - b. colorimeter.
   - c. spectrophotometer.
   - d. luminometer.

7. **What analyzer was introduced that enabled a microprocessor to process seven of the most commonly ordered STAT tests with automated pipetting?**
   - a. Creatinine 2
   - b. STAT7
   - c. ASTRA
   - d. none of the above

8. **The introduction of the processing of the seven common tests in a consolidated system enabled turnaround times to be reduced from 10 to 20 minutes to**
   - a. five minutes.
   - b. two minutes.
   - c. one minute.
   - d. one second.

9. **With continued improvements of new chemistry system generations, which feature has created efficiencies for laboratorians and physicians?**
   - a. internet-based remote diagnostics
   - b. automated maintenance processes
   - c. streamlined calibrations
   - d. all of the above

10. **The automation of chemistry analyzers has transformed the industry by enabling increased throughput, elevating quality, enhancing safety, and improving workflow.**
    - a. True
    - b. False

11. **The full automation of pre-analytical, analytical, and post-analytical tasks allows laboratorians to perform _____work using _____ labor and _____ resources.**
    - a. less; less; fewer
    - b. more; more; fewer
    - c. more; less; fewer
    - d. less; more; more

12. **What type of computer technology has allowed laboratories to improve uptime and avoid unplanned costs in inventory management?**
    - a. grid-based
    - b. utility-based
    - c. cloud-based
    - d. none of the above

13. **The implementation of which healthcare statistical system had a significant effect in clinical chemistry?**
    - a. diagnostic related groups
    - b. health resource groups
    - c. patient management categories
    - d. all of the above

14. **Federal legislative and regulatory factors have increased pressure on laboratories to produce fast and accurate results, while reducing costs.**
    - a. True
    - b. False

15. **The future development of chemistry analyzers will focus on**
    - a. instrument maintenance.
    - b. system troubleshooting.
    - c. consumables management.
    - d. all of the above

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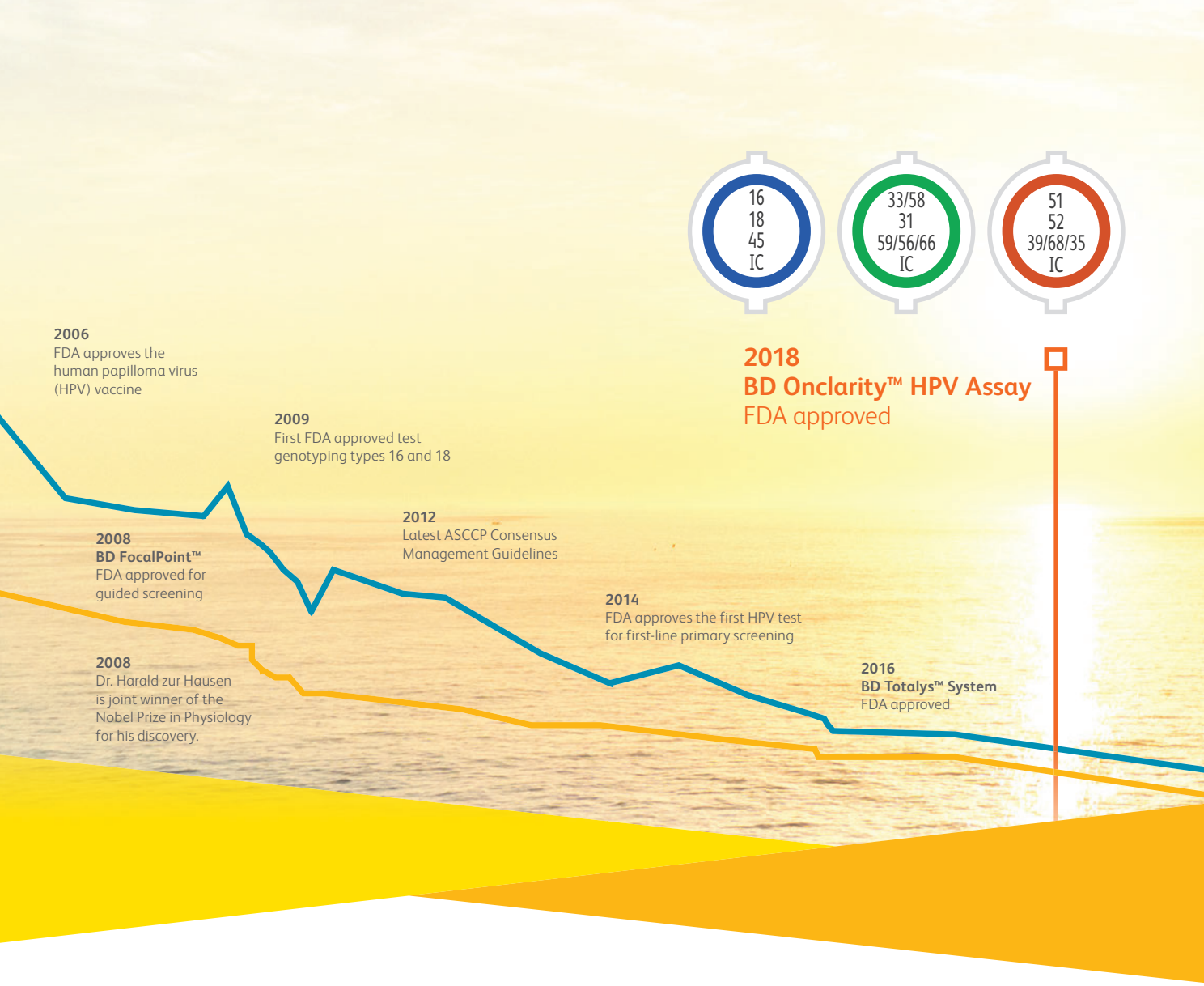

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2018 Lab of the Year: St. Luke's Health System's Core Laboratory

By MLO Staff

The competition was tough, the judging was not easy—but *MLO* is proud to present the 2018 Lab of the Year: St. Luke's Health System's Core Laboratory.

St. Luke's Health System (SLHS) is a not-for-profit, locally owned health system serving southern Idaho and eastern Oregon. St. Luke's Core Laboratory was established in 2011 and is a department of SLHS. The laboratory includes five physical locations in Boise, Idaho; one main testing site, and four outreach phlebotomy sites.

Prior to 2011, all laboratory testing was performed within the hospital environment; the creation of the core laboratory provided SLHS the opportunity to centralize outpatient and routine testing to improve efficiency across the corporation. The laboratory has 72 FTEs who provide five primary services: outreach phlebotomy; specimen testing; courier services; specimen processing/esoteric testing (send-outs); and client service.

Specimen testing is further subdivided into distinct departments:

- Hematology/Chemistry/Immunology
- Microbiology
- Molecular Biology
- Cytology.

Major testing platforms include technology provided by such industry leaders as Sysmex, Hologic, BD, Siemens, Beckman Coulter, Ortho Clinical Diagnostics, Diasorin, and Tosoh.

Test volume has increased 45 percent over the last four years, with 1,177,369 billable tests having been performed in FY17.

The laboratory has defined three strategic challenges—ones which, we suspect, are faced by many if not most of *MLO*'s readers:

- Reducing reimbursement: Insurance fee schedules continue to decline, limiting revenue for inpatient and outpatient testing.
- Volume to value: Networks and insurers are partnering with laboratories within per member, per month reimbursement models.
- Workforce shrinkage: The national average age of the technical workforce is 54, with more individuals leaving the field through retirement than entering as new graduates. More than half of the NAACLS-approved (National Accrediting Agency for Clinical Laboratory Science) medical lab scientist programs in place in 1980 have closed, with worker tenure reduced by half.

Those are the basics; now let's look at St. Luke's Health System's Core Laboratory more closely. *MLO* asked labs submitting nominations to discuss their lab in terms of six criteria: Customer Service, Productivity, Teamwork, Education and Training, Strategic Outlook, and Lab Inspections. To organize the rest of this article, we will use those categories as subsections and review some highlights.

Customer Service

Laboratory data is delivered according to provider preference. In addition to faxing and the U.S. mail, SLHS provides:

- EPIC Inpatient/EPIC Ambulatory: interfaced results directly to the inpatient and outpatient electronic medical records utilized by SLHS
- EpicCare Link: online portal for independent providers to access patient laboratory data
- Direct Interface to outside EHR: interfaced results between Epic Beaker and a contracted client.

Also, patient results are delivered via patient portal and can be accessible by patients or their proxies. The Idaho Health Data Exchange connects health systems, hospitals, providers, laboratories, and imaging centers in Idaho, eastern Washington, and eastern Oregon to electronically and securely share patient medical records.

Laboratory liaison. The lab also has a dedicated liaison that engages with customers in a variety of forms to listen, determine customer satisfaction, and capture information regarding opportunities to exceed expectations. The primary responsibilities of the liaison include:

- Clinic rounding: meets with clinic staff, leadership and providers discuss service and quality performance according to a scrupulously observed rounding schedule which has increased by more than 80 percent since FY16Q4.

- New product training: uses laboratorian background to provide expert knowledge on lab testing and products
- Lunch and learn: offers provider education on new testing and technology that is available at the core laboratory
- Customer quarterly business reviews: schedules face-to-face meetings with top 10 high-volume clinics to review call center, courier, testing volume, and error data
- Laboratory open house: schedules periodic open-house events for customers to view new technology and processes.

The laboratory liaison partners with the Community Connect liaison to meet with potential clients about using the EPIC ambulatory medical record and the availability of the Core Lab to provide interfaced high quality results to potential clients. Additionally, the physician liaison team facilitates quarterly continuing education events for the broader medical staff. The liaison partners on ensuring that appropriate laboratory medicine topics are integrated within the overall plan and ensures that potential customers are included.

The ***St. Luke's website*** includes information for both ordering providers and patients. Providers have access to the organization's complete test menu, which includes collection, transport, and turnaround time information. Patients can find laboratory locations and hours of operation.

Epic myChart is a patient portal that provides laboratory results directly to patients through a secure log-in.

Epic Care Link is an online portal for providers that enables access to patient results. Providers can access results for testing they have ordered or testing a colleague has ordered electronically.

The Physician Liaison team coordinates quarterly ***CME events*** for providers, in which key topics are discussed. Popular topics include laboratory testing best practices for renal disease, diabetes, and infectious disease.

The Core Laboratory operates a ***Client Service Center*** which ordering physicians can call to schedule a home draw, request or add on a test, communicate a concern, or obtain patient testing results. Performance is tracked with call quality audits that were implemented in FY18. SLHS is proud that abandoned calls are kept to a minimum; the industry best practice benchmark performance for call centers is an abandonment rate of below five percent, and the core laboratory has performed below this benchmark in both FY16 (2.9 percent) and FY17 (3.8 percent).

The Chief Quality Officer authors a monthly ***Provider Newsletter*** with key updates for physicians. Laboratory updates include new testing methodologies, new laboratory policies, and best practice updates. The ***Safety is Why I Care Newsletter*** is produced by the St. Luke's Quality & Patient Safety and Employee Safety teams and distributed to all hospital and clinic sites. Content focuses on safety opportunities in the SBAR format, encouraging staff discussion during staff meetings or daily huddles. Recently, a good catch by the core lab staff on erroneous STD results was highlighted.

Productivity

The core laboratory sets an annual budget built on internal and external benchmarking. Key monitors evaluated at the team and department level include:

- Worked and paid FTE
- Supply expense
- Total operating expense per test
- Total labor hours per test.

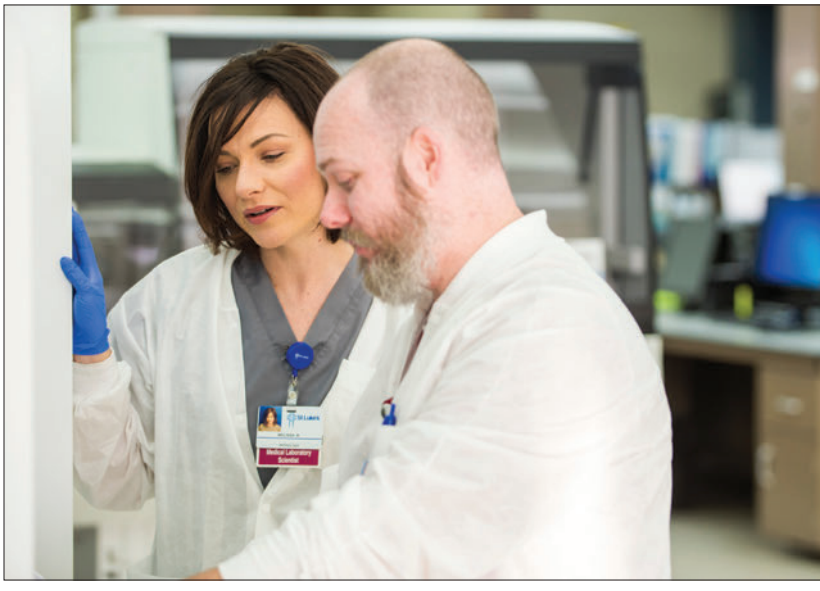
These metrics are reviewed during monthly 1:1 meetings, weekly leadership huddles, and monthly business review meetings with finance. Opportunities to optimize performance focus on technology solutions and workflow enhancements such as workstation alignment (processing), discontinuing low volume/high labor tests (microbiology), and test batching (molecular biology). These improvements/enhancements are considered when budget targets are set.

During the monthly business review meetings, cost management and customer needs are discussed, and sometimes hard choices are made. For example, the need to implement an additional courier route for a hospital customer was approved in support of improving turnaround times, even though it negatively impacted productivity. The laboratory has also transitioned away from traditional microbiology in support of molecular technology to reduce turnaround times; molecular technology can provide results in minutes, but is often three to four times more expensive. The laboratory has also continued to operate patient draw stations that perform at below benchmark productivity because having a convenient option for outpatient draws is important to their customers.

The core laboratory evaluates cycle time along the various steps in the testing process as indicators of process effectiveness. The first step in the process is specimen collection. SLHS has measured the cycle time in minutes from patient check-in through specimen collection for the core laboratory's three outreach phlebotomy sites. Performance is compared to a benchmark of 10 minutes, and performance has been consistently at or below benchmark performance for all sites.

The second step in the process is transporting the specimen to the Core Laboratory for testing; on-time courier transport of specimens for routine routes (regularly scheduled for non-STAT/urgent testing) at the Core Lab exceeded the industry benchmark of 90 percent for all of FY17.

The third step in the process is to perform the testing at the Core Laboratory. For the three highest-volume tests performed by the Heme/Chem/IA department during FY17, SLHS has come in under the national benchmark. The same is true for the cycle time for urine cultures in the Microbiology



Medical lab scientists Melissa Booth and Chris Taylor review specimen parameters, removing samples from cold storage unit.

department. The industry benchmark is to release results for urine cultures within 48 hours greater than 90 percent of the time, and the core lab has exceeded this standard since the beginning of 2017.

Improved cycle time performance, in addition to staff productivity, is supported by increased testing on automation lines. Both the Heme/Chem/IA and Microbiology departments have seen significant increases in automation since FY15.

Specimen testing ordered, but not performed, by the Core Laboratory is sent to an esoteric (highly complex) testing partner. The Core Laboratory tracks rejected specimens by such partners as an indicator of process effectiveness. Specimen rejection has been reduced from nearly four percent in October 2016 to 1.31 percent in October 2017.

Department productivity has improved significantly over the last three years. Supply cost improvements have positively impacted total cost-per-test improvements.

Teamwork

Lab leaders at SLHS strive to create an environment that is focused on optimizing performance both through a variety of internal processes and key collaborations. The internal processes include:

- ***Kola's board.*** Named after the department's director Kola Ogunrinola, PhD, the board displays service, quality, and financial performance for all work streams. The board is built upon three leadership commitments: know your process, know your numbers, and exceed expectations.
- ***Department scorecard.*** Tracking and analyzing of key metrics across all departments.

The St. Luke's Core Lab Leadership team poses in front of the Lab's operational metrics board. From left to right: Annette Monterrubio, Manager; Kara Dubin, Supervisor; Brittany Perez, Administrative Assistant; Kola Ogunrinola, PhD, Director; Angela Gambill, Director; Shannon Justice, Supervisor; and Jordan Harris, Supervisor.

- ***Weekly leadership huddles.*** The Core Laboratory leadership team huddles to review key performance indicators, goal progress, and organizational change management initiatives.
- ***Weekly team huddles.*** Leaders and staff meet to review key performance indicators and goal progress and to discuss opportunities for improvement.
- ***Monthly 1:1.*** Staff and supervisors meet to review key performance indicators, goal progress, leadership development, and staff issues/trends.
- ***All-staff meetings.*** These are utilized to deploy important information to the workforce. Service, quality, and stewardship measures are reviewed in alignment with project progress aimed at improvement.
- ***TEAMwork boards.*** Communication boards are displayed within each team environment and provide visibility to goals, performance, and improvement plans.
- ***LEAN tools.*** The Core Lab regularly utilizes Kaizen Action Sheets (KAS)—available on site—to facilitate the implementation of rapid change. More comprehensive process improvement utilizes the DMAIC framework, where problems are **D**efined, **M**easured, **A**nalyzed, **I**mproved, and **C**ontrolled.
- ***Emerging leaders breakfast.*** Implemented in 2017, the breakfast provides a leadership development opportunity for directors, managers, and supervisors within shared services on the Baldrige Excellence Framework. Attendees have engaged and supported the Core Laboratory's journey of excellence.
- ***Brilliant at the basics.*** In 2015, the laboratory implemented a Lean-based framework to support team learning and development within each Core Lab department. Each leader assessed their performance and set an improvement goal based on the following leadership fundamentals: put patient and employee safety above all else; know your customer, what they value, the processes that produce that value, and the numbers that reflect to what degree you are achieving that value; establish goals that align with the organization's goals, and report and escalate progress, issues, and barriers; foster a culture of continuous improvement by empowering your team, through education and support, to identify and solve problems; be a good steward of organizational resources; and ensure that work areas are well organized and conducive to optimal productivity and innovation.

The Enterprise Project Management Office (ePMO) is a key collaborator that supports the organization in successfully pursuing strategic opportunities and innovation. Leaders identify priorities and proceed through the project cycle: initial project review; business justification; prioritization and approval; and project implementation. Projects entered are evaluated against the organization's strategic objectives and action plans. New ideas or project proposals are documented and enter into the process.

The laboratory has engaged in the ePMO process successfully through the implementation of such innovations as courier redesign, automation in Microbiology, core line expansion, and, soon, utilization management.

Education and Training

The aging laboratory workforce requires effective approaches to both knowledge transfer and knowledge building. Specific strategies aimed at supporting knowledge transfer include:

- ***Levels built within job family.*** The laboratory has built a comprehensive job family that supports growth within roles and across roles as staff build their knowledge through degrees and certifications.
- ***Student rotations.*** SLHS participates with Idaho State University, Weber State University, University of Cincinnati, Oregon Health Sciences, and the University of South Dakota.

continued on page 26

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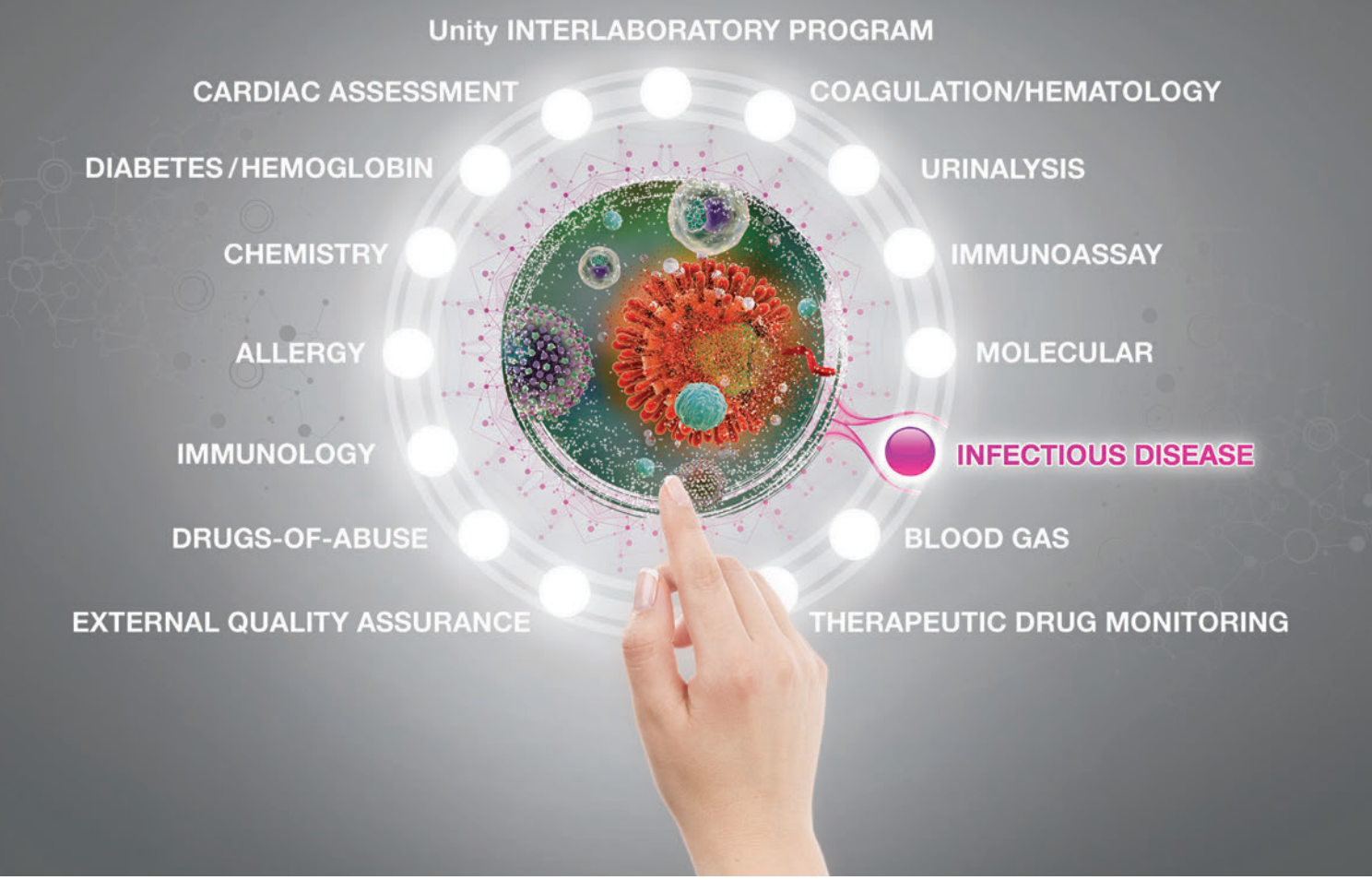

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continued from page 22

• ***Cross-training.*** A culture of cross-training within all laboratory teams is fostered.

Additionally, the laboratory is in the process of implementing a central processing department to support non-technical duties for Molecular, Microbiology, and ultimately Heme/Chem/IA.

The building of new knowledge is also fostered through various programs: local, regional, national, and international conferences; Continuing Education; networking with lab colleagues in a variety of regional and national forums such as the Health Trust Laboratory Board and Lab Leaders Conference; vendor presentations; and pathologist partnerships. Pathologists have extensive connections at teaching universities and are consulted to investigate unique or trending patient care issues.

Courier Services team members, accompanied by the Core Laboratory Director

Maintaining and measuring workforce capability is a priority at SLHS. The laboratory orientation process validates new employee initial competency in identified technical test systems and skill sets and determines where additional training and experience is needed to achieve competency. Annual competency assessment includes the six criteria identified by CAP and is outlined using test system criteria which are established by System Quality Councils for each clinical specialty. Documentation of both initial and ongoing (annual) competency follow a standardized hard copy and electronic process.

There has been significant focus within the core lab over the last two years on improving capacity through the following initiatives:

• ***Implementing automation.*** Non-value added tasks are identified and automation solutions investigated, with optimizations occurring as a result of total lab automation in Microbiology, core line expansion in Heme/Chem/IA, and Epic Beaker implementation in processing.

• ***Service consolidation.*** Opportunities are seized to consolidate functions to create additional capacity. For example, central processing has been expanded to cover microbiology specimens, and the microbiology and molecular biology teams have been aligned.

• ***Adjusting skill mix.*** Evaluation of staff time usage and ensuring performance at the top of each individual's certification and/or job description are ongoing. Opportunities are offered for staff to grow their competencies and skills and assume additional responsibilities.

At the organizational level, workforce change management is supported at SLHS through two main programs:

• The ***Employee Career Center*** was established within the career coaching program to support employee transitions. The program has evolved and now also supports employees looking for growth opportunities.

• ***HR business partners*** are embedded within each organizational unit to connect leaders with the appropriate human resources teams, processes, and tools to address workforce needs. The HR business partners were critical in compensation redesign and the organizational restructuring that occurred subsequent to the establishing of the acute care, medical, and post-acute care divisions in 2017.

The Core Laboratory has relied heavily on the partnership with HR to navigate changing workforce requirements. Implementing total lab automation within the Microbiology department required a workforce shift away from manual testing toward mechanical and information technology skills required to utilize the new equipment. This was accomplished through defining the skills and competencies required and working individually with staff and subject matter experts to define a pathway for success. The technical leads helped and supported staff who were struggling. A similar approach was employed as part of the effort to redesign central processing.

Workforce learning and development is also supported through initial and ongoing competency assessment, new/transition employee orientation, a preceptor program, facilitated classroom education, and team learning enhanced by simulation. The programs are a result of collaboration among the Learning and Development department, laboratory support team, and local core lab leadership.

Manager and leadership development is supported through SLHS's Organizational Effectiveness department via two programs:

Leadership Onboarding. All new leaders are provided a general management orientation to provide tactical tools within their first 90 days.

Leading at Luke's Fundamental. This program is designed to optimize and engage leaders across the organization covering communication, change management, HR policies, the Family and Medical Leave Act, Lean principles, and financial, meeting, and conflict management.

Strategic Outlook

SLHS's strategic planning process includes seven key milestones, occurs on a 12-month cycle, and aligns with the corporation's annual goal-setting process. The annual retreat, attended by laboratory leaders (directors, managers, technical leads, and supervisors) from across the operations division, includes a review and update of laboratory-specific core competencies. Each core competency has defined and described the behaviors for committing, developing, achieving, and leading along a maturity continuum.

During the retreat, each competency is scored for current performance and a year-end target is established. Level of impact is evaluated as primary, secondary, or tertiary, with the highest priorities reflected in the lab services' work plan.

The outcome of the laboratory's strategic planning process is the Laboratory Services Work Plan, which outlines the following four high-impact initiatives:

- ***Key performance indicators.*** understanding the data and using it to improve performance
- ***Policies and procedures.*** formalization of key documents across all sites
- ***Standardization.*** aligning performance and expectations in a standardized and consistent manner across all sites
- ***Waste.*** reducing non-value added tasks within laboratory work flows.

Within each high-impact initiative there are three to five goals. These goals are overseen by a laboratory leader with monthly milestones defined in support of successful implementation.

The Core Laboratory has implemented several successful strategies over the last three years:

The *courier redesign* initiative was initiated in FY15 with the goal of reducing transport cost by transitioning from an outsource model to an internal team. Monthly expense was reduced from $53,530 in November 2014 to $36,903 in September 2017, a 47 percent reduction.

Work was initiated in FY15 to accomplish *send-out reduction* by onboarding new methodologies to improve service and reduce cost. A reduction of eight percent was achieved in FY17 compared to FY14. The cost savings added up to an annual savings of more than $250,000. The Molecular department was established to support the send-out reduction activities, improve current methodologies, and support centralized testing performed across the organization. The cost savings for the top three assays was significant—an additional $250,000.

Laboratory Services utilizes a 10-year capital planning roadmap for platform replacement to *automate Microbiology*. In FY15 a comprehensive evaluation of microbiology testing systems was initiated, resulting in the decision to begin a significant automation transformation. When this was implemented in FY17, the Core Laboratory was the fourth lab in the country with this technology. As a result, microbiology productivity was cut in half, with a reduction from 0.25 in October 2015 to 0.12 in August 2017. The automation not only reduced cost, but also increased quality and service, including a six-hour reduction in result availability for bacterial isolate identification. This improvement puts results in the hands of the clinicians more quickly, getting patients on the right treatment faster.

A *utilization management* initiative is new—identified as part of the FY18 strategic planning process. The goal of the program is to ensure the right tests are ordered for the right patients at the right time. In September, the laboratory on-boarded a genetic counselor to provide consultation and order review support.

Accreditation

The core laboratory has received full CAP accreditation since inception in 2011. SLHS has been cited for a small number of deficiencies, mostly related to its rapid expansion into new areas. The *MLO* judges took that fact into consideration. What most impressed them, however, was the rapid, proactive way SLHS responded to the citations and corrected the deficiencies. Finally, the judges decided the ability to recognize a problem and act aggressively is a plus, not a minus.

Because no lab is perfect. But this lab is very, very good—as are the two runners-up in *MLO*'s 2018 Lab of the Year recognition. You can read about them on page 28 and 29. Congratulations to those labs and to all labs that submitted nominations.

"Quote...Unquote"

Here's what some SLHS Lab leaders say about the institution they serve.

"We've spent considerable time over the last three years maturing our approach to strategic planning. We know the lab is important. We also know that what has gotten us to this point will not sustain us. Our workforce is shrinking, our margins are compressing, and our reimbursement models are changing—so we must evolve. We must automate. We must drive out waste. We must engage our teams in innovative ways to improve. And we must do it now."

Mary Cronin, Senior Director, System Support Services

"We have spent a lot of time during the last two years on optimizing our productivity. Our staff are our greatest asset. Our focus has been on eliminating wasteful steps within our workflows and improving automation. Both of these efforts are aimed at promoting staff to practice at the top of their credential."

Kola Ogunrinola, PhD, Director, Core Laboratory

"Our entire team huddles weekly to review key metric performance and discuss opportunities for improvement. These huddles have made a difference by empowering employees to solve problems and impact the performance of the department as a whole."

Kara Dubin, Supervisor, Core Laboratory

"Our couriers aren't just specimen transporters. Our couriers are the face of our operation and relationship managers. As a result, we felt like outsourcing this function was a mistake. By bringing the role back in house, we not only saved the organization money, but we created eyes and ears within our customer base that we didn't have before."

Jordan Harris, Supervisor, Core Laboratory

"The Brilliant at the Basics program provided our leaders and teams a clear pathway for the implementation of Lean fundamentals within the lab. By clearly defining the behaviors for each concept, assessing current performance, and setting goals, we enabled teams to focus on the areas most impactful to them and manage the pace of change in consideration of other initiatives. We now have many Lean concepts hard-wired within our operations as part of our daily work."

Annette Monterrubio, Manager, Core Laboratory

Children's Medical Center Dallas Laboratory Leadership and Staff

First runner-up:

Children's Health Laboratory System

Children's Health Laboratory System consists of two physical laboratories: the lab at the main campus in Dallas, and the smaller lab at the Plano campus. Both offer specialized pediatric services to patients in the great state of Texas. The Dallas campus consists of 185 employees and performs 1.7 million tests annually, while the Plano campus, located 21 miles north, has 36 employees and performs 230,000 tests per year.

The two laboratories operate as one system under the same policies, procedures, instrumentation, and medical director oversight, and are **inspected** as a system by CAP and AABB. The leaders of Children's Health Laboratory System work to ensure that the two labs meet regulatory compliance and ensure quality not only when an inspection is near but 365 days a year. The labs undergo rigorous testing and evaluation to ensure that they are meeting or exceeding healthcare standards.

In 2017 Children's Health became the first organization with high level pediatric complexity to implement the Epic Beaker, a laboratory information system (LIS) whose software supports common workflows for clinical pathology (CP) labs as well as anatomic pathology (AP) labs. Beaker's barcode-enabled workflows allow laboratorians to track specimens within and across sites beginning at the point of collection and ensure efficient specimen handling. To ensure a unique and smooth transition, the Beaker building team selected six staff members to transition from the lab to the Beaker build analyst role. Everyone became Beaker-certified in the areas of the lab they were assigned to build. Children's **strategic outlook** involves continuing to optimize the new LIS system, while improving and streamlining processes.

Vaishali Patel, MT(AMT), evaluates Chemistry results at the Plano Lab

Children's Medical Center Plano Laboratory Leadership and Staff

With the new LIS implementation, **education** is a key area in Children's success. Custom training was developed for areas outside of the laboratory, including very specific workflows for ordering, collecting, receiving, specimen processing, and results. In addition, the laboratories work to provide education and training and work with staff to ensure that they understand the culture of the lab and what is expected from all levels of lab staff and leadership.

With regard to **customer service**, the system offers targeted genetic testing to extended families of the affected patient to interpret genetic changes of unknown significance. The labs also implemented the latest technologies to help in the diagnosis of inherited disorders. A lab genetic counselor, in conjunction with the genetics team, is involved, and the team has implemented processes that include benefits inquiry for insurance coverage to aid families in the process of deciding to have genetic testing. The lab genetic counselor performs daily review of the genetic test orders that are placed the day before to determine if a more appropriate or less expensive test is available, or if there was a duplicate or unnecessary test order. This has not only identified unnecessary testing and avoided unnecessary charges, but has continued to build a strong relationship between the lab and providers.

As an example of Children's emphasis on **productivity**, currently within Epic there is no module specific to genetics. The genetics leadership and medical director worked with Epic to develop a genetics module, creating a build that combines both AP and CP for the genetics department to document electronically within the patient chart and link to other testing for historical purposes. Prior to Beaker, the genetics lab was on paper, utilizing excel spreadsheets.

The labs value **teamwork** and strive to embody the following core values: Selfless Service, Commitment to Excellence, Passionate Advocacy, and Unwavering Integrity. The team writes and posts notes to recognize their peers on a quality board. Staff who receive recognition on the board receive a card from the manager or senior director. Once five recognition cards are collected, they can be used to redeem a gift card.

For more than 100 years, the mission of Children's Health has been to make life better for children. Established in 1913, Children's takes great pride in being the eighth-largest pediatric healthcare provider in the country, and the only academically affiliated pediatric hospital in the area. Children's Health Laboratory System leaders affirm that success and achievement would not be ossible without a combination of all six elements of customer service, productivity, teamwork, education and training, strategic outlook, and lab inspections. Their goal is to continue to strive for excellence in all of these areas while, "Making Life Better for Children, One Test at a Time."

Second runner-up:

Ronald Reagan UCLA Medical Center Laboratory

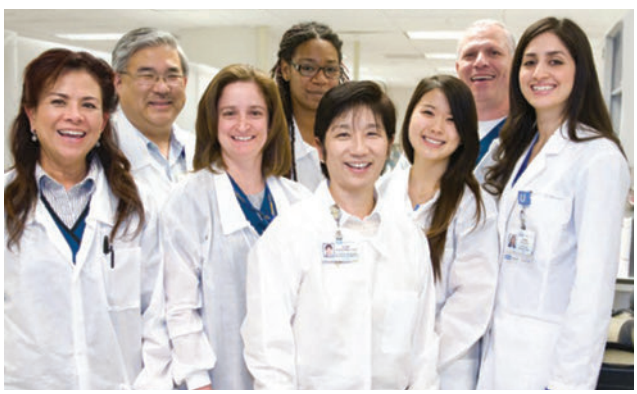
UCLA Health's Pathology and Laboratory Medicine Leadership and Staff

One of the shining stars of Los Angeles is not a movie or television personality, but Ronald Reagan UCLA Medical Center (UCLA Health). It is a Level 1 Trauma Center and has one of the nation's largest organ transplant programs.

UCLA Health consists of a main laboratory and ten offsite sections, which combined perform eight million lab tests annually. In addition, the UCLA Blood and Platelet Center falls under the purview of the laboratory. Of special note is the extraordinarily large and complex Point of Care Testing (POCT) program, with over 200 POCT sites in support of the Medical Center and surrounding UCLA medical clinics dispersed throughout local cities.

Due to its large size, the laboratory has a departmental section-based **customer service** outreach program. Each lab section interacts with its internal customers, stressing a win/win mentality focused on improving patient care, resolving issues, and providing the best lab support possible. Nursing staff are some of the lab's most important internal customers. "Outreach to our internal customers is the foundation of what we do to support our fellow healthcare professionals in their quest to heal patients," says Dr. Alyssa Ziman, Laboratory Medical Director.

With such a large and complex laboratory, it is essential that there are experts on hand to take care of laboratory-related business functions. UCLA Health's Clinical Laboratory Business Office created a **process improvement initiative** to reduce errors in billing practices in order to recoup money for tests performed but not billed. This led to a significant reduction in errors and a gain of $1.9M. "The Business Office is an essential part of the laboratory team. We provide administrative, supply, IT coordination, and financial support to all 35 of our cost centers to ensure that our laboratorians have the tools they need to provide outstanding patient testing," says Colleen Toten, Manager of the Clinical Laboratory Business Office.



Manager of Regulatory Affairs E. Tsukahara, Core Lab Staff, and interns

The UCLA Blood and Platelet Center is a large part of the laboratory team, collecting approximately 30,000 volunteer donations per year. These donations yield approximately 70 percent of the 73,000 blood products that are transfused by the laboratory. Treating more than 1,000 patients per year, the blood bank team created a rare whole blood inventory and transfusion program.

Having a high yielding donor center on a university campus is very unique for a hospital system. UCLA student recruiters work hand in hand with the donor center and student population to help save lives. "The UCLA Blood and Platelet Center **acts as a bridge between our community and our healthcare system**, resulting in safe, pure, and potent blood products for patients in need," says David Anthony, Director of the Center.

Pathology and Lab Medicine Leadership and Staff representing the Core Lab, Transfusion Medicine, Microbiology, Support Services, Regulatory and Lab Operations, and the BURL Outreach Lab

The laboratory is dedicated to fostering the next generation of laboratorians and has comprehensive training licensure programs available. It also offers free electronic CEUs for staff to maintain state licensure and ASCP certification and enhance managerial skills for future leadership roles.

"Our **strategic plan** helps us prioritize our resources, ensures our team understands our operational strategies, and provides focus to move our plans into actionable steps toward project and goal achievement," says Edward Griffin, MBA, Manager of Transfusion Medicine. "We have found that every minute spent in strategic planning saves at least ten minutes in execution."

UCLA Health has six lab compliance team members who perform full-time quality assurance oversight with an extensive auditing and continuous process improvement focus. "Quality is the hallmark of good healthcare," says Manager of Regulatory Affairs Elsa Tsukahara. "By focusing on quality we make sure that patients receive the trademark high-quality care that the UC Health system is known for."

Developing liquid biopsy diagnostic testing for cancer immunotherapy selection in NSCLC patients

By Gary Pestano, PhD, and Lisa Jensen-Long

More than 125,000 people are diagnosed yearly with lung cancer in the United States, and more than half die from the disease.[1] Non-small cell lung cancer (NSCLC) is one the most common forms of lung cancer, and it is most frequently diagnosed during advanced stages. Timely and appropriate precision diagnosis and treatment is critical for clinical management and patient survival. Blood-based liquid biopsy is gaining traction in clinical testing as an alternative to more invasive tissue biopsy for diagnosis and monitoring in patients with NSCLC.

Advances in immunotherapy

Advances in cancer immunotherapy research have enabled significant progress in the development of targeted therapies, with encouraging success in the clinic. Newly available immunotherapies, some referred to as checkpoint inhibitors, are today increasingly selected for treatment of advanced-stage NSCLC patients who cannot undergo surgical resection, as well as those who have failed to respond to platinum-based chemotherapy. Among the most promising targets of these checkpoint inhibitors are immune checkpoint proteins, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1).

Cancer cells can express PD-L1, which binds PD-1 on the surface of T cells and suppresses their ability to attack cancer cells. Inhibitors of PD-1 and PD-L1 have been designed to break this communication, thus restoring T cell anti-tumor activity. Positive PD-L1 expression of cancer cells is now considered a predictive and prognostic biomarker by clinicians, and it is used to determine which patients can benefit from PD-1/PD-L1 immunotherapy.[2] A variety of antibody-based inhibitors of PD-1/PD-L1 have obtained approval by the U.S. Food and Drug Administration (FDA), including nivolumab, pembrolizumab, and atezolizumab, and have shown great promise in patients whose tumor biopsies have tested positive for PD-L1.[3]

Drawbacks of IHC

Immunohistochemistry (IHC) of biopsied tumor tissue is currently the standard method to test for the presence of PD-L1 expression in cancer, to determine whether patients are likely to derive benefit from anti-PD-1/anti-PD-L1 immunotherapies over chemotherapy. IHC is a powerful tool. However, it can be variable in performance and requires invasive surgical procedures. The four IHC-based tissue assays approved by the FDA for PD-L1 use different antibodies, detection platforms, cutoff points, and scoring systems, which complicates standardization for clinical management.[4,5]

Researchers have also shown that there can be as much as 20 percent variability among pathologists in scoring when the cutoff is set at ≥1 percent positive tumor cells.[6] Furthermore, re-testing using IHC requires performing more than one surgical biopsy, which increases the burden on the patient and the cost of care, and may present additional clinical risks. Last, IHC test results may take weeks to be delivered, which could delay the administration of a targeted therapy.[7]

Two alternative test methods for measuring biomarkers relevant in immunotherapy that are drawing widespread interest are droplet digital PCR (ddPCR) and next-generation sequencing (NGS). In January 2018, a molecular testing company announced a partnership with PD-L1 IHC expert Fred R. Hirsch, MD, PhD, laboratory director of the Hirsch Biomarker Laboratory at the University of Colorado Cancer Center.[8] The company presented results on a newly-developed blood-based PD-L1 research assay at the 2018 American Society of Clinical Oncology and the Society for Immunotherapy of Cancer (ASCO-SITC) Clinical Immuno-Oncology Symposium.[9]

Improving PD-L1 diagnostics

Preliminary results compared the use of ddPCR technology to IHC for PD-L1 expression. The ddPCR test detected PD-L1 mRNA successfully in plasma and formalin-fixed paraffin-embedded (FFPE) tissue resections from the same individuals.[9]

The researchers used ddPCR technology, which partitions each sample into thousands of nanoliter-sized droplets, and enables absolute quantification of PD-L1 transcripts in each droplet, without need for standard curves as in traditional RT-PCR methods. ddPCR can be used to detect circulating nucleic acids from plasma, thus allowing the use of blood samples, which are much more easily obtained than tissue biopsies.

The results of this study concluded that this mRNA assay may require establishment of independent cutoff values, as IHC may not be the best validation measure for these assays. The ddPCR-based product concept was able to detect PD-L1 copies in the range of 6-1,272 copies from tissue, and 32-138 copies from plasma.[9] Overall, the study demonstrated the feasibility of testing for PD-L1 expression by ddPCR in plasma and in FFPE tissue sections.

Following these early results, a prospective study was initiated to continue to assess IHC and ddPCR testing for PD-L1, which includes performance measures of NSCLC patients after receiving PD-1/PD-L1 immunotherapy.

Related LDTs

The company has also developed and validated two prior, complementary laboratory-developed tests (LDTs), one of which is a ddPCR genomic test, and the other a Mass Spec proteomic test. These tests are used by clinicians to aid in the treatment of patients with NSCLC.

The genomic test detects cancer-driving mutations from liquid biopsy samples, including EGFR sensitizing (L858R

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and del19 E746-A750) and resistant (T790M) mutations, KRAS and BRAF mutations, and EML4-ALK, ROS1, and RET gene fusions.[7] Patients testing positive for any of these mutations may benefit from targeted therapies directed specifically toward these mutations or fusions.

The proteomics liquid biopsy test measures the chronic activation of complex proteomic pathways known to be associated with a poor prognosis and potentially limited response to therapy. A positive result provides prognostic information that a patient can derive maximum benefit from standard-of-care treatment options, such as platinum-based therapy, EGFR-TKIs, single-agent therapy, and immunotherapy. This may correlate with longer progression-free survival and overall survival after treatment.[10] A negative test result provides valuable clinical information that may be used to support patient-physician conversations regarding poor prognosis, as well as identifying a subset of patients who might benefit from other treatment strategies such as best supportive care or clinical trials.

Future outlook

Although further testing is required, PD-L1 in liquid biopsy that uses ddPCR technology has the potential to be a simpler and faster procedure that can return results in under 72 hours. Clinicians can use ddPCR-based LDTs as a rapid screening tool to look for tumor mutations or other biomarkers. PD-L1 testing by ddPCR could be especially favorable for patients with aggressive tumors, who may not tolerate tissue biopsy and could benefit from PD-1/PD-L1 immunotherapy.

As we continue to expand our understanding of the complex pathways cancers use to subdue the immune system, and to create increasingly targeted therapies against these molecules, we expect to see development of more sensitive and specific laboratory-developed tests based on liquid biopsy.

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What do we gain from liquid biopsy tests in lung cancer?

We asked Michael Apostolis, MD

By MLO staff

As a pulmonologist, why do you order liquid biopsies?

Dr. Apostolis: Liquid biopsy, in conjunction with tissue biopsy, provides further information on genetic mutations. Many lung cancers have genetic mutations that can be targeted with chemotherapy; therefore, it's very helpful to have a liquid biopsy to confirm the tissue analysis and inform personalized treatment.

In other cases, liquid biopsy is the only mode of getting the cells needed for a genetic diagnosis. For example, a pulmonary adenocarcinoma may not yield enough tissue for genomic analysis. To immediately re-biopsy is a difficult option. Repeated invasive procedures have increased risk, as opposed to a simple blood test. But liquid biopsy provides an alternative modality—usually a blood draw, though tests that use urine or other bodily fluids do exist—to collect molecular data from circulating nucleic acids, circulating tumor cells, or other biomarkers.

This is such an important tool in lung cancer diagnosis because bronchial aspiration and gestational bronchoscopy are very technical procedures that only give us limited access to tumor tissue. Capturing enough cells for genetic analysis is far from guaranteed. Furthermore, that tissue is a narrow view of the whole tumor's makeup, so the confirmatory use of liquid biopsy guards against false negatives.

Some forms of liquid biopsy can also give us information on whether or not a good response to chemotherapy is to be expected. Blood-based proteomic tests, for example, provide physicians tools to provide personalized counseling to families and help anticipate treatment complications.

There are several tests on the market now. To what factors do you give the most weight when deciding which test to order?

Dr. Apostolis: A robust test will have been validated to show strong correlation with other modalities, especially tissue testing. Because liquid biopsy is frequently ordered to complement tissue testing, there must be a high level of confidence that the two data sets can be compared in a meaningful way.

Close behind that, a fast turnaround time is very significant. Once we draw a blood sample, everyone involved rightly wants to get the results and start acting on them. As a critical care pulmonologist, I want to coordinate a treatment plan quickly with the pathologist and oncologist and communicate this to the patient. With a fast test, the patient feels at ease, tumor boards operate efficiently, and I can respond quickly if I need to modify treatment.

You might think fast turnaround time would come at the expense of sensitivity, but that's not necessarily true. The test I use most in my practice has a sensitivity at or above 90 percent, compared with tissue biopsy, and still returns results within 72 hours.

Physicians should also learn about some of the many testing platforms. PCR, for example, has been validated across multiple scientific fields and has become the standard for genetic molecular testing. Now, it's being used in medicine. Droplet digital PCR is an advancement that increases PCR sensitivity by dividing a sample into thousands of separate microreactions. Different platforms bring unique strengths and merits that should be considered with the needs of the situation.

What future improvements are you looking forward to? Would you like to see liquid biopsy replace tissue biopsy?

Dr. Apostolis: The next step will be expanding the portfolio of test targets. Right now, for example, there isn't a cell-free DNA test for PD-L1, though a few have been developed to measure PD-L1 on circulating tumor cells. The technical performance of many liquid biopsy tests is already solid, and we can expect to see steady improvements.

On a practical level, it would be astronomical if we can get to the point of using a finger stick of blood instead of a vial. As to whether a blood test will ever replace tissue biopsy, I don't see that happening any time soon because the two modalities support one another so closely. But there is potential, so we'll have to wait and see.

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Padlock probes

By John Brunstein, PhD

In last month's installment, we covered some of the ways in which a ligation step can be added into (or before) a PCR-based methodology to improve one or more aspects of the assay. While the topic of this month's article—padlock probes—also fits this description, it's unusual enough in its design and assay features to deserve its own column.

PCR reactions are, by and large, rather individualistic and temperamental things. Optimization of any reaction is a balance between sensitivity and specificity, chosen by tailoring reaction chemistry (components and concentrations) and conditions (times and temperatures of the thermocycling profile). In the context of a simplex (single-target) reaction, all of these can be optimized at will, but if the goal is a multiplex reaction, things get a lot more complicated.

Selecting all primer sets to have similar melting temperatures is probably the most crucial step, and to do so while ensuring uniqueness and thus specificity of primer binding sites generally leads to a range of amplicon sizes and differential amplification efficiencies of the separate amplicons in the mixture. While this can be compensated for to some extent by things such as differential primer concentrations, in the end a multiplex traditional PCR must be a sum of many compromises to reach acceptable (but almost certainly suboptimal) performance of each of the component singleplex reactions. It's just a natural consequence of the need for different primer sets, amplicon sizes, and dissimilar probe or hybridization capture regions within each singleplex.

Imagine now if there were a method that could multiplex large numbers of singleplex targets, but do it in such a way that a single common primer set could amplify every target (no more compromising on annealing temperatures); all targets could be the same length (no more compromising on extension times); and a real-time probe or hybridization capture tag sequence could be engineered in, assuring both that each possible amplicon would be readily distinguishable and that the probe or hybridization capture tags would all have very similar annealing behavior. It's as if you're promised a magical beast which does away with many of the classical challenges of multiplexing. Such an assay method does exist in the form of padlock probes. As always, though, there are costs; read on to discover the method, and what those costs are.

Padlock probe basics

The basic concept of a padlock probe is outlined in **Figure 1**. Essentially, it consists of a single-stranded synthetic DNA probe designed against each target of interest (a). The 5′ and 3′ termini of this probe are target-specific; they're designed to be complementary to two immediately adjacent sequences of the target nucleic acid, labeled here as R1 and R2. If the padlock probe is mixed with target nucleic acids containing these sequence complements, thermally denatured and reannealed, it can hybridize down to its target at both ends, effectively circularizing the probe and placing its 3′ and 5′ ends immediately next to each other, but with a nick—that is, missing the phosphodiester bond; see **Figure 1b**. If a DNA ligase is present—preferably, one from a thermostable organism so it could have been added during reaction setup, prior to thermal denaturation—it can now act at this nick, converting a previously linear padlock probe into a covalently closed circular molecule; see **Figure 1c**. In some versions of this type of assay, we will actually run a few cycles of denaturation / annealing / wait for possible ligation in an effort to drive formation of multiple copies of this circular product.

Of course, this doesn't occur to every padlock probe we added into the reaction, but only to a small fraction. That's fine, and to get rid of uncircularized probes we now add in single strand-specific DNA exonucleases. These "chew up" linear single-stranded DNA but leave any circular molecules intact. Now all we have to do is detect these.

That's where we switch back to classical PCR—eithker in a real-time format or upstream of a hybridization capture-based detection (that is, a microarray). If you look back at Figure 1, you'll note that on the padlock probe, internal to the target-specific R1 and R2 ends, are a pair of primer binding sites PB1 and PB2. The key here is that these work with a pair of primers; let's call them PB1′ (complement to PB1) and PB2 (identical in sequence to PB2; see Figure 1c). If we conduct a standard PCR reaction with these primers and have any circularized padlock probe present, consider what happens. PB1′ binds to the circularized probe and gets extended across the now-ligated R1/R2 junction, and out across PB2, creating a complement to PB2, and thus a binding site for the PB2 primer. Consider that if the padlock probe hadn't circularized, the nascent strand growing from PB1′ would have run out of template and stopped at the R1/R2 junction, thus never reaching PB2. Only a circularized template allows for PB1′ to extend across the PB2 site, creating what is now a "normal" linear PCR template for the PB1′ / PB2 primer pair. PCR amplification proceeds normally from there on.

Further observations

There are two things to observe at this juncture. First, note that any number of padlock probes could be used simultaneously with differing R1/R2 (target-specific) regions, but sharing a single PB1′/PB2 amplifying primer pair. That's where our promise above of using a single common primer set to amplify disparate targets comes from—so we only have to optimize PCR for this single PB1′/PB2 primer set (and note as well that we can design these sequences at will to have convenient thermal characteristics, lack of secondary structures, and other desirable characteristics; they aren't constrained to be part of any assay target sequence).

A second possible observation: what if instead of classical PCR, we used just the PB1′ primer, a polymerase,

and did an isothermal amplification? If you're guessing this would leave the polymerase racing around and around the closed padlock probe template and creating an ever-lengthening nascent strand consisting of concatemer linear copies of the circular sequence, you're right. Known as rolling circle replication or RCR, that's something we could do here as well. It would not be quite as specific as direct PCR (needing both primers PB1′ and PB2 to match) and wouldn't yield as much signal amplification as classical PCR, but it would effectively tether the growing product to the point of amplification. RCR-based padlock probe detection is therefore sometimes used for in situ molecular detection, where we want to know localization of targets to specific cell types such as in a tissue thin section. For the sake of brevity though, we'll stick to just the classical PCR-based detection of our padlock probe for the remainder of this article.

So that then brings us to the PCR detection part. If we assume we have probed a sample with several different padlock probes (remember, each type with unique R1/R2 regions but shared PB1/PB2), and all of identical or close to identical total length), how do we tell them apart after our PCR has amplified up any probes which circularized? The answer here is given in Figure 1 as well. Note that we've incorporated a unique tag sequence in each padlock probe. Much like the PB1/PB2 sequences, these are arbitrary and up to the whims of the designer, meaning they can be chosen to provide highly selective hybridization capture tags (that is, complements to a series of spots in a premade microarray) or binding sites for real-time PCR probes suitable for our choice of probe-based real-time chemistry. Again, we can pre-design a whole set of such probe sequences optimized for similar hybridization behavior with minimal cross-hybridization, bothersome secondary structures, or other problems. The answer to our method of detection then can be either of real-time PCR (probe based against the tag) or microarray hybridization (against the tag). Obviously, if we're going to multiplex more than four to six targets simultaneously—the practical limit imposed by spectral resolution issues in real-time PCR—then array-based detection is preferable. Keep in mind, however, that we needn't make a new array each time we want to change a target of our multiplex assay; we only need to change the target-specific R1 and R2 regions of the padlock probe which carries a predetermined array tag. Of course the same argument applies if we did use real-time detection, too.

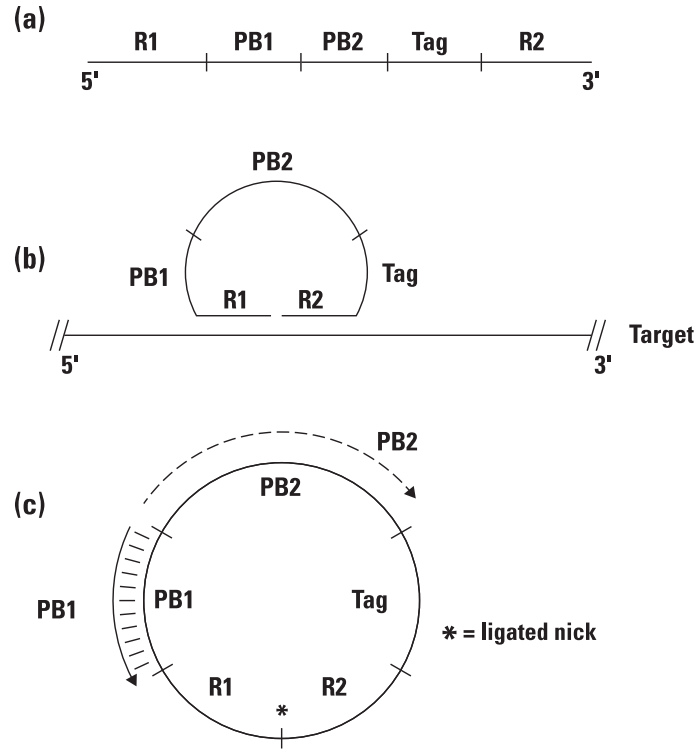

Figure 1. a) Padlock probe as synthesized. **b)** Padlock probe successfully annealed to target sequences at R1 and R2, awaiting ligation. **c)** Ligated, circularized padlock probe. (*) represents ligated nick, which now allows PCR primer sequences PB1′ and PB2 to amplify across the ligated junction. See text for additional details.

This final point—that we could premake a microarray, or set of real-time probes, and mix and match these against targets at will without redesign of the amplification primers or detection probes or array—is the icing on the cake, as it were, to our laundry list of desirable features which padlock probes have as a methodology over more traditional multiplex PCRs.

Considering the costs

The costs, then? These occur in the form of higher reaction complexity in terms of what has to go together and work in the reaction tube, not just PCR reagents but also a ligase and exonucleases. Since we don't want the ligase or the exonucleases working later on in the reaction, these have to be effectively inactivated, usually by an extended, high temperature step, after their point of action. The hybridization kinetics of a long padlock probe to target is not generally as fast or good as short, classical PCR primers, so lower limits of detection by this method may lag behind those of more direct PCR. Finally, synthesis of padlock probes, on the order of 100 bp in size, is more expensive and lower yield than synthesis of shorter, traditional PCR primer-sized molecules (However, compared to a few years ago, costs have decreased and yields increased significantly for longer oligonucleotides such as this, making that less of a hurdle than it used to be.)

Where is the laboratorian today likely to come across this type of assay? The most common application at present is probably in the detection of single nucleotide polymorphisms (SNPs). By placing the SNP of interest directly under either side of the R1-R2 junction, a mismatch to padlock probe will block ligation, or, conversely, a match will allow ligation and selective signal generation only when a perfect match occurs. Small insertions or deletions under the R1/R2 target area will also block effective circularization. Beyond such genotyping applications, other uses in the literature have included multiplex pathogen detection assays.

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A laboratory perspective on emerging and re-emerging infectious diseases in North America

By Linda L. Williford Pifer, PhD, SM(ASCP), GS(ABB), and Wyenona Hicks, MS, MT(ASCP), SBB

In the world of infectious diseases, recently there have been some new factors and some that are "déjà vu all over again," as Yogi Berra might have put it. Weather, natural disasters, poverty, crowding, unhygienic conditions, travel, contaminated food and water, proximity to animal vectors, and unknown elements have all given rise to surges in infection and increased the need for laboratory services as part of the response to them. One infectious agent was recently identified in the Western world, and several others are old enemies, but all deserve serious attention—because some will almost certainly present in your laboratory. In this article, we review some infectious agents that have made the news during the past year. Information from the U.S. Centers for Disease Control and Prevention (CDC) on how to report and process them is also included.

Acute flaccid myelitis

One of the most troubling emerging infectious diseases, causing concern to healthcare professionals and parents alike, is acute flaccid myelitis or AFM. This viral illness is strongly reminiscent of pre-vaccine polio, and it stirs memories of "iron lungs," heavy leg braces, and children on crutches in older "Baby Boomers." According to the CDC, AFM can be caused by multiple strains of RNA enteroviruses closely related to poliomyelitis, loosely termed EV-D68. Symptoms include fairly severe respiratory illness, muscle aches, and acute flaccid paralysis.[1] Dyda et al[2] have confirmed 120 cases of AFM emerging from various communities, and EV-D68 remains a frustrating mystery. Although enteroviruses are generally transmitted via a fecal-oral route, no common denominator environmental or other factor(s) have been uncovered to link these cases together epidemiologically.

Laboratory professionals will be crucial in contributing toward essential knowledge about this dangerous agent. Clinicians may be asking you to forward specimens to the CDC for confirmation of suspected cases. This website contains information on how to properly report, package and ship specimens: *http://www.cdc.gov/ncird/investigation/viral/specimen-collection.html*.

Seoul hantavirus

In February 2018, the first documented transmission of Seoul hantavirus from pet rats to humans in the United States was verified. It was detected in Tennessee, Georgia, Illinois, Missouri, South Carolina, and Utah, as well as in Canada.[3] Serologic results showed that 183 persons tested antibody-positive for Seoul virus. Of those, 12.5 percent were hospitalized; there were no fatalities. At the same time, humans were unknowingly fostering the virus in Norway rats (*Rattus norvegicus*) which were being sold as pets. Seventeen people in the U.S. were hospitalized, treated, and released.[4]

This was significant and alarming, because population health experts and others well recalled how, in 1993, hantaviruses caused an outbreak with numerous fatalities in the Four Corners region of the U.S. among members of the Navajo Nation. The dreadful outbreak, which took a number of young lives, was the subject of a major CDC investigation. The source of contagion turned out to be deer mice that had flourished due to a rich pinion nut harvest brought on by unusually heavy rains.[5]

Hantaviruses cause symptoms ranging from mild flu-like illness to severe respiratory disease, including shock, renal failure, and death, even in young, healthy persons. At this point, it is not known if the Seoul hantavirus is present extensively or at all in the U.S. wild rodent population. It is obvious that it could present a significant potential threat and challenge to public health nationwide, especially where rodent infestation is a serious problem.

Laboratory professionals and clinicians should consider testing for Seoul virus (and other hantaviruses) in patients with febrile illnesses who have had or may have had rodent contact. The CDC offers testing, as do some state and commercial laboratories. Complete information concerning specimen submission may be found at *https://www.cdc.gov/hantavirus/health-care-workers/index.html*.

Hepatitis A virus (HAV)

Hepatitis A virus (HAV), an old enemy, has re-emerged as a public health crisis in San Diego, California, to the extent that certain streets where the homeless congregate were necessarily pressure-washed with chlorine bleach to remove HAV-contaminated human fecal material.[6] Nearly 69 percent of San Diego's 580 patients required hospitalization, which is more than three times higher than normal. The mortality rate was 3.4 percent.[7]

Utah's index case of HAV was proven by molecular testing to have originated in California, and, since January 2017, the number of infected people has grown to 176 among the homeless population in Utah.[8] Vaccination drives in both states are aimed at containing the spread. A major concern is that it will amplify into the general population via infected food handlers as it has often done in the past. Laboratories in states including California, Utah, Michigan, Kentucky, and Colorado, and several others with substantial homeless populations without adequate sanitary facilities, will continue to see a surge in HAV testing.

Angiostrongylosis

Parasitology labs, particularly those in Hawaii and on the Pacific Coast, should be on heightened alert for queries concerning the rat lungworm parasite, *Angiostrongylus cantonensis*. This has become a serious problem because of the recent uptick in the

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population of this parasite's intermediate vector, the Southeast Asian semi-slug *Parmarion martensi*.[9]

This pain-inducing and frightening parasitic agent accesses the human body via raw, unwashed, or undercooked vegetables, fruits, seafood, frogs, or contaminated water. Larvae coughed up from the lungs of rats invade *P. martensi* (tiny slug-like snails). These slugs containing lung worm larvae are ingested by humans via raw vegetables or one of the aforementioned food items. Symptoms include nausea, vomiting, stiff neck, and headache. Human-to-human transmission is not known to occur. Most cases appear to resolve on their own, as the larvae eventually die because humans are a dead-end host. However, infection can be very painful and there is no specific treatment. Also rat lung worm infection is the world's leading cause of eosinophilic meningitis, which can leave the patient permanently impaired.[10]

Regrettably, there is no specific test for *A. cantonensis*. A few independent labs have developed serologic and PCR tests, but these are not commercially available. According to the CDC, it should be strongly suspected when symptoms resemble bacterial meningitis but results show eosinophilia in blood at >5 percent or in CSF at >10 percent, or travel to endemic areas has been verified, or dietary history supports this diagnosis. The larvae are rarely seen by microscopy of cerebrospinal fluid as they tend to attach to the meninges.[11] Ruling out other causes of meningitis is important, and MRI can be useful in this regard. Stool or biological specimens are of no value, as the parasite does not reproduce in humans.

Best tip to your clinicians: Watch eosinophils and consider the patient's recent personal history. Submission of specimens to the CDC is discouraged, but clinicians and laboratorians can call the Parasitic Diseases Hotline for advice and updates (404-718-4745).

Leptospirosis (Leptospira spp.)

We are increasingly reminded of the dramatic role that weather can play in emerging and re-emerging infections. The catastrophic winds and waves of Hurricane Maria unleashed a "perfect storm" of dozens of cases of Leptospirosis, and another 74 were being investigated in Puerto Rico as of this writing.[12] The corkscrew-shaped bacterial organism is transmitted by the urine of infected animals (most commonly rats) to humans by an oral route or through non-intact skin, eyes, or mucous membranes. It causes serious liver, kidney, and respiratory tract damage, muscle aches, meningitis and even death. Following a water-associated outbreak in 2015, the CDC reinstated Leptospirosis as a notifiable zoonotic infectious disease in the U.S. It claims nearly 60,000 lives every year worldwide, and its emergence can virtually be counted upon in endemic areas following flooding events.[13]

Vibriosis

Intensified toxic *Vibrio* illness (vibriosis) caused by *Vibrio vulnificus* and *Vibrio parahaemolyticus*, has also been documented scientifically as being associated with hurricane weather patterns. A study in 2014 of oyster beds in Chesapeake Bay first showed that virulence-associated genes in both *Vibrio* species intensified during post-Hurricane Irene environmental conditions.[14] Laboratories in Houston post-Hurricane Harvey cultured impressive numbers of both from patients. *Vibrio vulnificus* is a powerful food poisoning bacterium that is contracted from consuming contaminated raw oysters (primarily) and seafood. Dangerous bullous skin lesions and potentially lethal necrotizing fasciitis can occur as a result of infected cuts or abrasions sustained in brackish flood water.[15]

Vibrio parahaemolyticus is also associated with contaminated seafood and can cause dangerous infections in cuts and abrasions. Laboratory professionals should be on heightened alert for "storm surges" of these agents following hurricanes and other coastal flooding events involving brackish water. Both of these agents can prove rapidly lethal, and prompt identification is critical, especially in immunocompromised patients.[16]

Expecting the unpredictable

It is clear that emerging and re-emerging infectious diseases need not come from distant locales, as they can just as easily arise in the U.S. Chikungunya, Zika, and many exotic viruses still strike and come home with travelers to the Caribbean and points south and elsewhere. They make blood donor screening an ever more difficult task. It has been suggested that an overall deferral of travelling donors might be more effective than using targeted measures. For example, it might be best to defer all international travelers to known virus endemic zones for four weeks.[17]

In the world of infectious diseases, plagues that have lain dormant for decades can be reignited overnight. Examples are the current outbreak of bubonic plague (*Y. pestis*) in Madagascar, the occurrence of human anthrax (*B. anthracis*) in Africa,[18] and ongoing eruptions of smallpox-like monkeypox in residents of Nigeria.[19] It is noteworthy that the vast majority of these infectious diseases are zoonotic in origin. We also dealt with a norovirus disruption at the recently concluded Winter Olympics, recording nearly 200 cases with 1,200 staffers quarantined to prevent its spread.[20] In addition, a Royal Caribbean Cruise ship recently arrived in San Diego with 24 aboard suffering from norovirus gastrointestinal symptoms.[21]

All of which proves we must be eternally vigilant. Clinicians and laboratory professionals need to remain well-informed, aware, and prepared to meet every challenge presented by emerging and re-emerging infectious diseases. The lab provides our earliest alert, and therein lies one of laboratorians' most important responsibilities.

Please visit mlo-online.com for references.

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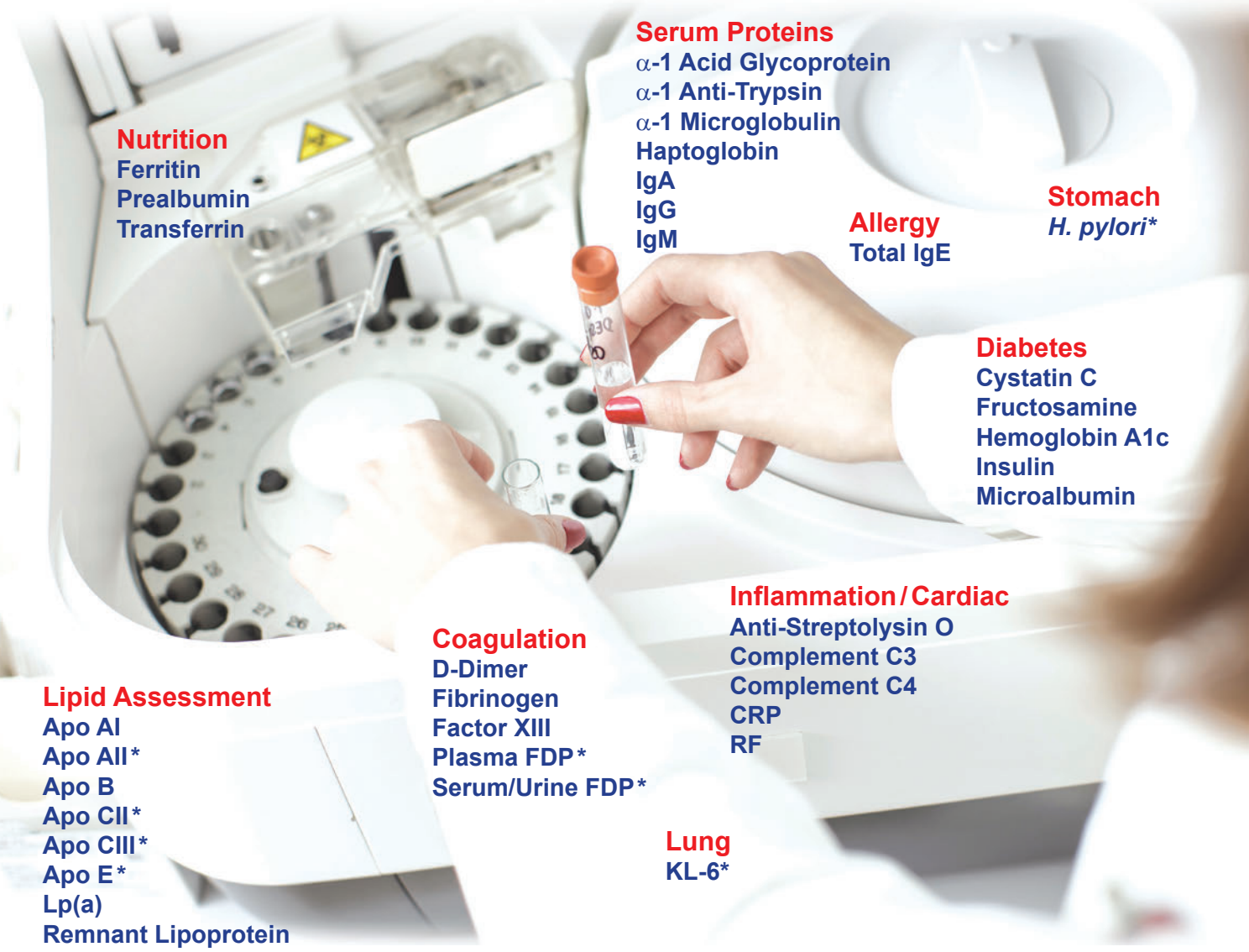

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Future prospects for flow cytometry

By Susan A. McQuiston, JD, MT(ASCP), CCy

The world of flow cytometry is rapidly evolving. During the past few years, there have been significant changes regarding the qualifications for personnel credentialed to perform flow cytometry, assays with revived clinical applications, more elegant fluorochrome development, and the size and sensitivity of instruments. There have also been many developments in reagents, instruments, and applications.

Staff credentials

Clinical flow cytometry laboratories now have an extended pool of expertise available thanks to the development of the Specialist in Cytometry Exam administered by the Board of Certification (BOC) of the American Society of Clinical Pathology (ASCP). The BOC had offered the "qualification in cytometry" (QCYM) designation for many years. In 2015, principal investigators and managers at cytometry core facilities were concerned about the retirement of personnel with extensive expertise. Development of the cytometry qualification exam occurred via collaboration among the International Society for Analytical Cytometry (ISAC), the International Clinical Cytometry Society (ICCS,) and the European Society for Clinical Cell Analysis (ESCCA), and sponsorship by the Wallace H. Coulter Foundation.

Successful qualification and completion of the International Clinical Cytometry Exam (ICCE) led to the credential "Certified Cytometrist" (C.Cy.). Continuing education was required to maintain the certification. In 2016, the original ICCE stakeholders agreed that the BOC would administer the exam. Individuals with ICCE or QCYM credentials became Specialists in Cytometry (SCYM). Highly skilled individuals from cytometry core facilities now have the credential necessary for cytometry positions within the hospital laboratory.

The return of cell cycle analysis

DNA ploidy and cell cycle testing of tumors could return to the clinical laboratory. Krishnan first published this method in 1975[1] using propidium iodide. Today, most solid tumor DNA testing tends to be performed using molecular DNA techniques. The current literature indicates the importance of tumor cell-cycle when selecting or designing clinical therapeutics.[2-5] At GLIIFCA 2016 [Great Lakes International Imaging and Flow Cytometry Association], Hedley presented data showing numerous, different mutated populations within a single pancreatic tumor.[6,7] Because each population may respond differently to various treatment options, accessing the molecular characteristics of each population could enhance clinical treatment and prognosis. The populations were isolated based upon ploidy and S-phase fraction. Therapeutic combinations targeting the different populations within a multivariate tumor could provide better outcomes.

Engineered fluorochromes

Polymer chemistry has developed several fluorochromes. A common example is composed of several light harvesting base polymers that transfer energy via fluorescence resonance energy transfer (FRET) to a reporter dye attached to the polymer.[8] These 405 nm excitable polymer dyes have six increasingly longer emission wavelengths dependent upon the polymer construction, starting at 421 nm and continuing up to 786 nm.[9] A new fluorochrome strategy constructs large organic molecules into a "cage" bound by platinum molecules.[10] Specific molecular assembly strategies tune the resonance frequency and fluorescence emission of the cage. Unlike most fluorochromes used today, these structures do not photobleach.

Smaller and more powerful instruments

The development of more sensitive fluorescence detectors has made smaller instrument footprints possible. This change has been occurring through the developmental history of flow cytometry instrumentation. There are clinical flow cytometry models that have the footprint of a standard laser printer. In the clinical laboratory, these smaller instruments usually have fewer lasers and fluorescence detectors.

One current research instrument has three lasers and 13 fluorescence detectors and is the same size as less powerful instruments. One technological advance used in this instrument is the avalanche photodiode detector. These detectors are more sensitive than other photodiodes, principally due to a built in electronic gain. Similar to a typically forward scatter photodiode, only the voltage changes. The avalanche photodiodes can detect emission signal as well as the standard photomultiplier tube but are as little as one-tenth the size of a photomultiplier tube.

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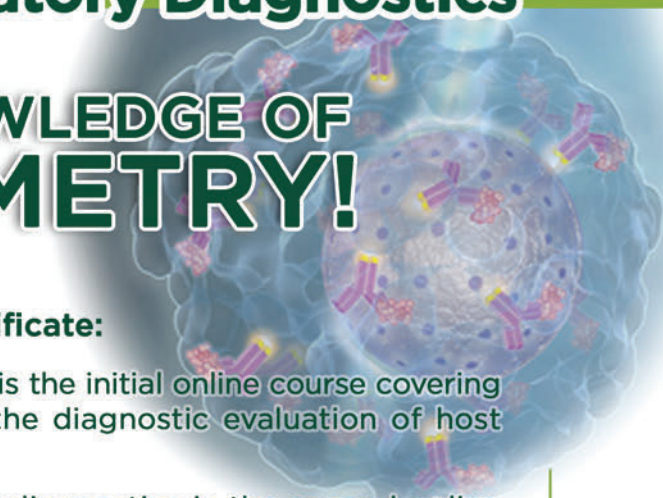

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Meet The Professor

Susan A. McQuiston
J.D., MT(ASCP), C.Cy

Dr. Sue McQuiston's experience in flow cytometry started in the Lab for Cell Analysis at the University of California San Francisco in 1989. Dr. McQuiston joined the faculty at the Biomedical Laboratory Diagnostics Program in May 2009 and has incorporated flow cytometry into all levels of undergraduate and graduate teaching.

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Establishing and implementing LDTs utilizing the Test Life Cycle Model

By Paula Ladwig, MS, MT(ASCP)

In the United States, there are two types of laboratory tests: U.S. Food & Drug Administration (FDA)-approved or laboratory-developed (LDTs). Most often, FDA-approved tests are marketed by a medical device company and purchased by a laboratory, hospital, or physician's office. Labs may also develop their own tests in-house: for example, when an FDA-approved test is not available, when an FDA-approved test is modified for a new sample type, or when a new test is more esoteric in nature. The Test Life Cycle Model can be followed by both commercial manufacturers and clinical laboratories to organize the establishment and implementation of either test type.

Definition of an LDT

The FDA considers an LDT to be an in vitro diagnostic (IVD) device that is intended for clinical use and designed, manufactured, and used within a single laboratory.[1] These LDTs are sometimes called in-house developed tests, or "home brew" tests.[2] The FDA does not consider these devices to be LDTs if they are designed or manufactured completely or partly outside of the laboratory that offers and uses them.[1] If a clinical laboratory modifies an FDA-approved test, for example, by changing sample type or intended use, then the test also becomes lab-developed. In the case of an LDT, the lab needs to establish acceptable performance through analytical and clinical validation, and then re-verify performance as part of implementation.

CLIA requirements and limitations

Under the Clinical Laboratory Improvement Act (CLIA), the Centers for Medicare & Medicaid Services (CMS) has regulated laboratories that develop LDTs. CLIA oversees and enforces the accreditation, inspection, and certification of medical laboratories. CLIA requirements address the laboratory's ability to perform laboratory testing accurately and reliably. CLIA prohibits the release of any test results prior to the laboratory establishing certain performance characteristics relating to analytical validity for the use of that test in the laboratory's own environment.[2]

Compliance with CLIA requirements ensures that clinical laboratory practices are of high quality and that the methodologies selected for clinical use have the capability of providing the quality of results required for patient care (42 CFR 493.1445(e)(1) and 42 CFR 493.1445(e)(3)(i–iii)). However, there are no requirements regarding the design, manufacture, and validation of the diagnostic device itself.[1]

FDA recommendations

Title 21, Section 820 of the Code of Federal Regulations (CFR) sets forth regulations for Quality System Regulation (QSReg) of medical devices and was expected to be applicable to the regulation of LDTs. In late 2014, the FDA issued draft guidance intended for its own staff, clinical laboratories, and the device manufacturer industry for the purposes of FDA notification and reporting for LDTs.[1] This guidance was not legally enforceable at the time of its posting, but rather outlined the FDA's recommendations. While implementation of these regulations for LDTs ultimately never came about, the FDA still has enforcement discretion.

Test Life Cycle Model

Whether a new laboratory test is created by a manufacturer or by clinical laboratorians, there are established measurement evaluations that both follow to ensure the quality and robustness of a laboratory test. The Test Life Cycle Model (**Figure 1**) can be used to organize the stages of establishment and implementation and the steps taken under both stages of the model needed to assure the development and implementation of a high-quality robust test.[3]

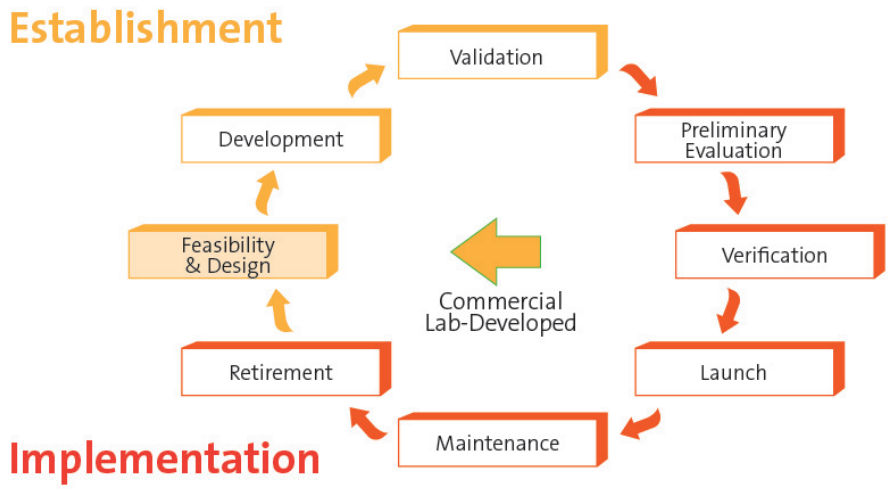

Figure 1. The Test Life Cycle Model. Reprinted with permission, Paula Ladwig, MS, MT(ASCP).

Establishment stage

The **Establishment** stage consists of the following steps: *feasibility* and *design*, *development*, and *validation*.

In *feasibility and design*, manufacturers or clinical laboratorians can perform a literature review, investigate the clinical usefulness and intended use, perform a feasibility assessment, and assess the legal right to use and perform a marketing assessment. These steps will help decision makers to decide if the appropriate resources should be invested to move the project forward.

The *development* step encompasses all the iterative steps a manufacturer or clinical laboratorian goes through in coming to a final product or test. Instrumentation is evaluated and chosen for fitness for purpose. Reagents, calibrators, and controls are either purchased or spiked in-house in appropriate matrix. The last steps of development involve the creation of standard operating procedures (SOPs) that will be followed through validation along with determining some preliminary performance characteristics to help again with decisions on whether resources should be invested into moving to the next step/stage. It is important to document each of these steps, conclusions, and decisions made.

In *validation*, before any method evaluations are performed, a plan should be written to ensure that the proper experiments are planned along with acceptance criteria used to evaluate each experiment/method evaluation. Critical experiments evaluate precision,[4] accuracy,[5] detection capability,[6] analytical specificity,[7] stability,[8] and clinical validation.[9] The measuring[10] and reference intervals[11] should also be determined. This is not an all-inclusive list; there may be test-, disease state-, or instrument-specific evaluations also. A validation summary should be written to summarize all experiments and determine whether acceptance criteria from the plan were met. The validation summary can also be thought of as a package insert for an FDA-approved test; both give the implementing clinical laboratory specifications to help decide if the test is appropriate for their purpose.

Implementation stage

Whether the assay in question is a commercial FDA-approved kit or an in-house LDT, a clinical laboratory needs to go through the **Implementation** stage. This stage consists of the following steps: *preliminary evaluation*, *verification*, *test launch*, *maintenance*, and *retirement*.

The *preliminary evaluation* encompasses familiarity and some early performance testing.[12] A new instrument, process, or assay may need a period of familiarity before moving further into a clinical laboratory. A clinical laboratory may need to evaluate whether the new kit/instrument fits into the process flow of the lab, and whether the performance criteria outlined from the manufacturer match what is obtained in real life.

Whether the test is purchased from a manufacturer or is an LDT, the implementing lab will need to perform *verification* to ensure that the test meets acceptance criteria set for the new test. Verification can be thought of as a small validation experiment, encompassing some of the same experiments but with smaller numbers over a shorter time span. A verification plan with pertinent experiments and acceptance criteria should be written. Precision, accuracy, and detection capability should be evaluated along with verifying the measuring and reference interval.

If verification is completed and experiments meet acceptance criteria, then a new test can be *launched* into the clinical laboratory.[13] A clinical laboratory will still perform test *maintenance* during the lifetime of the test. Finally a test may be *retired* due to implementation of a new version.

Meeting the standard

The goal of both FDA-approved test manufacturers and clinical laboratories that develop LDTs is to produce a test that meets a standard of high quality. Established measurement procedures are followed by creators of LDTs, whether the creator is a manufacturer or a clinical laboratorian. The Test Life Cycle Model organizes the establishment and implementation of a new or modified test and can be used to develop and implement a high quality, robust test.

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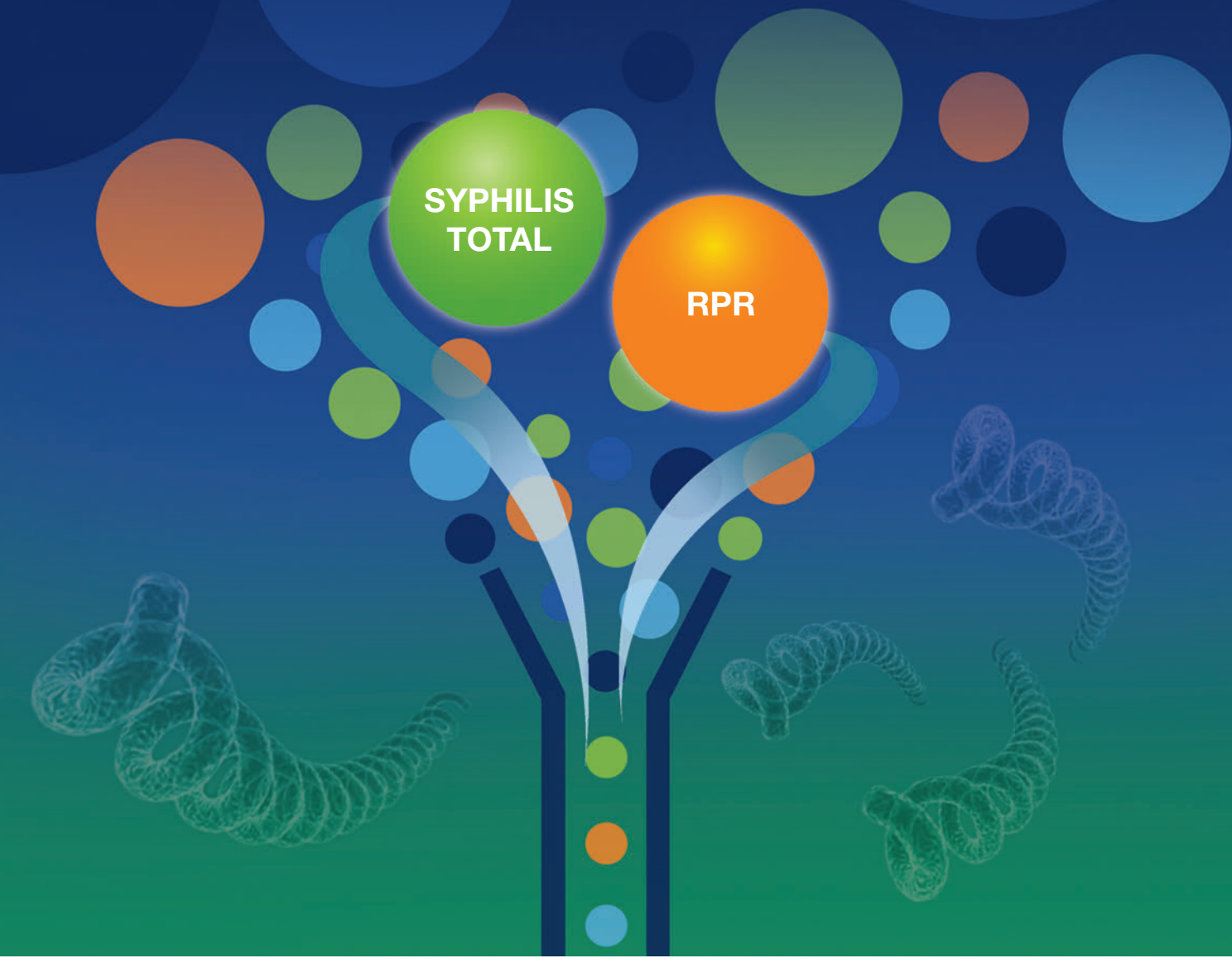

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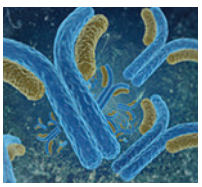

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Procalcitonin linearity and calibration verification kit

LGC Maine Standards' VALIDATE Procalcitonin linearity and calibration verification kit is used for Roche cobas analyzers. The kit, in a human-serum matrix, evaluates procalcitonin (PCT). Each VALIDATE Procalcitonin kit, liquid and ready-to-use and prepared using the CLSI EP06-A "equal delta" sample preparation, offers five distinct concentrations covering the reportable range. Laboratorians can dispense the solution from each dropper bottle directly into five sample cups, and run in replicates.

VALIDATE Procalcitonin allows clinical laboratories to complete their required procalcitonin linearity and calibration verification and maximize the reportable range while minimizing manual dilutions. Use of this product, while augmenting daily QC, assists with fulfilling various quality control requirements—such as Analytical Measurement Range (AMR) and Clinically Reportable Range (CRR)—for linearity and calibration verification under CLIA '88, CAP, COLA, JCAHO, JCI, and ISO 15189.

LGC Maine Standards manufactures VALIDATE linearity and calibration verification kits for more than 115 analytes, including General Chemistries, Urine Chemistries, Enzymes, Lipids, HbA1c, Therapeutic Drugs, Cardiac Markers, Thyroids, Serum Proteins, Vitamin D, Tumor Markers, Anemia, Fertility, Hemostasis, and Whole Blood Glucose.

LGC Maine Standards MSDRx data reduction software is available at no charge for real-time data analysis, or a laboratory can send its data to LGC Maine Standards where a technical specialist will complete the data analysis and return a report within five business days. Peer group comparison is also available upon request.

LGC Maine Standards
www.rsleads.com/804ml-156

Tri-level control for fetomaternal hemorrhage testing

Sure Tech Diagnostics FETALtrol is a tri-level control intended for laboratories having experience in test methods for fetomaternal hemorrhage. FETALtrol can be used to control both flow cytometry assays and manual stains (KB) for the detection of RBCs containing HbF or Rho (D antigen). FETALtrol has 105-day closed vial stability with an open vial stability of 25 thermal cycles, provided they are handled properly. Available in two sizes. Each kit contains three levels of controls. These whole blood controls are stored refrigerated. They are manufactured quarterly in January, April, July, and October.

FETALtrol
www.rsleads.com/804ml-157

INDEX OF ADVERTISERS

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Puritan Medical Products celebrates a century of service

If you were explaining Puritan Medical Products to someone who is not familiar with the organization, how would you characterize its primary areas of expertise? Puritan Medical Products is an American company in its 100th year of operation. We are the world's largest manufacturer of swabs and single-use sample collection devices. Puritan is well established yet small enough to maintain focus with a commitment to product development. We are staffed in all areas to help bring solutions to end users in healthcare, diagnostics, forensics, critical environments, and environmental specimen collection.

A fully integrated manufacturer, Puritan's primary area of expertise is innovation. Our R&D team of engineers and technicians design and build production systems that move materials from incoming QC to the production floor to packaging to the warehouse. We design the systems that produce the products, whether they incorporate a component of wood, plastic, wire, fiber, foam, or flock—or a medium for specimen transport. Our sister company mills the wood to our exacting specifications and we acquire spun fiber in bales to card onsite, all in order to control the absorbency and performance of the finished specimen collection device.

Timothy Templet
Executive VP of Sales and Managing Partner
Puritan Medical Products

Professional
As Executive VP of Sales since 1987, my role has greatly expanded from expertise in critical environment products to developing and promoting an entire line of diagnostic devices sold worldwide.

Education
University of Maine

Personal
I treasure family time with my wife Elise, our two daughters, and our dog, Henry. We enjoy skiing in winter and cruising the beautiful coast of Maine in summer.

Every step of our production process, from raw material to labeling, is closely monitored by QA personnel using tools that cutting-edge technology makes possible to assure that products are uniform and meet complex specifications. Puritan knows very well each product it manufactures, whether used for patient care, diagnostics, forensics, environmental sampling, or critical environment applications. Many of the materials and methods employed in our manufacturing process are proprietary.

What are the major categories of solutions that the company provides for the clinical lab? Collection swabs of various tip materials—cotton, polyester, rayon, flock, and calcium alginate; specimen transport media—traditional configurations as well as liquid and custom formulations for molecular testing; transport tubes—engineered and produced by Puritan to assure ease of use and specimen integrity; custom solutions—custom swabs, media fills, or combinations to deliver the specimen collection and transport device needed.

In addition, the trend of the expanding need for DNA specimens dictates that swabs used in that area must be free of cross-contamination and protected from inadvertent contamination at every step of production as well as in use and transport. Puritan is ISO 18385 compliant.

What should clinical lab directors know about Puritan's customization capabilities? About the technology that lies behind your flock swabs? Puritan works closely with its customers to define the requirements of a collection device in order to develop a new product for specific applications. We can customize a swab handle with various sizes and breakpoints, offer various tip shapes and materials, and develop unique transport media to preserve or improve viability of a specimen during transport to the clinical laboratory.

Our patented HydraFlock and PurFlock Ultra swabs utilize a unique proprietary fiber and manufacturing process. These flock swabs offer superior collection and elution of specimens for more accurate and reliable results which outperform the standard nylon flock swabs historically supplied to the market.

What are trends in specimen collection that our readers should consider when making their own short- and long-term plans? With lab personnel retiring and fewer being trained as specialists, automated processing is bound to be the rule before long. Central labs will make this move economically viable and ease the crunch at the bench of smaller healthcare facilities. We are also seeing the steady march toward molecular assays in many areas. DNA/RNA assays will further distance the methods of diagnostics away from the traditional. Specimen collection and transport devices are evolving with this trend.

This year's rough flu season underscored the importance of swabs and related products, and the need for lab personnel to use them properly. How does Puritan address this, particularly in the context of emerging infectious diseases? Puritan works closely with national manufacturers of rapid influenza diagnostic tests; many millions of the swabs Puritan produces are intended for use in many of these. As our established original equipment manufacturer (OEM) customers develop kits and instrumentation in response to rapidly emerging infectious diseases, Puritan will design the swabs that assure these novel methods perform as intended. As demand increases, so does our production. We are continually expanding our manufacturing capacity to ensure we meet some of these unprecedented demands, particularly for the flu season. Our marketing team provides blogs and infographics with "How-To" demonstrations of our products.

Puritan is a contract manufacturer to some major global diagnostics companies. What has enabled you to recruit and retain such customers? What kind of feedback to you get? Contract manufacturers—OEMs—have come to rely on Puritan for product development partnerships with fair pricing, quality, and reliable availability. They must have product to meet the demands of the market with unparalleled quality. Puritan understands these requirements. Add to that the guarantee of a personal connection with a dedicated staff member who is well versed in their requirements and responsive to their needs. We constantly hear Puritan delivers on all points.

What is new in your pipeline—or what might be coming in the near future? R & D projects are a constant at Puritan. In the near future, we will be introducing another proprietary flock specimen collection device ideal for the molecular market. Stay tuned for more innovative products.

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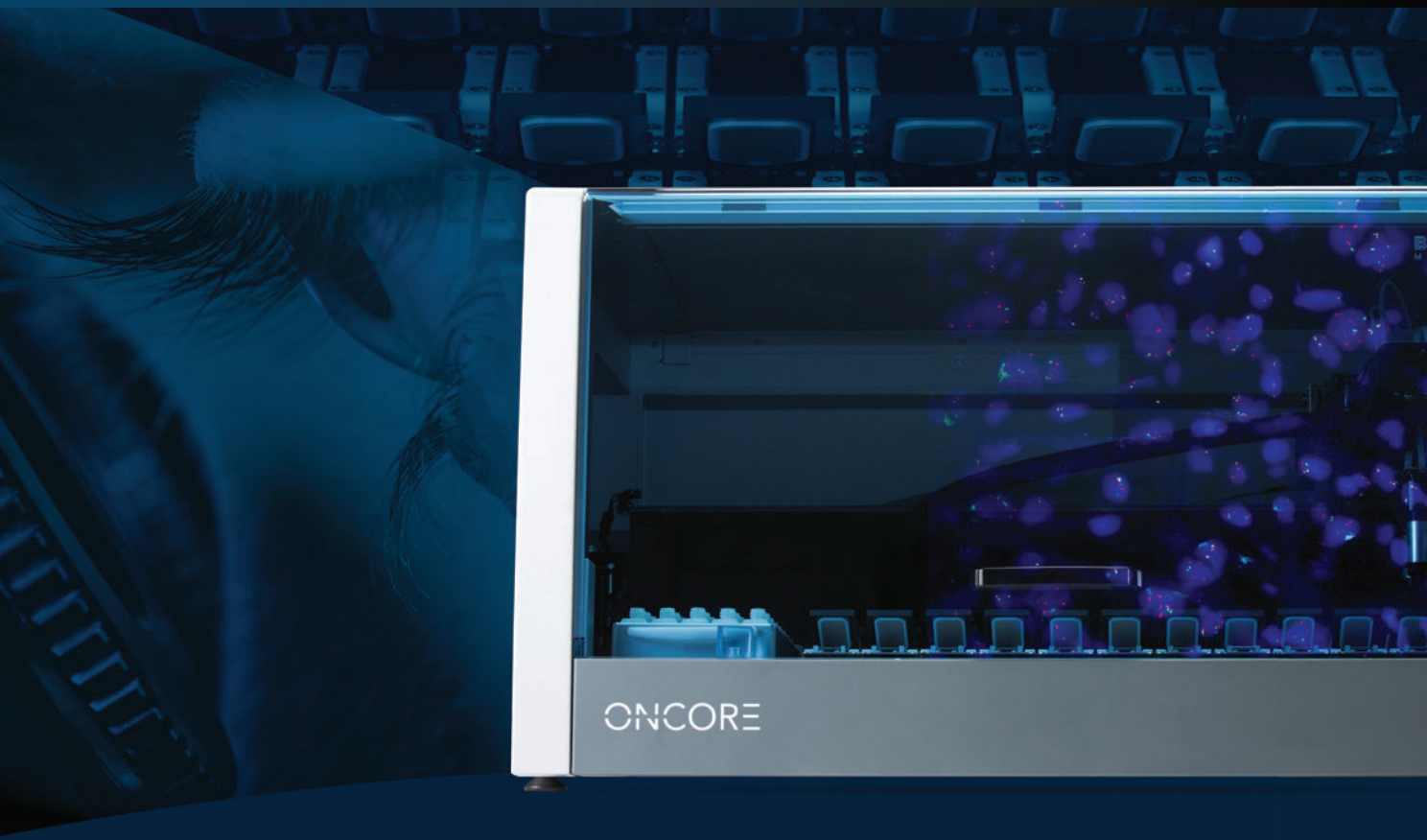

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