PEDIATRIC AND MATERNAL-FETAL DIVISION NEWS
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AACC Better health through laboratory medicine.

FROM THE MIND OF THE CHAIR

Hello and Happy New Year!

I am so excited to be serving as Chair of the PMF Division! I would like to start by thanking Shannon Haymond for all of her hard work as chair the last two years! Thanks also to outgoing board member, David Carpentieri, for many years of dedication to PMF.

Our Division had a memorable 2017 and were able to participate in a number of important AACC initiatives. We began work with our members to develop pediatric-focused laboratory medicine educational material, an AACC Symposium on newborn screening, and a joint webinar with SYCL dedicated to non-invasive prenatal testing. We also focused on member engagement through increased participation on the artery, a joint mixer with the clinical translational sciences, informatics, and industry divisions at the AACC Annual Meeting, and several recognition awards. Our advocacy efforts are ongoing as we work to educate our leaders on Capitol Hill on the importance of pediatric laboratory medicine. We also reinvigorated the discussion of a large clinical study focusing on pediatric reference intervals!

We have a number of exciting activities planned for 2018. We will continue our mission to further educational awareness surrounding pediatric and maternal fetal laboratory medicine through development of educational curricula, Q&A articles, and sponsored symposia at the annual meeting. We will also continue our research efforts in the areas of Pediatric Reference Intervals as well as a benchmarking study for clotted specimens. Finally, we plan to continue our partnership with the AACC Science and Practice Core Committee by contributing to their test utilization initiative. We have so many exciting goals and could not accomplish these without your help. If you would like to get involved, please contact me or another member of our leadership team!

I am excited to introduce this month's edition of the PMF Division Newsletter! We start back with A in our ongoing series, The ABCs of Pediatric Laboratory Medicine. This time A is for the timely topic of Acute Kidney Injury. This article provides a nice discussion of the disease with an up to date summary AKI biomarkers. Next is Shannon Haymond's interview with our new AACC president and PMF division member, Dennis Dietzen. They discuss his goals for AACC and pediatric laboratory medicine. The newsletter rounds out with citations of recent publications in the field of pediatric and maternal fetal medicine.

I hope you enjoy this edition as much as I did! If you have any ideas for future newsletter topics please contact our editor Van Leung-Pineda.

Alison Woodworth

Chair, AACC PMF Division

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THE ABC'S OF PEDIATRIC LABORATORY MEDICINE:

"A" is for Acute Kidney Injury in Children

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Acute kidney injury (AKI) is a common condition, occurring in up to one third of hospitalized children. In this setting, AKI is associated with significantly adverse acute and chronic outcomes, including mortality, in both critical care and non–critical care settings. In-patient AKI-related mortality is estimated to be as high as 25 and 30% in high risk subgroups. Previous studies on sequelae of AKI in children admitted to hospital had focused on these high-risk patient populations, i.e. those with nephrotoxic medications, cardiac surgery, sepsis, or admission to an intensive care unit. The severity of the renal insult and the development of multiple AKI episodes is associated with an increase in morbidity and mortality. However, several studies have shown that between 20 and 30% of cases of AKI are preventable.

Furthermore, animal studies have identified several agents to treat AKI, which have not been translated to humans. More importantly, a barrier to performing AKI clinical therapeutic trials has been the lack of early diagnosis of AKI, which might allow for the implementation of novel treatments within the narrow therapeutic window. A key requirement for AKI prevention or treatment strategies is precise diagnosis and categorization of stages. Clinically, several AKI clinical definitions are utilized including the Kidney Disease Improving Global Outcomes (KDIGO), the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) and the pediatric RIFLE (pRIFLE) (Akcan-Arikan) definitions as well as the AKIN (Acute Kidney Injury Network) (Lopes). These definitions have salient nuances, but have overlapping features.

With this in mind, several advances in the field of early AKI detection and monitoring are increasingly being employed to significantly reduce or prevent hospital acquired AKI (HA-AKI). Amongst the various developments in this arena, there are two topics that have seen significant advance over the last few years. ***One*** such area is the field of novel, early AKI bio-marker discovery and validation, while the ***second*** is the utilization of information technology (IT) and Big Data analytic approaches for enterprise wide early monitoring, prevention and intervention. This article will summarize a few salient features and/or examples in these two evolving areas that are converging and being increasingly employed synergistically to reduce HA-AKI burden in pediatric patients.

Renal function and AKI biomarkers

The laboratory direct measurement of glomerular filtration rate (GFR) has been historically considered the gold standard for the evaluation of renal function. The most accurate methods to measure GFR include Inulin, Iohexol (Schwartz, Shihabi), Iothalamate and creatinine clearances. Among these, the 12h and 24h urine creatinine clearance analysis have been proposed (Pong) as better markers when compared to the Schwartz equation but are not widely employed as an AKI preventive tool. Indirect GFR estimates based on equations (eGFR) utilizing serum creatinine (sCr) or cystatin C have been suggested as a replacement but these equations are not accurate or reproducible for all populations (Kim) and have been mostly used in the setting of chronic kidney disease monitoring (Schwartz). Cystatin C appears to be a better predictor than sCr for AKI (Lau). In fact, standardized sCr lacks the necessary sensitivity to detect AKI at an early clinical stage creating a gap to be filled by new markers.

Given this background, there has been considerable effort to identify AKI biomarkers in urine and blood over the last decade. Several markers are under evaluation under the oversight of TRIBE (Translational Research

Investigating Biomarker End-Points) (Parikh) and SAFE-T (Safer and Faster Evidence-based Translation) among other consortia. A partial list of biomarkers undergoing validations include: Neutrophil gelatinase-associated lipocalin (NGAL); Symmetrical dimethylarginine (SDMA); Calprotectin, Hepatocyte growth factor (HGF); Insulin-like growth factor binding protein-7 (IGFBP-7), tissue metalloproteinase-2 (TIMP-2); Interleukin-18 (IL-18); Kidney Injury Molecule-1 (KIM-1); Liver-type fatty acid-binding protein (L-FABP); α1 Microglobulin; Monocyte chemoattractant peptide-1 (MCP-1); N-acetyl-β-d-glucosaminidase (NAG); Osteopontin, Trefoil Factor 3 (TFF3), Clusterin (CLU), CXCL16, Osteoactivin, Calbindin (CALB1), Interferon gamma-induced protein 10 (IP-10), MIF, VCAM-1 and VEGF-A. Importantly, some biomarkers may be better suited for the AKI diagnosis in children versus adults or with specific pathophysiological mechanisms. Also, different medical conditions may affect biomarkers differently (Table 1). The few biomarkers that are commercially available for clinical (NGAL, IGFBP-7 and TIMP2) and veterinary care (SDMA) are highlighted below:

Neutrophil gelatinase-associated lipocalin: NGAL is the most extensively studied biomarker in pediatric patients (Goldstein, Hassanzadeh). It is a protein extruded in the urine from proximal tubular cells as a result of injury (Bolignano). NGAL is involved in tubular cell injury and repair and acts as an iron chelator. Following different types of insults to the kidneys, intrarenal NGAL expression is upregulated and it is secreted into the urine. Proximal tubular cells have been shown to secrete NGAL in response to ATP depletion. After AKI, plasma NGAL also increases, and is freely filtered in the glomeruli and reabsorbed in the proximal tubules of the kidney. Thus increased plasma NGAL in AKI may result from tubular leak, and/or reduced glomerular filtration. Similarly, elevated urinary NGAL may reflect induced renal expression, glomerular filtration of plasma NGAL from renal or extra-renal sources and/or impaired tubular reabsorption. It is speculated that urinary NGAL is more sensitive with histological damage, whereas blood levels might be more sensitive for changes in clearance. Urine and plasma NGAL assays have been recently reviewed (Kift) and clinical studies have demonstrated the utility of this marker in children (Du, Meersch, Pedersen). Currently, FDA approval is pending and a point of care test is only available in Europe.

Tissue inhibitor of metalloproteinase-2 & Insulin-like growth factor-binding 7: These markers recently received FDA approval as a combined test in the adult population. TIMP2 is an inhibitor of matrix metalloproteinases and is involved in cell cycle arrest, particularly the suppression of endothelial cells proliferation. IGFBP7 regulates the availability of insulin growth factors in body fluids. In a recent study focused in children after cardiac surgery (Meersch), TIMP-2 and IGFBP7 along with NGAL, predicted AKI based on the pediatric modified RIFLE and follow up elevation of sCr.

Symmetric dimethylarginines: Symmetric dimethylarginines (SDMA) (El-Khoury, Shafi) is a methylated form of the amino acid arginine (i.e.: mono-methylarginine, asymmetric dimethylarginine, and SDMA). All are derived from intranuclear methylation of L-arginine by protein-arginine methyltransferase and released into the circulation. SDMA is a nitric oxide synthase inhibitor which is primarily eliminated through the kidneys by filtration; therefore it has been evaluated as potential marker of GFR and is closely correlates with measured GFR. (El-Khoury, Schwedhelm, Kielstein, Fleck). SDMA is a more sensitive and specific marker of renal function compared with sCr and is not affected by muscle mass and a number of other confounding factors that affect NGAL and cystatin C. In human patients SDMA levels were strongly associated with predicted renal function and clinical outcome in specific scenarios such as: after ischemic stroke and after renal transplant (Lüneburg, Kielstein). Pediatric AKI studies are lacking.

Information Technology for AKI early detection and monitoring

As mentioned, HA-AKI is being increasingly recognized to have significant consequences like increased morbidity, mortality and health care costs in pediatric health care facilities.

Electronic health records (EHRs) and clinical information systems (CIS) are becoming increasingly common in hospitals and can be leveraged to detect changes in sCr according to current definitions for AKI (including KDIGO, RIFLE and AKIN) (Sawhney, Sutherland). These systems have the potential to increase AKI recognition, and reduce the time to therapeutic interventions to prevent progression, and thereby improve outcomes of AKI. More importantly, an efficient data monitoring system has the potential to facilitate the management of subgroups of patients who are at a higher risk of developing AKI (Sawhney, Sutherland). At our institution, a novel enterprise wide EHR based real-time surveillance system for automated AKI detection and generation of curated alerts was created (Fig. 1). The software program was designed to provide enterprise-wide data analysis by querying the EHR every 6 hours for AKI risks, including baseline sCr, % change and rate of rise in sCr, nephrotoxic medications (NTM), therapeutic drug levels (TDxM), and renal replacement therapy as well as nephrology service intervention. Quick links to the patient charts are also available. The analytic output is automated and made available on a self-updating dashboard. Data analysis is based on algorithms utilizing existing AKIN staging criteria. The dashboard is utilized to generate curated AKI risk alerts by the enterprise nephrologists.

The dashboard generates color coded signals for stage I, II and III AKI, plots weekly change in sCr, NTM exposure and duration, TDxM listing, day(s) since last sCr and documented nephrology intervention. It detects both NTM and non NTM associated AKI and risk factors. It is also programmed to detect AKI with sCr <0.5 mg/dl. An AKI surveillance team (consisting of pharmacist and nephrologist) reviews the dashboard daily to direct AKI prevention and treatment strategies through curated alerts to the responsible healthcare providers through “two way” integrated Vocera® secure messaging system. This avoids “alert fatigue” and has led to a proactive change in provider’s approach to HA-AKI prevention.

This novel EHR dashboard and AKI alert system serves as an early warning tool for enterprise wide application. The alerts in our enterprise (Figure 1) are traceable, auditable and are HIPAA compliant. This automated tool allows the HA-AKI prevention team to track at risk patients, provide early detection and prevention of HA-AKI. Some of the AKI biomarkers mentioned above (i.e. NGAL) have been incorporated in the dashboard while others are being planned to be incorporated in near future. The planned outcome is to develop automated AKI alerts which would be designed to enable early detection of AKI and provide opportunities to link AKI detection to clinical decision support tools for management, in order to mitigate avoidable propagation of AKI and associated harms in children.

In summary, the development of effective biomarkers for the early diagnosis of AKI has received significant attention from the research community, clinicians as well as biotech companies in recent years. These stepping stones are leading to a paradigm shift in the evaluation of renal function from assessment of function towards a preventive approach. Unfortunately, there is a need to expand the validation of these biomarkers in pediatrics and future studies should address the needs at various hospitalized settings to better guide early therapeutic intervention. When possible, the integration of these new biomarkers in EHR data monitoring systems should be considered a priority.

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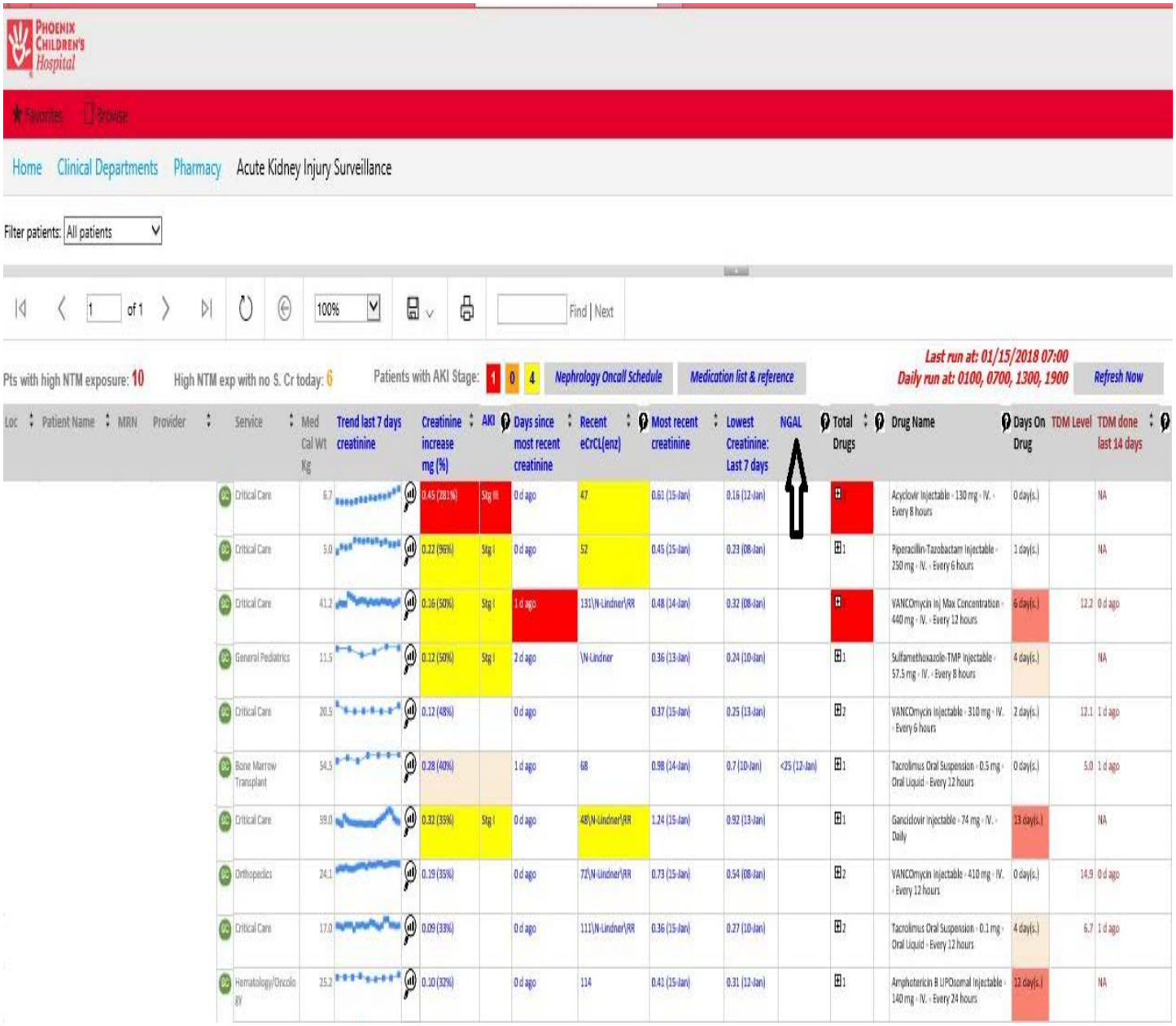
Table 1: AKI biomarker characteristics

*IBD=Inflammatory bowel disease, UTI=Urinary tract infection, CKD=Chronic kidney disease, RCC=Renal cell carcinoma, PCKD-Polycystic kidney disease

AKI biomarker	Description	Medical conditions affecting AKI biomarkers*
Calprotectin	Cytosolic calcium-binding complex of two proteins of the S100 group (S100A8/S100A9); derived from neutrophils and monocytes; activator of innate immune system	IBD
		UTI
		CKD
Cystatin C	13 kDa cysteine protease inhibitor produced by all nucleated human cells and released into the plasma at a constant rate	Systemic inflammation
		Malignancy
		Thyroid disorders
		Glucocorticoids
		Hyperbilirubinemia
		Hypertriglyceridemia
		HIV disease
Hepatocyte growth factor (HGF)	Anti-fibrotic cytokine produced by mesenchymal cells and involved in tubular cell regeneration after AKI	Advanced heart failure
		Hypertension
		IBD
Insulin-like growth factor binding protein-7 (IGFBP-7), tissue metalloproteinase-2 (TIMP-2)	Metalloproteinases involved in cell cycle arrest	
Interleukin-1 (IL-18)	18 kDa pro-inflammatory cytokine	Inflammation
		Sepsis
		Heart failure
Kidney Injury Molecule-1 (KIM-1)	Transmembrane glycoprotein produced by proximal tubular cells after ischemic or nephrotoxic injury	RCC
Kidney Injury Molecule-1 (KIM-1)		Chronic proteinuria

Liver-type fatty acid-binding protein (L-FABP)		CKD
		SCN
	14 kDa intracellular lipid chaperone produced in proximal tubular cells and hepatocytes	CKD
Liver-type fatty acid-binding protein (L-FABP) α1 Microglobulin		PCKD
		Liver disease
		Sepsis
	Low molecular weight protein produced in liver	Sepsis
Monocyte chemoattractant peptide-1 (MCP-1)	Peptide expressed in renal mesangial cells and podocytes	Variety of renal diseases
N-acetyl-β-d-glucosaminidase (NAG)	>130 kDa lysosomal enzyme; produced in proximal and distal tubular cells and non-renal cells	Diabetic nephropathy
Neutrophil gelatinase-associated lipocalin (NGAL)	Three different types:	Sepsis
Neutrophil gelatinase-associated lipocalin (NGAL) Symmetrical dimethylarginine (SDMA)	• Monomeric 25 kDa glycoprotein produced by neutrophils and epithelial tissues, including renal tubular cells • Homodimeric 45 kDa protein produced by neutrophils • Heterodimeric 135 kDa protein produced by renal tubular cells	Malignancy
		CKD
		UTI
		Pancreatitis
		Pancreatitis Endometrial hyperplasia
	Isomer of endogenous asymmetrical dimethylarginine (ADMA).	Nephrolithiasis

Figure 1: Electronic Medical Record Dashboard for AKI detection and monitoring



A screen capture of AKI dashboard being employed at Phoenix Children's Hospital. The dashboard is color coded for different AKI stages (*yellow*: stage 1; *orange*: stage II; *red*: stage III) as well as AKI monitoring criteria in different colored fonts (from left to right: *gray font:* patient identifiers; *blue font:* AKI markers including NGAL (arrow); *black font:* NTM exposure; *brown font:* drug level monitoring).

Interview with a Distinguished Colleague

By Shannon Haymond, PhD

Dennis J. Dietzen, PhD, DABCC, FAACC
2018 AACC President.
Professor of Pediatrics and Pathology and Immunology, Medical Director of Laboratory Services, Saint Louis Children's Hospital. Washington University School of Medicine in St. Louis. St. Louis, Missouri, USA.

What are some challenges you see currently facing the field of laboratory medicine?

The field of lab medicine has a number of ongoing challenges within the greater challenge of providing affordable care to all Americans. Challenges include the shrinking workforce, diminished reimbursement, and heightened regulation. Without adequate personnel and reimbursement, delivery of service will continue to be stressed across the care spectrum that includes both outpatients and inpatients. Heightened regulation will add cost and inhibit the development and adoption of new tests and new technology that will benefit patients. For the time being, these regulatory challenges have been tabled, but we must remain aware and continue to advocate for sensible regulation, particularly in the realm of laboratory developed tests. The final hurdle to mention is making sure that clinicians, regulators, payers, and administrators recognize the vital role that laboratory professionals play in the provision of care to patients of all backgrounds. It is incumbent on individual members all the way up to AACC Board of Directors to highlight the indispensable role of the laboratory in delivering the right care at the right time regardless of the environment in which we practice.

What changes do you see in the future of pediatric or maternal fetal laboratory medicine?

I am not big into crystal balls but I will tell you what I hope to see. I hope to see pediatric lab medicine begin to drive development of new tests and new technology. Throughout my realm of experience, pediatric practitioners have had to make due with testing platforms in environments for which they were not designed. That is why we have automation systems that don't work with tiny samples and why we have some pretty important assays that are not very resistant to things like hemolysis that we deal with commonly in pediatric practice (ammonia assays come to mind). Small sample sizes make sense for all patients, not just kids. While the experience with Theranos provided no shortage of negative lessons, one positive takeaway is that there is truly a need for revolutionary technology that will decrease the volume of blood necessary to make testing more accessible for kids and adults. I think we should dare to think big and demand big solutions when it comes to the smallest patients.

Advocacy for children's health, and therefore, pediatric laboratory medicine, has been an area of focus for AACC. Are there plans for the upcoming year to continue to promote or support pediatric laboratory medicine among policymakers?

Children's health remains a top advocacy priority for the Association in 2018. This is not really an accident. I am, after all, the third consecutive AACC President with a pediatric bent following Drs. Patti Jones and Mike Bennett. The Association continues to promote newborn screening programs both domestically and abroad. Avenues to utilize the residual specimen bank from the National Children's Study are ongoing. Exciting new directives are being explored to gain access to specimens with an aim toward refining our improving database of pediatric reference intervals. The

larger ongoing efforts of the Association to promote the use of residual specimens for research purposes and the sensible regulation of the LDTs that we all rely on daily, are also important to ensure the very best delivery of pediatric care through laboratory medicine.

Excerpts from the Literature

Kelly Doyle, PhD, DABCC, FAAC, Clinical Chemist, Intermountain Healthcare, Salt Lake City, UT, USA

Predictive Analytics at Work in Pediatrics: Kidney Failure Risk Equation Now Validated for Children

As clinical laboratorians we persistently seek to optimize the value of test results streaming from the lab so as to improve efficiency, patient outcomes, and cost-savings. Successful efforts are more often coordinated, standardized, and patient-centered across integrated health systems.

Predictive analytics— the effort of identifying variables from large data sets that can then be extrapolated to predict future events—has generated a number of risk scores for cardiovascular, renal, and diabetic health, even for mortality. While the verdict is still out as to whether these risk scores are effective in motivating patients to commit to life-long lifestyle changes, they are an effective way for clinicians to identify patients of greatest need or who are at increased risk of long-term disease progression and to provide coordinated care for these patients.

In 2011, Tangri et al published “A predictive model for progression of chronic kidney disease to kidney failure” [1] highlighting the utility of lab tests in predictive risk models and in this case, allowing clinicians to effectively plan for renal replacement therapy, dialysis needs, and preemptive kidney transplantation [2, 3]. This is substantial because while eGFR is useful in identifying those with chronic kidney disease (CKD), effective clinical intervention is better determined when the clinician understands the patient’s risk of progressing to end stage renal disease (ESRD).

In 2016, a meta-analysis of data from 31 cohorts representing over 700,000 adult patients from 30 countries shows the 4-variable kidney failure risk equation based on age, sex, eGFR, and the ratio of urinary albumin to creatinine, is accurate in predicting 2- and 5-year probability of progressing from CKD to ESRD [4].

Most recently in 2017, Winnicki et al [5] found that by substituting in the Bedside Schwartz eGFR into the 4-variable risk calculator, it worked well to predict 1-, 2-, and 5-year risk of ESRD in a cohort of 603 children from the Chronic Kidney Disease in Children Cohort Study (CKID). Risk discrimination is expressed as “C-statistic” where a value greater than 0.80 suggests strong discrimination. Risks of ESRD in this study were found to be 0.90 (1-year risk), 0.86 (2-year risk), and 0.81 (5-year risk).

Interestingly, while children often have quite different etiologies of CKD than adults, the 4-variable equations based on nearly identical criteria appear to work well in both populations in predicting risk of progression to ESRD.

Because children with CKD have a high lifetime risk of ESRD they also have a significant reduction in lifespan. Laboratories have a significant opportunity to help facilitate the implementation of these equations in electronic medical record systems or provide links to online calculators in test result reports. As pointed out by Allison Dart, MD, “The use of the Kidney Failure Risk Equation could…improve transitions in care, decrease unnecessary procedures, and improve quality of life” [6].

1. JAMA 2011, 305(15) 1553-1559
2. Am J Kidney Dis. 2017; 69 (4):514-520
3. Kidney Int. 2007(71) 555-561
4. JAMA 2016, 315(2) 164-174
5. JAMA 2017, Dec 18th, E1-E7
6. JAMA, 2017 Dec 18 E1-E2

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Diagnostic Errors in Primary Care Pediatrics: Project RedDE (BS-L)

Rinke ML, Singh H, Heo M, Adelman JS, O'Donnell HC, Choi SJ, Norton A, Stein REK, Brady TM, Lehmann CU, Kairys SW, Rice-Conboy E, Thiessen K, Bundy DG.. Acad Pediatr. 2017 Aug 10. [Epub ahead of print]

Diagnostic errors (DE) cause adverse outcomes in patients and occur at different frequencies in different medical specialties. Pediatrics is no exception, in two surveys, 35-54% of pediatricians reported monthly occurrences of DEs while a slightly lower percentage reported an annual occurrence of DEs that resulted in patient harm. Compared to adult primary care, little progress has been made in identifying and reducing DEs in pediatric primary care.

This study called Project RedDE (Reducing Diagnostic Errors in Pediatric Primary Care) aimed at identifying and defining DEs across a broad range of pediatric ambulatory clinics. A total of 25 pediatric practices participated in this study. One of the DEs addressed was abnormal laboratory values leading to a missed opportunity for diagnosis (MOD). This is a very important DE as previous studies show that, 40% of ambulatory primary care visits include laboratory testing, however, about 83% of physicians report delay in reviewing laboratory results at least once in the previous 2 months, while 40% report missing results even with computerized result delivery. In this study, MOD rates in pediatric primary care was found to be 11% for patients with abnormal laboratory values (n = 381). In addition, 9% of these patients did not have documentation that the abnormal value had been noted and that appropriate timely action was taken.

This study shows that DEs, including DEs linked to the use of laboratory results, occur in pediatric primary care at a considerable frequency and can contribute to delays in patient care and even patient harm. Laboratory professionals can certainly play a role in reducing DEs. In a recent *Clinical Laboratory News* interview with the corresponding author on this publication, Dr. Rinke pointed out that one thing laboratory professionals can do to facilitate clinician identification of abnormal laboratory results would be to have highlighted abnormal results show up first at the top of the laboratory report. This way, clinicians don't have to dig through a long list of normal results to get to abnormal results. In addition, one way for laboratories to improve test results reporting and communication will be to use the Test Results Reporting and Follow-up SAFER Guide to conduct a risk assessment.

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