The Monitor

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From the Mind of the Chair

Greetings from the Chair!

The holidays are within sight, and we are again pleased to have a Division newsletter for your reading pleasure.

Our principal feature in the ABC's of Laboratory Medicine in this issue is: S is for Send Outs, prepared by Mark A. Cervinski, Ph.D., DABCC, FACB. Mark directs Clinical Chemistry and Point-of-Care Testing at Dartmouth-Hitchcock Medical Center and is a faculty member at the Geisel School of Medicine at Dartmouth. I am very impressed with Dartmouth's national leadership in innovative, fiscally responsible and progressive approaches to health care delivery systems. It is also a spectacular place to visit if you have the opportunity to visit Hanover, NH—a quintessential New England experience, and this recommendation comes from a New Englander and former Dartmouth student! The medical school--founded in 1797 as the fourth-oldest school in America--was recently renamed after the late Theodor Geisel (better known as Dr. Seuss, also a Dartmouth student) and his wife Audrey, a former nurse.

For our regular feature, the interview with a distinguished colleague series, we have unique perspectives from our current AACC President Robert H. Christenson, Ph.D. who is the Director of Clinical Chemistry Laboratories and Professor of Pathology and Medical and Research Technology at University of Maryland.

The Reference Interval Corner feature offers a review of troponin reference intervals—an under-recognized issue for our collective consideration when serving pediatric patients.

Our election ballots are available for PMF Division member voting, with a fine roster to carry forth the AACC's mission: to provide leadership in advancing the practice and profession of clinical laboratory science and its application to health care, and our Division's particular mission, for the care of pregnant women and children -- from fetus to adolescent.

I would like to thank our Executive board for their many hours on behalf of the Division; from contributing their time as volunteers for conference calls, reviewing or creating educational proposals, judging abstracts, contributing to the website and newsletter, and keeping our books straight, I have been most fortunate as Chair to enjoy this wonderful support. Our talented and collegial board includes: Sihe Wang, Treasurer; Angela Ferguson, Newsletter Editor; Shannon Haymond, Secretary; Members-at-large Jon Nakamoto, Christina Lockwood and Linda Rogers; Webmaster Olajumoke Olubukola Oladipo; Past Chair Nathalie Lepage; and Chair-elect, David Carpentieri, who will take the helm come January!

The past year's activities and successes would not be possible without your support of the Division as members, your attendance at our annual meetings and webinars, and your expertise freely offered in educational programs and in our listserv for the benefit of colleagues and patients everywhere.

You can make a difference for 2014 by actively participating in our listserv, by contributing to our newsletter, attending and/or offering an educational program, or getting involved with the leadership of our Division.

With best wishes to you and your families for a rewarding and healthful holiday season 2013,

Sharie Geaghan M.D.

Chair, Pediatric Maternal Fetal Division

Reference Interval Corner

Cardiac Troponin in Pediatrics

Shannon Haymond, PhD, DABCC
Director, Clinical Chemistry and Mass Spectrometry, Ann & Robert H. Lurie Children's Hospital of Chicago

The indications for measurement of cardiac troponin (cTn) in pediatrics include evaluation of chest pain (in patients who were previously healthy and those with known history of cardiac disease) and monitoring for cardiac injury in patients administered cardiotoxic drugs and those undergoing cardiac surgery. The most common reasons for chest pain in pediatrics are not cardiac in origin; however, ruling out cardiac causes is necessary and this may warrant measurement of cTn. Additionally as assays improve and more data is collected using high sensitivity cTn (hs-cTn) assays, it is clear that the presence of detectable cTn in blood is not necessarily pathologic or reflective of myocyte injury (1).

What is an elevated cTn in children?

Few cTn reference range studies exist but large, longitudinal pediatric reference interval studies using current and state-of-the-art assays are beginning to investigate this question (2,3,4). A previous study has also shown that there is age dependence, where cTn is highest in newborns and decreases over the first several months of life (5). In a survey on utilization of cTn, 24 pediatric hospitals indicated that 55% use a cutoff validated internally, 40% use the 99th% cutoff defined by their assay manufacturer and 5% use the 10% CV defined by their assay manufacturer (unpublished results). The third universal definition of myocardial infarction describes the cutoff for increased cTn concentration as a value exceeding the 99th percentile of a normal reference population (6). An obvious question is whether or not the 99th% values are applicable to a pediatric population, since there were likely few pediatric patients included in the method validation set and reports are clear that the selection of the population is critical to establishing a relevant cutoff (7,8,9). Recent data from the CALIPER study using a cTnI assay is shown in

Table 1 (4). There was no difference between genders but an age-dependent increase was observed. Calculation of the 99th% in this population shows that the 99th% cutoff provided in the manufacturer's package insert for the assay used in the study is reasonable for children older than 3 months. Data reported from the Australian LOOK study using a hs-cTnI assay, highlights the importance of population selection on establishing the 99th% cutoff and reveals that transient illness in otherwise healthy children (8, 10 and 12 y) caused elevations in hs-cTnI above the 99th% cutoff (2). These authors further examined the distribution of hs-cTnI after exclusion of 2 data points due to transient illness and found that in both males and females, the distribution was Gaussian (3). The authors conclude that there is a background physiological release of troponin and that in a truly healthy population concentrations of hs-cTnI can be described by a Gaussian distribution. This suggests that a traditional 95% reference interval may be applicable for cTn in children. In current practice, there is a high degree of variability around how cutoffs are being defined for cTn in pediatrics but as data is collected from large cohorts of healthy children, we will continue to understand what is 'normal' for cTn in children. This information will be of particular importance given the fact that elevations in cTn indicating myocyte damage will be rare in the pediatric population with chest pain. Many pediatric hospital labs are using cutoffs that exceed the 99th% because of this reason, so transitions to lower cutoffs will need to be evaluated and managed carefully.

Table 1. Reference ranges for cTnI using Abbott ARCHITECT i2000 assay in healthy children of the CALIPER study. (Clin Chem. 2013 Sep;59(9):1393-405.)

Analyte	Age	Male RIs						Female RIs					
		No. of samples	Geometric mean	Lower limit	Upper limit	Lower limit CI	Upper limit CI	No. of samples	Geometric mean	Lower limit	Upper limit	Lower limit CI	Upper limit CI
TnI, ng/L**	5 to <15 days	46	73.63	2.97	936.35	1.33 to 9.55	742.46 to 1083.83	46	73.63	2.97	936.35	1.33 to 9.55	742.46 to 1083.83
	15 days to <3 months	35	13.75	NA	NA	NA	NA	35	13.75	NA	NA	NA	NA
	3 months to <19 years	691	NA	NA	<9	NA	6.0 to 17.0	691	NA	NA	<9	NA	6.0 to 17.0

** Corresponding 99th percentiles for TnI obtained by linear interpolation: 968 ng/L (5 days to <15 days); 59 ng/L (15 days to <3 months); 21 ng/L (3 months to <19 years).

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The ABC's of Pediatric Laboratory Medicine- S is for Send Outs

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Clinical laboratories have been faced with a number of challenges over the past few years, most notably reduced reimbursement for the routine tests ordered on many of our patients. This is most evident in the decreases in the Medicare Part B clinical laboratory fee schedule (1). Coupled with this challenge has been the tremendous growth in referral laboratory tests known colloquially in the laboratory as send-outs or mail-outs. In the U.S. the referral laboratory business is a $70 billion dollar industry (2) that is growing by approximately 8% per year (3). Within this 8% increase, the largest driver has been the growth of expensive "boutique" molecular laboratory testing for constitutional developmental disorders, cancer genetics and neurological conditions. Consequently, the combination of these financial pressures has led many clinical laboratories to evaluate strategies to reduce their financial liability in an effort to stave off layoffs and other drastic financial austerity measures.

One such strategy has been to rely heavily on the Laboratory Medicine/Clinical Pathology faculty to develop a send-out review strategy to lessen the financial burden associated with this testing. We, like many other laboratories, have also noticed the dramatic increase in the growth of these referral tests, and with it, our financial liability. To respond to this growth, we have moved to develop a referral test utilization committee to address this serious threat to our solvency. Not only are these activities important to the continued success of individual laboratories and hospital systems, they should also be a priority for those of us in laboratory medicine to ensure that our patients are receiving testing along the lines of the Clinical Laboratorians three "R's": The Right Test, for the Right Patient, at the Right Time. In

this article I will be sharing with you the strategies we have used to develop a test utilization committee from a conceptual vision to a program in its adolescence. Throughout this article I will also reveal the successes that we have managed to achieve and discuss what our next steps are to develop our system into a self-sustaining program that enhances the training our pathology residents receive during their clinical pathology rotations.

Our Impetus and Our Target

As mentioned we have seen our financial liability to referral laboratories increase in the past few years. A rather shocking increase in volume (Fig 1A) and cost (Fig 1B) was noted between 2008 and 2011 wherein our send-out volume increased from 160,703 to 275,110 tests with a concomitant increase in expense from $4,965,955 to $7,928,310 annually. We had noted this trend prior to 2011 and had moved to address the increase proactively by working with the major reference laboratories in the U.S. in a Request For Proposals (RFP) process between the 2009 and 2010 fiscal years to consolidate as much of our business as possible to net a reduction in the cost per reportable result. While this activity did reduce our cost per reportable result, it was not enough to stem the increase. In 2011, the Department of Pathology leadership at Dartmouth-Hitchcock Medical Center convened a meeting to formulate a plan and an aggressive cost reduction target of $2.5 million a year by the end of fiscal year 2015.

While this target was and is aggressive, our main challenge has been how to be fiscally responsible with our limited resources without impacting patient care. To manage both of these goals we've approached this task with a three-pronged strategy. The three strategies are: Make vs. Buy Decisions; laboratory consolidation and price negotiation; and test utilization review.

Make vs. Buy Decisions

Undoubtedly this is the strategy that all laboratorians have employed at one point or another in their careers. In the view of many, testing is best done in a facility that is closely associated with the physician and patient; however the cost of testing does need to be factored in. The most logical place to start a make vs. buy analysis is to generate a list of the instrumentation currently available department wide and the assays that all available platforms can accommodate. Given that information you can compare the assay menu of your department/laboratory to the list of assays currently sent to reference laboratories and highlight those tests that have a combination of cost per test and volume. Most national reference laboratories will provide their laboratory customers with a monthly test utilization report that highlights the number of tests ordered as well as the cost per test. Using this strategy you can identify those targets that can have the greatest impact on your budget.

Once targets for internalization are identified, it is important to get an accurate determination of your estimated cost per test in order to decide if it is financially feasible to internalize the test. Because of the economies of scale, reference laboratories can command a much lower cost per reportable result than a typical hospital laboratory. At times, some targets for internalization are not financially viable due to higher reagent cost. An illustration of two Make vs. Buy calculations are included in Figure 2. Hypothetical test "A" has a monthly volume of 2000 orders at a purchased cost of $20 per reportable result. Test "A" is an available assay on one of our analyzers and our vendor has quoted us a reagent

cost of $500 per a kit containing enough reagents to perform 100 tests. In working up a cost per test it is important to remember to include the number of quality control samples you will be running as well as a certain re-run rate to account for samples that will need to be diluted or re-run for various reasons. When we factor in all of the disposable reagents that will go into analyzing this test in-house our cost per reportable result for only the reagent and associated disposables is $6.53 per test. While this cost is significantly lower than the reference laboratory price, it is also important to work with your administration to determine the amount of technical labor and overhead per sample as well as this will add to the cost. As you can see in the example our final cost per test is $7.00 and with the test volume we could save approximately $312,000 annually with this plan.

Not every test you identify as a potential target will work out. For test "B" on the same instrument platform, we can see that the cost per reportable calculation was not favorable, and internalizing this test would result in a net loss of $5,040 annually. When considering the internalization of a test it is also crucial that the stability of the reagent is considered as well. If the reagent once opened is only stable for a short time there may be significant reagent wastage. It is important to point out that both of these examples assumed that I already had the appropriate instrumentation on site and that I would be using existing staff to implement the new testing. If new instrumentation needs to be purchased/leased or new staff would be needed, it is implicitly understood that the costs of the new instrumentation, service contracts, fit-up/construction costs, and salaries for technologist positions need to be included.

Using this strategy as a department, we identified a small number of tests that were internalized at the midpoint of FY 2012. Two of these tests alone, 25-hydroxyvitamin D and the Chromosome SNP array, accounted for an approximate $800,000 annual reduction in our send-out costs. This reduction in send-out volume and cost staved off a further increase in FY 2012 (Fig 1A and 1B) and for the first time in four years we did not experience a significant increase over the previous years' volume and cost. The full effect of these internalization efforts and additional tests accounting for an additional $200,000 is clearly seen between FY years 2012 and 2013.

Laboratory Consolidation and Price Negotiations

We, like many other laboratories, send out to a significant number of reference laboratories. At the outset of our strategy to reduce costs, we had our general chemistry/microbiology testing split between two large national reference laboratories. This not only added to our cost per test as we weren't commanding enough volume at either to benefit from a volume based price reduction, but it also led to a significant amount of confusion as to where the requested assays should be directed. As expected we undertook a request for proposal (RFP) process in order to compare several national reference laboratories. In the RFP process, it is not sufficient for the laboratory medicine faculty to be merely involved in the process. In order to assure that the quality of testing, turnaround time and other value added features between laboratories is considered, the laboratory medicine staff needs to be key players in the RFP process.

Prior to the first presentations by the various vendors we elected to explore, the committee consisting of both laboratory medicine faculty and departmental administration developed a scoring tool with

which to evaluate the vendors. This scoring tool took into consideration many factors in addition to the cost per reportable test (Table 1). As part of this process, the group placed a weighting factor to each category that reflected our departmental mission and cost reduction goals. The RFP process is a large and time consuming process that will involve many individuals. To manage this group and coordinate the schedules of all involved, it is wise to enlist the help of a project manager to keep the group on task and working towards a common goal. Changing reference laboratories is a time consuming process that can involve a significant amount of work following the RFP process. This in and of itself will have a cost associated with it, and as such the RFP process is not done frequently.

Our RFP process was completed at the end of FY 2010 and this process was an important component in our strategy to reduce our send-out expense. While our total send-out volume and expense increased in FY 2011 we were able to realize a drop in our cost per test ratio (Fig 1A and 1B). This reduction in cost per test was maintained until FY 2013 when our cost per test ratio again climbed above the pre-RFP levels. This increase was largely due to the internalization of the high volume, low cost vitamin D testing.

Test Utilization Review

One potent tool in reducing the financial liability associated with reference laboratory testing that is not utilized at most hospitals and academic medical centers is using the laboratory medicine faculty for test review and consultation. In many laboratories, including ours, there was little if any review structure in place. Large panels of serum antibodies or genetic markers were frequently ordered by our physicians when alternative strategies could have been employed to save the facility and our patients a considerable amount of money. Knowing that this was an area that we needed to come up to speed on quickly, we circulated a large database of tests to all laboratory medicine faculty for review. The goal of this review was to identify candidate tests that were likely misordered, over ordered, or of limited clinical utility.

This review identified many test panels, such as celiac disease testing, that were sent to highly specialized laboratories that could be replaced with sequential testing profiles from our main reference laboratory for a significant financial savings. In addressing changes in reference laboratory testing such as this, we elicited the help of clinical colleagues. For celiac testing we reviewed the panel approach vs. the sequential testing profiles with Gastroenterology and presented them with the diagnostic and financial evidence. Once we had reached an agreement with our clinical colleagues, it was a matter of removing the large panel from our test catalog and following up with providers who continued to order the large antibody panel.

Using this same strategy, we also noted a number of lower volume tests of limited clinical utility such as the use of adenosine deaminase on pericardial fluid for the diagnosis of extraplumonary tuberculosis. We also noted that a number of providers were ordering both a TIBC as well as a transferrin simultaneously. Our first step in addressing tests such as these was to remove them from the Computerized Physician Order Interface (CPOE). While we occasionally still get miscellaneous laboratory

test requests for these tests, simply removing the offending test can have a profound effect on ordering patterns.

Unsurprisingly, we also identified a few tests that had a high likelihood of being ordered in error such as 1,25-dihydroxyvitamin D in place of 25-hydroxyvitamin D or Parathyroid Hormone related protein (PTHrP) in place of Parathyroid Hormone (PTH). In fact, in the case of 1,25 dihydroxyvitamin D, we noted an increase in the number of requests that coincided with the advent of CPOE at our institution (Figure 3). Knowing that direct physician education would likely have limited effect on ordering patterns as we continually have new resident physicians each year, we chose a separate approach. Tests that had a high potential of being ordered in error such as PTHrP and 1,25-dihydroxyvitamin D, as well as all miscellaneous laboratory test requests, were collated into a spreadsheet by our laboratory information system program three times a day Monday through Friday. This spreadsheet is then reviewed by a combination of laboratory staff, pathology residents and pathology faculty.

As part of the review process for commonly mistaken orders such as 1,25 dihydroxyvitamin D, the laboratory staff will cull out certain requests such as those on known renal failure/transplant patients. The remaining requests are reviewed by the pathology resident and/or faculty. Then if it is determined that the physician likely meant to order the 25-hydroxyvitamin D, an email template directing physician to the correct order in CPOE is sent. This activity combined with creative test naming schemes, such as renaming 1,25-dihydroxyvitamin D to 1,25-dihydroxycholecalciferol, successfully reduced the number of incorrect tests being performed on patients for whom this testing was unnecessary (Figure 2).

Review of Molecular Testing

While these small steps can have profound effects on patient care and cost, there is a whole other area of testing that many laboratorians have not yet begun to tackle: the requests for large gene panels. In addressing this challenge we sought to hire a content expert to help in the review of these requests as suggested by others (4). Although these requests are not as frequent as others the cases are often complex and the interpretation of clinical symptoms and presentation can be lost in clinical notes. To aid us in this complex area we were fortunate to work with a Medical Geneticist with a background in connective tissue disorders. When a request for a large gene panel is received, the case is summarized and sent to a team of laboratory medicine faculty including the Medical Geneticist. Following a review of the case, if a conversation between the laboratory and the ordering physician is necessary the conversation is typically led by the Medical Geneticist. In our experience the majority of these requests upon review are either cancelled or reordered in a tiered or sequential manner with the highest prevalence genes targeted first.

At times the requests are quite simple, such as a request for whole gene sequencing when there is a known familial mutation. Requests such as this do not require consultation via the Medical Geneticist, and the physician is typically consulted by either a Pathology Resident or other Laboratory Medicine faculty to amend the order to query the gene for the known familial mutation.

In addition to the RFP process previously mentioned, we've also been actively monitoring the cost of our esoteric molecular tests. Traditionally we've not directed our physicians to particular laboratories for

molecular testing. However it became apparent that significant disparities exist in pricing between laboratories. In order to address this challenge as part of the test utilization process that will be described below, we also query the Gene Tests online data base for locations that perform the requested test (www.genetests.org). Once the various laboratories are identified, the cost of the test is determined either through their online test catalog or via a phone call with a laboratory representative. This data is currently being collected and our preferred laboratory for various esoteric tests will eventually be included in our test catalog/laboratory test formulary.

The test review strategy is the most labor intensive activity of all three strategies but it does hold immense potential in reducing unnecessary testing. While our test utilization review only fully came into being in the latter half of FY 2012, we noted significant reductions in our send- out volume and expense. Approximately half of the $2 million dollar reduction in our send-out expenditures between FY 2012 and FY 2013 (Figure 1A and 1B) can be accounted for by internalization of certain assays. The remainder, approximately $1 million dollars, is due partly due to direct intervention in cases of large gene panels and a change in our physicians ordering patterns once the magnitude of the cost of testing was realized.

Summary

We've approached a reduction of our reference laboratory volume in three ways. We've internalized high volume and/or high cost testing, we've negotiated test pricing and we've initiated an active review process. While the active review of physician orders requires a significant investment of time, it does fulfill the mantra of many in laboratory medicine: the Right Test, for the Right Patient at the Right Time. These strategies cannot be done by one person working alone. A team of committed individuals is needed to drive the process from various positions. We would not have been able to achieve the early successes we have it had not been for the work done by departmental administration, laboratory staff, departmental faculty and especially without support from the department chair and hospital administration.

Our next steps along this process are to create an interdepartmental test utilization committee to discuss new testing strategies and to develop approved form letters and procedures to codify the test review process. These activities will be necessary as we move from a fee for service era into accountable care and for the review of requests for Whole Exome and Whole Genome testing.

The significant increase in reference laboratory costs for many hospitals is growing to such a level that it may soon threaten our ability to provide care to all of our patients. To that end we live by one last mantra: No Margin, No Mission. It is imperative that this challenge is faced, and while we are a not-for-profit facility, we are seeking new ways of delivering effective and efficient care to our patients so that we may continue to provide care for those who need it most.

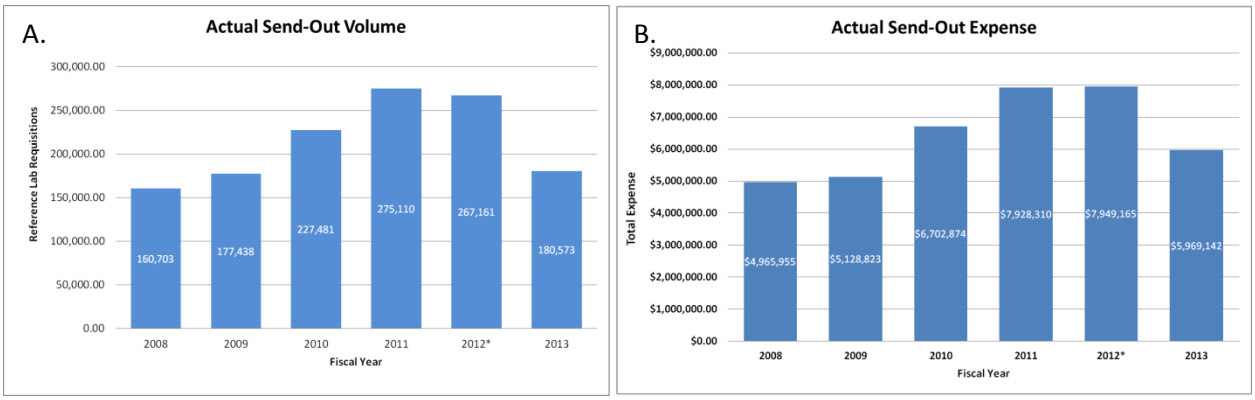

Figure 1: Send-out volume and expense trend. Test volumes (A) and cost (B) increased from FY 2008 to FY 2011. Test utilization plateaued and decreased in FY 2012 and FY2013 as a result of our test utilization strategies.

Test "A"

2000	*orders per month*
100	*5 % repeat rate*
68	*QC based on 4.5 weeks and repeats*
2168	*Samples and QC/mo*

Assuming:
3 levels of QC per testing day *5 days a week
Repeat level 5% (worst case scenario)

Reagent Cost/Test	Quantity	price/unit	Cost
Reagent (100/kit)	22	$ 500	$ 11,000
Cuvettes	3	$ 350	$ 1,050
Wash	1	$ 100	$ 100
System Buffer	2	$ 100	$ 200
Triggers	3	$ 150	$ 450
CCs pack	1	$ 150	$ 150
Control Set	1	$ 100	$ 100
			$ 13,050
		Samples/Month	2000
		Cost/Test	$ 6.53

	Annual Vol	Cost/Test	Annual Cost
Ref Lab A	24,000	$ 20.00	$ 480,000
DHMC	24,000	$ 7.00	$ 168,000
		Potential Savings	$ 312,000

Test "B"

60	orders per month
3	*5 % repeat rate*
14	*QC based on 4.5 weeks and repeats*
77	*Samples and QC/mo*

Assuming:
3 levels of QC per testing day once a week
Repeat level 5% (worst case scenario)

Reagent Cost/Test	Quantity	price/unit	Cost
Reagent (100/kit)	1	$ 1,500	$ 1,500
Cuvettes	0.1	$ 350	$ 35
Wash	0.1	$ 100	$ 10
System Buffer	0.1	$ 100	$ 10
Triggers	1	$ 150	$ 150
CCs pack	1	$ 150	$ 150
Control Set	1	$ 100	$ 100
			$ 1,955
		Samples/Month	60
		Cost/Test	$ 32.58

	Annual Vol	Cost/Test	Annual Cost
Ref Lab A	720	$ 29.00	$ 20,880
DHMC	720	$ 36.00	$ 25,920
		Potential Savings	$ (5,040)

Figure 2: Comparison of two assays being evaluated for internalization. Test “A” on the left demonstrates an assay that would be ideal for internalization while Test “B” on the right represents an assay that would cost more to perform internally.

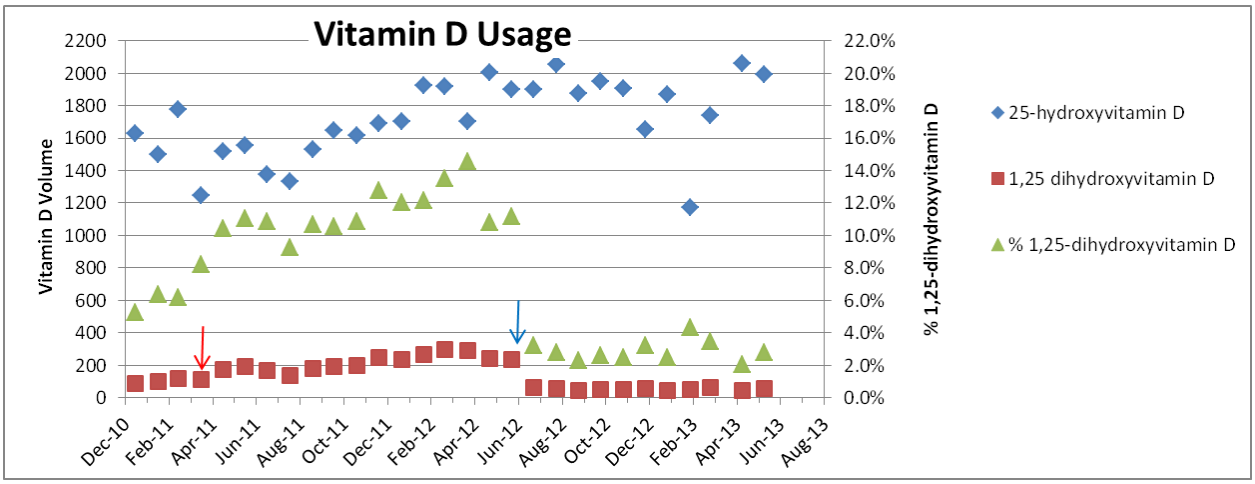

Figure 3: 1,25 Vitamin D utilization trend. We noted that following the advent of a new CPOE program (red arrow) that our requests for 1,25-dihydroxyvitamin D (Red Squares) and the % 1,25-dihydroxyvitamin D (Green Triangles) increased disproportionally to our 25-hydroxyvitamin D volumes. Following the institution of a review process (blue arrow) the volume of 1,25-dihydroxyvitamin D tests dropped considerably.

Reference Lab Selection Criteria

Criteria	Weighting Factor*
Test Menu/Breadth of Testing/Quality	**0.2**
Customer Service	**0.1**
Price	**0.3**
Value Added Activities	**0.05**
Interface	**0.1**
Specimen Handling/Tracking	**0.2**
Implementation Plan	**0.05**

Table 1 Reference Lab Selection Criteria

*These weighting factors are for demonstration purposes only. Each laboratory should choose weighting factors based on their goals.

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2. Paxton A, How Labs are Taming Test Utilization. CAP Today, June 2013
3. Paxton A, The Sense and Cents of Send-Outs. CAP Today, February 2012

4. Dickerson JA, Cole B, Conta JH, et al. 2013. Improving the value of costly genetic reference laboratory testing with active utilization management. Arch Path Lab Med. In Press.

Other Suggested Reading:

Kim JY et al. Utilization management in a large urban academic medical center. AJCP. 2011;135:108-118

Dickerson J, et al. Ten Ways to Improve the Quality of Send-out Testing. Clin Lab News. 2012;38(4): 12-13. www.aacc.org/publications/cln/2012/april/Pages/SendOutTesting.aspx#

Excerpts from the Literature

Articles of interest compiled by the editorial board. Please welcome our new member of the editorial board, **Van Leung Pineda, Ph.D, DABCC**.

Whole genome and exome sequencing using archived neonatal dried blood spot samples (UG)

Hollegaard, M, Grauholm J, Nielsen R, Grove J, Mandrup S and Hougaard DM.

Mol Gen Metabol 110 (2013): 65-72

Dried blood spot (DBS) is the most commonly used sample in newborn screening. Commonly used screening markers are biochemical pathways intermediates, and less commonly used markers are proteins and DNA. With the availability of next-generation sequencing coupled with advances in data handling and analysis at a reasonable prices per sample, this technology is becoming widely used in clinical genetics, and entering into newborn screening. Since DNA is very stable and most newborn screening programs have repositories, DBS provide access to large cohorts of well-characterized patients and healthy controls. The authors previously demonstrated that DNA extracted from archived DBS can be whole genome amplified (wgaDNA) and used for accurate array genotyping. In this paper the authors demonstrated that wgaDNA from DBS can be used for accurate whole genome sequencing (WGS) and exome sequencing (WES). The results of DBS (archived and fresh) were compared with DNA from whole blood. The overall performance of the archived DBS was similar to the whole blood reference sample. The study demonstrates the use of neonatal DBS in genetics research, diagnostics and screening projects.

Low prepregnancy adiponectin concentrations are associated with a marked increase in risk for development of gestational diabetes mellitus. (JS)

Hedderson MM, Darbinian J, Havel PJ, Quesenberry CP, Sridhar S, Ehrlich S, Ferrara A. Diabetes Care. 2013 Aug 29. [Epub ahead of print]

The prevalence of gestational diabetes mellitus (GDM; elevated blood sugar concentrations during pregnancy in an individual not previously diagnosed with diabetes) has increased sharply in the past 20 years. While most discussions of the increased incidence of diabetes are centered on the obesity epidemic, up to 50% of women who develop GDM are not classified as overweight or obese. Women with GDM are at increased risk of both maternal and fetal morbidity, as well as developing type 2 DM at some point after the pregnancy. Additionally, their children are at increased risk of becoming obese and developing DM themselves. Identifying those at risk is therefore an important step to provide timely treatment for the eventual prevention of GDM.

Adiponectin is a hormone produced by adipocytes that plays a role in modulating metabolic responses and increasing insulin sensitivity. It is (paradoxically) inversely associated with body fat, it decreases during pregnancy and it is found in lower concentrations in type 2 DM patients. This article by Hedderson et al sought to determine if prepregnancy adiponectin concentrations might be predictive of GDM.

Samples collected up to 6 years prior to pregnancy were used to address this question. 256 women who went on to develop GDM were matched with 497 control women that did not develop GDM during pregnancy. Results were adjusted for differences in body mass index, number of pregnancies, race/ethnicity, smoking, glucose and insulin concentrations, fasting status, and family history of diabetes. After eliminating these differences, the authors observed increasing risk for developing GDM with decreasing adiponectin. Compared with the highest adiponectin quartile, the odds ratios increased from 1.5 to 3.7 to 5.2 in the lowest quartile. In other words, women with the lowest adiponectin concentrations had a more than 5-fold increased risk for developing GDM. The combination of adiponectin concentrations below the median and an overweight or obese BMI increased the odds ratio for developing GDM to 6.8.

The authors concluded that low prepregnancy concentrations of adiponectin may identify women at higher risk for developing GDM. This data may help target individuals for early therapies or intervention. It also highlights the importance of the preconception period for an eventual healthy pregnancy and may identify individuals that would benefit from increasing their health status prior to conception.

Obesity and diabetes related plasma amino acid alterations (VP)

Yong Zhou et al. Clin Biochem 46(2013)1447-1452

This article describes using a test familiar to biochemical genetics laboratories to compare a normal population to diabetic patients. Although the population studied was not pediatric, their pathologies are becoming well known in the pediatric population.

In this study, Zhou et al. analyzed and compared the amino acid profiles of normal individuals to individuals diagnosed with Type 2 Diabetes. In addition, within each group the authors also subdivided them in the categories of lean vs. obese participants. Fasting plasma specimens were obtained from

study participants and analyzed for 42 amino acids using LC-MS/MS. Furthermore, the specimens were also tested for glucose, HbA1c, cholesterol, lipid profile and insulin. The patient population studied was 100 normal subjects, of which 80 were obese, and 126 type 2 diabetics, of which 31 patients were obese.

The authors found that when lean individuals were compared to obese individuals in the normal group, the obese subgroup 19 elevated amino acids, 15 of which are essential. This suggested to the authors that essential amino acids were not metabolized efficiently in obese subjects and led to plasma accumulation. In contrast, in the diabetic group, obese persons only had 3 amino acids increased when compared to lean diabetic patients, suggesting that the differences in obese vs. lean in terms of amino acid metabolism were less than in the normal group. When comparing normal vs. diabetic, the diabetic group showed increases in 16 amino acids and decreases in 11 amino acids. Multivariate regression revealed certain associations between changes in amino acid concentrations to alterations in the metabolism of diabetics. For example, changes in glycine, proline and sarcosine were related to HbA1c alterations.

Limitations of the study included the relatively small sample size and the age difference between the normal subjects (mean age early 30s) and the diabetic population (mean age early 60s). However, it is a good example of the expansion of an established biochemical genetic test to pathologies different than the classical inborn errors of metabolism. In this case amino acid profiling could provide prognostic and monitoring information for diabetic patients.

Interview with A Distinguished Colleague: Dr. Rob Christenson

Sharon Geaghan, MD

I had a chance to catch up with Rob via a virtual interview, and he shares his insights with you as the next in a series of conversations with distinguished colleagues in our discipline

Q1. How did you come to the career decision to choose Clinical Chemistry as your profession?

I started college as Physical Education major (and baseball player) after less than sterling academic performance in high school. By chance my roommate was a pre-med / chemistry major. We made a great life-long friendship and I changed my major to chemistry after one semester. He's now a thoracic surgeon on the faculty at Columbia. We both took a histology course as college seniors, which really hit

home for me about biological changes that occur with disease, diagnosis, etc. When entering graduate school I was interested in organic chem. I soon found an interest in biochemistry and analytical chemistry, which led me down the path to clinical chemistry and laboratory medicine.

Q2. Did you have a mentor and if so what did he/she teach you?

My mentors have been many. Two that have had a big influence are John Shelburne, who was head of labs at Duke University, and Joe Keffer, both pathologists who very encouraging in my early academic years and taught me a great deal about love of work ethic, self-confidence and a passion for learning and asking questions about clinical science and medicine.

Q3. For newly-minted chemists, do you have any pearls of wisdom for career development?

Successful people focus. Find a niche for your research interests while at the same time remaining enthusiastic about the general nature of laboratory medicine. Never stop learning. When asked by colleagues to help with something try to never say no. Although one must be careful to not get over committed, good things (i.e. luck) comes to those who are collegial and make good use of their time. Never compromise the quality of your work and enjoy what you do.

Q4. What is the most enjoyable part of your professional work?

A bit corny, but the warm feeling of satisfaction gained when the work you has the potential or reality of making a difference in people's lives. This can be through implementation of new or better processes and service in the clinical lab or through clinical research.

Q5. What is the hardest part of your professional work?

Completing all of the tasks I've agreed to in the timeframes specified. I always say that busy is good, and I (like many) have a hard time saying no. The problem is that if you have 50 tasks and you complete 49, it's that single one unfinished item that makes me feel regret. Trying not to be over committed is my biggest challenge.

Q6. The next generation of chemists has been characterized as looking for work-life balance. Do you have advice for them in managing that balance from your experience ?

Strive to be well organized and happy in both your personal and professional life. Decide who you are and what it is you really want to be. At the end of the day, family and friendships are most important, but for me professional satisfaction is also necessary for happiness. Make sure you have hobbies, and save something for yourself, without making it all about you.

Pediatric and Maternal-Fetal Division Elections

The election for Division Officers is complete. The new members of the executive board are listed below, along with a short biography.

Chair-Elect: Shannon Haymond

I am the director of the Clinical Chemistry and Mass Spectrometry laboratories at the Ann & Robert H. Lurie Children's Hospital of Chicago. In this capacity I also hold a faculty appointment as an assistant professor of pathology at Northwestern University's Feinberg School of Medicine. Like many laboratory directors, my job is a mix of providing clinical service, teaching pediatric clinical chemistry to residents and fellows and performing clinical research. My research interests include general lab process improvement and correlations to 'value' metrics, method development and quality initiatives for LC-MS/MS applications and the utilization and investigation of biomarkers in pediatric cardiovascular and renal disease. I have served on the PMF board as a member-at-large and am currently serving as the secretary of the PMF division. I have also been actively involved with AACC at both the national (current SYCL committee and nominating committee member and AMOC 2010 brown bag coordinator) level and in a variety of capacities within my local section (Chicago), including serving as chair in 2010. My experiences serving AACC have been rewarding and fun and, therefore, I am grateful for your consideration to serve as the PMF division chair-elect.

Secretary: Christina Lockwood

I am delighted to be considered to serve as Secretary for the Pediatric Maternal-Fetal division. After joining AACC in 2006, I was pleased to be elected Member-at-large of the PMF division in 2011. I finished my Clinical Chemistry fellowship at Washington University in St. Louis in 2009. I am currently an Assistant Professor in Pathology and Immunology at Washington University in St. Louis where I am Director of the Molecular Diagnostics Laboratory at Barnes-Jewish Hospital.

A vital component of my fellowship training was a rotation as acting medical director at St. Louis Children's Hospital under the supervision of Dr. Dennis Dietzen, where I learned firsthand that children are not little adults! Since completing my training, I have participated in several clinical projects relating to maternal-fetal and pediatric medicine. In my current position in the Molecular Diagnostics Lab, I continue to be engaged in testing for both maternal-fetal and pediatric populations.

The sustained commitment to pediatric reference intervals, active listserv and outstanding newsletter with valuable educational updates are highly visible ways the PMF division has promoted clinical laboratory science. Our mission of advancing PMF laboratory medicine is also evident in the numerous division awards. Enhancing the division's visibility and clearly articulating our goals will be important in maintaining and increasing our membership. The AACC has been an invaluable resource for my professional development. I look forward to more opportunities to serve our organization, and I hope to do so within the PMF division.

Treasurer: Sihe Wang

Dr. Sihe Wang is Section Head and Medical Director of Clinical Biochemistry and Director of Clinical Biochemistry Fellowship Training Program, Cleveland Clinic, Cleveland, Ohio. He also chairs the clinical chemistry integration effort for the Cleveland Clinic Health System which includes 1 Florida hospital, 8 community hospitals and 18 family health centers in Northeast Ohio. Additionally, he is Clinical Chemistry Professor, Cleveland State University. Prior to his current position, Dr. Wang was Assistant Professor at Northwestern University; Director, Clinical Chemistry Laboratory and Referred Testing Laboratory, Children's Memorial Hospital, Chicago, Illinois. Dr. Wang is a diplomate of the American Board of Clinical Chemistry (DABCC) and a fellow of the National Academy of Clinical Biochemistry (FACB).

Dr. Wang is a member of several professional organizations, including the American Society for Mass Spectrometry and the American Association for Clinical Chemistry (AACC). He served as chair of AACC Northeast Ohio Section in 2008 and 2009 and the president of North American Chinese Clinical Chemistry Association (NACCCA) 2008-2009. Currently he serves as the advisor for NACCCA, the treasurer for the Pediatric and Maternal Fetal Division of AACC, the delegate for AACC Northeast Ohio section, commissioner for The Commission on Accreditation in Clinical Chemistry, and AACC's Strategies Online Editorial Advisory Board member. The AACC presented him with the 2005, 2008, and 2010 Clinical Chemist Recognition Award. He is also the recipient of the 2006 Lemuel J. Bowie Young Investigator Award for the Chicago Section of the AACC. Dr. Wang has authored over 140 journal articles, book chapters, and abstracts. He also serves on several editorial boards of peer reviewed journals.

Member At Large: Brad Karon

Dr. Karon completed his MD and PhD (Biochemistry) degrees at the University of Minnesota, followed by a residency in Clinical Pathology at Barnes Hospital (Washington University). He is certified in clinical pathology by the American Board of Pathology; and is also a fellow of the National Academy of Clinical Biochemistry, College of American Pathologists, and American Society for Clinical Pathology.

Dr. Karon is an Associate Professor of Laboratory Medicine and Pathology at Mayo Clinic in Rochester Minnesota. As medical director for Hospital Clinical Laboratories and Point of Care Testing at Mayo Rochester, he oversees a system of stat and physician office laboratories as well as a large point of care testing program. Dr. Karon has published extensively in the field of clinical chemistry; including five peer-reviewed publications relating to effective screening strategies for neonatal hyperbilirubinemia, one of his primary academic interests. He also holds multiple education leadership positions at Mayo Rochester including Vice-chair for Education in the Department of Laboratory Medicine and Pathology, Program Director of the Pathology residency, and Medical Director of the Medical Laboratory Sciences program.

Member At Large: Alison Woodworth

Dr. Alison Woodworth received her Ph.D. in Cell Biology from Washington University in St. Louis, where she went on to complete fellowship training in clinical chemistry. Dr. Woodworth is currently the Director of Esoteric Chemistry, Associate Director of Clinical Chemistry, and Assistant Professor of Pathology, Microbiology and Immunology at Vanderbilt University Medical Center in Nashville, Tennessee. She is a Diplomate of the American Board of Clinical Chemistry. She serves as Director of the ComACC certified clinical chemistry fellowship program at Vanderbilt, where she also teaches residents, medical students and medical technologists. Dr. Woodworth has been actively involved in AACC since 2003 and the AACC Southeast section since 2007 where she has served as section vice chair and chair. She is also very active on the national level for AACC, serving as an abstract reviewer, editorial board member for the AACC Press board, and was a member of the 2012 annual meeting organizing committee. She was recently awarded the SYCL Service Award for outstanding contributions to the AACC. She is a fellow of the National Academy of Clinical Biochemistry and currently serves as chair of the editorial board for the NACBlog and was recently elected to the Board of Directors. She is also a member of the Academy of Clinical Laboratory Physician Scientists, where she serves on the nominating committee. Her noteworthy contributions to clinical and translational research in the areas of and Maternal/Fetal Medicine and Sepsis have resulted in multiple publications and awards, including the NACB distinguished abstract award and best abstract awards from the Industry and Maternal/Fetal Medicine division. Dr. Woodworth enjoys speaking about clinical chemistry; she has been invited to speak at several local, regional and national meetings and has won the AACC outstanding speaker award for the past three years.

Introduction of the Trainee Member of the PMF Board

The trainee member of the PMF Division is a newly created position that allows a current fellow of a laboratory medicine program with an interest in pediatrics or maternal-fetal medicine to become more involved with the division. The trainee position is appointed by the board and carries a term of 18 months. If you would like to nominate someone for this position, please contact a division officer for information.

Joe M. El-Khoury, PhD

Clinical Chemistry Fellow, Department of Clinical Pathology, Robert J. Tomsich Pathology and Laboratory Medicine Institute, Cleveland Clinic

Dr. El-Khoury received his B.Sc. in Chemistry from the American University of Beirut (Lebanon, 2008) and his Ph.D. in Clinical and Bioanalytical Chemistry from Cleveland State University (2012). Dr. El-Khoury was the recipient of the 2012 Past President's Scholarship ($100,000) from the American Association

for Clinical Chemistry (AACC), which is funding his appointment as Clinical Chemistry Fellow at Cleveland Clinic (2012-present). He also served as Adjunct Lecturer in the Department of Chemistry at Cleveland State University (2013).
Dr. El-Khoury has over 5 years experience in the field of laboratory medicine and mass spectrometry and has presented and talked at AACC and Mass Spectrometry Applications to the Clinical Lab meetings. His expertise is in liquid chromatography-tandem mass spectrometry, renal disease biomarkers and vitamin D.

Dr. El-Khoury is a member of the AACC and its society for young clinical laboratorians (SYCL, 2009-present). He was recently appointed to the Pediatric and Maternal-Fetal division as a trainee board member, but also serves on SYCL 360 (2012-present), Northeast Ohio-AACC local section (2011-present), and as the Scientific Program Chair for the Ohio-Collaborative Laboratory Conference (2012-present). He is a reviewer for Clinica Chimica Acta.

Save the Date

Abstract Submission for the AACC 2014 Annual Meeting

Call for Abstracts for the 2014 AACC Annual Meeting
July 27 – July 31, 2014
Chicago, IL

The website for submitting abstracts for the 2014 AACC Annual Meeting is now open. The deadline for abstract submission is **February 26, 2014 at 6:00PM New York Time.** There will be no extensions of this deadline. Submitters may also apply for various AACC Division and Student Awards when submitting abstracts. All abstracts are peer reviewed and the best are eligible for the NACB Distinguished Abstract Award and for possible oral presentation during the Annual Meeting.

Click here to submit your abstract.

ICPLM 2014

The ICPLM 2014 will be June 20th-22nd, 2014, prior to the IFCC-WorldLab in Istanbul, Turkey. The exciting symposium program can be accessed using the link below. Please save the dates for this exciting pediatric focused meeting which would be ideal for both the specialist and non specialist laboratory medicine professional. The names of the plenary speakers have been announced, and the deadline for abstract submission is **February 15th, 2014.**

http://www.icplm2014.org/

So long…farewell…

Several members of the board are finishing up their terms, and we would like to extend our thanks for their service to the PMF division.

Nathalie Lepage

Stan Lo

Michael Metz

Thank you!