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ASCLS and other laboratory groups are alert to trends in Medicare payment, often the largest source of payment for a laboratory or a hospital. Developments in Medicare payment policy, such as competitive bidding, freezes to the Medicare Outpatient Laboratory fee schedule, threats of instituting a co-pay for Medicare beneficiaries, and others, have been the focus of advocacy efforts at the Legislative Symposium and in other campaigns.

Legislators, businesses, and the public remain concerned about the rising cost of healthcare and the growing number of uninsured citizens in the United States. Many proposals have been made to control the rate of increase in healthcare costs. Laboratorians often feel that the laboratory is unfairly singled out for more than a fair or proportionate share of freezes or cuts in reimbursement.

Concern from Congress about Medicare spending on Part B (outpatient) laboratory services stems from a significant increase in total dollars spent for laboratory services, despite the fact that the individual fees for tests have been frozen in 11 of the last 15 years. In the years 1991 and 1998, Medicare spending for laboratory services was $3.6 billion. There was a slight increase to $4.3 billion in 1993 and 1994, then a gradual decrease back to $3.6 billion in 1998. Since 1998, however, there has been an increasingly steep rise in total spending for laboratory services, averaging 8.8% annually, to $6.0 billion in 2004, the latest year for which data is available. (Data from the 2005 Medicare Trustees Report) Despite this growth, laboratory spending is still just 4.4% of Medicare Part B expense, and 2.0% of total Medicare expense.

The reasons for the increase in laboratory expenses are a combination of the aging population swelling the numbers of beneficiaries needing services, and new technology providing additional tests. With these factors and the additional expense to Medicare of the Part D prescription drug benefit, we know that the Medicare program officials will continue to look to the laboratory for cost savings.

But what about other payers? Many of us have already experienced, in our employer-provided plans, the movement toward consumer-directed health plans (CDHPs). CDHPs may take a number of forms, but the common theme is to get away from “first dollar” coverage and place more financial responsibility on the individual.

Health insurance was introduced in the US in the 1930’s, and employer-provided health insurance became common during World War II, when wages were frozen and employers offered insurance as additional compensation to attract workers. Utilization of healthcare services increased in the 1950’s through 1970’s as technology boomed. In the 1980’s and 1990’s, managed care slowed the growth of healthcare expenditures, but apparently only temporarily. In the 2000’s, attention has focused on the contribution of lifestyle-induced chronic diseases to the utilization and expense of healthcare. There is a belief that the cost of employer-provided insurance has made US businesses less competitive in the global marketplace. Many businesses have increased the amount of employee contribution to their insurance premiums, added co-pays and co-insurance, and generally provided plans that place responsibility for more out-of-pocket expenses on the employee.

Congress has facilitated the consumer-driven movement by providing for health reimbursement accounts (HRAs) and health savings accounts (HSAs). The assumption is that the individual will take on more responsibility for healthcare decisions and finances when more expenses are out of pocket. The psychology changes from “use it or lose it” (HRAs) to “use it or keep it” (HSAs).

The consumer-driven movement raises many questions and concerns:

- Do consumers have the necessary knowledge and information to make appropriate choices about their healthcare?
• Will consumers forgo or postpone needed care, and ultimately need more complex and expensive care?
• Will cost reductions or stabilization be permanent?
• Will lower socio-economic groups and less well-educated consumers be unfairly harmed?

While it is too early to be able to answer these questions definitively, early research suggests some interesting trends. A survey from the McKinsey consulting group finds that only 40% of those covered by traditional employer-paid plans ever ask about the cost of any aspect of their care, as contrasted with 64% of those in a CDHP and 70% of the uninsured. Patients are much more likely to ask about the cost of their prescription drugs than about procedures or tests, however. In addition, patients in a CDHP are significantly more likely to consider alternative treatment options, such as those found by doing independent research on the Internet. A majority of patients say that they do not have enough information about quality of care and price to make informed decisions.

So far, only a small percentage of patients admit to forgoing needed care – four percent of those covered by traditional plans versus six percent of those in CDHPs. These individuals cite cost as the primary factor for these decisions to forgo care. CDHP participants are much more likely to choose a less expensive treatment (excluding medications), such as a less expensive home glucose meter for a diabetic patient.

Preliminary data also indicates that CDHP participants are more likely (69% to 55%) to engage in healthier lifestyle behavior (diet, exercise, non-smoking) than those covered by traditional employer plans. If this trend proves to be true over the long term, it is possible that costs of managing chronic illness long-term could indeed be reduced.

CDHP participants are more likely to state that they have annual physicals because it is important for long-term health, whereas those in traditional plans are more likely to say that their reason is because it is covered by their health plan.

Finally, CDHP members with a chronic disease (such as hypertension or diabetes) are more likely to “very carefully” follow treatment regimens than those with traditional insurance. An impressive difference of 51% to 31% is seen in those with hypertension.

Is it true that “you get what you pay for” – that more expensive care is better care? A study published in Health Affairs, February 2002: Dartmouth Atlas examines cost and quality of Medicare services in five metropolitan areas. Total spending varies by over 100% among the five areas studied, with Minneapolis being lowest and Miami highest. Specialist visits vary six-fold. But a measure titled “effective care index” is almost identical in all five.

What will be the impact of all of this on the laboratory? Hospitals and laboratories are already experiencing more difficulty in collecting those patient co-pays and co-insurance amounts from individuals. Despite all the rules involved in billing Medicare and insurance companies, they are still easier to collect from than individuals. For self-pay patients, there will be pressure for “retail” charges to more realistically reflect costs, rather than being marked up to cover discounts taken by insurance companies, as has been common. Hospitals and laboratories are likely to experience more bad debt; this then results in pressure on laboratories and other departments to operate more efficiently.

Laboratories, along with other healthcare providers, will continue to face new challenges in getting paid for the vital services we provide, as pressure continues from both the government payers and from the private payers.

1 Presented at the Executive War College on Laboratory and Pathology Management; 2006 May; Miami (FL).
NCA and BOR Consider New Credentialing Agency

GEORGE A FRITSMA

The National Credentialing Agency for Laboratory Personnel, Inc. (NCA) and the Board of Registry (BOR) of the American Society for Clinical Pathology (ASCP) may unite to form a new credentialing agency. Patricia Ellinger, MSED, Chair of the BOR Board of Governors, and Kathryn Doig, PhD, President of the NCA Board of Directors jointly announced the effort at the ASCLS Clinical Laboratory Educators’ Conference, March 2, 2006 in San Antonio. By invitation, E. Blair Holladay, PhD, BOR Executive Director, addressed the NCA board at its regular meeting, November 4, 2005, leading to the development of a letter of intent signed December 12 at BOR headquarters by Drs Doig and Holladay and Ms Ellinger and by BOR Vice-chair Cynthia Johns and NCA Executive Director Sheila O’Neal. The non-binding letter opens the opportunity for consideration of a new agency.

NCA was chartered in 1978 as a peer-review credentialing agency in response to concerns for pathologists’ control of the clinical laboratory science (CLS) profession and has functioned as an independent agency sponsored by the American Society for Clinical Laboratory Science (ASCLS) and the Association of Genetic Technologists. Generalist certifications through NCA lead to the Clinical Laboratory Scientist [CLS (NCA)] and Clinical Laboratory Technician [CLT (NCA)] credentials. The BOR is an agency of ASCP and BOR generalist certifications are Medical Technologist [MT (ASCP)] and Medical Laboratory Technician [MLT (ASCP)]. There were 976 BOR MT examinees in the first half of 2005; NCA examined 521 CLS candidates in all of 2005.

Conference attendees voiced enthusiastic approval. Concern for clinical pathologists’ constraint of clinical laboratory scientists’ practice has moderated in the years since ASCP became independent from the College of American Pathologists and as the CLS profession has grown in numbers, representation, and stature. The existence of parallel, competing agencies creates confusion among employers and graduates, consumes resources, and weakens our profession’s public voice. Unity would establish consistent standards for professional entry, reduce confusion, and enhance our influence on state licensure laws, federal regulations, and employment standards. It would assemble our talented professionals serving both agencies to strengthen credentialing activities, and enhance the financial security of both agencies, which has held steady but not grown during the recent dip in certificant numbers.

What unification issues face us? The technical issues include, but are not limited to…

- What form do the new exams take?
- What exam delivery agency do we employ?
- How do we resolve tax status differences?
- What does a new agency mean for present credential-holders?
- How do we resolve differences in certification maintenance programs?
- How does the new agency blend the various specialty and certificant credentials and exams?

Perhaps more important, we must address credential name, the makeup of the agency board, and autonomy.

What name do we want? Medical Technologist? Clinical Laboratory Scientist? Medical Laboratory Scientist? The internationally recognized title, Biomedical Scientist? What does a new credential name mean to employers, state licensing boards, and federal agencies that regulate laboratories? What about federal and state agencies that provide funding and that currently recognize the terms CLS and MT? Do current certificants change their credential name? What name would be best recognized and respected by the public?

How would the new board look? What constitutes peer leadership and review? How many pathologists should be included, how many clinical laboratory scientists? Should it be chaired by a clinical laboratory scientist? A clinical pathologist? Who gets to vote, who serves as an advisor?
And finally, to whom would the new agency report? ASCP? ASCLS? Perhaps the best approach, expressed at the educators’ meeting by Lucy J. Randles, MA, CLS is the “NAACLS model”. The National Accrediting Agency for Clinical Laboratory Sciences, which audits and accredits clinical laboratory science schools throughout the world, is an independent agency supported in part from dues paid by member organizations. The NAACLS board includes representatives from its member organizations and the profession’s constituency. An independent credentialing agency like NAACLS would be responsive to, and best represent, the needs of the profession.

We’ve got insightful, cautious leaders willing to hammer out the details for the new agency, and we know the answers will not appear overnight. The decisions we make have serious implications for the future of our profession, and your input will help. Please send questions and suggestions to Sheila O’Neal or Kathy Doig at nca-info@goamp.com and to Pat Ellinger, Cindy Johns, or Blair Holladay at BORNCA@ascp.org. We’ve got an opportunity to contribute to the future of our profession.

George A Fritsma MS MT(ASCP) is Clinical Laboratory Science Continuing Education Editor.
Validating the Assessment of Glucose-6-Phosphate Dehydrogenase (G6PD)

CHARLES ASOWATA MAJOR, LESTER PRETLOW, EMILY FINCHER, VERNON KOZIATEK

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme of clinical significance to the Armed Services. The ability to determine accurate erythrocyte concentrations of G6PD is imperative for the prophylaxis and treatment of service members against a variety of opportunistic hemolytic infectious diseases, such as malaria, which might be encountered during deployment. G6PD catalyzes the first oxidation reaction in the pentose phosphate shunt, in which glucose-6-phosphate is dehydrogenated to 6-phosphogluconolactone with the concurrent reduction of nicotinamide adenine dinucleotide phosphate (NADP). This reaction is the only source of the reduced form of NADP, NADPH, which provides the reducing power to change oxidized-glutathione into reduced-glutathione. Reduced glutathione acts as a reducing agent against oxidative insults to the erythrocyte.

G6PD deficiency is expressed when individuals with decreased reduced-glutathione concentrations are administered oxidant drugs such as quinine, analgesics, and sulfonamides. The decrease in reduced-glutathione leads to the inability of erythrocytes of these individuals to endure the oxidative assault of these drugs. As a consequence, erythrocytes lose their structural integrity, resulting in hemolytic anemia that can be moderate to life threatening. G6PD deficiency is the most widely distributed enzyme defect of erythrocytes in humans, therefore, it is important to screen all service members for the enzyme deficiency before they are prophylaxed in preparation for deployment. This potential for drug induced hemolytic complications demands screening and for that reason, the analytical procedures for assessing G6PD concentrations must be rigorously validated to ensure the best quantitative determinations. Most methods for the analysis of G6PD are based on the enzymatic activity of erythrocyte G6PD.

In analyzing erythrocyte G6PD in whole blood specimen on the Roche Cobas Mira Plus™, it was noticed that the enzyme activity (U/g Hgb) for a group of specimens decreased concomitantly as the number of specimens per run was increased. The purpose of this study was to discover the reason for the decrease in erythrocyte G6PD activity seen in the sequential assessment of whole blood specimens. To accomplish this, four objectives were targeted: (1) The G6PD assay by Sigma Diagnostics was validated for precision, linearity, and correlation on the Cobas Mira Plus instrument. (2) Since College of American Pathologists (CAP) survey material was not available, proficiency testing was performed using whole blood specimens by correlating the assay periodically.
with the clinical laboratory at Fort Sam Houston, Texas. Fort Sam Houston’s laboratory used the Cobas Mira Plus for the determination of erythrocyte G6PD activity. (3) The stability of erythrocyte G6PD specimens was tested by storing whole blood specimens for different time intervals and then retesting the specimens to determine any difference from the original assessment. (4) Within-batch stability of the assay was tested by varying the number of specimens assessed per analytical run.

The Cobas Mira Plus was chosen because it has onboard lyses of red cells and because of its ability to deliver the hemoglobin concentration as well as the enzyme activity in a single analysis. Comparable instruments required that the hemolsate be prepared offline before specimens were placed on the instrument. The Cobas Mira Plus was refurbished and distributed by Spectron (Burlington, WA) and was acquired specifically for the analysis of G6PD.

MATERIALS AND METHODS
Validation of G6PD assay on the Cobas Mira Plus

Precision, linearity, and correlation determinations were performed on the Sigma Diagnostics G6PD reagent adapted to the Cobas Mira Plus. Within-run precision was tested by combining several previously analyzed specimens and then allocating the mixture into forty separate samples. Varying the number of specimens per run, the specimens were then analyzed on the Cobas Mira Plus and the resulting data were evaluated by entering it into the EP-5 Evaluator™ software (Rhoads, Kennett Square, PA) version 5.0 for simple precision to obtain a mean, standard deviation, and coefficient of variance. Varying the number of specimens per run assessed the length of analytical run that had the best within-run precision.

To test for linearity, seven pre-assigned controls were run. The Accumark controls were purchased from Sigma Diagnostics. Using the EP-5 Evaluator software, assigned values were plotted against measured values. Regression statistics with slope and Y-intercept were calculated.

A correlation study was conducted by split sample comparison with the assay performed at a large reference laboratory that also utilized the Sigma reagent to assay G6PD. Seventy whole blood specimens were aliquotted and analyzed by each laboratory. The set of specimens sent to the large reference laboratory was processed through the laboratory’s shipping and receiving department where the set was wrapped in plastic, packed on ice in a Styrofoam container, placed in a cardboard box, and overnighted to the shipping and receiving department of the large reference laboratory for analysis. Data from these two assessments of G6PD were analyzed using the EP-5 Evaluator software for alternative method comparison. The EP-5 Evaluator software calculated the correlation coefficient, slope, Y-intercept, and standard error estimate.

Error analysis for the assay was calculated using appropriate statistical analysis. The statistical Allowable Error (E_y) was determined as fifteen percent of the medical decision level (MDL) of G6PD deficiency, 10.0 U/g Hb. Fifteen percent was half of the acceptable performance for several enzymes of clinical significance which had a performance criterion of ten to thirty percent. Random Error (R_y) was calculated as four times the standard deviation (SD) as determined from the simple precision for the assay. Systemic Error (S_y) was calculated around the MDL as the absolute value of Y minus X for the MDL. The regression equation obtained from the split sample comparison with the large reference laboratory was used to calculate the Y-value for our assay as compared to the MDL. The SD as a percentage of E_y was then plotted against the S_y as a percentage of E_y on a medical decision chart (MDC).

The medical decision chart is a graphical tool that considers a method’s random and systemic error simultaneously. It classifies a method by how easily its errors can be controlled to keep it below the allowable error. A MDC is constructed by labeling the x-axis “SD as % of Allowable Error” and scaling the x-axis from zero to fifty in increments of ten. The y-axis is labeled “Bias as % of Allowable Error” and scaled from zero to one-hundred in increments of ten. A line is drawn from the one-hundred percent on the y-axis to the 50% on the x-axis, labeling the region as unacceptable; additional lines are drawn from the 100% on the y-axis to the thirty-three percent, twenty-five percent, and sixteen-point seven percent on the x-axis and labeling the regions marginal, fair, good, and Six Sigma, respectively. The labeled regions judge the performance of a method based on the location of the operating point.

Periodic correlation of G6PD enzyme activity with another facility

Due to the unavailability of proficiency survey material, our G6PD method was periodically (as required by CAP)
validated against a similar methodology to assess the laboratory’s technical competency, instrument, and reagent accuracy/precision. For this study, only the enzyme activity was validated and not the enzyme activity per grams of hemoglobin. Twenty-two specimens were collected in EDTA tubes. The specimens were aliquotted. One set of specimens was then sent to the laboratory shipping and receiving department where it was wrapped in plastic, packed on ice in a Styrofoam container, placed in a cardboard box, and sent overnight to the shipping and receiving department of Fort Sam Houston facility for analysis. Once specimens arrived at Fort Sam, they were unpacked and refrigerated overnight before being analyzed the next day. Both laboratories utilized the Sigma Diagnostic G6PD reagent and the Cobas Mira Plus instrument for the quantitative determination of G6PD in whole blood at 340 nm. Data from this study was evaluated using the EP-5 Evaluator software utilizing the alternate method comparison to determine the correlation coefficient, slope, Y-intercept, and standard error.6

**Stability of G6PD in whole blood specimens**

To look at specimen integrity over time, six whole blood specimens were collected in EDTA tubes and then aliquotted. An initial G6PD activity was determined at the time of collection for one of the aliquotted specimens. The other specimens were then refrigerated at 4 °C – 8 °C for seven, nine, ten, 11, 14, and 23 days. At the end of a given time period, the stored specimens were retested with the Sigma Diagnostic reagent adapted to the Cobas Mira Plus instrument.

The analytical run length was observed by visual inspection during run lengths of four to 12 specimens. The purpose of this activity was to document any problems that could be visually noted during the analytical phase of G6PD assessment. Additionally, a group of specimens was combined and then allocated into 16 specimens. Observations of any problems seen during these analytical runs were noted.

**RESULTS**

The precision of the Sigma Diagnostic reagent when adapted to the Cobas Mira Plus was determined by measuring or calculating the mean, SD, and CV from the simple precision experiment. It was determined that analytical runs of four specimens had the best precision. The mean was determined to be 14.3 U/g Hgb, with an SD of 0.15 U/g Hgb, and a CV of 1.0%. The assay was linear with a slope of 1.087 and a Y-intercept of 0.320. The assay correlated with a reference assay at a large reference laboratory with a correlation coefficient of 0.9667, a slope of the regression line of 0.968, a Y-intercept of -0.291, and a standard error estimate of 0.521. Figure 1 shows the scatter plot from the method comparison.

Allowable error was calculated as 15.0% of the medical decision level of 10.1 U/g Hgb and was determined to be 1.5 U/g Hgb. The $S_E$ was 0.60 U/g Hgb and the $T_E$ was 1.2 U/g Hgb. $S_E$ and $R_E$ expressed as percentage of the allowable error were 40.0% for $S_E$ and 10.0% for $R_E$. These results were plotted on a medical decision chart with random error ($R_E$) on the X-axis and the bias ($S_E$) on the Y-axis (see Figure 2).

Periodic correlation of the assay with the laboratory at Fort Sam Houston obtained the following data. The correlation coefficient was 0.9483; the slope of the regression line was 0.990; the Y-intercept was 104.8; and the standard error estimate was 66.6. Figure 3 shows the regression line for the two facilities.
A minimal difference was found between specimens retested after being refrigerated for one to three weeks, showing little change in G6PD activity. The difference was close to one enzyme activity unit for any specimen in the study. Table 1 shows the change in activity over time.

Two observations were seen as the number of specimens in the analytical run was increased. In the experiment with four to 12 specimens, when the run length was greater than four specimens, the enzyme activity decreased. In the experiment with 16 aliquots, the enzyme activity began to decrease at the fifth specimen. As the run was increased, red cells appeared to settle out of solution while on the instrument.

**DISCUSSION**

In validating the G6PD assay, the precision, linearity, and correlation are acceptable. A CV of 1.0% shows that the R_E of the reagent and instrument system is very precise with only a small difference in error between replicate samples when the length of the analytical run is optimized. The linearity experiment for the system shows that the difference between assigned and measured values is small and closely approximates a 1:1 ratio with a slope of 1.087. The bias between the assigned and measured values, 0.60 U/g Hgb, is well within the E_A of 1.5 U/g Hgb. The correlation of the assay with the assay as performed at a large reference laboratory is also acceptable.

The R_E, S_E, and T_E for the G6PD assay are less than the E_A and therefore are acceptable. Plotting the S_E and the R_E as a percentage of the E_A on an MDC shows that the system is likely to perform well and that errors can be controlled within the allowable margin. The data plotted on the border of the Six Sigma and good range. The means that the method meets quality requirements and can be well managed in routine service with a reasonable amount of quality control.9

Periodic correlation of the assay with the laboratory at Fort Sam Houston shows that the system is performing acceptably. The regression statistics are acceptable.

Whole blood specimens appear to be very stable. Our results show that whole blood specimens collected in EDTA tubes are stable up to three weeks with a maximum loss of G6PD activity of approximately 1U. Changes in G6PD enzyme or whole blood specimen integrity appear to be noncontributory in the assessment of enzyme activity.

Analytical processing appears to be a major contributor to problems experienced in our facility. The observation of decreasing enzyme activity in batch runs of greater than four specimens is significant and is likely due to red cells settling out of solution while specimens are on the instrument. As always, in any reagent/specimen driven analysis, the analytical procedure of mixing cannot be underemphasized. Our standard operating procedure includes the rocking of specimens for ten minutes before they are placed on the instrument. However, the Cobas Mira Plus, with its onboard hemolysis feature, does not remix specimens before they are sampled. We observed, in case of large batches, that erythrocytes consistently settled out of solution, causing the observation of decreasing G6PD activity (U/g Hemoglobin) as the number of specimens in the run was increased. This observation affects the qualitative and quantitative use of the Cobas Mira Plus for G6PD screening.

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**Figure 2.** Evaluation of Sigma Diagnostics reagent on the Cobas Mira Plus analyzer

The MCD shows that the reagent and system meet reasonable quality requirements for allowable error.
This observation clearly impacts the number of specimens that can be run per day and thus the workload for the test. In our case, this means that only 120 specimens can be run in an eight hour day. Furthermore, it requires that a technician be dedicated to the instrument, since our facility receives several hundred specimens per week. With this system, onboard lysis of erythrocytes is clearly a trade off for the number of specimens that can be assayed per day. Preparing the hemosylate offline and then placing the specimens on the instrument would likely prevent the observations we have seen with our system. The question that needs to be answered is which method is really the most time-management friendly...preparing the hemosylate offline or using this system with onboard red cell lysis? This will require further investigation.

However, our findings confirm that as long as the number of specimens is optimized the Cobas Mira Plus using the G6PD reagent by Sigma Diagnostics is accurate, user friendly, and easily maintained. We recommend the system as a good method for the qualitative and quantitative assessment of G6PD activity and effective in keeping soldiers who may have a G6PD deficiency out of harm's way.

### REFERENCES


### Table 1. G6PD activity when whole blood specimens were collected in EDTA tubes, refrigerated, and retested after one to three weeks

<table>
<thead>
<tr>
<th>Specimen</th>
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<th>Retest G6PD activity</th>
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<td>18.0</td>
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</table>
Texas Tech University Health Science Center (TTUHSC) supports a strong undergraduate honors program. Students are required to enter the Honors College as freshmen and enroll in at least 24 hours of honors-designated classes. Some of the clinical core courses in the clinical laboratory science (CLS) program are designated as honors courses so students can continue their contract agreement with the Honors College to enroll in at least six hours of honors credit at the junior and senior level. By providing further educational experiences out of class, these honors students are able to meet the requirements needed to graduate with highest honors. A CLS honors program not only benefits the student but also the faculty involved and the program curriculum.

ABBREVIATIONS: CLS = clinical laboratory science; SOM = school of medicine; TTUHSC = Texas Tech University Health Science Center.

INDEX TERMS: CLS program; curriculum; honors college.

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Historically, when undergraduates in the Honors College declared a CLS major and entered the TTUHSC CLS program at the beginning their junior year, they had to abandon their designation as honors students and graduating with distinction as an honors student. Our CLS curriculum was not linked to a basic education through an honors program, and none of our courses were designed to contain an extra component of study that was acceptable to the administration of the Honors College as deserving of honors credit. Four years ago the TTUHSC CLS program applied for affiliation with our institution’s Honors College. Some of the CLS clinical core courses were then designated as honors courses in which honors students could continue their agreement contract with the university’s Honors College to enroll in a set number of honors credit hours at the junior and senior level. These courses include participation in a special project that honors students are required to complete over a period of several semesters. Since the initiation of the CLS honors curriculum, 8% to 10% of enrolled CLS junior students each
year have opted to take some of the CLS courses as honors courses and have completed research projects in forensic autopsy, clinical and surgical urology, and surgical robotics, in addition to their traditional course work load.

BACKGROUND AND REQUIREMENTS

The honors program administered by our institution’s Honors College sets forth high standards that a student must meet before being accepted as an honors student. Entering freshman must have a minimum SAT score of 1200, or a composite ACT score of 26 or higher. The student can also apply if they were in the top 10% of their high school graduating class. For transfer students who wish to participate in the honors program, the minimum requirement is a cumulative college GPA of 3.4 or higher on transferred credit.2 There are no restrictions on the minimum number of hours transferred.

Students accepted into the honors program are required to sign a contract with the Honors College stating that they agree to take a minimum of 24 hours of Honors College designated classes. Students must earn an “A” or “B” in each course they take to receive honors credit and to graduate with honors. Of the total 24 credit hours of required honors courses, six hours must be taken at the junior or senior level. Most CLS honors students have only upper division honors credits remaining when they enter the program at the beginning of their junior year. CLS students in the university’s honors program are able to pursue graduation with highest honors, provided they write a senior thesis and complete a senior project.

Prior to registration each semester, all honors students are required to be advised by a staff member of the university’s Honors College as well as a CLS faculty honors course mentor. Continued honors advisement is necessary to ensure students are making progress toward completion of their honors requirements.

DEVELOPMENT OF THE TTUHSC CLS HONORS PROGRAM

For a CLS course to hold the distinction of an honors course, the course director must include a higher level component in their course, such as a topic-related project. Honors students are required to complete the regularly assigned work in addition to investing time outside of class to complete the assigned honors project. The faculty course director mentors and advises the honors students as they perform their projects. The project assigned to the student usually is broad enough in detail and requirements to involve more than one course and may take up to two semesters for completion and presentation of results.

Since the implementation of the TTUHSC CLS honors program, four classes of CLS students have completed a variety of unique honors projects. Each project was designed to represent the same amount of student effort, time, depth, and uniqueness. A vital role of the CLS faculty mentor is to serve as a liaison between the CLS honors students and any physicians and clinical staff not directly affiliated with the TTUHSC CLS Program who volunteered to participate in the project. The following are examples of projects that were found to be broad enough in complexity and detail, but unique enough to stimulate student interest and give the honors student a greater appreciation of CLS and the medical community.

Example 1. Investigation of autopsy methods

One group of honors students enrolled in the TTUHSC CLS program completed a project investigating autopsy methods. The project included library research, reading assignments, observation of one or more autopsies, the reporting of findings, writing a thesis, and giving an oral presentation. Students assigned to this project worked individually as well as within a group. The project included some assistance and instruction from physicians and staff in the Department of Pathology at TTUHSC as well as the county medical examiner. The willing cooperation of the pathologists and the pathology department was vital to the success of this project. The students were allowed to observe select autopsies at the forensic pathologist’s discretion, with the understanding that students arrived on time for the scheduled autopsies. The following textbook was provided for students assigned to this project: Hutchins GM. Autopsy Performance and Reporting. Northfield, IL: College of American Pathologists; 1990.

Textbook readings were assigned by chapter and date. Students were required to hand in a two to three page summary of each chapter assigned. Summaries were formatted in narrative form. At the conclusion of the project, a comprehensive written thesis was required as a group effort. The format of the thesis, highlighted in Table 1, included an extensive bibliography of the subject, summaries of each assigned chapter, a report on the history and purpose of autopsy, general autopsy procedures, personal observations of an autopsy, a case study of a selected autopsy including an official autopsy report worksheet, and conclusions.

At the end of the second semester, the students were also required to present their thesis orally to an audience that included peers, CLS faculty, participants from the pathology department, and administrators from the Honors College.
Example 2. The practice of clinical and surgical urology
The second project involved the investigation of a clinical urology practice and common surgical urological techniques. An urologist and his staff allowed students to shadow the physician during his daily rounds at the clinic. The urologist allowed the students to observe several surgeries, in addition to serving as mentor in the participants’ education in urological surgical techniques.

Honor students assigned to this project were required to complete a set number of physician shadowing hours as well as observe one or more urology-related surgeries. This provided the opportunity to observe how a specialist’s clinic operates and the duties of an urologist. Students were encouraged to keep a journal to record their observations. During their personal observation period, students were directed to pick an interesting case study to work-up and include in their final report. Urology text books and additional references were provided by the urologist and made available to the students. As part of the urology project, students were required to complete a literature review on the history of urology, surgical techniques for removal of kidney stones, and renal transplantation techniques. Students were allowed to work on this project individually and as a group. To ensure timely completion of the project and the continuous flow of topic research materials, students were given a schedule of dates and times to meet with the CLS faculty advisor to submit completed sections of the project.

The case studies selected by the students and their physician mentor focused either on kidney stone surgery or a renal transplantation. The importance of maintaining patient confidentiality in their written report and oral presentation was emphasized. The students’ case study report was required to include a case history including age, sex, initial clinical history and physical findings of the patient, laboratory results, and other supporting diagnostic information. In addition, case studies were to include the patient diagnosis, the basis of diagnosis, a brief explanation of the selected patient’s disorder, and the patient’s treatment and prognosis.

As with other honors projects, reference book research and written summaries were assigned by topic and date of completion. At the completion of the project assignment students presented a written thesis that was required to be a minimum of 100 pages. The required format of the written thesis and presentation are listed in Table 2. In addition, an oral presentation was given to an audience as above.

Example 3. The use of surgical robotics in the treatment of urological disorders
The third project was based on computer and surgical robotics used in surgery to correct urological disorders. Students shadowed physicians on their daily clinical rounds, observed patients in a clinical setting, and viewed surgical techniques that involved computer interfacing with surgical robotics. Honors students selecting this project were assigned a research thesis and an oral presentation that included an extensive literature search and bibliography, sections on the general history of urology, the history of surgical robotics, and renal disorders corrected with surgical robotics. Each student had the opportunity to include in the thesis a case study

Table 1. Required format of autopsy thesis
A. Title page (including all student names)
B. History and purpose of autopsy
C. Autopsy procedures
D. Discussion of observations
E. Discussion of autopsy reporting
F. Autopsy report worksheet case studies
G. Chapter summaries
H. Conclusions
I. References
J. Hard copy of PowerPoint™ presentation

Table 2. Required format of renal surgical techniques thesis
A. Title page (including all student names)
B. Table of contents
C. History and purpose of urology
D. Renal stone and transplant-related disorders
E. Common urology procedures of stone treatment and transplantation
F. A discussion of observations
1. Physician shadowing
2. Surgical procedures
G. Related case study
H. Conclusions
I. References
J. Hard copy of PowerPoint presentation
workup of an actual pathologic case that was corrected by robotic techniques. The highlighted case study was required to include all of the components previously described. The required format of the written thesis and presentation are shown in Table 3.

**BENEFITS OF AN HONORS PROGRAM**

Being a CLS honors student places the student on an academic track that provides many benefits not available to the typical CLS undergraduate student. At TTUHSC, Honors College students experience an elevated level of education in which they are personally involved and receive exposure to a stimulating academic environment. By working on their assigned projects, they have the opportunity to participate closely with professors and clinicians. The honors students have increased access to non-academic medical professionals in private practice who take a personal interest in them and their medical education. They are encouraged to pursue cutting edge topics outside of the normal CLS class routine that will broaden their academic horizons. A CLS honors education requires more intensive writing and increased active engagement in the learning process.

Access to information and opportunities not readily available to the typical undergraduate student is another benefit. All honors students have access to information about education, travel, scholarships, and intellectual opportunities across the nation and in other countries. A support system is available to help with application to competitive national scholarship programs or for financial support in the pursuit of further research opportunities. In addition, these students enjoy special benefits at the university library, access to an honors student computer laboratory, and guaranteed first day registration for classes.

In the typical TTUHSC CLS classes, at least one third of students declare themselves as pre-med and begin application to medical school upon graduation from the CLS program. The majority of our pre-med students apply for medical school admission during their senior year with the intent to enter medical school the fall after their graduation from our CLS program. Working closely with TTUHSC’s medical school, Honors College students can take advantage of an early acceptance program. This program allows these students to waive the Medical College Admissions Test and to apply to TTUHSC’s School of Medicine (SOM) before they complete their junior year if they demonstrate excellent academics. Successful early acceptance applicants are notified of their acceptance into the SOM in late January, and complete their baccalaureate degree prior to admission into the SOM. Criteria of a successful applicant in the early acceptance program include entrance into the university’s Honors College as a freshman, in-state residency, and a composite score of at least 1300 on the SAT or at least 29 on the ACT. It has been observed in our program that involvement in the Honors College actually enhances the honors student’s chance of successful admission into medical school.

Participation in a scholastic honors program not only benefits our CLS students but also benefits the CLS program as a whole. Being involved in the university’s Honors College program gives the CLS program a higher level of academic credibility for scholarly activity and serves as an excellent recruiting tool. By serving the academic needs and requirements of honors students, the CLS program attracts students with higher levels of scholastic preparedness and increases overall student enrollment. Many top pre-med students have been honors students who majored in the biology or chemistry disciplines. By offering junior and senior level clinically-based honors classes in the CLS curriculum, many of the honors students who desire a clinical education at the undergraduate level choose CLS as their major. CLS faculty have the satisfaction of knowing that these students will not only become exceptional clinical laboratory scientists and ambassadors, but also exceptional doctors whose first love is the clinical laboratory.

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**Table 3. Required format of renal surgical robotics thesis**

A. Title page (including all student names)
B. Table of contents
C. General history and purpose of urology
D. History of the use of surgical robotics
E. Renal disorders corrected with surgical robotics
F. Urologic surgical procedures using robotics
G. Discussion of observations
   1. Physician shadowing
   2. Surgical procedures
H. Related case studies
I. Conclusions
J. References
K. Hardcopy of PowerPoint presentation
CONCLUSION
The CLS honors program recruits, retains, rewards, and enriches the intellectually curious and academically capable student through participation in a variety of clinical research projects and learning experiences. These students have entered the institution’s Honors College at the freshman level having met the university’s high academic standards. The benefits of this program are shared by the students, the faculty, and the academic program itself. The TTUHSC CLS honors students strengthen the program by exploring, defining, and pursuing unique clinical opportunities in a way that will maximize their academic and personal growth.

The faculty in the TTUHSC CLS program have designed projects that not only challenge honors students, but provide new opportunities to interact with and observe other medical professionals. Students learn writing and presentation skills that would ordinarily be reserved for graduate education. By providing educational experiences such as forensic autopsy procedures, physician shadowing, and the observation of cutting edge surgical techniques, these students are able to more than meet the requirements needed to graduate with highest honors.

Honors students receive a broader medical education than the traditional CLS student and are encouraged to develop self-discipline and to engage in self-directed learning. CLS honors students continue to enjoy all of the perks of being a member of the Honors College. Faculty share the opportunity for growth and mentor students as they learn the newest advances in the medical profession. Finally, the CLS program collectively benefits by providing unique experiences to unique students who learn to think “outside the box”. Honors College educational programs that require extra time, imagination, and opportunities are worth the investment.

ACKNOWLEDGEMENT
We thank Mr. Joel Walker with the Texas Tech University Honors College for his guidance and cooperation with our CLS program and honors students. His willingness to work with our students is greatly appreciated.

REFERENCES
This paper reviews antiphospholipid syndrome (APS), also known as Hughes syndrome, which is a potentially life-threatening auto-immune disorder where the body produces antibodies directed toward phospholipids and phospholipid-binding proteins. Diagnosis of this syndrome relies on both clinical and laboratory criteria. Laboratory testing used for diagnosing APS includes coagulation assays for the detection of lupus anti-coagulant (LA) and enzyme-linked immunosorbent assay (ELISA) for antiphospholipid antibody (APL) detection.

**ABBREVIATIONS:** APL = antiphospholipid antibodies; APS = antiphospholipid syndrome; APTT = activated partial thromboplastin time; β₂-GPI = beta₂-glycoprotein I; dRVVT = dilute Russell’s viper venom time; ELISA = enzyme-linked immunosorbent assay; Ig = immunoglobulin; KCT = kaolin clotting time; LA = lupus anti-coagulant.

**INDEX TERMS:** antiphospholipid syndrome; antiphospholipid antibodies; laboratory techniques and procedures; lupus anti-coagulant.

 APS, which was first described by Graham Hughes in 1983, is an auto-immune disorder that is characterized by the presence of APL, arterial and/or venous thrombosis, and repeated pregnancy loss. The syndrome is categorized as primary or secondary based on whether it occurs alone (primary APS) or in the presence of other diseases (secondary APS), primarily auto-immune disorders such as systemic lupus erythematosus. Patients with APS progress seldom to the catastrophic form of this disorder which is characterized by multiple organ infarcts transcending to multiple organ failure within days. The syndrome is more commonly noted in young to middle-aged adults and exhibits a female predominance. APL can occur in connective tissue disorders, infectious disease states such as syphilis and AIDS, and may be drug induced. They can also occur incidentally in healthy individuals and as a result, APL are considered clinically significant only when present in APS.

**Mechanisms of pathogenicity**

In APS, APL consist of LA, anticardiolipin antibodies, and anticardiolipin antibodies that recognize specific target molecules such as beta₂-glycoprotein I (β₂-GPI), prothrombin, protein C, protein S, and annexin V. The exact mechanism in which these antibodies cause or promote thrombosis is not known; however, it is clear that multiple mechanisms are involved. One study was aimed at determining the IgG subclass distribution of anticardiolipin and anti-β₂-GPI antibodies and the clinical manifestations of each subclass. This study found that different IgG subclasses (anti-β₂-GPI IgG₂, anti-β₂-GPI IgG₃, anticardiolipin IgG₂), which differ in their effector functions, were associated with the same syndrome manifestations (arterial and/or venous thrombosis and fetal loss). A second study investigating the genetics of β₂-GPI, a naturally occurring anticoagulant, found that β₂-GPI concentration varied in healthy populations and even identified β₂-GPI congenitally deficient siblings. Interestingly, the siblings did not exhibit a history of thrombotic episodes. This leads to the conclusion that thrombosis in patients with anti-β₂-GPI antibodies can not be explained merely by the secondary β₂-GPI deficiency caused by circulating APL.

It is theorized that these antibodies bind cell surface phospholipids or phospholipid-binding proteins, thereby interfering with the clotting process or promoting it. Some of the proposed mechanisms of pathogenicity are stimulation of...
platelet function, interference with the function of phospholipid-binding proteins, and activation of endothelial cells. APL stimulate platelet function by binding to their phospholipid surface membranes. During platelet activation, there is an increase in exposure of anionic phospholipids on the external cell membrane, making them more reactive to APL and creating a repetitive cycle of activation and spontaneous aggregation. β2-GPI and annexin V are serum phospholipid-binding proteins that are believed to be naturally occurring circulating anticoagulants. Both bind endothelial cell surface anionic phospholipids rendering them unreactive for coagulation reactions. APL directed at these proteins interfere with their anticoagulant abilities and result in a procoagulant state. Activation of endothelial cells by APL causes upregulation of the expression of adhesion molecules (E-selectin, intracellular adhesion molecule-1 and vascular cell adhesion molecule-1) and secretion of cytokines (interleukin-1, and interleukin-6) promoting adhesion and inflammation. Obstetric complications of APS include fetal death, pregnancy-induced hypertension, intrauterine-growth retardation and fetal heart block and are a result of thrombosis in the vasculature of the uterus and placenta.

Clinical features
As previously stated, APS is characterized by arterial and venous thrombosis and consequently clinical features of the syndrome can vary widely and can involve any organ system. The features for both primary and secondary APS

Figure 1. Definitive diagnosis of APS*

* Modified from the “Criteria for the classification of definite antiphospholipid syndrome” †
† Pregnancy morbidity must fall in the following categories:
1. One or more unexplained death of a normal fetus at or beyond the tenth week of gestation
2. One or more premature births of a normal neonate before the thirty-fourth week of gestation due to severe preeclampsia or severe placental insufficiency
3. Three or more unexplained consecutive spontaneous abortions before the tenth week of gestation with parental chromosomal and maternal anatomic or hormonal causes excluded
‡ Antibodies must be present on two occasions tested at least six weeks apart

‡ Antibodies must be present on two occasions tested at least six weeks apart.
are identical. Features involving the central nervous system most commonly include stroke, and less commonly cerebral dysfunction that can range from poor concentration or forgetfulness to severe dementia. The more important cardiac features of APS include manifestations of coronary artery disease (atherosclerosis and myocardial infarction) and valve disease which presents as vegetative masses and valvular wall thickening. Hypertension, present in 70% of patients, caused by renal and/or pulmonary involvement is a major clinical feature of APS. Manifestations that cause hypertension include pulmonary embolism, renal artery thrombosis and intrarenal vascular lesions. Skin features most frequently include livido reticularis, a purple-mottled fishnet pattern of the skin, and skin ulcers.

Mild to moderate thrombocytopenia, with platelet counts that range from 50-100 x 10^9/L, is present in 25% of APS patients but is rarely severe enough to cause bleeding. Other hematologic features include hemolytic anemia and a positive direct Coombs’ test. The primary and most significant obstetric complication is fetal loss occurring in the second and third trimester; however, it is not uncommon for the loss to occur in the first trimester.5

Diagnosis
Consensus criteria for the classification of definite APS were developed during the Eighth International APS Symposium held in Sapporo, Japan in 1998. Initially designed for selecting patients for research protocols, these criteria are commonly used for definitive diagnosis of APS. Keeping in mind that the criteria are not inclusive of all of the clinical manifestations known to occur in APS, a diagnosis can still be made if a patient demonstrates clinical features despite not meeting the criteria exactly. Definitive diagnosis is confirmed by the presentation of at least one clinical and one laboratory criterion as seen Figure 1.11

Laboratory testing
Laboratory diagnosis is based on detection of LA or moderate to high levels of IgG or IgM cardiolipin antibodies. Results should be positive on two or more occasions, at least six weeks apart, because APL levels have been known to rise, fall, and even disappear.5 Testing is indicated in all patients with spontaneous venous thrombosis, young patients (under 50 years) with stroke or arterial thrombosis, and in women with three or more consecutive pregnancy losses.12

It is recommended that LA be initially screened using tests such as modified activated partial thromboplastin time (APTT), kaolin clotting time (KCT), and dilute Russell’s viper venom time (dRVVT). In vitro, LA interferes with the phospholipid dependent steps of coagulation thus producing prolonged results. If results are prolonged, mixing studies with normal plasma (APTT) and correction procedures (KCT, dRVVT) should be performed to determine whether the results are due to an inhibitor or factor deficiency.12

Anticardiolipin antibodies are detected using solid phase enzyme-linked immunosorbent assays (ELISA) coated with cardiolipin. These tests permit diagnosis of APS when LA is absent or if its presence can not be established (due to oral anticoagulation).12 More specific testing, ELISA for the detection of β2-GPI, may be required for a reliable diagnosis in the presence of infection or other diseases known to produce APL.13 Retesting by a different laboratory may be indicated in patients with symptoms indicative of APS but who demonstrate negative or equivocal results because interlaboratory variation of test results can be high. One study undertaken to determine the variability of anticardiolipin assay results of 20 positive samples among ten laboratories revealed a mere 55% result concurrence. Their study results were found to mirror the results noted in the 2003 College of American Pathologists ACL-B survey for anticardiolipin antibody proficiency testing where an 80% consensus was reached for only five of the nine (55%) samples distributed for testing.14

Treatment and prognosis
Because it is not known if or when a thrombotic event will occur in patients with detectable levels of APL prophylaxis is not generally prescribed. Once a thrombotic event does occur, initial treatment with heparin followed by life-long oral anticoagulation with a target international normalized ratio (INR) of 3.0-3.5 is initiated.13 Successful medical management relies on the prevention of future thrombosis. Pregnant women with APS are commonly treated with subcutaneous heparin because it does not cross the placenta. Low dose aspirin can also be used in addition to heparin up until the thirty-fourth week of gestation.9

Prognosis of APS is influenced by the severity and recurrence of thrombosis. Clinical manifestations of the syndrome that are associated with a poor prognosis include pulmonary or renal hypertension, cerebral ischemia, and myocardial infarction. If APS progresses to the “catastrophic” form, the prognosis is worse still. The catastrophic form of APS carries a mortality rate of 50% and most patients die from cardiac or respiratory failure.13 Conversely, prognosis in pregnant
women can be favorable when treatment is started immediately upon pregnancy confirmation.

Summary

APS is a disorder that is characterized by the presence of APL, recurrent thrombosis, and fetal loss. It can occur in the absence of disease (primary APS) or in combination with other diseases (secondary APS). The exact pathogenic mechanism in which these antibodies cause thrombosis is not known; however, several hypotheses have been proposed such as activation of platelet and endothelial cells and interference with $\beta_2$-GPI. Clinical features of the syndrome may include stroke, livido reticularis, cardiac-valve disease, pulmonary embolism, thrombocytopenia, and hemolytic anemia. Diagnosis is based on the presence of at least one clinical and one laboratory criterion. Clinical criteria include one or more thrombosis events in any organ, unexplained miscarriages at or before ten weeks of gestation, one or more premature births before 34 weeks of gestation, or three or more spontaneous abortions before ten weeks of gestation. Laboratory criteria include medium to high positive IgG or IgM anticardiolipin antibodies or detection of LA. Tests utilized to diagnose APS include coagulation assays (APTT, KCT, dRVVT) and ELISAs for the detection of cardiolipin and $\beta_2$-GPI antibodies. Unfortunately, the risk of thrombosis can not be predicted, and therefore treatment is not initiated until a thrombotic event occurs. Indefinite anticoagulation is prescribed once a thrombotic event occurs and anticoagulation therapy during gestation is prescribed to those with a history of recurrent spontaneous abortion. Prognosis primarily depends on the severity of the clinical manifestations. Some manifestations that confer a poor prognosis are pulmonary embolism and cerebral and myocardial ischemia.

REFERENCES

Molecular techniques are playing an ever-increasing role in all areas of anatomic and clinical pathology. The field is currently in need of well-trained technologists in this area of the clinical laboratory who are situated to bridge the current state of practice and the continuing developments in high complexity testing. For the close term, use of “home-brew” and analyte specific reagents (ASR)-based tests will require well-trained personnel with strong biomedical science backgrounds and a thorough understanding of technologies used in assay development. Here, we discuss the selection and evaluation of molecular diagnostic training preceptor sites and tasks indicated for trainees that most meet the needs of the newest facet of the laboratory. We present evaluation tools developed over the course of four years of clinical education used to assess practical performance of trainees in a molecular diagnostic pathology laboratory and conclude with considerations for future training of laboratory technologists.

**ABBREVIATIONS:** ASR = analyte specific reagents; BMC = below minimum competency; DMS = diagnostic molecular scientist; MSMP = Master of Science Program in Molecular Pathology; NAACLS = National Accrediting Agency for Clinical Laboratory Sciences; PAS = performs above standards; PCR = polymerase chain reaction; TTUHSC = Texas Tech University Health Sciences Center.

**INDEX TERMS:** clinical education; molecular; training.

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Over the past few years, the clinical laboratory has seen an explosion in the number of tests based upon DNA and RNA analysis. For the first time in the history of the diagnostic laboratory, molecular pathology is extending the range of information available to physicians, research scientists, and other health professionals. The completion of a draft sequence of the human genome and the wealth of technology to arise out of that effort has moved from the research bench to the clinical laboratory bench with swift success. It is now commonplace for a molecular diagnostics laboratory to have the capability to provide diagnostic services ranging from the analysis of the fundamental genetic makeup of an individual which indicates the development of a pathology later in life1-3 to the ability of a physician to monitor the response of an individual to therapy4 to the determination of viral load5 or a nascent public health concern6.

A problem unique to this area of practice is the paucity of FDA-approved assays currently on the market. The majority of molecular diagnostic assays currently exist as ASRs or as in-house developed “home-brew” tests, original and unique to a facility. The complex nature of molecular diagnostic testing and the nature by which testing is brought to fruition therefore requires that technologists have not only well-developed clinical laboratory skills, but also a strong background in basic molecular biology and genetics. Individuals trained specifically in molecular diagnostic testing are uniquely situated to bridge the gap between the current state of practice in the clinical laboratory and an area expected to continue rapid growth over the next few years. The goal of molecular diagnostic practice is to enhance the value of clinical laboratory services by providing an environment in which new tests can be developed, validated, and implemented in practice based on the application of knowledge and new techniques at the most basic biological level.

To address this particular need, a graduate-level Master of Science Program in Molecular Pathology (MSMP) was devel-
oped in the Spring of 2001 within the Department of Laboratory Sciences and Primary Care at the Texas Tech University Health Sciences Center (TTUHSC) School of Allied Health Sciences. The program was developed with a focus on training technologists who are well-prepared to step into bench- and higher-level roles in a molecular diagnostics laboratory, with a strong emphasis on clinical skills. The curriculum was developed to meet the standards set forth by the National Accrediting Agency for Clinical Laboratory Sciences (NAA-CLS) for the diagnostic molecular scientist (DMS). To date, the MSMP program at TTUHSC remains the only graduate program to have been granted accreditation by this body (2004). Briefly, the didactic portion of the curriculum consists of courses in cell biology, biomedical ethics, pathophysiology and human molecular genetics, and training in high complexity molecular biology methods specific to the diagnostic environment. Students receive hands-on training in molecular diagnostic methods and clinical assays in a functioning clinical molecular pathology laboratory at TTUHSC during the entirety of the program as a complement to classroom instruction. The program concludes with clinical training at one of ten affiliated institutions performing molecular diagnostic testing in a Clinical Laboratory Improvements Act and College of American Pathologists-accredited facility (the exception is a combined rotation at two sites). The purpose of this article is to present tools that may be used for evaluation of student performance at clinical training sites.

The MSMP program currently enrolls a maximum of 16 students per year. To date, a total of 33 students have graduated from the program and 16 are enrolled for 2005-2006. This is hardly adequate to address the shortage of well-trained personnel and projected shortfalls in the laboratory sciences. However, a small class size does ensure a very high level of technical training and depth of understanding of basic biomedical concepts upon graduation. The ultimate goal of the program is the production of individuals who are capable of stepping into, at the very least, a bench position and more likely, a supervisory position in the laboratory upon graduation.

With the exception of reference laboratories and very large hospital systems, it is not common for a molecular diagnostics laboratory to offer a menu of services that spans the range of services commonly regarded as the scope of molecular diagnostics and pathology. Briefly, this includes human identity testing, hematology/oncology, genetics, and infectious disease/microbiology, and the associated technologies of each. The scope of molecular diagnostic practice coupled with the ever-changing technological innovations initially made selection of training sites a challenging task. During the first two years of the MSMP program, every effort was made to select sites that had a comprehensive test menu, including at least one test from each of the previously mentioned areas of practice. It was decided that this strategy was largely ineffective, primarily because the test volume of an individual laboratory was not high enough in any one area to adequately train students beyond the level of a bench technologist. We found that an assay may have only been run one time in an eight week period and rarely led to the discussion of higher-level considerations of a technology or the special clinical considerations unique to the test.

<table>
<thead>
<tr>
<th>TASK</th>
<th>BMC*</th>
<th>PAS†</th>
<th>N/A‡</th>
<th>Comments</th>
<th>Instructor initials</th>
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Legend for Tables 1, 2, 4:
* performs below minimal competency
† performs at or above minimal competency/above standards
‡ not applicable
Not surprisingly, it was found that at sites specializing in only one type of testing (e.g., infectious disease), the depth of knowledge gained by students far exceeded that of their peers. Because the profession is highly technology-oriented, it has been most effective to train technologists with this in mind, regardless of the clinical condition being assayed. The nature of molecular diagnostics laboratories across the nation is varied with regards to the areas of testing offered by a given facility. However, the technology platforms used in testing are relatively constant, regardless of clinical condition. Currently four of our affiliates offer a comprehensive test menu, i.e., one that spans the spectrum of disease. We therefore found it important to develop standardized tools that would provide a comprehensive assessment of the training provided and student performance during the clinical rotation. This unique perspective on training has allowed us to better resolve the difficulty associated with the diverse climate of molecular diagnostic training and ensure that all students acquire the same level of competency upon graduation. This is a philosophy shared by NAACLS, as reflected in the July 2005 revision to standard 9B2 in the DMS training criteria.

Each student is evaluated on performance and professional skills by the clinical training site. In turn, the students provide feedback on their experience. Together, this information is used to assess the clinical competency of each student and to further refine the MSMP program. All students are evaluated on areas of basic competency in molecular diagnostic practice: nucleic acid extraction and quantification, reagent preparation, gel preparation, polymerase chain reaction (PCR) preparation, probe preparation, and assay quality control. It is required that all students perform these tasks during the course of testing (Table 1). Additional required tasks are enumerated in Table 2. These skills are evaluated as they relate to specific areas of practice – genetics, oncology and/or microbiology/infectious disease.

A score of “performs above standards” (PAS) or “below minimum competency” (BMC) is assigned in each category and comments are solicited from the clinical instructor, as appropriate. These task lists refer back to the objectives set forth in the NAACLS DMS standard and by those developed specifically in the MSMP program relating to clinical training with criteria for evaluation of performance. Table 3 contains our current training sites and the areas of testing provided at each. Tables 1 and 2 describe the areas of laboratory competency assessed at the training site for each student.

Overall, student performance evaluations indicate a high level of affiliate satisfaction with student training upon completion of formal coursework and upon completion of clinical training. To date, the external certification rate for all graduates taking either the CLSp(MB) or (MP)ASCP exam is 100%. All training sites evaluated trainees using the worksheets represented in Tables 1

Table 2. Molecular pathology student task list: specific discipline

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<th>TASK</th>
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<td>Sequencing</td>
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<td>Viral load</td>
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§ polymerase chain reaction
In 2005, all students (100%) were scored as PAS at all sites. In addition to evaluation of individual trainees and certification rate, affiliate satisfaction can be inferred from offers of employment to graduates upon program completion. In 2005, students were made offers of employment at 66% of affiliated laboratories. Initial selection of affiliates included laboratories in Texas and outside of the state. While the employment outlook for molecular technologists within the state is expected to be positive for the next several years, diverse opportunities for employment within the field are available across the nation. Seeking affiliates at distant sites has also increased awareness of the program among out-of-state laboratory directors and medical centers.

As mentioned previously, the philosophy of the MSMP program emphasizes a focus on technology platform secondary to clinical condition to ensure appropriate training for all students. Provided an affiliate covers all areas of appropriate technology, it is not necessary for all students to receive the same training experience to receive an equivalent training experience. Note that the characteristic common to all sites is an active program of research and development of new assays and validation of new assay platforms. The business climate and very nature of molecular diagnostic testing requires that laboratories investigate the design and validation of novel “home-brew” assays and analyte specific reagents. It was this need for individuals prepared to participate in research and development activities that guided the development of new performance evaluation tools used within the MSMP program. In response to strategic needs of clinical laboratories, we are currently constructing an additional skills assessment checklist to be used for evaluation of research and development tasks. This list will include “home-brew” assay design and validation, crossover study data analysis, and other skills required for implementation of novel testing platforms.

In the first two years of the MSMP program, additional tasks were included for evaluation of students with a focus on Southern blotting and hybridization and PCR. Other technologies were to be enumerated by the affiliate and a pass/fail grade assigned as appropriate. For purposes of evaluating student performance, a brief listing of additional tests performed in a laboratory was adequate. However, we were often unable to determine the specifics of the training provided. We felt that such information would be helpful in refining our clinical training, as well as in making initial assignments of students to sites in future classes that would best “round out” their technical training. Keeping in mind that clinical instructors often have additional job responsibilities and that students may rotate through several instructors in a laboratory, an evaluation task list was constructed to obtain more specifics with a minimal amount of required narrative.

We prepared a separate table of tasks for each practice area: infectious disease, oncology/hematology, and genetics. The skills to be evaluated were common amongst all three areas and now include an area for the instructor to provide the methodology (instrument) and disease tested for each skill, as well as a section for brief comments. An example of this worksheet is provided in Table 2. In the first year of implementation, from these worksheets we were better able to determine the scope of testing in which each student actually participated, areas for remediation and additional study before certification, and the trends of technologies currently utilized in the laboratory. This last point has proven particularly helpful in curriculum development and in strategic planning.

### Table 3. MSMP training sites and areas of testing

<table>
<thead>
<tr>
<th>Clinical affiliate</th>
<th>Genetics</th>
<th>HID*</th>
<th>Oncology</th>
<th>Microbiology</th>
<th>R&amp;D†; new assays</th>
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<tbody>
<tr>
<td>Affiliate 1</td>
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<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Affiliate 2</td>
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<td>Affiliate 3</td>
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<tr>
<td>Affiliate 4</td>
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<td></td>
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<td>X</td>
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<td>Affiliate 7</td>
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<td>Affiliate 9</td>
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<td>X</td>
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<td>Affiliate 10</td>
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</table>

* Human identity testing
† Research and development
Areas of service provided at each laboratory are indicated by an “X”
Because graduates may seek or be expected to step into a supervisory position, additional training in laboratory management was added to the task list in the second year of the MSMP program (2003). The expectation of this training experience is for students to be given an overview of human resources management for the organization, quality assurance and management, laboratory accreditation, and any other supervisory issues the affiliate finds appropriate to discuss. In the first year of implementation in the clinical curriculum, we observed that no clinical training sites addressed management tasks as described in the task list in 2004. This may have merely been due to their position on the task list – they were added at the end of a large table of items. In the most recent revision of evaluation criteria, these competencies were expanded and included as a separate, freestanding worksheet (Table 4). In 2005, 33% of students were evaluated for performance/training in management tasks and 100% were scored as PAS. Emphasizing these tasks as a separate area of focus increased the number of affiliates that addressed these tasks with trainees. It is expected that this number will further increase in subsequent years as we pursue improvements through personal communication with clinical educators.

In summary, narrative commentary from clinical educators has been overwhelmingly positive as it relates to both student performance and structure of evaluation tools (e.g., task lists). Students are demonstrating mastery of laboratory tasks and in most cases exceeding initial expectations. Continuous refinement and utilization of appropriate evaluation criteria are critical to the development of excellence in clinical laboratory education. The implementation of these task lists has provided us valuable data that will allow us to evaluate the quality of student training and plan for future developments in the field of molecular diagnostics.

**ACKNOWLEDGEMENTS**

This work was supported by the Texas Tech University Health Sciences Center Molecular Pathology Graduate Program.

**REFERENCES**


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**Table 4. Molecular pathology student task list: management**

<table>
<thead>
<tr>
<th>TASK</th>
<th>BMC‡</th>
<th>PAS†</th>
<th>N/A‡</th>
<th>Comments</th>
<th>Instructor initials</th>
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<td>Applicant hiring process</td>
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<tr>
<td>Employee performance appraisal</td>
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<tr>
<td>Ordering and purchasing for lab</td>
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<tr>
<td>Sit in on supervisory meeting</td>
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<tr>
<td>Understand quality management program</td>
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<tr>
<td>Maintenance of laboratory accreditation</td>
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<tr>
<td>Marketing strategies</td>
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<tr>
<td>Participation in laboratory meetings</td>
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<tr>
<td>Other</td>
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The following abstracts have been accepted for presentation at the 2006 American Society for Clinical Laboratory Science (ASCLS) Annual Meeting and Clinical Laboratory Exposition to be held July 25 through July 29 in Chicago, IL. The preliminary meeting program was published in the Spring 2006 issue of *Clinical Laboratory Science*. Abstracts are reviewed by appropriate representatives of the ASCLS Abstract Review Committee. They are the final authority in selecting or rejecting an abstract.

Papers and posters will be presented during the following times at the annual meeting. Room assignments will be listed in the final program.

**ORAL RESEARCH AND CASE STUDY PRESENTATIONS**
McCormick Place
Wednesday, July 26, 2006, 2:00 p.m. – 3:00 p.m. and 3:45 p.m. – 5:15 p.m.

**POSTER PRESENTATIONS**
McCormick Place
Tuesday and Wednesday, July 25 and 26, 2006, 10:00 a.m. – 4:30 p.m.; Thursday, July 27, 2006, 10:00 a.m. – 12:30 p.m.

Authors will be present on Wednesday, July 26, 2006 from 1:00 p.m. – 2:00 p.m. to discuss their posters.

**ORAL RESEARCH PRESENTATIONS**

Are Quality Laboratory Services Related to Personnel Credentials?
*Maria D Delost PhD CLS (NCA), G Andy Chang PhD, Youngstown State University, Youngstown, OH; Teresa S Nadder PhD CLS(NCA), W Greg Miller PhD DABCC, William J Korzun PhD DABCC MT(ASCP), Virginia Commonwealth University, Richmond VA.*

Proficiency test (PT) performance provides an objective and consistent evaluation of laboratory quality. A retrospective review of existing PT results (2003) from six clinical laboratories in northeastern Ohio and western Pennsylvania was conducted to determine the relationship of PT performance to the personnel credentials of the testing personnel. Predictor variables were the practitioner’s major area of study, degree, certification, and years of laboratory experience. The sample consisted of 174 testing personnel and 11,233 valid PT results of which there were 11,120 results graded acceptable (99.0%) and 113 unacceptable results (1.0%). Technical problems were the most common type of error reported (35, 31.0%). Logistic regression analysis (n = 11,233, $\chi^2 = 20.416$, $p = 0.002$) with all predictors included revealed that a clinical laboratory major was a statistically significant predictor of successful PT performance ($p = 0.018$). Those individuals without a clinical laboratory major ($\exp \beta = 2.810$) were almost twice as likely to produce an unacceptable result compared to those individuals with a clinical laboratory major. The study supports the hiring of laboratory personnel who have completed a formal clinical laboratory education program. Healthcare facilities should investigate the benefits of partnering with clinical laboratory education programs to maintain quality in the face of personnel shortages.

Grade Inflation in Clinical Laboratory Science
*Shirlyn B McKenzie PhD CLS(NCA), Linda A Smith PhD CLS (NCA), University of Texas Health Science Center at San Antonio, San Antonio TX.*

The purpose of this study was to describe clinical laboratory science (CLS) students’ GPAs in pre-professional and CLS courses over the period 1995-2004. University grading patterns have periodically come under fire because of perceptions of grade inflation. Although there is much anecdotal evidence, there is little empirical data showing that grade inflation is real. In this study, electronic surveys were sent to program directors of the 239 NAACLS-accredited CLS programs. There was a 41% (99) response rate. The survey asked for grade data for classes entering in 1995, 1999, and 2003. Data indicated that average GPA of admitted classes showed an upward trend between 1995 and 2003 with 26% having an average GPA > 3.25 in 1995 and 40% having an average GPA > 3.25 in 2003. Average GPA of the graduating class during this time remained stable in hospital-based programs. However, the percentage of university-based programs reporting an average graduating class GPA > 3.0
increased from 63% to 80%. Hospital-based programs had higher graduating class GPAs than university-based programs. Despite the increase in average admission GPA, <25% of respondents thought students were better prepared for the CLS curriculum. Thus, there appears to be evidence of grade inflation in prerequisite courses and some CLS courses.

Health Professions Workforce Partnership Can Be the Answer
Barry Eckert PhD, Hassan Aziz PhD, Armstrong Atlantic State University, Savannah GA.

With increased demand for clinical laboratory scientists, academic institutions are finding themselves facing a different and a unique challenge. Limited funds and constrained instructional resources such as number of qualified faculty and appropriate laboratory space are forcing educational administrators to seek opportunities outside the traditional operating methods. Armstrong Atlantic State University, together with three healthcare systems in the southeast region of Georgia, established a “Health Professions Workforce Partnership” for the purpose of assessing and responding to health workforce needs in the region. The partnership not only provides a mechanism for communication of current and projected workforce needs but also enables the university to respond through program enhancements. This process results in long term financial benefit to the healthcare systems and has allowed the university to expand its medical technology and other health professions programs. This poster will present the details of the partnership and will illustrate steps taken to establish and maintain this project. With active audience participation, the interactive presentation will conclude with a focused question and answer discussion to explore the prospects and consider potential issues in structuring an ongoing collaborative effort.

Medical Errors and Patient Safety: State Legislation and Recommendations
Leticia J San Diego PhD CLS (NCA), Healthcare Management Development Center, Clinton Township MI.

The issue of medical errors and patient safety is of great importance to Michigan’s Governor Jennifer Granholm and the legislature. A 1999 report by the Institute of Medicine showed that medical error is the eighth leading cause of death and biggest challenge in US healthcare. Public Act 119 was developed and signed into law to create a commission on patient safety. The legislation allows the governor to designate the Michigan Health and Safety Coalition to act as the commission to examine ways to improve patient safety and reduce errors. In an effort to improve patient safety in the state, the commission solicited testimonies and recommendations from the public, professional organizations including the Michigan Society for Clinical Laboratory Science, academia, stakeholders, and experts who are interested in patient safety. Recommendations included a system approach to emphasize that prevention not punishment is the best method, to create a culture of safety within organizations and non-punitive systems for reporting errors, and to establish performance standards for education, licensing and credentialing organizations, and training and implementation of patient safety systems. Diversified approaches and commitment among professional organizations and coalitions will strengthen implementation of initiatives in reducing medical error and provide directions in enhancing patient safety in Michigan.

Methicillin-resistant Staphylococcus aureus in a Texas County Jail
Rodney E Rohde MS SV (ASCP), Texas State University-San Marcos, San Marcos TX; Marilyn Felkner DrPh, Ana Marie Valle PhD, Tamara Baldwin BA, LP (Sky) Newsome CHES, Texas Department of State Health Services, Austin TX.

Methicillin-resistant Staphylococcus aureus (MRSA) in correctional facilities has garnered the attention of public health officials since 2000. This study assessed nasal carriage rate and strain-relatedness of MRSA among inmates incarcerated for fewer than two weeks in a Texas county jail using a cross-sectional design for surveying and obtaining nasal swabs and pulsed field gel electrophoresis (PFGE) to determine strain relatedness. Four hundred three (61.6%) of 654 inmates screened allowed questionnaires and nasal swabs to be collected. One hundred fifteen inmates (28.5%) carried S. aureus. Of the 403 inmates tested for nasal carriage of MRSA, 18 were positive for a carriage rate of 4.5% (95% CI = 2.7-7.1). PFGE identified ten different strains: four subtypes of each other, apparently USA300 (638, 703, 774, 776); two additional strains (775, 800) related to each other but not subtypes of the previous four related strains; and four strains, totally divergent from each other and from the other six strains (773, 799, 805, 772).

This is important because our data suggest that MRSA is endemic in persons coming into correctional facilities. Healthcare workers in correctional facilities should be prepared not only to prevent outbreaks through control of transmission within the facility but to treat MRSA infections that are unrelated epidemiologically arising from exposures prior to inmates’ incarceration.
Nutritional Assessment of Alzheimer’s Patients Using Homocysteine, Folate, and Transthyretin Levels: Laboratory Identification of Alzheimer’s Disease

Eileen Carreiro-Lewandowski MS CLS, University of Massachusetts Dartmouth, Dartmouth MA.

Routine identification of patients suffering from Alzheimer’s Disease (AD) pre-autopsy consists of cognitive assessment, clinical symptoms, imaging studies, and assessment of functional abilities consistent with this type of dementia, often making early differential diagnosis difficult. As part of a clinical trial for therapeutic treatment of AD, 218 clients in assisted living facilities given a provisional diagnosis of AD by their primary care practitioner were initially selected. Each candidate’s medical history was reviewed, and laboratory studies were performed as part of a qualifying physical examination. Participants were further divided based on co-morbidities and other trial exclusion criteria. As expected in an elderly population, there was an increased incidence of increased homocysteine and decreased folate levels. However, in those candidates meeting more stringent criteria for the larger trial, there was also an increased incidence of decreased transthyretin (pre-albumin) levels despite the fact that these clients have meal preparation as part of their care. This case study will review the findings of this data and discuss a possible future role the laboratory may have in the early identification of AD.

Understanding of and Opinions about Licensure for Laboratory Personnel among Laboratory Professionals in the United States

Tim R Randolph, MS CLS(NCA), Kathleen Solomon CLS(NCA), Saint Louis University, St. Louis MO.

The purpose of this study was to ascertain the current understanding of registration, certification, and licensure among laboratory professionals in the US and to determine their views regarding licensure of laboratory personnel. Several threats to laboratory medicine currently exist, upsetting the balance between supply and demand of laboratory professionals. Licensure is one strategy to address these problems. Four hundred thirty two surveys were sent to laboratory professionals throughout the US (72.5%) with a concentration in Missouri (27.5%). Surveys received (70.6%) represented mostly middle aged (63.7% over 40 years old), Caucasian (89.8%) females (83.4%) primarily employed in urban (61.6%) hospital (84.7%) laboratories. Although about half (49.1%) claimed a moderate degree of understanding about registration, certification, and licensure, only 16.9% correctly indicated the number of states with laboratory licensure laws and 50.5% knew the number of other healthcare professions listed that had licensure in most US states. The majority of respondents (57.8%) were in favor of licensure with 19.1% opposed and 23.1% unsure. Nonetheless, 77.7% of respondents are willing to get involved with licensure initiatives at some level. Although there is confusion regarding registration, certification, and licensure, most laboratory professionals favor licensure and are willing to get involved even if unsure.

CASE STUDY PRESENTATIONS

Importance of Patient History in a Case with Antibody to High Frequency Antigen

Christina Thompson, EdD CLS(NCA), Texas A&M University-Corpus Christi, Corpus Christi TX.

A 55-year-old female with a history of anemia was admitted to the hospital for elective surgery. A crossmatch for two units of blood was ordered. The patient tested as O positive with a positive antibody screen at the antiglobulin phase only. All panel cells and units of blood crossmatched were also incompatible at the antiglobulin phase. The patient had not been previously transfused at this hospital and the patient’s history did not indicate previous antibody problems. The sample was sent to a reference laboratory and the antibody was identified as anti-Diβ. After the antibody was identified, the laboratory supervisor informed the doctor of the problem and was informed that the patient knew about the Diego b antibody. The patient was transfused with compatible Diego b negative cells. Although the Diego b antigen is a high frequency antigen, the Diego b negative phenotype is found in increased numbers in the Mexican American and southwest Native American population and occasionally the patients are cognizant of their antibody problems. A recent study also indicated an increased incidence of the Diego antigen in donor population and anti-Diβ in previously transfused patients.

Transfusion-related Bacterial Sepsis

Linda A Smith PhD CLS(NCA), Yvette Esparza BS, University of Texas Health Science Center, San Antonio TX.

Transfusion-related bacterial sepsis is most commonly associated with the infusion of contaminated platelet concentrates. However, contamination of packed red blood cells (PRBC) can also cause this type of transfusion reaction. In cases of
contaminated PRBC, the causative organism is usually a gram-negative rod capable of growing at 1 °C - 6 °C. This case presentation is that of a 60 year old male who was admitted for chronic anemia and complications of femoral bypass surgery. Two units of PRBC were ordered. During the infusion of a unit he developed shaking chills, elevated pulse rate and blood pressure, and a temperature spike to 103 °F. Investigation of the reaction revealed no clerical or patient identification errors or serologic incompatibilities. The initial Gram stain of the unit demonstrated no bacteria. However, culture of the unit grew an organism subsequently identified as *Serratia marcescens*. Despite treatment, the patient expired two days after the incident.

**POSTER PRESENTATIONS**

**An Atypical Antibody Event**

*Paula M Szuflad MS MT(ASCP)SBB, Alan Weiner BS, VA Boston Healthcare System, West Roxbury MA.*

A surgical patient presented for compatibility testing. Results showed a positive antibody screen (AS) and direct antiglobulin test (DAT) negative, consistent with prior results. Four units of compatible red cells were transfused over a period of nine days. On the tenth day after the first transfusion, the patient’s hemoglobin dropped from 11.2 g/dl to 9.3 g/dl, and two units of red cells were requested. At this time, the patient demonstrated a positive AS (2+ reactivity at AHG) and DAT (2+ with anti-IgG). Anti-M was identified in both the serum panel and the eluate. The patient’s pre-transfusion sample tested negative for the M antigen. Two of the four units transfused were confirmed positive for the M antigen. Anti-M is typically found as an IgM class antibody, reactive at room temperature. There are few reported cases of this antibody being involved in delayed transfusion reactions. It is likely that this patient had a pre-existing anti-M that was not detected and that it was re-stimulated by transfusion. The patient subsequently was transfused with two units of M negative, cross-match compatible red cells without incident. Eight days after the antibody was identified, the patient’s AS and DAT reverted to negative.

**Are Different Tests of Platelet Function Comparable When Taking Aspirin?**

*David L McGlasson MS, Michael Chen MD, Z Knight, M Dobbs MD, Wilford Hall Medical Center, Lackland AFB TX.*

The purpose of this protocol was to study platelet sensitivity to aspirin (ASA) resistance with four assays using single doses of ASA. Whole blood (WB) platelet aggregometry was run using collagen and arachidonic acid (AA) as agonists. The PFA-100 system using EPI/COLL cartridges and an AccuMetrics instrument with AA cartridges measured ASA resistance. An ELISA urine method measured the level of urine 11-dehydrothromboxane (11-DHT) in pg/mg creatinine. Fifty normal subjects who met the inclusion criteria were consented into the study. Blood and urine were obtained at baseline and then each subject was given an 81 mg enteric-coated ASA. Twenty-four hours later blood and urine specimens were recollected. In two weeks the process was repeated with a single dose of 325 mg enteric-coated ASA. The results in percent resistance to both concentrations of ASA are as follows:

<table>
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<tr>
<th>DOSE ASA</th>
<th>WB Collagen</th>
<th>WB AA</th>
<th>PFA EPI/COLL</th>
<th>ACCUMETRICS AA</th>
<th>11-DHT</th>
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<tr>
<td>81 mg ASA</td>
<td>74.4%</td>
<td>79.6%</td>
<td>77.0%</td>
<td>83.6%</td>
<td>51.1%</td>
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<tr>
<td>325 mg ASA</td>
<td>28.2%</td>
<td>11.6%</td>
<td>19.1%</td>
<td>14.5%</td>
<td>16.7%</td>
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</table>

There were no statistical or clinically significant differences between the WB assays at either dose of ASA. However, the urine 11-DHT was more sensitive at 81 mg ASA. There were no clinical differences evident in all assays at 325 mg ASA.

**β-2-Microglobulin Compared with Thirteen Other Tumor Antigens for the Serodiagnosis of Pancreatic Cancer**

*Margot Hall PhD FAIC FACB FRACI CChem (MRSC) CPG, Sabrina Bryant, MS MT(ASCP) CLS(NCA), James T Johnson PhD, Slobodanka D Manaveca PhD, Paul Sykes MD PhD, Margaret Jackson MD MT(ASCP), Harold Schultz MS, Raisheeda Crowell, Tammy Sims-Davis, Sharae Johnson, Mary Guo, Wileen Cooksey MT (ASCP), CLS(NCA), Shawn Clinton, MT(ASCP) CLS(NCA), Kevin Beason MT(ASCP) CLS(NCA), Debbie Fortenberry MT(ASCP) CLS(NCA), Cynthia Bright MS, Helen Hua MS MT(ASCP), Jiaron Ying MS MT(ASCP), University of Southern Mississippi, Hattiesburg MS; Kay Hollifield MT(ASCP), Charlton Vincent MD, Laurel Clinic for Women, Laurel MS; Cynthia Wilson MT(ASCP), University Medical Center, Jackson MS.*

The purpose of this study was to compare β-2-microglobulin with 13 other tumor antigens for diagnostic efficacy in pancreatic cancer. With 32,180 new cases and 31,800 deaths estimated during 2005 and an insidious onset, pancreatic cancer is an important pathology in the USA. A non-invasive, early diagnostic method is urgently sought and tumor antigens have been used for diagnosis. Sera from 554 patients (16 pancreatic cancer, 343 other cancers, and 195 non-can-
cer) were assayed for the presence of tumor antigens and the results correlated with diagnoses established pathologically. Immunoassay test kits from Diagnostic Automation (β-2-Microglobulin, NSE, Ferritin, CA242), Hybritech (CEA, CA195), Centocor/FujiRebio Diagnostics (CA125, CA19-9, CA72-4, CA15-3, CA27.29, Cyfra21-1), CIS BioInternational (CA50), and Abbott (AFP) were used to test for the concentration of these antigens. Using the manufacturers’ decision values the following diagnostic sensitivities were obtained: β-2-microglobulin 50.0%, NSE 0.0%, Ferritin 50.0%, CEA 37.5%, CA19-9 66.7%, CA195 100.0%, CA50 66.7%, CA242 66.7%, CA72-4 31.3%, CA125 40.0%, CA 15-3 26.7%, CA27.29 40.0%, AFP 18.2%, Cyfra21-1 26.7%. Diagnostic specificities were > 75%. We concluded that β-2-microglobulin was inferior to CA195, CA19-9, CA50, CA242 but equal or superior to all other markers studied for pancreatic cancer.

Clinical Laboratory Sciences Curriculum Re-development: An Application of Change Theories
Lillian Mundt MHS CLS(NCA)SpH MT(ASCP)SH, Janet Vanik MS MT(ASCP), Rosalind Franklin University of Medicine and Science, North Chicago IL.

Problem and reasons for investigating. Closure of MLT programs has lead to a decline in the availability of associate-degreed applicants. Most prospective students hold an undergraduate degree and express interest in obtaining entry-level skills but desire a higher degree. In 2005, the CLS department awarded no Bachelor’s degrees, with no hope of reversing this trend. Change was imminent in order to guarantee the department’s survival.

Method. The faculty employed multiple models to implement a productive change process. Traditional models no longer served the department’s needs, therefore a transformational model was used. Transformational change includes visioning, market focus, and involving all stakeholders.

Result. The result of this process is the entry-level MS CLS degree (ELM). Offering this program increased enrollment in the CLS department from seven (BS level) to 18 students for the 2005-2006 academic year. All additional students entered the ELM program. The projection for the 2006-2007 academic year is 23 new students.

Conclusion. The CLS faculty recognized external and internal change forces that drive the need for change, applied appropriate change models to implement change and overcome barriers, and transformed the CLS curriculum. The creation of the entry-level masters has saved the CLS department from extinction.

Diagnosis of Invasive Pulmonary Aspergillosis: Molecular vs. Culture
Ryan D McGough MT(ASCP), University of Cincinnati, Cincinnati OH; Deborah Josko PhD CLS(M), SM(ASCP), University of Medicine and Dentistry of New Jersey, Newark NJ.

This work was done to fulfill a course requirement at the University of Medicine and Dentistry of New Jersey.

Invasive Pulmonary Aspergillosis (IPA) is of particular interest to physicians treating immunocompromised and immunosuppressed patients due to its complicated diagnosis and high mortality rates from inadequate treatment. Because of inherent complications with IPA diagnosis from bronchoalveolar lavage (BAL) fluid specimens, and the toxic effects of prophylactic anti-fungal therapy, quicker and more efficient diagnostic methods are necessary. This review focuses on studies that directly compare molecular methods of fungal detection (such as PCR) in BAL fluid to culture, radiograph, computed tomography, and other traditional diagnostic methods in an effort to determine whether sufficient evidence exists for molecular methods to replace these methods in IPA diagnosis from BAL specimens. Several databases were searched and 12 articles were retrieved which passed defined inclusion and exclusion criteria. The results analyzed in this review indicate that many of the intrinsic advantages of molecular based assays, like extremely high functional sensitivity, actually acted to decrease the clinical utility of many of the assays because of problems with contamination and colonization. Thus, to date, sufficient evidence does not exist for molecular methods to replace traditional diagnostic methods in suspected cases of IPA.

The Effect of Ozone on Common Environmental Fungi
William J Korzun PhD, Jeffrey M Hall MS, Ronald L Sauer MA, Virginia Commonwealth University, Richmond VA.

Fungal contamination of occupied buildings can cost building owners large sums of money to remediate and can contribute to a condition referred to as Sick Building Syndrome. One potential form of building remediation is treatment with ozone. This study was designed to test the null hypothesis that there is no significant difference in viability between fungal spores treated with ozone and fungal spores not treated with ozone. Freshly prepared suspensions of Cladosporium spp.,
Stachybotrys spp., and Aspergillus niger spores were diluted and plated onto the surface of solid agar plates. The plates were exposed to room air or to different concentrations of ozone for up to four hours, as were uninoculated plates. All plates were then incubated at 25 °C until quantitative colony counts could be performed. There was a significant ($p < 0.05$) decrease in viable spores of all three fungi, at ozone concentrations of 5.0 – 12.8 parts per million, by four hours of exposure. However, in every case, some spores remained viable even at the highest level of exposure. These data suggest that ozone must be used in conjunction with other methods of remediation in order to eliminate fungal contamination of buildings.

Improved Rapid Fluorescent In Situ Hybridization Protocol for Testing of Newborns for Possible Chromosomal Aneuploidy

PA Lennon PhD CLSp(CG), PHu MS CLSp(CG) CLSp(MB), University of Texas MD Anderson Cancer Center, Houston TX; SW Cheung FACMG, A Patel FACMG, Baylor College of Medicine, Houston TX.

It is often desirable to rapidly determine if a newborn in the NICU is suffering from one of the more common chromosomal aneuploidies, such as trisomy 13 and 18 (or their mosaics), by performing FISH on cultured blood cells or directly on a blood smear. Blood smears, however, cause cells to lie upon one another or especially to fold, causing the fluorescent signals to lie in differing depths of field, leading to error. We present a rapid blood FISH technique for use with the AneuVysion (Vysis: Des Plaines, IL) kit for chromosomal aneuploidies of chromosome 13, 18, 21, X, and Y. We use the hypotonic and cell fixation solutions of conventional cytogenetic blood culture harvest on fresh uncultured blood in a 1.5 ul Eppendorf tube. This allows white blood cells to swell and their DNA to spread, and allows the cells to be dropped onto a slide flat, reducing cell folding. Our technique also increases probe hybridization from 37 °C to 42 °C, so that the locus specific probes for 13 and 21, which usually require six hours for hybridization, can hybridize in only two hours. Turnaround time from sample receipt to reporting is less than five hours.

Integrated Metabolism and Low Carbohydrate Dieting

Lester G Pretlow PhD CLS(CC) NRCC(CC), Medical College of Georgia, Augusta GA.

The enzymatic and regulatory controls of low carbohydrate dieting have been misunderstood. The reason for this investigation was to explain the biochemistry and physiology of low carbohydrate dieting by presenting the key regulatory points of integrated metabolism. Integrated metabolism is defined as the sum of the metabolic pathways required to produce life sustaining energy in the form of ATP. An extensive literature review of the current understanding was conducted and compiled. The investigation addressed the regulation of hormonal control and the enzymatic (allosteric) controls of glycolysis, gluconeogenesis, glycogenesis, glycogenolysis, lipogenesis, and lipolysis. Additionally, hormonal and metabolic processes impacted energy consumption at specific organs – such as brain, muscle, liver, and adipose tissue. The results of this investigation showed that recidivism, the tendency of individuals to regain weight, suggested that adipose tissue may in fact regulate itself through the secretion of leptin, a protein important in regulating body weight, metabolism, and reproductive function. A low carbohydrate environment inhibited lipogenesis. Also, exercise and the utilization of glycogen stores versus lipolysis had different effects on fast-twitch and slow-twitch muscles. In conclusion, this investigation demonstrates that understanding the controls of integrated metabolism can provide knowledge for maintaining health and weight.

An Introductory Pathology Course in a Medical Technology Curriculum

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Medical technology students tend to be detail-oriented. Although this characteristic is essential for performing laboratory work, it presents a challenge to medical technology educators who must ensure that the students assimilate and integrate voluminous factual information into a “big picture”. They must also develop the critical thinking skills that allow students to interpret data and apply it clinically and to be aware that every specimen represents a person. The West Virginia University medical technology program developed a new course, Introduction to Pathology, as a foundation course to encourage the students’ ability to integrate and apply information from all of their coursework. Twenty-seven medical technology students were enrolled in the class the first semester of their junior year. Twenty-four dental hygiene juniors and eleven athletic training seniors also participated in the course, adding an interdisciplinary component. The course was taught by medical technology faculty. Course evaluation included questions rated on a Likert scale. The responses of more than 90% of the class indicated strong agreement that the course helped integrate knowledge from other courses, provided a good foundation for future courses, and was helpful in promoting basic understanding of the body in health and disease.
Investigation of Knowledge and Attitudes of African American High School Students toward Clinical Laboratory Science

Lynda Britton PhD CLS(NCA), Karrie Hovis MHS CLS(NCA), David Irwin PhD, Louisiana State University Health Sciences Center, School of Allied Health, Shreveport LA; Louann Lawrence DrPH CLS(NCA), Louisiana State University Health Sciences Center, School of Allied Health, New Orleans LA.

Currently, there is a shortage of minorities in the health professions and a shortage of clinical laboratory science (CLS) professionals. In their strategic plan, the Coordinating Council on the Clinical Laboratory Workforce recommended recruiting middle and high school students into the CLS profession. A web-based educational module, LabPartners, was designed and tested in New Orleans to recruit middle and high school students into CLS (Haun, Leach, Lawrence, Jarreau, in press). This study tested the knowledge and attitudes of low socioeconomic African American high school students toward clinical laboratory science using the LabPartners module. Twenty-four low socio-economic African American high school students were in both the experimental and control groups. Each group was tested for prior knowledge and attitude toward CLS. The experimental group was presented the web-based instructional module and tested for post knowledge and attitudes. We found a statistically significant difference in the subjects’ knowledge of CLS ($p < 0.05$) but not in their attitudes towards the CLS profession ($p > 0.05$). The LabPartners educational module is a useful tool for exposing students of different ethnicities to CLS but may not be sufficient to influence their career choices.

A “Proficiency Assessment Process” for Clinical Hematologists

Linda C Beck PhD MT(ASCP), Kimberly Rainbow Parra MS MT(ASCP) CLS(NCA), Virginia Commonwealth University/Medical College of Virginia, Richmond VA.

Training and proficiency assessment of new employees in the performance of the manual leukocyte differential is a challenge faced in the clinical hematology laboratory. The test’s complexity and interpretative nature, combined with the current shortage of job applicants holding degrees and/or certifications in clinical laboratory sciences, augments this challenge. Little published guidance is available on the subject of proficiency testing tools. The intent of this project was to develop a “proficiency assessment process” that is more applicable for use in the current laboratory workforce environment. The process consists of a two tier evaluation system, ensuring proficiency in normal morphology before progressing to tier two, abnormal morphology evaluation. Tier one was developed and contains ten peripheral blood smears of normal morphology, with corresponding case histories and related study questions. An answer key was developed by four “expert” hematologists and the results formulated into graphs. Ten employees with fewer than two years experience participated in the project. They plotted their results for a visual representation of their competency. A questionnaire was completed to evaluate the effectiveness of the tool. In conclusion, the rating for the proficiency assessment tool was positive and the answer key graphs worked well for the intended use.
Urinary 11-dehydrothromboxane B2 Levels in Healthy Individuals Following a Single Dose Response to Two Concentrations of Aspirin

David L McGlasson MS, Michael Chen MD, Z Knight, M Dobbs MD, Wilford Hall Medical Center, Lackland AFB TX.

The purpose of this protocol was to determine the aspirin (ASA) effect on urinary 11-dehydrothromboxane B2 levels (11-DHT) in normal individuals who ingested a single dose of aspirin. Fifty normal volunteers over 18 years of age that had not ingested aspirin or other NSAIDs for 14 days were enrolled in this study. Each subject had a baseline urine specimen obtained and was then given an 81 mg enteric-coated ASA. Twenty-four hours later a second urine was obtained. Two weeks later the process was repeated with 325 mg enteric-coated ASA. Platelet function was assessed using an ELISA 11-DHT kit. Aspirin response was established by determining a 50% difference of the levels of 11-DHT from baseline and 24 hour specimens with both concentrations of ASA. Twenty-two of the 48 subjects of the 81 mg ASA group showed ASA sensitivity (46%). Forty of the 46 (85%) of the subjects that finished the 325 mg dose displayed an ASA response. The 325 mg ASA dose shows a significantly greater platelet response sensitivity. Previous studies have shown that non-responders to ASA have a greater risk of cardio-vascular problems. However, do we know if normal subjects taking ASA are protected?

Young Adults’ Perceptions of an Ideal Career and a Career in Medical Laboratory Science

Christine G Griffin MS MT(ASCP)SH, Mary Val Palumbo DNP APRN, University of Vermont, Burlington VT.

The purpose of this study was to explore young adults’ perception of an ideal career compared to a career in medical laboratory science in order to develop an effective recruitment campaign in the state of Vermont. Many strategies are currently needed to address the shortage of competent medical laboratory scientists. Subjects were invited to participate at various locations throughout Vermont. All 720 subjects, ages 18 to 24, completed the ideals career section and of these 720 subjects, 120 subjects also answered questions specifically about a career in medical laboratory science while the remainder answered questions about five other healthcare careers. The instrument developed by May and others (1991) measures 18 items on a five point Likert scale and has been tested for reliability in previous studies. The significant differences found between ideal and medical laboratory science careers were appreciation, respect, job security, and a safe workplace. Characteristics most important to an ideal career were respect and appreciation, whereas the respondents identified that “using your brain”, “knows a lot”, and “working with high technology” most strongly described a medical laboratory science career. The findings of this study suggest a recruitment campaign that highlights a medical laboratory scientist as a respected and appreciated professional.

2007 Annual Meeting Abstract Deadline

The deadline for abstracts for oral or poster presentations of research or case studies at the 2007 ASCLS Annual Meeting is January 15, 2007. Submission instructions and the proposal form may be found at www.ascls.org/conferences. The completed proposal form and abstract must be submitted electronically by the deadline.

The 2007 Annual Meeting will be held July 17-21 in San Diego, California. Additional meeting information will be available at the ASCLS Conferences webpage.
The association between Down syndrome and acute myelogenous leukemia (AML) has been well documented.\textsuperscript{1,2,3} AML in Down syndrome is usually a specific type of megakaryoblastic leukemia (M7, AMKL).\textsuperscript{1} A myelodysplastic syndrome generally precedes this malignancy. Down syndrome patients with AMKL have a much better prognosis than other children with AML.\textsuperscript{5}

A case study of a 22-month-old female with Down syndrome and myelodysplastic syndrome of a megakaryoblastic lineage is presented here. Upon admission to a pediatric hematology/oncology clinic, flow cytometry results reported a distinct population of phenotypically abnormal myeloblasts expressing myeloid antigens and the immature cell markers.

The patient was placed on a national research group study and began chemotherapy treatment. To date she has received two courses of cytarabine (ara-c) and daunorubicin therapy, which were tolerated well, and is awaiting her third course. Her blood counts stabilize for a while after treatments and her prognosis is good.

**ABBREVIATIONS:** AMKL = acute megakaryoblastic leukemia; AML = acute myelogenous leukemia; BMT = bone marrow transplant; CBC = complete blood count; CMV = cytomegalovirus; RSV = respiratory syncytial virus; TAM = transient abnormal myelopoiesis.

**INDEX TERMS:** acute megakaryoblastic leukemia (M7, AMKL); acute myelogenous leukemia (AML); Down syndrome.
count of 8000/uL. A differential showed a predominance of lymphocytes and a few blasts. She was promptly referred to a pediatric hematology/oncology clinic for myelodysplasia with severe anemia and thrombocytopenia.

At the pediatric oncology clinic a physical examination revealed a positive umbilical hernia and pinpoint petechia on her lower extremities and left forearm. All other vital signs proved unremarkable. She then received transfusions of packed red blood cells and platelets. The peripheral blood smear revealed a predominance of small, mature lymphocytes. There were a few blasts with round to oval nuclei, partially condensed chromatin, several tiny prominent nucleoli, and blue cytoplasm. Only occasional platelets were seen. The red cell morphology showed anisocytosis, poikilocytosis with occasional teardrop cells, spherocytes, ovalocytes, and a few schistocytes. There were also several mononuclear cells with oval nuclei, blue cytoplasm, and irregularities in shape that appeared to be monocytes. Her CBC and differential results from the pediatric hematology/oncology laboratory are shown in Table 1.

A battery of tests ensued including bone marrow biopsies taken from the right and left posterior iliac spine. The biopsies were reviewed using para-aminosalicylic acid and haematoxylin and eosin stains. Marked megakaryocytic hyperplasia and reticulin fibrosis were noted along with marked erythroid and myeloid hypoplasia. Small lymphoid aggregates were also seen. Reticulin fibrosis is common in AMKL.

Cytogenetic studies were also performed. Chromosome analysis from cultured bone marrow cells revealed the presence of an abnormal, mosaic pattern consistent with a neoplastic process. Using Giemsa banding techniques, 20 metaphase cells were examined and all of them contained an extra chromosome 21 (trisomy 21). In addition, seven of the 20 cells contained an additional isochromosome 8q resulting in an 8q tetrasomy. The trisomy 21 is a constitutional abnormality because the patient was already known to have Down syndrome. Isochromosome 8q is not known to be diagnostic of any specific neoplasia but is probably the result of some dysplastic event occurring in the bone marrow.

A clinical flow cytometry laboratory performed cytometric immunophenotyping of a bone marrow aspirate from the patient. The results showed that the specimen contained a mixture of cell types with a relative lymphocytosis. The laboratory reported a distinct population of phenotypically abnormal myeloblasts expressing myeloid antigens and the immature cell markers CD34 and CD117 (c-kit). CD61, which stains positively in disease states of AMKL and also stains positive for blasts in transient myeloproliferative disorder, demonstrated a weak 1+. However, it is important to note that in AMKL CD13, CD33, and CD71 all stain variable, and all were positive on this patient. In addition, CD14 and CD64 stained negative which is also suggestive of AMKL. Results of myeloid related CD markers are seen in Table 2.

The pathology report described the patient’s bone marrow to be abnormal. Marked megakaryocytic hyperplasia and reticulin fibrosis were noted along with marked erythroid and myeloid hypoplasia. A diagnosis of acute leukemia could not be made because no clusters of blasts were detected. However, clinical correlation was recommended. Her condition was diagnosed as Down syndrome with myelodysplastic syndrome and severe cytopenias.

**TREATMENT**

The patient was given irradiated apheresed leukocyte reduced platelets on four separate occasions during her initial hospital stay. She also was transfused with 100 cc of irradiated cytomegalovirus negative packed red blood cells on three separate occasions. She was placed on a national research group study

| Table 1. Initial presentation CBC/differential data |
|----------|--------------|---------------|
| Test     | Result       | Reference     |
| WBC      | 5.3 x 10^9/L | 4.5 – 17.5 x 10^9/L |
| RBC      | 3.18 x 10^12/L | 3.7 – 5.3 x 10^12/L |
| HGB      | 10.6 g/dL    | 10.5 g/dL – 16.0 g/dL |
| HCT      | 28.8%        | 33% – 49%     |
| MCV      | 90.4 fl      | 70 fl – 102 fl |
| MCH      | 33 pg        | 22 pg – 35 pg |
| MCHC     | 37%          | 30% – 37%    |
| RDW      | 15.0         | 11.5 – 14.5  |
| RETIC    | 2.4%         | 0.8% – 1.2%  |
| PLATELETS| 69 x 10^9/L  | 150 – 400 x 10^9/L |
| SEGS     | 14%          | 42% – 75%    |
| LYMPHES  | 79%          | 25% – 46%    |
| MONOS    | 5%           | 0% – 6%      |
| BLASTS   | 2%           | 0% - 0%      |
and began chemotherapy treatment. Complying with protocol, she received Cytarabine (ara-C) and daunorubicin for four days and also ara-C intrathecally (IT) medications. The patient tolerated the chemotherapy well with few side effects. She was given speech therapy, physical therapy, and occupational therapy following her treatment. A post-treatment physical examination showed her to be playful and active, and all vital signs were within normal limits. Her blood counts appeared to stabilize and a CBC indicated a WBC of 3750/µL, hemoglobin 11.7g/dL, hematocrit 31.8% and a platelet count of 100,000/µL. She was discharged and scheduled to return two weeks later for a second course of chemotherapy.

**DISCUSSION**

It is believed that many cases of AMKL in Down syndrome may have been misclassified as undifferentiated AML (M0), so the incidence might actually be much higher than previously believed. The median age at diagnosis for AMKL is 22 to 23 months of age. Down syndrome patients with AMKL have a much better prognosis than other children with AML. The majority of Down syndrome patients with AML/AMKL can be cured and seem to have a considerable advantage over non-Down syndrome children. A four year event-free survival approaching 75% has been documented. Non-Down syndrome patients who are fortunate enough to receive a bone marrow transplant have about a 50% survival rate as opposed to a rate of only 35% for those who do not receive a bone marrow transplant.

Some Down syndrome children develop transient abnormal myelopoiesis (TAM) at or soon after birth. TAM is generally unique to Down syndrome and produces a blood and bone marrow picture that is indistinguishable from leukemia. TAM spontaneously resolves within three to four weeks. Down syndrome neonates presenting with these symptoms are left untreated and monitored closely to see if the condition goes away. Only if the condition does not spontaneously resolve can the patient be diagnosed with AML and begin a treatment regimen. Approximately 20% to 30% of patients with TAM will develop AML at some point later in life.

**CASE RESOLUTION**

The patient returned to the pediatric oncology clinic as scheduled for her second course of chemotherapy. Upon admission, she presented with a fever of 101.7 °F and moderate nasopharyngeal congestion. She was placed on broad-spectrum antibiotics pending the result of cultures. Cultures returned negative and her condition was determined to be of viral origin. Her condition improved during her hospital stay and she received blood product transfusions to support her platelet and erythrocyte count. It was determined that her second course of chemotherapy be postponed until the upper respiratory tract infection had resolved. She was given an additional transfusion of one half of a unit of CMV negative, apheresis, and irradiated platelets to boost her platelet count and was then sent home.

**Table 2. Myeloid CD markers**

<table>
<thead>
<tr>
<th>CD Marker</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD11b</td>
<td>3+</td>
</tr>
<tr>
<td>CD13 (LeuM7)</td>
<td>pos</td>
</tr>
<tr>
<td>CD14 (LeuM3)</td>
<td>neg</td>
</tr>
<tr>
<td>CD15 (LeuM1)</td>
<td>neg</td>
</tr>
<tr>
<td>CD33 (LeuM9)</td>
<td>pos</td>
</tr>
<tr>
<td>CD34 (My10)</td>
<td>2+</td>
</tr>
<tr>
<td>CD45 (HLE)</td>
<td>pos</td>
</tr>
<tr>
<td>CD61 (gp3a)</td>
<td>1+</td>
</tr>
<tr>
<td>CD64</td>
<td>neg</td>
</tr>
<tr>
<td>CD71</td>
<td>pos</td>
</tr>
<tr>
<td>CD117</td>
<td>pos</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>neg</td>
</tr>
</tbody>
</table>

**Table 3. Post-treatment CBC data**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>3.9 x 10⁹/L</td>
<td>4.5 – 17.5 x 10⁹/L</td>
</tr>
<tr>
<td>RBC</td>
<td>3.02 x 10¹²/L</td>
<td>3.7 – 5.3 x 10¹²/L</td>
</tr>
<tr>
<td>HGB</td>
<td>9.8 g/dL</td>
<td>10.5 g/dL – 16.0 g/dL</td>
</tr>
<tr>
<td>HCT</td>
<td>29.1%</td>
<td>33% – 49%</td>
</tr>
<tr>
<td>RDW</td>
<td>20.0*</td>
<td>11.5 – 14.5</td>
</tr>
<tr>
<td>RETICS</td>
<td>7.9 %</td>
<td>0.8% – 1.2%</td>
</tr>
<tr>
<td>PLATELETS</td>
<td>174 x 10⁹ /L</td>
<td>150 – 400 x 10⁹ /L</td>
</tr>
<tr>
<td>SEGs</td>
<td>85%</td>
<td>42% – 75%</td>
</tr>
<tr>
<td>BANDS</td>
<td>2%</td>
<td>0% – 9 %</td>
</tr>
<tr>
<td>LYMPHS</td>
<td>10%</td>
<td>25% – 46 %</td>
</tr>
<tr>
<td>MONOS</td>
<td>3%</td>
<td>0% – 6 %</td>
</tr>
</tbody>
</table>

* Slight to moderate poikilocytosis and anisocytosis were also indicated.
Three weeks later the patient returned in healthy condition to resume her second round of chemotherapy. A bone marrow aspirate, lumbar puncture, and administration of intrathecal Ara-C were performed and treatment proceeded without difficulty for a course of five days. She tolerated the second course remarkably well with only mild, brief emesis shortly after the onset of her treatment. She exhibited no significant nausea, vomiting, or intolerance, and remained playful and interactive. A post chemotherapy assessment determined her to be in no apparent distress and all of her vital signs were within normal limits. She was discharged with instructions to return in one week to evaluate her peripheral blood picture.

Complete blood counts and manual differentials were performed weekly after completion of her second course of chemotherapy. Her CBC/differential at one month post second treatment produced the results in Table 3.

Currently, the patient is preparing to begin her third course of chemotherapy. Her blood counts are being monitored on a weekly basis and she will continue to receive chemotherapy treatments for an unspecified length of time. Each case is unique to the individual and the treatment regimen may require modification as different situations arise. She also continues to receive blood product transfusions as needed to help stabilize her red blood cell and platelet counts. She continues to be very active and playful which is encouraging to both her parents and her physician. Fortunately, her disease was caught at an early stage before it had time to progress into AML (M7), which is a significant benefit. Early detection is paramount to the recovery process of any malignancy. In addition, given the fact that the vast majority of Down syndrome patients completely recover from AML and myelodysplastic syndrome, it is believed that her prognosis is good.

REFERENCES
Co-inheritance of α and β-Thalassemia in a Jordanian Family

AYMAN A AL QADDOUMI

Additional α-genes may increase the severity of heterozygous β-thalassemia. Conversely, the co-inheritance of α-thalassemia with homozygous β-thalassemia and the consequent reduction in α-globin chain excess often results in a milder clinical and haematological phenotype. This study describes the hematological and the molecular data resulting from the interaction between α and β-thalassemia determinants in a Jordanian family. The parents are double heterozygotes for α and β-thalassemia. DNA analysis of four children characterized homozygosity for β-thalassemia (IVS 1.6 thalassemia mutation) in three of them. Co-existing heterozygosity for α-thalassemia determined by the -α 3.7 mutation was detected in two of them (Children 1 and 2). Those two children have a less severe clinical course than that of the third child (Child 3) with homozygosity for β-thalassemia only. The co-existence of -α 3.7 mutations with homozygous β-thalassemia may have converted a transfusion-dependent thalassemia major to non transfusion-dependent thalassemia intermedia. The fourth child (Child 4) was heterozygous for -α 3.7 but lacked β-thalassemia IVS 1.6 mutation and appeared normal.

ABBREVIATIONS: MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PCR = polymerase chain reaction.

INDEX TERMS: α-thalassemia; β-thalassemia; co-inheritance; Jordan; PCR.

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Human globin-gene mutations are amongst the most common genetic disorders observed in human populations. At the molecular level β-thalassemia comprises a heterogeneous group of hemoglobin disorders resulting from mutations eliminating (β0) or reducing (β+) the β-globin gene expression. Over 200 different mutations can cause β-thalassemia phenotype.

Of the numerous mutations that have been described to cause α-thalassemia phenotype, deletions at the α-gene locus account for the vast majority of α-thalassemia alleles. The most widely occurring single-gene deletions are the -α 4.2 and the -α 3.7, while the double α-gene deletions in cis, such as the -αSEA, -αFIL, and -αTHAI alleles are most common in Southeast Asia and the -αMED and the -αTHAI double gene deletions occur most frequently in the Mediterranean area.

Imbalance in the relative amounts of β and α-globin chains plays a major role in the pathophysiology of thalassemia. In homozygous β-thalassemia, the excess α-chains precipitate in the red blood cell precursors causing membrane damage, red cell destruction, ineffective erythropoiesis, and consequently anemia.

In heterozygous β-thalassemia, the deleterious effects of excess α-chains have been implicated through the correlation of β-thalassemia mutations with the mean corpuscular volume (MCV) of the red blood cells.

Unlike β-thalassemia, the detection of α-thalassemia carrier status has always been problematic because of the limitations in traditionally existing techniques in molecular characterization of α-thalassemia carriers. Currently, polymerase chain reaction (PCR) based assays provide a simple, sensitive, and rapid detection of α-thalassemia trait carriers.

It has been shown that the excess α-genes increase the severity of heterozygous β-thalassemia. Conversely, heterozygousity for α-thalassemia in conjunction with homozygous β-thalassemia ameliorates the clinical condition.
In the present study we reported the clinical, hematological, and molecular data resulting from the interaction between α and β-thalassemia in a Jordanian family of six affected members.

MATERIALS AND METHODS
Blood samples were vacuum collected in Na–EDTA. Hematological parameters were obtained from an automated counter Sysmex SE 9000™ ( Sysmex-Toa Medical Electronics Co.: Kobe, Japan). Red cell lysates were examined on cellulose acetate electrophoresis at pH 8.6. Hb A2 and Hb F fractions were measured by High Performance Liquid Chromatography using BioRad. Variant II™. Genomic DNA was isolated by commercial DNA isolation kit (instagene genomic isolation kit, BioRad.: USA). Samples were tested for 22 most common β-thalassemia mutations by reverse hybridization (β-Globin StripAssay, ViennaLab: Vienna, Austria). Positivity for β-thalassemia mutations was confirmed by a micro well hybridization technique MDX- Beta Gene 1 Kit™ (BioRad.: USA) according to manufacturer instructions. Detection of α-thalassemia mutation –α 3.7 was achieved by PCR-based technique using published primer sequences6 with some modifications to the original technique. Each 50 μl reaction contained 200 μM of each dNTP, 1.5 μM MgCl2, 2.5 μg BSA, 10% DMSO, 250 ng – 500 ng of genomic DNA, and two units of Taq DNA polymerase (Ampli Taq Gold polymerase, Perkin Elmer) in the supplied reaction buffer. Reactions were performed in a Perkin Elmer 9600™ thermal cycler. The program was initiated with denaturation at 96°C for 12 minutes followed by 32 cycles of 96°C denaturation for two minutes, 62°C for 75 seconds, and 72°C extension for 135 seconds. The reaction was completed with final extension at 72°C for ten minutes. After amplification, 10 μl of product was electrophoresed through one percent agarose gel in 1x Tris-EDTA-Borate-buffer at 10 volts/cm for one hour. The ethedium bromide stained gel was visualized and photographed under a UV transilluminator.

RESULTS
Clinical picture and hematological data

Parents
Both parents were apparently normal. Their Hb and Hct levels were normal for their ages. Only mild reduction in their MCV and mean corpuscular hemoglobin (MCH) values was noticed. The blood picture of both parents including red cell morphology was consistent with thalassemia trait. Cellulose acetate electrophoresis (pH 8.6) showed mild increase in the Hb A2 values for both parents with no other abnormal hemoglobin fraction. DNA analysis (Figure 1) revealed that both parents were double heterozygotes for β-thalassemia mutation β+ IVS1-6 and α- thalassemia mutation -α 3.7. The hematological data and genotypes for the family are shown in Table 1. Figure 1 shows the PCR amplification product for the -α 3.7 mutation.

Children
Children 1 and 2: These two children were referred to the pediatric hematology clinic at the ages of three and four years respectively. They were presented with similar clinical and hematological phenotype consistent with a diagnosis of thalassemia intermedia. Both children showed mild splenomegaly with occasional requirement for blood transfusion. The hematological data for Children 1 and 2 were as follows; (MCV = 62 fl and 50.5 fl, MCH = 15.8 pg and 20.2 pg, Hb A2 = 5.2% and 7.2%, Hb F = 1.8% and 3.1% respectively). Genotype analysis for the two children demonstrated homozygosity for β+ IVS 1-6 mutation and heterozygosity for -α 3.7 mutation.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age years</th>
<th>Hb (g/dl)</th>
<th>Hct%</th>
<th>MCV (fl)</th>
<th>MCH (pg)</th>
<th>HbA2%</th>
<th>HbF%</th>
<th>Serum ferritin ng/ml</th>
<th>β-globin genotype</th>
<th>α-globin genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>30</td>
<td>12.1</td>
<td>30.7</td>
<td>70.1</td>
<td>22</td>
<td>3.7</td>
<td>0.4</td>
<td>64</td>
<td>Het IVS1-6</td>
<td>-α/αα</td>
</tr>
<tr>
<td>Father</td>
<td>41</td>
<td>15.3</td>
<td>46.5</td>
<td>72.1</td>
<td>23.7</td>
<td>4.1</td>
<td>0.3</td>
<td>124</td>
<td>Het IVS1-6</td>
<td>-α/αα</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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Child 3: At the age of one year, this child presented with clinical manifestations consistent with thalassemia major: severe anemia, splenomegaly. This child was diagnosed as β-thalassemia major based on the increase in Hb F fraction, the typical red cell morphology, and the suggestive family history. He showed consistent requirement for blood transfusion almost every month. This child was found to be homozygote for β⁺-thalassemia mutation IVS 1-6 while the -α³.⁷ mutation was not detected.

Child 4: DNA analysis for this apparently normal child revealed the presence of -α³.⁷ mutation with the absence of β⁺- IVS1-6 mutation. He had a hemoglobin value of 12.4 gm/dl, MCV value of 65 fl, MCH value of 22.8 pg, Hb A2 concentration of 2.8% and Hb F concentration of 0.3%. Child 4 was diagnosed as -α³.⁷ trait carrier.

DISCUSSION
Homozygosity for β-thalassemia mostly results in thalassemia major, characterized by severe anemia, splenomegaly, and requirement for regular blood transfusion from early infancy. However, some homozygotes present with mild hematological and clinical phenotype without requirement for regular blood transfusion. This condition is called thalassemia intermedia.¹ Thalassemia intermedia may result from the inheritance of mild β-thalassemia mutations, or as a result of interaction between triplicated α-globin gene with heterozygous β-thalassemia, compound heterozygosity for β-thalassemia, or as a result of co-inheritance of α-thalassemia with homozygous β-thalassemia.¹¹

Except for mild reduction in the MCV and MCH, both parents are phenotypically normal, with α-thalassemia genotype of -α/αα indicating the loss of a single α-gene. Both parents also are heterozygotes for the β⁺ IVS1-6 mutation, which is of mild severity, thus, the ameliorating effect resulting from the interaction between these two mutations in heterozygotes might explain the borderline Hb A2 levels (Mother Hb A2 = 3.7%, Father Hb A2 = 4.1%). It has been suggested that the levels of Hb A2 in α-thalassemia are lower than in normal individuals,¹² raising the possibility that the level may be lower in double heterozygotes for α and β-thalassemia than in those with β-thalassemia alone.

Both Children 1 and 2 presented with β-thalassemia intermedia phenotype. Their symptoms were considerably less severe than those seen in Child 3. Both children were found to be homozygous for β⁺-thalassemia mutation IVS 1-6 and heterozygous for -α³.⁷ mutation. Both children have received only occasional blood transfusions. The hematological data and the clinical phenotypes may seem quite mild compared to Child 3 with homozygosity for β-thalassemia only. The clinical and hematological findings for Child 3 were consistent with the diagnosis of β-thalassemia major. These findings include severe anemia, splenomegaly (4 cm below the coastal margin) and iron overload. DNA analysis for this child showed homozygosity for β⁺-thalassemia mutation IVS 1-6 mutation while the -α³.⁷ mutation was not detected. His Hb F is moderately increased (14%), which is relatively lower than that usually observed in β-thalassemia homozygotes. This is not uncommon in case of the inheritance of the mild β-thalassemia mutation IVS1-6.¹ This child receives regular blood transfusions at monthly intervals.

Child 4 represents a typical case of α-thalassemia trait. His MCV and MCH are slightly reduced (MCV = 65 fl, MCH = 22.8 pg). DNA analysis confirmed heterozygosity for the -α³.⁷ and the absence of β⁺-thalassemia mutation IVS 1.6.
Hb F levels for Children 1 and 2 (1.8 % and 3.1 % respectively), are significantly less than that seen in Child 3 which agrees with the concept that Hb F level is decreased when a deletional α-thalassemia mutation coexists with other β-globin gene mutations and the value of HbF is conversely related to the degree of anemia.13

These findings demonstrate clearly that the co-inheritance of α-thalassemia plays an important role in modifying the clinical course of homozygous β-thalassemia.

It seems highly probable that many of thalassemia intermedia phenotypes can be explained by the co-inheritance of α-thalassemia,14,15 and the co-inheritance of triplicated α-globin gene with heterozygous β-thalassemia. Local studies in Jordan estimated the prevalence of β-thalassemia at three percent to four percent, with a wide range of β-thalassemia mutations existing in the country.16,17,18 The homozygous β-thalassemia patients in Jordan resemble a group with significant clinical heterogeneity. It is important to determine whether the presence of single α-thalassemia determinant explains the clinical heterogeneity among those patients. Our study suggests that this may be the case, but it will be necessary to analyze a series of transfusion dependent homozygotes for β⁻ and β⁰-thalassemia and compare the incidence of α-thalassemia in that group with a large series of patients known as mild homozygotes for β⁻ and β⁰-thalassemia. This will enable us to define fully the clinical spectrum resulting from the interaction between α and homozygous β-thalassemia.

Furthermore, in fetuses homozygous for β-thalassemia, the detection of α-thalassemia determinant should become an important part of the program for the prevention of these disorders, especially with the development of PCR technology which allows an easy identification of α-thalassemia trait carriers making it now possible to predict more accurately the clinical outcome of the interaction between different α and β-thalassemia determinants.

This case represents an extremely rare condition, as both parents are double heterozygous for α and β-thalassemia. Furthermore, the two determinants were clearly defined. Such co-inheritance of α and β-thalassemia might be due to the high prevalence of thalassemia determinants, and the high rate of consanguineous marriages among Jordanians.19 The parents in this case are first-degree relatives from both sides.

REFERENCES
A Model for Educational Enrichment and Employment Recruitment for Clinical Laboratory Science Students

LM KASPER, AE SCHULTZE

An educational partnership was initiated between a pharmaceutical company and a university-based clinical laboratory science program to achieve mutually beneficial objectives. This external enrichment site provides a unique educational experience for the students that cannot be duplicated anywhere else in the community. The framework for the educational experience was established with a full day’s schedule of visits and presentations guided by a list of twenty learning objectives. Clinical laboratory science students interact with laboratory professionals who are employed by the pharmaceutical company and assigned to a variety of traditional and non-traditional roles. During the visit, pharmaceutical company employees observe student interactions in small group settings and assess the learners’ interest in the work environment and specimen testing process. Employee feedback may be applied to future employment decision making. This article describes how employer outreach goals and initiatives and educational enrichment objectives can be met through cooperative team work.

ABBREVIATIONS: GLPs = good laboratory practices; RIA = radioimmunoassay.

INDEX TERMS: alternative careers; employment recruitment; partnership; pharmaceutical industry; off-site enrichment.


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The constant emphasis on cost efficiency combined with the shortage of qualified laboratory personnel in today’s hospital laboratories presents a challenge to laboratory science education program administrators in securing adequate clinical education sites. Cearlock and others described a major curriculum revision effort motivated by the need for additional clinical sites.1 While the most desired clinical education sites are well-equipped hospital laboratories with some diversity in their patient populations, programs frequently pursue educational opportunities that are outside the routine laboratory testing environment to facilitate and augment student learning. External educational sites that fit into this latter category include molecular diagnostics laboratories, newborn screening clinics, public health facilities, sexually transmitted disease clinics, blood centers, private diagnostic laboratories, rural community hospitals, contract research organizations, and pharmaceutical research laboratories. Vittetoe summarized learning outcomes from rural hospital enrichment sites to include work environments, institutional philosophies, healthcare, and career opportunities.2 Ackall described deployment of clinical laboratory students to primary care settings in underserved communities to participate in multidisciplinary healthcare teams. In this setting, students enhanced their skills in phlebotomy, interpersonal communication with patients and team members, instrument trouble-shooting, and participation in research projects.3 This manuscript describes a model developed as a joint venture between a pharmaceutical company (Lilly Research Laboratories) and a university-based clinical laboratory science program (Indiana University) to increase exposure of students to traditional and non-traditional employment opportunities for clinical laboratory scientists.

The peer-reviewed Research and Reports Section seeks to publish reports of original research related to the clinical laboratory or one or more subspecialties, as well as information on important clinical laboratory-related topics such as technological, clinical, and experimental advances and innovations. Literature reviews are also included. Direct all inquiries to David G Fowler PhD CLS(NCA), Clin Lab Sci Research and Reports Editor, Dept of Clinical Laboratory Sciences, University of Mississippi Medical Center, 2500 North State St, Jackson MS 39216. (601) 984-6309, (601) 815-1717 (fax). dfowler@shrp.umsmed.edu
DISCUSSION
The Clinical Laboratory Science Program at the Indiana University School of Medicine in cooperation with Eli Lilly Research Laboratories offers students an inside view of pharmaceutical research and potential employment opportunities for graduates. Small groups of four or five students, accompanied by a program representative, spend one day at the Lilly Research Laboratories. To prepare for the visit, students participate in two lectures presented at the program facility by a Lilly Veterinary Clinical Pathologist. This individual also serves as host for the students’ visit to the pharmaceutical research laboratories. The lectures are titled Introduction to Toxicology with a Focus on Animal Models for Drug Development, and Comparative Veterinary Hematology. Emphasis is placed on understanding the role of the clinical laboratory scientist in the drug development process. To avoid concerns with advertisement to a captive audience, no Lilly products are included in any aspect of this program, and advertising for such is not offered. The integrity of the educational process is maintained throughout the event. The program has been in existence for six years, and a total of 81 students have participated in the educational experience.

Students interact with clinical laboratory scientists employed in traditional and non-traditional positions within a large pharmaceutical company. While students do not participate in or work on actual toxicity studies, they gain valuable knowledge through demonstrations, observations, and small group interactions with the various employees of the Departments of Pathology and Non-clinical Safety Assessment within the Toxicology Division.

While the National Accrediting Agency for Clinical Laboratory Science does not require written objectives for environments that are clearly identified as enrichment sites, the host site personnel developed a list of twenty educational objectives to guide staff presentations for the day’s events and to assure consistency among the groups. Students receive the objectives and schedule prior to the visit. The two documents provide learners with a preview of the day’s events as well as the sponsor’s expectations. The objectives serve as a guide for the staff to use in discussions with the students and focus on content such as principles of instrument operation, species variation in peripheral blood smear findings among research animals, and issues related to sample collection and method development for animal studies. A post-visit quiz was developed from these objectives.

Prior to the students’ entry into the first laboratory setting, the host impresses upon the student the absolute necessity of consistently wearing protective eye wear in all laboratory settings, and each student is provided with a pair of style-dependent safety glasses, based on whether he/she wears eyeglasses. Students begin the day in the clinical pathology laboratory with a discussion on the unique challenges of specimen processing for animal subjects and compare and contrast how these requirements differ from human subjects. Following this introduction, students rotate to hematology, coagulation, and urinalysis testing sections of the laboratory. Students review principles of cell counting instrumentation (e.g., Advia systems) and cellular variations that are unique to research animals (rats, dogs, and monkeys). In addition, students are introduced to urinalysis testing using online reagent strip readers and to coagulation testing using Diagnostica Stago instrumentation. The instruments noted here are not available to students in the hospital laboratories where most of the clinical education occurs (Figure 1).

In the chemistry testing area, students learn that testing methods for numerous routine analytes, while accomplished on Hitachi instruments, use many of the same chemical reactions that are found in hospital laboratories (Figure 2). Frequently, only the sample sizes and reference intervals for selected analytes vary. In addition, species-specific differences in clinical chemistry analytes are identified, and students are exposed to alternative test selections that might not occur in a hospital setting.

In the clinical pathology laboratory, students have an opportunity to interact with the laboratory supervisor and examine

Figure 1. Cathy Durbin AS MLT(ASCP) (right) explains proper use of the STA coagulation instrument to clinical laboratory science students.
how the supervisor’s role in a research setting compares with the similar role in a hospital setting. The supervisor provides unique information regarding the challenges of providing clinical pathology services for toxicity studies and clinical trials. Discussion topics often include sample volume limitations associated with laboratory animals, sample collection methods, appropriate scheduling for sample collection at toxicology study termination and challenges associated with analyzing large numbers of samples efficiently, laboratory testing capacity, and efficient flow of work within the clinical pathology laboratory. Clinical laboratory science students often take this occasion to inquire about opportunities for employment in the non-hospital setting. They frequently ask about specific types of jobs available for clinical laboratory scientists in the pharmaceutical industry, qualifications needed for application and any additional training that might be beneficial to application, and prior student experiences that might provide an additional incentive to hire clinical laboratory science graduates.

Species-specific assays used in toxicology testing are one area of focus for the special procedures laboratory, where the clinical laboratory scientist emphasizes radioimmunoassay (RIA) methods, Luminex, and Flow Cytometry analyses. While many hospital laboratories continue to reduce their reliance on RIA methodologies in favor of other types of immunoassay procedures, RIA is often the method of choice in the pharmaceutical testing environment where samples from multiple species of animals need to be analyzed accurately in a time limited manner, and where procedures and data documentation comply with good laboratory practices (GLPs) guidelines. The Bio-plex workstation uses a fluorescent-dyed polystyrene bead-based microplate system equipped with flow cytometric detection that accommodates simultaneous analysis of as many as 100 different analytes (Figure 3). This technology is particularly useful for volume-limited samples. Point-of-care cardiac readers that perform troponin T analyses are also discussed.

Students spend time with the scientist who coordinates all study protocols and monitors progress to assure adherence to timelines. They learn the importance of organizational as well as written and oral communication skills. The importance of written communication skills is emphasized in their discussion with a technical writer, also a clinical laboratory scientist (Figure 4).

The quality assurance officer discusses the importance of establishing and maintaining quality to meet and exceed regulations of global regulatory authorities. Emphasis is placed on compliance with GLPs throughout the preclinical study process. The details of GLPs are not emphasized by many clinical laboratory science programs, and these types of interactions expand the students’ knowledge of the regulatory compliance issues involved in laboratory testing for drug development.

Figure 2. Bruce Beechler BS MT(ASCP)(right), lead medical technologist in the clinical chemistry section, discusses the chemical reactions used in the Hitachi Clinical Chemistry Analyzer and similarities and differences compared to other chemistry analyzers.

Figure 3. Connie Powers BS MT(ASCP) (left) describes use of the Luminex in the special procedures laboratory. She emphasizes the difficulties incurred when analyzing specimens of small volume.
Students close out the day with the host veterinary clinical pathologist (who is also a clinical laboratory scientist) (Figure 5). Using selected cases with clinical pathology data sets, tissues, blood smears, and body fluid preparations from animals used in pre-clinical studies, he conducts an interactive session that helps students gain a global view of the important contribution that clinical laboratory scientists make in animal studies used for drug development. Clinical laboratory science students are challenged to apply principles of medical technology, to integrate knowledge from numerous disciplines (hematology, clinical chemistry, coagulation, urinalysis, histopathology), and to practice a variety of skills learned in the clinical laboratory science training program to assure safety in drug development.

Throughout the educational program, students learn about various agencies that regulate hospital operations. At Lilly Research Laboratories, students are reminded that the Food and Drug Administration plays a major role in regulating pharmaceutical research laboratory operations. In addition, the roles for other regulatory agencies including the United States Department of Agriculture, Public Health Services, Environmental Protection Agency, and Association for Assessment and Accreditation of Laboratory Animal Care, are discussed. Students are given an overview of GLPs as they pertain to laboratory testing. Students are reminded that the intention of the GLPs is to document quality and validity of test data. GLPs encompass all study organizational processes including study planning, test performance, monitoring of the study progress, and recording and reporting of results. Each Lilly Research Laboratory employee who shares an area of expertise with the students holds education and certification credentials as a laboratory practitioner. Approximately 16 members of the toxicology division are involved in the program. This program was initiated at the request of Lilly Research Laboratories. This opportunity for the clinical laboratory science students is one of several included in the Pathology Academic Outreach Program. Other educational offerings include the Lilly Fellows (a three year research post-doctoral training endeavor), Pathology Internship (summer research program for medical professionals), Veterinary Student Externship (one month rotation in Pathology and Laboratory Animal Medicine designed for students in the third and fourth years of veterinary school), and Resident/Graduate Student Visitations (one or two day visits within the Department of Pathology shadowing a Veterinary Clinical or Morphologic Pathologist.) These programs serve to achieve a goal of educational outreach to the community, and the students provide a well educated and trained prospective pool of future employees for the organization.

For the clinical laboratory science students, the venture offers an opportunity to observe the laboratory testing environment of a premier place of employment, to interact with a group of laboratory practitioners assigned to diverse roles, and to

**Figure 4.** Kathy Piroozi BS MT(ASCP) (center right), toxicology study director, explains the necessity of excellent oral and written communication skills to clinical laboratory science students visiting in the toxicology division.

**Figure 5.** Eric Schultze DVM PhD Diplomate ACVP MT(ASCP) (left) discusses the importance of blood smear morphology assessment in the conduct of toxicology studies in animals.
develop an understanding of how their individual interests and skills might fit into the research environment. Students have expressed an appreciation for the opportunity to visit the facilities, to interact with numerous laboratory professionals at work, and to learn how employment in a pharmaceutical company contrasts with employment in a hospital laboratory. For example, students encountered non-traditional employment opportunities available to clinical laboratory scientists, technology and laboratory instrumentation not commonly found in hospital laboratories, and work practices that strictly follow GLP guidelines. A brief multiple choice quiz is administered by the Indiana University Clinical Laboratory Science Program faculty to assess student learning from the experience. The 2004 class average on the quiz was 85%, the 2005 class average was 97%, and the 2006 class average was 92%.

After the day’s activities are completed and students have left the premises, the Lilly Research Laboratory staff members who interacted with the student group complete an informal evaluation with particular emphasis on each student’s perceived interest in and attitude about the work processes as well as his/her oral communication skills. The evaluation summary serves as a future reference in the event that the student applies for employment at the host site. When asked for feedback on the value of the educational experience, pharmaceutical employees noted that student questions provided scientific stimulation and that participation in the event gave a sense of greater pride in each individual’s work and a feeling of ownership of the effort.

CONCLUSION
This educational partnership furnishes a unique learning experience for the clinical laboratory science students through the opportunity to interact with laboratory professionals employed in a variety of positions in a pharmaceutical organization. These interactions occur as the pharmaceutical employees engage in their daily work tasks, giving students an authentic view of the challenges of the workplace. Additionally, students’ knowledge of analytic options is broadened when they encounter testing instruments and technologies not included in the hospital laboratories that serve as clinical education sites. The positive feedback provided by students in an informal exit question-and-answer period and student performances on the post-visit quiz suggest that students are achieving the goals agreed upon by the partnership entities.

The pharmaceutical host also receives benefits. In addition to addressing a community educational outreach goal, individuals responsible for participating in the initial employment decision-making can evaluate how each student interacts in small group settings as well as assess the student’s interest in the work environment and testing processes. This evaluation summary becomes a valuable tool in future employee selection processes. Hence, the endeavor achieves mutually beneficial objectives for both the corporate and educational institutions.

REFERENCES
RESEARCH AND REPORTS

Searching for Hereditary Hemochromatosis

REBECCA J LAUDICINA

OBJECTIVE: To detect hereditary hemochromatosis (HH) in low-income residents of a medically underserved region through free screening and confirmatory laboratory testing and to raise awareness of HH in the general population.

DESIGN: Two-tiered reflexive laboratory testing was used to screen for HH. Participants evaluated the project by written survey upon its conclusion. Data were analyzed by descriptive techniques.

SETTING: Local public health departments in 18 counties in western North Carolina (WNC).

PARTICIPANTS/SUBJECTS: Phase 1: adult volunteers age ≥ 20 without previous diagnosis of HH; Phase 2: Phase 1 participants with elevated screening results and adult family members of Phase 2 participants found to have HFE mutations; Phase 3: randomly-selected Phase 1 participants (Survey A) and all Phase 2 participants with HFE mutations (Survey B).

INTERVENTIONS: Phase 1 (initial screening): non-fasting blood collection by venipuncture with testing for transferrin saturation (TS). Phase 2 (confirmatory testing): fasting blood collection by venipuncture for TS, serum ferritin (SF), and cheek swab for DNA analysis for two HFE mutations (C282Y and H63D). Phase 3: written Surveys A and B.

MAIN OUTCOME MEASURES: Total number participants screened for HH; prevalence of elevated TS in Phase 1 participants; prevalence of HFE genotypes consistent with HH (C282Y/C282Y and C282Y/H63D) in Phase 2 participants; prevalence of elevated SF in subjects with HFE mutations; number of family members tested; number of participants being treated for HH as a result of screening; increase in awareness of HH among Phase 1 participants.

RESULTS: 2,034 total subjects participated in screening events and/or family member testing. Of the 1,976 Phase 1 participants, 130 (6.6%) had elevated TS (≥ 45%). Twenty of 130 (15.4%) Phase 2 subjects were homozygotes for C282Y. The prevalence of the C282Y/C282Y genotype among the Phase 1 participants who were tested in Phase 2 was 20/1976 (1.0%). Fourteen of 20 (70%) C282Y homozygotes had elevated SF. Eleven of 130 (8.5%) Phase 2 subjects were compound heterozygotes for C282Y and H63D, and none had elevated SF. Of 58 family members tested, two (3.4%) were homozygotes for C282Y and eight (13.8%) were compound heterozygotes for C282Y and H63D. One of two (50%) family members homozygous for C282Y had an elevated SF. No compound heterozygotes had elevated SF. Sixty-four of 120 (54.2%) Phase 1 subjects responded to Survey A. 53.1% of respondents were unaware of HH prior to the screening event. 92.1% of respondents told their family and friends about HH after participating. 73.4% discussed their laboratory results with their healthcare provider. Twenty of 41 participants (48.8%) found to have HFE mutations associated with HH responded to Survey B. Eleven of 20 (55.0%) stated that they were being treated for HH.

CONCLUSION: The prevalence of the major genetic mutation, C282Y/C282Y, associated with HH among Phase 1 study participants in WNC was 1%, more than three times the national prevalence of approximately 0.33%. Results suggest that free screening using laboratory tests in a two-tiered reflexive approach may be an effective means of detecting HH, especially in high-risk populations. Early detection through free laboratory screening tests may reduce morbidity and, ultimately, healthcare costs for low-income individuals. Awareness of HH as a health concern may increase as a result of publicity generated by screening events.

ABBREVIATIONS: HESP = Hemochromatosis Education and Screening Project; HH = hereditary hemochromatosis; PHD = public health department; SF = serum ferritin; SI =
Hemochromatosis is a progressive disease that results from iron overload. It can have genetic or non-genetic causes. Most cases of hemochromatosis in the United States are linked to mutations of the \textit{HFE} gene and are referred to as hereditary hemochromatosis (HH). Genetic mutations associated with HH occur more frequently than those associated with other genetic disorders such as cystic fibrosis and sickle cell disease in which there is greater public familiarity. Very importantly, HH often goes unrecognized and undetected by healthcare providers during routine primary care. It is estimated that only ten percent of affected individuals are actually being diagnosed at the present time, suggesting that there is a need for educating healthcare providers about HH.\cite{1}

HH is a disorder of iron regulation that may lead to an abnormal increase in dietary iron absorption. Iron in excess of normal storage capacity is toxic to cells. Progressive loading of iron can be seen in parenchymal cells in the liver, heart, pancreas, and other organs of some individuals affected by HH. Early detection and treatment of iron overload is important to prevent the serious morbidity that occurs in some patients.

In its early stages, clinical symptoms of HH are vague and nonspecific, posing a diagnostic challenge for clinicians. Early signs and symptoms may include fatigue, depression, irritability, joint pain, elevated liver enzymes (AST, ALT), amenorrhea, and impotence. Over time as iron is increasingly deposited in tissues, signs and symptoms associated with organ damage may appear. Late stage signs and symptoms include diabetes mellitus, gray or bronze skin tone, cirrhosis, hepatocellular carcinoma, joint disease, congestive heart failure, arrhythmias, hypotuitarism, increased incidence of bacterial infections, and chronic abdominal pain.\cite{2} Results of biochemical tests for iron and DNA tests for \textit{HFE} mutations coupled with clinical signs and symptoms provide the means for an accurate diagnosis of HH.

Several mutations of the \textit{HFE} gene have been identified.\cite{3} Two mutations, C282Y and H63D, have been studied extensively and are linked to HH. In studies of persons diagnosed with clinical HH, 90\% or more of individuals are homozygous for C282Y. A small number of affected persons are compound heterozygotes for C282Y and H63D. A few affected individuals are homozygous for H63D, compound heterozygotes for C282Y and other mutations, or single heterozygotes for either C282Y or H63D.\cite{4,5,6}

The C282Y/C282Y genotype is present in approximately 0.2\% to 0.5\% individuals in the United States. Ten percent to 12\% of the US population may be carriers of a single C282Y mutation.\cite{4,7} The highest prevalence is found in Caucasians, primarily those of northern European or Celtic descent, and HH is most prevalent in persons with Irish, Scottish, French, and Scandinavian ancestors.\cite{8} The overall prevalence of the C282Y/C282Y genotype was found to be 0.33\% in a recent study of almost 100,000 subjects in a diverse population. \textit{HFE} mutations associated with HH were also found in other ethnic groups such as Hispanics and African Americans, although at much lower prevalence.\cite{9}

Based on current data, at least 50\% of males and 25\% of females homozygous for the C282Y mutation will develop organ-damaging and life-threatening disease unless treated.\cite{10} However, not all persons carrying \textit{HFE} mutations develop symptoms of iron overload. Also, some individuals diagnosed with HH in screening studies are asymptomatic, in spite of laboratory evidence of iron overload.\cite{2,11} One study found that persons diagnosed with HH through screening did not have a higher rate of symptoms than normal controls.\cite{12} The penetrance of the C282Y/C282Y genotype, or proportion of persons with the genotype who develop clinical disease, is thought to be considerably less than 100\%.\cite{5,11} The penetrance of the other known \textit{HFE} mutations is very low.\cite{13} It may be that environmental or as yet unknown genetic factors interact with known \textit{HFE} mutations to enhance or suppress phenotypic expression.

Therapeutic phlebotomy provides a low-cost, safe, and effective treatment for iron overload in HH. Through a series of periodic phlebotomies, excess iron is gradually removed from the tissues as it becomes incorporated into developing...
erythrocytes. Therapy must be continued throughout the individual’s lifetime to prevent excess iron from re-accumulating. Effectively treated individuals diagnosed early with HH have been found to experience normal lifespans.14

Primary iron overload due to HH must be differentiated from secondary or acquired iron overload caused by iron-loading anemias, liver disease, and other conditions. Clinical findings, patient history, and laboratory test results are used in the differential diagnosis of various forms of hemochromatosis.

The only reliable means of detecting and confirming a diagnosis of HH is through the use of appropriate laboratory tests. Biochemical tests for iron provide simple and inexpensive laboratory screening tests for iron overload associated with HH. An elevated fasting transferrin saturation (TS) > 45% provides the earliest evidence that iron overload is present and should be the initial screening test.15 TS is based on measuring the serum iron (SI) and total iron binding capacity (TIBC) and calculating by the formula:

\[ \text{TS} = \left( \frac{\text{SI}}{\text{TIBC}} \right) \times 100 \]

A single, elevated TS should be followed by a repeat TS and serum ferritin (SF) performed on a fasting blood specimen. SF levels reflect iron stores and if elevated, provide evidence that iron is accumulating in the tissues. When coupled with an elevated TS, an SF >200 μg/L in pre-menopausal women or >300 μg/L in men or post-menopausal women is considered elevated and warrants confirmation of HH.15

SF levels are associated with the clinical signs and symptoms of HH, with higher SF levels found for persons with clinical manifestations.16 It should be noted that ferritin is an acute-phase reactant and may be elevated in other disorders, notably inflammation, infection, and malignancies. These conditions should be ruled out in order to properly evaluate an elevated SF.

Confirmation of hemochromatosis in persons with elevated screening results (TS and SF) may be achieved by one of three methods: laboratory testing for \( HFE \) mutations, quantitative phlebotomy, or liver biopsy. Quantitative phlebotomy documents the number of units of blood, and thereby amount of iron, removed over time and is performed as part of iron overload therapy. Iron accumulation in tissue has traditionally been confirmed by liver biopsy, but biopsy is now recommended only if liver disease is suspected.15

The presence of \( HFE \) genotypes associated with HH such as homozygosity for C282Y or compound heterozygosity for C282Y and H63D, coupled with laboratory evidence of iron overload, typically confirms a diagnosis of HH. DNA analysis for \( HFE \) mutations is most useful in confirmatory testing of individuals with documented iron overload (increased TS and SF), in testing pre-symptomatic persons (increased TS, normal SF, and normal liver enzymes), and in screening family members of individuals diagnosed with HH. Genotyping of first degree relatives of affected family members is recommended, but testing of children can be postponed until age 20 because of typical lack of organ damage before this age.17 DNA testing for \( HFE \) mutations alone can not predict severity of HH. At the present time the College of American Pathologists, Centers for Disease Control and Prevention, and other consensus groups do not recommend the use of genetic tests for routine screening of asymptomatic persons (population screening).15,18,19

Lack of access to healthcare may prevent some individuals from being tested for HH. Without regular health assessments, some persons with early HH may progress to develop significant iron overload, seeking healthcare only when serious and costly medical conditions arise. It has been estimated that at least 40 million Americans are without health insurance. Increasing access to laboratory screening tests may lead to earlier detection of HH, thus improving health and reducing healthcare costs in the long term.

The goal of the Hemochromatosis Education and Screening Project (HESP) was to provide free laboratory screening tests for HH to low-income residents of WNC. This area of the southern Appalachians is inhabited predominantly by persons of northern European descent, including Scots, Irish, and English.20 The percentage of white residents in the 18 WNC counties included in this study was 93.3.21 Because HH is found in the highest prevalence in persons of Celtic descent, it was thought that there might be many cases of HH among WNC residents.

WNC is a region with low per capita income and is considered a medically underserved area. The per capita income for the 18 counties participating in HESP is $23,254, which is well below the North Carolina state average of $27,785. Over 20% of residents are enrolled in Medicaid, and 12.9% live below the poverty level. There is, on average, one primary care physician per 1,513 residents, considerably below the state average of one per 1,193.21 Due to lack of primary healthcare or medical insurance, many residents of WNC may have limited access to testing for HH.
Funding for HESP was obtained from a grant by a private foundation, the Kate B. Reynolds Charitable Trust (Winston-Salem, NC). Laboratory Corporation of America (Burlington, NC) and Kimball Genetics (Denver, CO) significantly discounted charges for the laboratory screening and confirmatory tests, respectively. Additional personnel support came from the NC Department of Health and Human Services Genetic Health Unit, 18 county health departments in WNC, and the Department of Allied Health Sciences at the University of North Carolina at Chapel Hill.

Members of an advisory board composed of clinical laboratory scientists, geneticists, public health directors, physicians, health educators, and patients reviewed all materials and evaluated methods prior to implementation. The Institutional Review Board of the University of North Carolina at Chapel Hill School of Medicine approved this project.

MATERIALS AND METHODS

Procedure

The Hemochromatosis Education and Screening Project was divided into three phases conducted over an approximate 15-month period (Figure 1).

Phase 1 (screening) consisted of 19 one-day screening events held at local public health department (PHD) facilities in 18 counties in WNC during 2001. In order to reach the widest audience, screening events were publicized several weeks in advance through the local PHDs. Methods of notification included flyers posted at PHDs, places of employment, churches, senior centers, and other locations. Public service announcements in local newspapers and on radio and television were also used. PHD staff advised HESP staff on suitable methods for promoting local screening events and assisted with distribution of promotional materials.
Each participant spent approximately 45 minutes completing all HESP requirements. Typically two HESP staff members administered informed consent, completed laboratory test requisitions and other paperwork, and answered subjects’ questions. One to three phlebotomists, hired by HESP, were scheduled for each event in order to perform venipunctures on the subjects. PHD staff assisted with directing participants and other functions such as specimen processing.

Venipunctures were performed on all subjects participating in Phase 1. Most subjects were non-fasting, as appointments were scheduled throughout the day of the screening event. Code numbers were used to identify subject samples. HESP staff later matched coded test results to subjects’ identities for purposes of reporting. Blood specimens were sent by courier to a single reference laboratory in NC for testing.

Both subjects and their healthcare providers were notified in writing by HESP staff of the Phase 1 screening test results, including numerical results and a brief interpretation. Two copies of the letter were mailed to subjects who had not identified a healthcare provider. Primary healthcare was provided by local PHD staff for many subjects. Healthcare providers of participants with elevated TS results were sent additional materials on diagnosis and treatment of HH.

A regional genetic counselor telephoned each participant with elevated TS results to discuss HH and to determine the individual’s desire to undergo further laboratory analyses including biochemical and genetic testing. Subjects could elect to withdraw from the study at this point.

Phase 2 consisted of conducting confirmatory laboratory tests on Phase 1 subjects who had elevated screening results. Participants in Phase 2 were asked to schedule an appointment for venipuncture and report to the local PHD after a 12 hour fast. PHD staff completed paperwork, collected blood, and sent specimens to the reference laboratory for the relative small numbers of subjects requiring Phase 2 testing. At this time, Phase 2 participants were also given home collection kits for DNA testing and instructions for collecting and mailing specimens to the reference laboratory.

Phase 2 subjects were mailed results of their confirmatory tests along with detailed interpretive information provided by the reference laboratory. Phase 2 participants were urged to share these results with their healthcare providers; however, providers were not given Phase 2 testing results by HESP.

Participants with HFE mutations associated with HH were advised by the regional genetic counselor to discuss these findings with their blood relatives. First-degree family members (mothers, fathers, siblings, and children) were invited through their relatives to participate in Phase 2 testing. HESP provided them with printed information for distribution. Testing was limited to only those relatives residing in the project’s service area of WNC. PHD staff conducted Phase 2 activities on participating family members, including collecting blood and obtaining informed consent. The regional genetic counselor also contacted family members who consented to undergo Phase 2 testing in order to provide additional information about HH and genetic testing.

Phase 3 consisted of the administration of written surveys to study participants. Survey A (Table 1) was mailed in January 2002 to a random sample of 120 Phase 1 participants: 60 with normal TS and 60 with elevated TS (≥ 45%). Survey B (Table 2) was mailed in March 2002 to 41 subjects with mutations associated with HH.

HESP assumed the cost of laboratory testing of all subjects, but did not pay for transportation, medical care, or treatment of participants. HESP staff assisted participants with locating healthcare providers if needed. Genetic counseling was provided by the State of North Carolina regional genetic counselor. Participants received no financial incentives or inducements to join this study.

Laboratory analyses
Tests performed on Phase 1 participants were serum iron (SI), total iron binding capacity (TIBC), and the calculation of transferrin saturation (TS). Because screening events took place throughout the day, participants in Phase 1 had not been instructed to fast. Subjects with TS ≥45% were referred for Phase 2 confirmatory testing.

Tests performed on Phase 2 participants included SI, TIBC, TS, serum ferritin (SF), and DNA tests for two HFE mutations commonly associated with HH: C282Y and H63D. Participants were instructed to fast for 12 hours prior to Phase 2 blood collection. Subjects were given cheek cell home collection kits supplied by Kimball Genetics for DNA analyses.

Subjects who were found to be homozygous for C282Y or compound heterozygous for C282Y and H63D were considered to have HFE genotypes consistent with HH.
Subjects with these $HFE$ genotypes and elevated SF were considered to have HH. SF levels >200 $\mu$g/L in pre-menopausal women or >300 $\mu$g/L in men or post-menopausal women were considered elevated. Subjects were not assessed for clinical signs and symptoms of HH as part of the study.

**Subjects**
Subjects for Phase 1 were adult volunteers age ≥ 20 who were not known to have HH. Knowledge of health status with regard to HH was by self-report on the Participant Information Sheet. Two participants with previously diagnosed HH were tested, but were excluded from data analyses.

Subjects for Phase 2 consisted of two groups. One group was composed of Phase 1 participants with TS results ≥45%. A second group consisted of family members of the Phase 1 participants who had $HFE$ mutations consistent with HH. All subjects in Phase 2 were adult (age ≥ 20) volunteers.

Subjects for Phase 3 were participants in Phases 1 and/or 2. Subjects were randomly selected to complete Survey A. All participants identified through testing as having HH mutations were mailed copies of Survey B.

Subjects gave written informed consent for participating in all phases of HESP.

**Materials**
A one page participant information sheet was used to collect subjects' demographic and contact information. Participants were also asked to list the name and address of their healthcare providers so that Phase 1 results could be directly mailed. An informed consent document was used to explain the project’s methods, benefits, and

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**Table 1. HESP Phase 3 Survey A**

Please circle the correct answer for each question.

1. I knew about the disease hemochromatosis before I took part in this project.
   - YES
   - NO

2. I first learned about hemochromatosis when I went for my blood test.
   - YES
   - NO

3. The videotape I watched was helpful in learning about hemochromatosis.
   - YES
   - NO

4. The printed information I got was helpful in learning about hemochromatosis.
   - YES
   - NO

5. Talking to the project staff was helpful in learning about hemochromatosis.
   - YES
   - NO

6. I told my friends and family about hemochromatosis because of this project.
   - YES
   - NO

7. My hemochromatosis test result (transferrin saturation) was
   - NORMAL
   - LOW
   - HIGH

8. I talked to my health care provider (doctor or nurse) about my test results.
   - YES
   - NO

9. I talked to project staff on the phone about my test results.
   - YES
   - NO

10. Talking to project staff was helpful in understanding my test results.
    - YES
    - NO

11. I am now being treated for hemochromatosis.
    - YES
    - NO

12. I heard about the hemochromatosis testing event from.
    - FRIEND
    - RADIO
    - TV
    - CHURCH
    - WORK
    - DOCTOR
    - HEALTH DEPARTMENT
    - BULLETIN BOARD
    - OTHER

Comments:
potential risks, and to give contact information for the study’s sponsor and principal investigator. A copy was given to each participant for his/her personal records. A two-page brochure was used to provide printed information about HH for the participants to take home. All documents were written by HESP staff at appropriate literacy levels to reflect those of the target population.

A ten minute videotape was shown in order to give potential participants additional information on HH prior to giving informed consent. The Institutional Review Board of the University of North Carolina at Chapel Hill School of Medicine approved all materials.

RESULTS

Nineteen screening events were held in 18 counties in WNC over a 12-month period. The number of participants per one-day screening event ranged from 31 to 241, with an average of 92 subjects per event. Two events were held in one county to accommodate the large number of residents interested in being tested. A total of 1,976 subjects completed Phase 1 of the project by undergoing screening for HH.

The number of Phase 1 participants with elevated TS (≥ 45%) was 130 of 1,976 (6.6%). Participants with elevated TS were found in all but two counties. These were the two with the lowest number of participants: 31 and 39.

Table 2. HESP Phase 3 Survey B

Please circle YES or NO to the following questions

1. I saw my doctor (or nurse or other healthcare provider) and gave him/her the results of the laboratory tests for hemochromatosis.
   YES   NO

2. I am being treated for hemochromatosis.
   YES   NO

3. I am not being treated for hemochromatosis, but my doctor (or nurse or other health care provider) is aware of the laboratory test results.
   YES   NO

4. I have told my family members about hemochromatosis.
   YES   NO

5. This project provided useful information about my health.
   YES   NO

Please feel free to add comments:

Of 129 Phase 1 subjects taking part in Phase 2, 31 (24.0%) had HFE mutations consistent with HH. Twenty of 129 (15.5%) subjects were homozygous for C282Y, and 11 (8.5%) were compound heterozygous for C282Y and H63D. The remaining 98 participants (76.0%) were homozygous for H63D, heterozygous for C282 or H63D, or had normal HFE genotypes. Of 1,976 total Phase 1 participants, 31 (1.6%) had HFE mutations commonly associated with HH. The prevalence of HFE mutations commonly associated with HH among all Phase 1 study participants was .016.

Of the 20 subjects who were homozygous for C282Y, 14 (70%) had elevated SF levels. The mean SF level for this group was 485.4 μg/L, and the range was 312 to 1,077 μg/L. None of the 11 compound heterozygotes demonstrated elevated SF. Fourteen participants in Phase 1 testing thereby met both criteria for a diagnosis of HH in this study: presence of an HFE mutation and elevated SF.

Fifty-eight family members of Phase 1 subjects with HFE mutations took part in Phase 2 testing. Ten of the 58 family members (17.2%) were found to have HFE genotypes associated with HH, including two who were homozygous for C282Y and eight who were compound heterozygous for C282Y and H63D. Twelve family members were unable to complete biochemical testing as they resided outside of the project area. Of the 46 family members undergoing biochemical testing for iron, 12 (26.1%) had either an elevated TS or SF or both. One family member, a C282Y homozygote with an elevated SF, met both criteria for a diagnosis of HH as defined by this study.
A total of 2,034 subjects were screened for HH, including 1,976 Phase 1 participants and 58 family members. The mean subject age was 53.0 years, and the range was 20 years to 96 years. 70% of study participants were female. Race was indicated as white by 98.2% of subjects.

Sixty-four of the 120 (54.2%) randomly selected Phase 1 subjects responded to Survey A. 53.1% of respondents were unaware of HH prior to the screening event. 92.1% of respondents told their family and friends about HH after participating. 73.4% discussed their laboratory results with their healthcare provider. Twenty-four of 41 Phase 2 participants (73.4%) discussed their laboratory results with their healthcare provider. Twenty-four of 41 Phase 2 participants (58.5%) found to have HFE mutations responded to survey B. Eleven of 24 (45.8%) were being treated for HH.

DISCUSSION

Screening volunteers using free laboratory tests was found to be an effective way to detect undiagnosed hereditary hemochromatosis (HH) in a population of adults in a medically underserved region of western North Carolina. Fourteen previously undiagnosed subjects met the criteria for a diagnosis of HH through participation in this study. Eleven participants stated on a follow-up survey that they were currently being treated for HH.

Through the promotion of free screening events by local PHDs, over 2,000 individuals were tested for HH during a one-year period. HESP staff considered the average of 92 subjects recruited per event adequate to justify using this approach. In one county, a second screening event was needed to accommodate the number of residents requesting screening. HESP staff believed that planning and working with PHD staff was crucial to the project’s success and attests to the key role played by these agencies in delivering primary care to medically underserved residents. In all counties, HESP was viewed as providing a vital service to PHD patients. PHD directors serving on the HESP advisory board indicated that screening for HH in this population could not have been undertaken without the services of HESP.

The prevalence of the major mutation associated with HH, homozygosity for C282Y, was found to be 0.10% of the participants screened in Phase 1. This is considerably higher than the prevalence reported in other population screening studies. There are two possible interpretations of the high prevalence determined by this study. It may be that the true prevalence in the population of Caucasians residing in WNC, many of whom are descended from early settlers of Celtic ancestry, is actually 0.10%. An alternate explanation is that publicizing the screening events was effective in recruiting volunteers at greater risk for HH, in which case the study’s findings over-estimate the true prevalence. Approximately 47% of Phase 1 participants responding to Survey A indicated they were familiar with HH before enrolling in the study. Because data were collected on volunteers who attended HH screening events and were not collected on a random sample of the area’s population, the prevalence cannot be generalized. Only additional studies on random samples will adequately address this issue.

During Phase 2, fourteen participants in Phase 1 screening were found to have HFE mutations associated with HH and elevated SF. These subjects, along with one family member, meet the criteria for diagnosis of HH as defined by this study. Furthermore, 11 Phase 2 participants indicated on a self-report follow-up survey that they were being treated for HH. It should be noted that case definition of HH may take into account the presence of clinical signs and symptoms and that clinical findings were not included in this study. Inclusion of clinical findings could alter the number of persons diagnosed with HH.

The two-tiered reflexive approach used in this study appears to have been successful in that 129 of the 130 Phase 1 participants with elevated TS returned for confirmatory testing. Using a two-tiered reflexive approach with relatively low-cost biochemical tests may have kept the costs of screening lower than if more expensive genetic tests were included in Phase 1 testing of 2,034 subjects. Theoretically, screening could be more cost-efficient by also ensuring that subjects were fasting for Phase 1 testing, thereby eliminating the need for repeating TS. Determining the actual cost-effectiveness of screening for HH was not included in this project and could be the subject of future studies.

HESP appears to have been moderately effective in increasing awareness of HH as a health concern among participants. A substantial number, 53.1%, of respondents were unaware of HH prior to the screening event. Very importantly, 92.1% of respondents told their family and friends about HH after participating, and 73.4% discussed their laboratory results with their healthcare providers. Efforts to publicize HESP screening events may also have increased public awareness of HH. Laboratory results and information about HH sent to participants’ healthcare providers may have contributed to increased awareness of HH in the medical community. The true impact of the project on increasing public awareness is difficult to assess.
The overall benefits of this screening project to the medically underserved residents of western North Carolina are also hard to quantify. Given the current belief that only 10% of affected persons are likely to be diagnosed, it is possible that many of 11 HESP participants who are currently being treated for HH would not have sought medical care for HH without this project. One can also speculate that they benefited from an earlier diagnosis. For the 15 participants identified with laboratory results consistent with HH, early diagnosis may have prevented the development of serious medical conditions associated with the late stage iron overload of HH and thereby reduced morbidity and associated healthcare costs.

Of concern is the project’s inability to pay for treatment or to follow-up with subjects found to have HH. It is encouraging that 11 subjects stated on the survey that they were being treated. This finding suggests that resources are available, even in a population considered to be medically underserved. Another concern is that because a biochemical marker for iron, TS, was used as an initial screening test, it may be that some younger HESP participants will develop iron overload later in their lives. This project did not provide for future re-testing of younger participants.

Anecdotal evidence gathered from the follow-up surveys is supportive of the benefits of HESP. One participant commented, “This HESP project probably helped save my life and I greatly appreciate the effort it took to see this project through.” A 28-year-old participant stated, “Because of all this, my mother, aunt, and uncle have also been diagnosed with hemochromatosis and are being treated. If it were not for the screening, none of us would have ever been aware of the disease.” Another remarked that the project “really helped my family”. One participant commented, “I wish I had been diagnosed earlier in life, as this disease has damaged my body considerably.”

HESP could serve as a model for future efforts to provide screening for genetic disorders to targeted populations through collaboration between clinical laboratory scientists, public health agencies, the private sector, and others. HESP demonstrates that there is an important role for clinical laboratory scientists in directing the appropriate use of laboratory tests in a public health setting. However, the problem of long-term funding for such projects is unresolved. It is unlikely that state legislatures will fund screening for adult-onset disorders as they have for newborn screening. In general, while other studies have shown that screening for HH can be cost effective, questions about the likelihood that persons with HFE mutations will develop iron overload will also have an impact on the advisability of population screening. Education of healthcare providers to enhance case finding in symptomatic persons through the use of appropriate laboratory tests may afford another approach to improving detection of HH.

ACKNOWLEDGEMENTS

The author wishes to acknowledge the following individuals and organizations for their outstanding contributions to HESP and the residents of western North Carolina: Sally K. Zwadyk MS, HESP Director; Robin Fletcher MS, Regional Genetics Counselor, NC Department of Health and Human Services; the Kate B. Reynolds Charitable Trust, Health Care Division; Laboratory Corporation of America; Kimball Genetics; and the Public Health Directors of the 18 participating counties.

REFERENCES

DEPARTMENT OF CLINICAL LABORATORY SCIENCES
SCHOOL OF ALLIED HEALTH PROFESSIONS
VIRGINIA COMMONWEALTH UNIVERSITY

FACULTY POSITION

The Department of Clinical Laboratory Sciences at Virginia Commonwealth University invites applications for a full-time, 12 month, tenure-track faculty position. The Department, located on the MCV Campus of VCU, is one of nine departments in the School of Allied Health Professions. VCU is a large urban, research-extensive institution with a richly diverse university community and commitment to multicultural opportunities. The Department offers both B.S. and M.S. degree programs in Clinical Laboratory Sciences and provides the CLS specialty track in the Ph.D. program in Health Related Sciences.

The successful candidate will be responsible for teaching clinical immunology and immunohematology/blood banking courses on-campus and on-line at the undergraduate and graduate levels, interacting with clinical faculty at affiliated clinical sites, and student mentoring. Also expected are scholarly activities/ research, university service responsibilities and professional activities.

Applicants must have a Master’s degree (Ph.D. preferred), national certification as a generalist in the clinical laboratory, clinical or college teaching experience, excellent interpersonal and written/oral communication skills, and demonstrated scholarly productivity. Preference will be given to applicants with specialist certification in blood banking and a record of active participation in professional societies.

Salary and rank will be commensurate with education and experience.

Review of applications will begin immediately and continue until the position is filled. Send a letter of interest, curriculum vita and the names of three references to: William Korzun, Ph.D., Department of Clinical Laboratory Sciences, Virginia Commonwealth University, P O Box 980583, Richmond, VA 23298-0583.

Virginia Commonwealth University is an equal opportunity/affirmative action employer. Women, minorities, and persons with disabilities are encouraged to apply.
OBJECTIVE: Upon completion of this article, the reader will be able to describe learning objects (LOs) and discuss their use in clinical laboratory sciences instruction.

DESIGN: Through a questionnaire, educators evaluated clinical laboratory sciences-related LOs for accessibility, usability and instructional qualities.

SETTING: LOs were presented on a password-accessed website. Evaluations were completed on the website.

PARTICIPANTS: Nine educators participated in the evaluation.

INTERVENTIONS: The LOs were made available to participants for use in their own instructional material.

MAIN OUTCOME MEASURE(S): The evaluation measured educators’ interest in and perceived usefulness of LOs in clinical laboratory sciences curriculum.

RESULTS: On a scale of one to five with one equal to poor and five equal to excellent, participants rated LOs as accessible (4.68) and usable (4.61). Ninety-eight percent stated that they would use LOs in their curriculum. Fifty-seven percent stated that they could attribute improved learning performance on student exposure to LOs.

CONCLUSION: LOs are useful, relevant, and time-saving resources to clinical laboratory sciences instruction.

ABBREVIATIONS: CLS = clinical laboratory sciences; LO = learning object.

INDEX TERMS: instruction; Internet; teaching.

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Yasmen Simonian PhD is the Focus: Educational Technology II guest editor.

Focus Continuing Education Credit: see pages 191 to 192 for learning objectives, test questions, and application form.

Learning objects (LOs) are elements of a new type of computer-based instruction grounded in the object-oriented paradigm of computer science. LOs are instructional components that can be reused in different learning contexts to communicate material that is jointly used in the presentation of many topics. These elements can be delivered over the Internet, and accessed by a number of individuals simultaneously. LOs often represent autonomous, fundamental concepts presented by most instructors. Through joint preparation and review, creators standardize the content element while reducing instructional preparation time. Individuality is retained by the instructor through the choice of context in which the LO is used.

Key to the development of LOs is the ability to name and easily retrieve the object. Although all LOs have certain
properties, it is their differences that aid in categorization. Several taxonomies may be used to differentiate LO types. Bloom provides a system of differentiating statements by cognitive levels. Proponents of LOs suggest a system of differentiating LOs on the basis of the instructional design, technology, and interactivity of the object:

- Fundamental – a JPEG of a hand playing a chord on a piano keyboard
- Combined-closed – a video of a hand playing a chord on a piano keyboard with accompanying audio
- Generative-presentation – a chord identification problem
- Generative-instructional – instructs and provides practice for any type of procedure

Properties that add to ease of use for LOs include consistent use of terminology, use of comprehensible formats, absence of references to other LOs, uniformity of grammar and tone, consistency of language level and the use of searchable keywords. Content management of LOs is aided by the use of a metatag, or descriptive information about the LO. Metatags facilitate storing, searching, and retrieval of content by technological databases.

Traditional instructional media, such as an overhead or videotape, may be used by one instructor at one time. LOs may be used by thousands of instructors and students at one time. Instructors may collaborate on the creation of LOs for increased standardization and time savings. Such object-orientation is grounded in instructional theory. Reigeluth and Nelson suggest that when teachers organize instructional materials, they break the content down into fundamental components. They reassemble the components to support their own context. Burns and Parlett describe expert performance as the process of disintegration of complex performances into progressively simpler performance units. It is a natural step to apply this expert performance to the creation of digital technology. In this model, instructors do not have to develop their own instructional components. Instead they can use objects developed by others, bypassing the step of breaking down lessons to repackage in their own lesson format. This allows for increased speed and efficiency of instructional development and decreased faculty preparation time. Merrill applies an algorithmic model of computing to instruction, in which knowledge is represented by data and instructional strategies are represented as algorithms.

The use of LOs applies the learning theory of constructivism. Constructivism describes learning as an active process of constructing rather than acquiring knowledge, and it describes instruction as a process of facilitating that construction. Constructivists propose that the learner individually interprets experience from a knowledge base that permits reference, reuse, and reconfiguration of knowledge objects. They suggest that the same knowledge objects can be configured into different types of instructional formats including presentation, practice, and learner evaluation. Central to the theory of constructivism is the belief that learners perceive knowledge objects differently, based on their own set of experiences.

LEARNING OBJECTS FOR CLS INSTRUCTION

In clinical laboratory sciences (CLS), the body of knowledge expected of CLS graduates has been defined on a national level. Given that the contents of curricula across CLS programs are comparable, high-quality, easily accessible, digital multimedia that can be incorporated into CLS program materials and lessons could be advantageous for CLS educators. Although the idea of sharing resources seems reasonable, design for effective implementation in a variety of settings can make the task seem overwhelming. The variety of models that exist in CLS education creates a challenge for collaborative efforts among programs. Course scheduling becomes difficult for programs interested in sharing courses and faculty resources. For example, in a one year CLS hospital-based program, specific course content may be integrated into the clinical preceptorship time or presented in short seminars, whereas a two year university program may teach this content in specific courses. Additionally, with the decrease in CLS programs, an effort to provide more educational opportunities for students through distance learning is being made. A major difficulty in providing education has been the lack of quality educational materials that are easily shareable. In a review of electronic educational materials available to CLS programs, very little can be found in a format that is easily identifiable and transferable between programs. Limited image collections on DVD and CD are available from a few textbook publishers and professional associations. These collections are not user friendly for faculty teaching courses, have not been appropriately cataloged for easy faculty accessibility, and are not readily available to students without additional expense. Existing materials are primarily embedded in platform specific course delivery systems, are course specific, and are not readily sharable.

Because LOs are visual in nature, they could be an asset for the development of lesson structure in distance learning, computer-assisted, and traditional classroom environments.
The use of CLS LOs may reduce the preparation time for lectures, examinations, and remediation materials, freeing instructors to focus on other tasks. This article will discuss the results of a survey of CLS and microbiology faculty members who have reviewed a series of newly created LOs for accuracy, clarity, interactivity, and durability. Data from these reviews will guide final preparation of each LO for distribution.

MATERIALS AND METHODS
The University of Texas Medical Branch CLS Program partnering with the University of Nebraska Medical Center CLS Program received a Fund for Improvement for Postsecondary Education grant to create LOs for CLS and disseminate them via an online repository. The CLS repository is currently focused on microbiology and immunology. Partners in the project divided instructional material into autonomous content. Content was deemed appropriate for development of LOs if it could be used in a variety of presentations and it was visual in nature. The instructional content includes biochemical reactions, organism identification and panel selection, and gram stain quality control. These LOs were created, maintained, and stored for use as resources for lectures, reviews, or tests that may be used individually or with other LOs to create interactive content. They include a combination of drawings, still photographs, animations, videos, audio clips, and text components. The partners in the CLS project have chosen to differentiate LOs in a modification of the Wiley system:

• Level 1 LOs display simple graphics. A photo of a gram-negative bacillus or an agar plate showing *Escherichia coli* colonies are examples of Level 1 LOs.

• Level 2 LOs consist of an animation or video clip showing a specific mechanism. A positive oxidase test with text describing the procedure is an example of a Level 2 LO.

• Level 3 LOs provide instruction and practice requiring student interaction. A Level 3 LO might be an animation requiring the student to drag and drop agar plates in the correct incubation environment or an exercise requiring interpretation of a biochemical panel, in which the student must add specific reagents. This level includes one to two objectives and a short unit of instruction including the interactive component.

Partners in the CLS project prepared and categorized LOs. Learning objects were categorized by several partners to maintain inter-rater reliability. Reviewers were recruited through Internet-based listserves and presentations at professional conferences. Nine educators evaluated 105 LOs. Not all evaluators evaluated all LOs. Reviewers accessed the project via a website, http://webcls.utmb.edu/lo/, and obtained a user identification and password. Through the descriptive terminology of the storage database, reviewers chose LOs, which could be downloaded to the reviewer’s electronic storage. After examining the LO, the reviewer completed an online FOCUS: EDUCATIONAL TECHNOLOGY evaluation.

Table 1. Results of the evaluation survey

<table>
<thead>
<tr>
<th>Question/Evaluation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate the learning object (LO) for</td>
<td></td>
</tr>
<tr>
<td>Accessibility</td>
<td>4.68*</td>
</tr>
<tr>
<td>Usability</td>
<td>4.61*</td>
</tr>
<tr>
<td>Instructional qualities</td>
<td>4.55*</td>
</tr>
<tr>
<td>Overall evaluation</td>
<td>4.33*</td>
</tr>
<tr>
<td>Using the LO saved time</td>
<td>yes, 90%</td>
</tr>
<tr>
<td>Time saved by using the LO</td>
<td>1 hour</td>
</tr>
<tr>
<td>Areas in which time was saved†</td>
<td></td>
</tr>
<tr>
<td>Lesson or course development</td>
<td></td>
</tr>
<tr>
<td>Student learning</td>
<td></td>
</tr>
<tr>
<td>Gain in learning attributed to LO</td>
<td>yes, 57%</td>
</tr>
<tr>
<td>Performance gain attributed to LO†</td>
<td></td>
</tr>
<tr>
<td>Improved performance on assessment of didactic</td>
<td></td>
</tr>
<tr>
<td>content, content comprehension</td>
<td></td>
</tr>
<tr>
<td>and competency</td>
<td></td>
</tr>
<tr>
<td>Will use LOs again</td>
<td>yes, 98%</td>
</tr>
</tbody>
</table>

*Average of rating responses to all LOs, rating scale 1 through 5 where 1 = poor and 5 = excellent
† Subjective evaluation by individual reviewers
questionnaire. Each LO was reviewed separately. Reviewers were rewarded with free use of these LOs. The evaluation questions are indicated in Table 1.

RESULTS
Evaluation ratings and comments were stored within the website database and accessed as cumulative data. Table 1 shows the results of the survey. Average responses were computed on the basis of responses to all LOs.

DISCUSSION
LOs offer the ability to share resources. They are fundamental elements of a model for content creation and distribution. The survey results show that LOs are useful and accessible elements of high quality technology. Fifty-seven percent of the educators stated they could attribute some aspect of increase in learning to student exposure to LOs. Several educators stated they were not able to determine this factor because they had not yet evaluated their students.

Anecdotally, reviewers suggested that the partners needed to develop LOs in more commonly used formats to ease LO downloading. Instructions for downloading programs for viewing and using the LOs must accompany each LO that relies upon the program. The project will continue to develop LOs for the CLS repository and encourage submission of LOs to the Internet repository by other educators.

LOs provide fundamental knowledge through technology-based, searchable resources. However, knowledge is not enough; the educator’s goal is to engender student understanding. Only with understanding will the student have the ability to think and act flexibly while using that knowledge. LOs provide elements of knowledge; educators facilitate understanding. Shared resources providing the knowledge component allow educators the time and flexibility to accomplish understanding more readily and in a variety of educational settings.

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REFERENCES
Teaching and Assessing New Method Verification Skills Using Interactive Simulations

Leonard Gary Nielsen

ABBREVIATIONS: CLIA = Clinical Laboratory Improvement Amendments; CLS = clinical laboratory science; CMS = Centers for Medicare and Medicaid Services; WSU = Weber State University.

INDEX TERMS: education; laboratory simulations, new method verifications.

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Focus Continuing Education Credit: see pages 191 to 192 for learning objectives, test questions, and application form.

Since the introduction of the Clinical Laboratory Improvement Act of 1988 every laboratory has faced new regulatory compliance challenges including Clinical Laboratory Improvement Amendments/Centers for Medicare and Medicaid Services (CLIA/CMS) pre-use verifications of the manufacturer’s performance claims of each new instrument and method used in the laboratory. Skills in planning and conducting such verification studies are among those which should be taught to students preparing for careers as clinical laboratory scientists.

I present a method to teach and assess student skills in planning and conducting a new method verification that is being successfully utilized in my CLS-3314 Advanced Clinical Chemistry course of Weber State University’s (WSU) CLS program, both on-campus and online. The method, which does not impact actual patient care or the laboratory workflow or significantly affect program budget, uses an interactive simulation approach in which each and every student has the opportunity to design and direct a customized verification study. In a prerequisite course, the students first define the components of method verification prescribed by the current CLIA/CMS regulations. They learn the requirements for verifying accuracy, precision, analytical measurement range, sensitivity, and that the reference range used is appropriate for the patient population being served. Next, in the Advanced Clinical Chemistry course these verification skills are assessed and enhanced. The course requires that student assume the role of a technical consultant to a laboratory, plan and design each verification experiment, and create explicit written instructions on how each experiment should be conducted.

This simulation follows this concept: “If one can teach someone else to do something, then the teacher has mastered the task” (source unknown). As a former technical consultant to a large reference laboratory who has directed and designed numerous instrument and method verifications, I rarely performed the actual testing. Rather, I developed very detailed experimental designs and assay instructions that allowed others to perform it. After the actual testing had been performed, I evaluated the results of each experiment using appropriate statistical analyses, and then made the appropriate decisions or recommendations regarding the use of the method for patient care. I believe that the most critical method verification skills involve:

- knowing exactly what experimental studies must be done.
- carefully designing each verification experiment.
FOCUS: EDUCATIONAL TECHNOLOGY

- developing explicit written instructions for others to follow.
- evaluating the test data and performing appropriate statistical analyses on that data.
- drawing the appropriate conclusions about each verification experiment.
- documenting the verification process and conclusion as a formal report.

Actually performing the analytical testing is the least significant of all the method verification skills. During this simulation the students follow the critical steps outlined above. The students are assigned to serve as a “technical consultant” to some hypothetical laboratory in this simulation exercise. They develop very detailed experimental design instructions that are submitted to a fictitious bench technologist who supposedly actually performs the testing according to those experimental designs. The test results are then returned to the student, who must evaluate the results of each experiment using appropriate statistical methods, and then make appropriate decisions or recommendations regarding the adoption of the method for patient care.

VERIFICATION TOOLS
During the simulation, both the students and the teacher use Microsoft Excel™ and Microsoft Word™ for the simulation.3 Excel is used for the statistical analysis using the Analysis ToolPak library, and Word is used to generate the experimental designs and assay instructions, method performance summary, and the final validation report. Alternate spreadsheet and word-processing software can be used, as well as specialized tools such as EP Evaluator™ if desired.4 For simplicity the simulation involves verifying an alternate commercial reagent to be used on a specific analyzer platform for a specific analyte, such as magnesium. In our simulations we use the Roche Cobas Mira S™ platform since these instruments are used in our student laboratories.5

PERFORMING THE SIMULATION
In the simulation, a new hypothetical reagent (“NuLab” magnesium reagent, as an example) is being considered for use on the analyzer, and the students are told that it has already been Food and Drug Administration/CMS-approved for use on that analyzer. The students are given the pertinent manufacturer’s performance claims for this reagent, and the verification involves documenting that the new reagent meets or exceeds the Food and Drug Administration-approved minimum performance criteria as specified in the manufacturer’s package insert. If so, the use of the new reagent can be implemented. If not, adoption of the reagent must be rejected.

The students must develop clear, detailed experimental designs for each validation experiment addressing accuracy (by recovery, calibration verification, and correlation with a reference method), analytical measurement range, within-run and run-to-run precision, minimum detection limit, and reference range (transference of an existing range or a reference range study, if required). The student’s instructions are then sent to the fictitious bench technologist. The teacher uses a spreadsheet to generate representative test results for each experiment, based upon each student’s experimental design. The raw data (test results) are returned to the student for review. Each student then evaluates the data from each experiment and performs the appropriate statistical analysis. The experimental results from each experiment are then compared to the performance specifications of the reagent manufacturer. At the completion of the simulation, each student must generate and submit a method performance summary sheet (to be an appendix to the method’s standard operating procedure), and a final verification report, for use during laboratory inspections to document the entire validation. The final verification report must summarize the experimental design of each experiment and the experimental findings. Each experiment must be included as an attachment to the report, complete with statistical analysis conclusions and charts, when appropriate. The students are instructed to format their spreadsheet printouts so that they are “report quality” in order to earn maximum points.

DISCUSSION
This simulation provides each student with all the challenges of an actual verification study, with the exception that the student does not actually perform analytical testing. This simulation is “interactive” from the standpoint that the faculty must generate raw data in accordance each student’s unique experimental design. Unfortunately, there can be considerable variation in acceptable designs among students. Some students may choose to follow Clinical and Laboratory Standards Institute (formerly the National Committee for Laboratory Standards)6 evaluation protocols, while others may follow alternate protocols. The students are given the charge to perform the verifications under conditions that maximize the efficiency of the verification (minimize reagent and labor costs while maintaining acceptable sample sizes, etc.), and complete sufficient studies so that the verification would ultimately “pass” an actual College of American Pathologists’ laboratory accreditation inspection. If a student submits an experimental design which is inappropriate or incomplete, the teacher should generate the corresponding data for the student. The teacher should then consult with the student in order to cor-
ect the mistake and provide retraining. Appropriate points may be deducted from the student’s project grade under the rationale of “unnecessary reagent/labor costs” at the discretion of the teacher. The written instructions for each experiment must be absolutely clear and complete to the extent that any technologist or technician could follow the instructions and correctly perform all necessary testing, which reinforces the need for developing excellent technical writing skills. If the instructions are not of sufficient quality, the instructions are returned to the student for clarification, and points may be deducted from the student’s final project score.

Since there can be a wide variation in experimental designs for each experiment, data sets for several common variations may be created ahead of time (for good designs as well as common substandard designs). For example, for the within-run precision study, several sample size variations might be specified by the students (n = 20, n = 30, n = 40). Additionally, there are several acceptable ways to assess accuracy. With expected variations such as these, the creation of additional data sets ahead of time will allow giving raw data back to the students in a timely manner. If the student’s design differs from those already created (forbid the thought), existing data sets may be modified quickly to match the student’s experimental design. Our CLS program uses simulations for 16 different analytes which allows every student to have their own “customized” verification project. While this approach requires considerable “up-front” developmental work by the teacher, our program’s faculty believes that the quality of the individualized learning process makes the extra effort worthwhile.

Grading each verification experiment is accomplished by the teacher’s assessing the appropriateness of each experimental design and performing the statistical analysis and evaluation in tandem with the student. This assesses (1) the student’s skills in method verification and (2) the student’s correct performance and interpretation of the statistical analyses.

CONCLUSION
The simulation presented is one tool which can be used to teach and assess new method verification skills. In the past our CLS program utilized student verification projects that involved actual assay work using our instrumentation, involved considerable reagent, control, calibrator, and disposable costs, and included the need to acquire large numbers of human serum or plasma specimens from our affiliated hospitals and clinics. After using this interactive verification simulation process, we have found it also to be effective in assessing and documenting CLIA/CMS pre-use verification skills. The costs for the simulation process are minimal since there are no reagent, control, calibrator, or disposable costs, nor is there any need to acquire actual human specimens. Even when done in an actual hospital setting, the simulation process causes no interference with actual patient care, since no “real-time” analyzer use is required. Equally important is the fact that each and every student has the unique opportunity of designing and directing a customized verification study.

My previous work experience in performing new method/instrument validations and verifications in actual hospital laboratories has contributed to the success of this validation simulation at WSU. Faculty interested in using a simulation process such as the one presented are encouraged to network with those in actual clinical laboratories who are conducting ongoing pre-use verifications. Such collaboration can generate a source of verification data and experimental design information from which to develop future simulations for student use.

REFERENCES
7. College of American Pathologists, Laboratory Accreditation Program, 325 Waukegan Road, Northfield IL 60093.
Continuing Education Questions

SUMMER 2006

To receive 1.0 contact hour of intermediate level P.A.C.E.® credit for the Focus: Educational Technology II questions, insert your answers in the appropriate spots on the immediately following page; then mail a photocopy of the form as directed.

NOTE: There may be more answer spaces on the sheet than needed. If so, please leave them blank.

LEARNING OBJECTIVES
After reading the two Focus: Educational Technology II articles in this issue, the reader will be able to:

1. Define the term “learning object”.
2. Describe the purpose of learning objects in the presentation of educational material.
3. Distinguish between educational levels of learning objects.
4. Discuss the retrieval and use of learning objects by clinical laboratory sciences educators.
5. Choose material that may be suitable for a learning object format.
6. Explain how new method verification simulations have educational advantages over actual verifications being performed in a working hospital laboratory.
7. Identify the major and minor parts of carrying out an actual new method verification.
8. Explain the verification tasks required of students performing new method verification simulations.
9. Discuss what the instructor must do upon receiving the experimental design for a verification experiment from a student.
10. Discuss what action the teacher should take if a student submits either incomplete verification instructions or an inappropriate/incomplete experimental design.
11. Explain what pre-verification work the teacher should do to accommodate acceptable variations in the experimental designs developed by the students.

CONTINUING EDUCATION QUESTIONS
1. Learning objects are:
   a. small, reusable, technology-based elements.
   b. textbooks.
   c. Internet-based curriculum templates.
   d. complete, stand-alone lessons.
2. Learning objects may be used for all of the following instructional events except:
   a. as a component of a lecture.
   b. sequentially, to create a presentation.
   c. as a component of a computer-based training system.
   d. as an example of the context.
3. Metatags facilitate:
   a. visual properties of learning objects.
   b. student interactivity with learning objects.
   c. the ability to use learning objects sequentially.
   d. retrieval and storage of learning objects.
4. A learning object that requires student interaction is an example of a Level ______ learning object.
   a. 1
   b. 2
   c. 3
   d. 4
5. A learning object that is a photograph is an example of a Level ______ learning object.
   a. 1
   b. 2
   c. 3
   d. 4
6. A learning object that is a statement of process illustrated by a video clip is an example of a Level ______ learning object.
   a. 1
   b. 2
   c. 3
   d. 4
7. Characteristics of learning objects include all of the following except:
   a. use of consistent terminology.
   b. use of reproducible formats.
   c. references to other learning objects.
   d. uniform grammar and tone.
8. Select the best example of CLS instructional material that would be appropriate to use as a learning object:
   a. presentation of a lecture on liver function
   b. textbook chapter on microbial pathogens in blood
   c. animation of antigen-antibody agglutination
   d. student laboratory exercise of the glucose oxidase procedure

9. The creation of learning objects models the preparation of instructional material by an expert in:
   a. providing the situational background for a concept.
   b. breaking instructional content into smaller and smaller concepts.
   c. linking facts to context.
   d. referencing statements of opinion.

10. Learning object is to instructional context as:
    a. instruction is to resources.
    b. words are to pictures.
    c. digital data is to algorithm.
    d. Internet is to webpage.

11. New method verification simulations have educational advantages over actual laboratory validations because:
    a. they do not impact patient care.
    b. they do not affect the actual laboratory workflow.
    c. they offer each student an opportunity of experiencing the entire validation.
    d. All of these are educational advantages.

12. According to the author of the verification article, which of the following verification processes is considered to be the least significant from an educational standpoint?
    a. performing the actual analytical testing
    b. designing the verification experimental designs
    c. reperforming appropriate statistical analyses on the data.
    d. writing explicit instructions for other technologists to follow

13. The verification tasks required of students performing new method verification simulations include all of the following with the exception of:
    a. developing each validation experimental design.
    b. writing explicit instructions for other technologists to follow.
    c. selecting the appropriate statistical tool to use for evaluating the data.
    d. determining whether or not observed differences in the new method compared to a reference method are clinically significant.

14. According to the article, what should the instructor do upon receiving the experimental design from a student for a verification experiment such as a within-run precision study?
    a. wait until the run-to-run precision design is also received before acting
    b. send test data back to the student which matches the instructions
    c. send test data to the student which differs from the instructions
    d. All of the above should be done by the instructor.

15. According to the article, identify the action the teacher should take when a student submits inappropriate or incomplete experimental design and/or assay instructions.
    a. refuse to accept the student submission
    b. give the student test data in accordance with the faulty design
    c. require the student to resubmit corrected design instructions
    d. Answers “b” and “c” should both be done by the teacher.
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Answers

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12. a b c d  
13. a b c d  
14. a b c d  
15. a b c d

1. Is this program used to meet your CE requirements for: (a) state license (b) NCA (c) employment (d) other

2. Did these articles achieve their stated objectives? (a) yes (b) no

3. How long did it take you to complete both the reading and the quiz? _____________minutes

4. What subjects would you like to see addressed in future Focus articles?
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