AMERICAN SOCIETY FOR CLINICAL LABORATORY SCIENCE
6701 Democracy Blvd, Suite 300
Bethesda, Maryland 20817
(301) 657-2768, (301) 657-2909 (fax)
www.ascls.org

Contributing Editors
Eileen Carreiro-Lewandowski/N Dartmouth MA
Deborah Josko/Newark NJ
Elaine Kohane/Newark NJ
Rebecca Laudicina/Chapel Hill NC
Connie Mahon/San Antonio TX
Linda Smith/San Antonio TX
Michelle Wright-Kanut/Galveston TX

REVIEW BOARD
Richard Bamberg/Greenville NC
Dianne Gearlock/DeKalb IL
Peter Colaninno/Jamaica NY
Jo Ann Fern/Salt Lake City UT
Ellis Frohman/St Louis MO
Mildred Fuller/Norfork VA
Abraham Furman/Portland OR
Richard Gregory/Indianapolis IN
Jesse Guiles/Newark NJ
Lester Hardegree/Bluffton SC
Denise Harnening/Baltimore MD
Daniel Hoeftner/Elon, NC
Linda Hogan/Wichita KS
Virginia Hughes/Montgomery AL
Linda Kasper/Indianapolis IN
Nancy Konopka/Gettysburg PA
Robin Kretetz/Cherry Hill NJ
Linda Laatsch/Milwaukee WI
Hal Larsen/Lubbock TX
Donna Larson/Gresham OR
Louann Lawrence/New Orleans LA
Marcia Lee/Oxford OH
Craig Lehmann/Stony Brook NY
Elizabeth Kenimer Leibach/Augusta GA
Lynn Little/Dallas TX
Carol McCoy/Minneapolis MN
David McGlasson/Lackland AFB TX
Sharon Miller/St Charles IL
Isaac Montoya/Houston TX
Harriette Nadler/King of Prussia PA
Joan Prince/Milwaukee WI
Margaret Reinhart/Philadelphia PA
Stephen Sodeke/Tuskegee AL
Lori Woeste/Normal IL

ASCLS Mission/Vision Statement
The American Society for Clinical Laboratory Science serves as the voice of all clinical laboratory professionals, creating a vision for the advancement of the clinical laboratory practice field, and advocating the value and role of the profession ensuring safe, effective, efficient, equitable, and patient-centered healthcare.

ASCLS Core Values
Core Values include enhancing quality standards and patient safety; providing professional development opportunities; promoting expanded roles and contributions of clinical laboratory professionals to the healthcare team; increasing the diversity in the profession; and expanding the voice and role of under-represented individuals and groups.

ADDRESS CHANGES
Postmaster: Send address changes to
Clinical Laboratory Science
6701 Democracy Blvd, Suite 300
Bethesda MD 20817

ASCLS MEMBER EDITORS
Editor-in-Chief
David G Fowler PhD CLS(NCA)
Office of the Associate Vice Chancellor for Academic Affairs
University of Mississippi Medical Center
2500 North State Street
Jackson MS 39216
601-815-1149, fax 601-984-2970
dfowler@acadaff.uams.edu

Continuing Education Editor
George A Fritsma MS MT(ASCP)
The Fritsma Factor
http://www.fritsmafactor.com
153 Redwood Drive
Trussville AL 35173
205-821-5641, fax 205-975-7302
geroge@fritsmafactor.com

Clinical Practice Editor
Bernadette Rodak MS CLSpH(NCA)
Clinical Laboratory Science Program
Indiana University
Clarian Pathology Laboratory
350 West 11th Street, 6002F
Indianapolis IN 46202
317-491-6218, fax 317-491-6163
brodak@iupui.edu

Research and Reports Editor
David L McGlasson MS CLS(NCA)
59th Clinical Research Division/SGRL
2200 Berquist Dr., Bldg. 4430
Lackland AFB TX 78236-9908
210-292-6555, fax 210-292-6053
david.mcglasson@lackland.af.mil

Advertising for CLS is accepted in accordance with the advertising policy of the ASCLS. Contact the CLS advertising representative at (301) 657-2768.

Manuscript Submissions: To encourage consistency in style, refer to guidelines in Scientific Style and Format – The Council of Science Editors Manual for Authors, Editors, and Publishers, 2006. Detailed instructions for authors are available on the ASCLS website. Contact the CLS Editorial Office for more information.

Inclusion in the journal of product names or author opinions does not constitute endorsement by either Clinical Laboratory Science or ASCLS.

Clinical Laboratory Science (ISSN 0894-959X) is published quarterly by the American Society for Clinical Laboratory Science, 6701 Democracy Blvd., Suite 300, Bethesda MD 20817; (301) 657-2768; (301) 657-2909 (fax).

Annual Subscription Rates:
USA Canada Non-USA
Individuals $60 $75 $125
Institution $75 $75 $125

Questions related to subscriptions should be addressed to: SherryM@ASCLS.org. The cost of single copies is $15. Requests to replace missing issues free of charge are honored up to six months after the date of issue. Send requests to ASCLS headquarters. Annual membership dues of ASCLS are $92, $40 of which is allocated to a subscription of CLS.

Periodical postage paid at Bethesda, MD and other additional mailing offices.

Postmaster: Send address changes to
Clinical Laboratory Science
6701 Democracy Blvd, Suite 300
Bethesda MD 20817

Correspondence related to editorial content should be mailed to: IC Ink, 858 Saint Anne’s Drive, Iowa City IA 52245; (319) 354-3861; (319) 338-1016 (fax)
ic.ink@mchsi.com
www.ascls.org/leadership/cl/index.htm

Managing Editor
Margaret LeMay-Lewis MFA

PRODUCTION
BB Design Studio
1608 Mountain Avenue
West Des Moines IA 50265

© Copyright 2007 American Society for Clinical Laboratory Science Inc. All rights reserved.
WASHINGTON BEAT

Competitive Bidding Demonstration Site Announced and Repeal Efforts Continue

PAULA GARROTT

Not long ago I was presenting a session at a regional ASCLS meeting entitled “Legislative and Regulatory Issues Impacting the Practice of Clinical Laboratory Science”. One of the participants, who also happens to be a good friend and colleague, after looking quickly at the handout said, “These look like the same issues we discussed last year.” I laughed and told him he was absolutely correct! Although there are many exciting developments in the advancement of the knowledge and technology impacting clinical laboratory science, on the legislative and regulatory side, it seems trying to enhance and protect reimbursement for clinical laboratory services is always at the top of our professional “issues” list. Without appropriate reimbursement for our services, clinical laboratories cannot provide the quality our patient public deserves!

The Medicare Clinical Laboratory Competitive Bidding Project is the current threat to assuring appropriate reimbursement for laboratory services. In my last article, I provided an update on the status of the project as well as initiatives to repeal the competitive bidding mandate. Much has happened since that writing.

The Centers for Medicare and Medicaid Services (CMS) announced that the site for the first of two competitive bidding demonstration projects, scheduled to run for three years each, would be the San Diego-Carlsbad-San Marco Metropolitan Statistical Area (MSA) in California. The Bidders Conference was originally scheduled for October 31, 2007. However, due to rampant fires producing emergency situations in that area, the conference was postponed. It has now been re-scheduled for December 5, 2007. The demonstration project requires all hospital outpatient and independent clinical laboratories in the MSA billing more than $100,000 annually in Medicare testing to bid if they want to continue to do such testing. Exemptions include physician office laboratories and laboratories that provide services exclusively to beneficiaries entitled to Medicare by reason of end-stage renal disease or in skilled nursing facilities. (Complete information regarding the demonstration project is available at the CMS website: www.cms.hhs.gov)

The bid package is based on 303 Health Care Procedure Coding System codes which represent approximately 99% of the tests reimbursed under the Part B Clinical Laboratory Fee Schedule according to CMS volume and payment data. According to CMS, multiple winners will be selected based on their ability to offer lower prices than the current fee schedule, provide quality services, and demonstrate testing capacity, as well as other quality thresholds. Laboratories not required to bid will be paid the competitively-set price for each test code. Non-winning laboratories will be allowed to serve as reference laboratories to the winning facilities but will not be able to bill Medicare directly.

ASCLS, along with other professional organizations, is planning a pre-conference session to be held the night before the Bidders Conference, to help laboratory professionals representing their laboratories in the competitive bidding process prepare by discussing the process, answering questions, and assisting in the formulation of questions that will need to be answered by the CMS representatives.

While the competitive bidding demonstration project continues, the efforts to repeal this mandate have escalated. In the last Washington Beat, we reported HR 3453, the Community Clinical Laboratory Fairness in Competition Act of 2007, had been introduced by Representative Nydia Velazquez (NY), chair of the House Small Business Committee. This bill amends Title XVIII of the Social Security Act to repeal the Medicare competitive bidding demonstration project for clinical laboratory services. Due to the grassroots efforts of clinical laboratory professionals contacting their Congressional representatives, support for this bill is gaining momentum. Additional co-sponsors include key members of the House Energy and Commerce Health Subcommittee.

Washington Beat is intended to provide a timely synopsis of activity in the nation’s capitol of importance to clinical laboratory practitioners. This section is coordinated by Paula Garrott, Co-chair of the ASCLS Government Affairs Committee; and Don Lavanty, ASCLS Legislative Counsel. Direct all inquiries to ASCLS, (301) 657-2768 ext. 3022, (301) 657-2909 (fax); or mail to ASCLS, 6701 Democracy Boulevard, Suite 300, Bethesda MD 20817, attn: Washington Beat.
In addition, on September 26, 2007, Senators Ken Salazar (D-CO), Pat Roberts (R-KS), and Maria Cantwell (D-WA) introduced S.2099, the Preserving Access to Laboratory Services Act of 2007. This companion bill to HR 3453 would also repeal the Medicare competitive bidding demonstration project for laboratory services.

Clinical laboratory professionals must continue to contact their members of Congress to educate them regarding the potential impact of competitive bidding for laboratory services on our ability to provide timely and high quality laboratory testing and diagnostic information. Please urge your congressional members to support HR 3453 and S.2099. Meanwhile, ASCLS is committed to work with our members in the San Diego MSA in an attempt to assure that should the demonstration project go forward, it will be implemented in a way that will minimize the negative impacts on laboratories and the healthcare providers and patients they serve.
It's a new year and there are some changes occurring with the Clin Lab Sci journal editorial staff. First let me begin by stating as the new editor-in-chief, I find myself in a situation with some very big shoes to fill. As you are probably aware, Dr. Susan Leclair is “retiring” from this position after serving the profession for two very productive terms. She has served admirably and has led the way to make the journal become more recognized as a first-rate journal. Clin Lab Sci is somewhat unique in its efforts to meet the needs of the members of our profession. Many journals only print research manuscripts. While these journals are recognized in the academic world as the premiere format, the Clin Lab Sci journal has a much more diversified readership. Thus, we offer not only research articles but also clinical practice manuscripts for the practitioner and a Focus section to provide continuing education opportunities for the entire profession. Susan has done a great job in ensuring that the quality of the journal has continuously improved. I believe this journal offers something for everyone. There is still work to be done to further our efforts and I just hope I will be able to continue with the standards Susan has set. I wish her the very best and hope to see some great manuscripts in hematology.

I have served as the Research and Reports editor for the past couple of years and now this position is being filled by a very capable new editor, Dave McGlasson. Many of you may know Dave as a well-respected expert and researcher in the field of coagulation. I know he will serve the journal well and I look forward to working with him along with our other editors, Bunny Rodak and George Fritsma. I would like to encourage each of you to help them out by providing us with Research and Reports, Clinical Practice, and Focus manuscripts. We can’t publish a journal without your valuable input.

The Clin Lab Sci journal is one of our links to other professions to be recognized as a legitimate player in healthcare. Lack of recognition is one of the problems our profession has always experienced, with not only the public but also other healthcare practitioners. Over the years we have worked hard to put our profession more in the forefront. Our educational programs have continued to improve and include more complex scientific theories, techniques, and methodologies. However, in the past few years I’ve noticed some troubling changes to our academic programs within many universities. Several of our programs are being merged into other departments and losing recognition as an independent profession. Although I understand administrators’ efforts I do not agree with them. They are hurting the profession.

In academics, as in many healthcare areas, administration must show fiscal responsibility. This means getting the most out of your money. In the business world this is known as return on investment or ROI. In the academic world this is measured by how many students can be educated for the least amount of money. Since CLS programs have small enrollments, the financial model used in academia is not in our favor. CLS education is expensive. Therefore, healthcare programs with small enrollments are merged into single departments with some generic healthcare title resulting in larger student numbers at the expense of a loss of our presence as an independent healthcare profession.

So what do we do? I think there are two areas that need to be addressed. We need to have more CLS faculty moving into dean positions in schools and colleges of health professions. This is where the decisions are made, and it is imperative to have individuals who truly understand health care education. The other area is the academic ROI model. Education funding by state legislatures does not really look at investment returns. Basically, they measure how many students can be educated with a certain level of funding. A true ROI model should measure the financial return the graduates of the programs make to the state. I believe if we determined this payback by practicing CLSs it could easily be shown that the financial return is much greater than by other majors such as biology and chemistry. A CLS degree puts tax-paying individuals into local jobs while other science degrees create individuals looking for jobs that do not exist.

Once again our profession is facing another major obstacle to becoming a valued member of the healthcare team – one I believe we will overcome. I look forward to doing my part to ensure that our profession moves forward by making this journal the very best it can be in promoting our profession within the healthcare industry.

David G Fowler PhD CLS(NCA) is editor-in-chief of Clinical Laboratory Science.
The position statement of the American Society for Clinical Laboratory Science (ASCLS) regarding the doctorate in clinical laboratory science (DCLS) begins:

Missing within the continuity of healthcare are enough scientists and physicians within the clinical laboratory or elsewhere on the healthcare team who are totally dedicated to and who have the breadth of knowledge and assigned authority essential to the ordering of appropriate laboratory tests, the effective use of laboratory test information, effective consultation with other healthcare team members, direct communication with patients, review of patient records, and interpretation/application of laboratory-generated information in reference to clinical signs and symptoms. A clinical laboratory science professional holding a doctoral degree (DCLS) is needed to provide the critical interface across the healthcare system in order to assure improved patient outcomes and cost effective patient care.¹

This succinct introduction defines the practitioner needed “to assure improved patient outcomes and cost effective patient care.” To identify, describe, measure, provide for, and improve the ordering, dissemination, and utilization of medically effective and cost-efficient clinical laboratory information defines the objectives of quality in clinical laboratory science as well as the focus of clinical laboratory science (CLS) evidence-based practice.

The Institute of Medicine (Crossing the Quality Chasm, http://www.iom.edu/CMS/8089.aspx) has challenged the healthcare delivery system to refocus on appropriate use of healthcare services. The clinical laboratory by every cost, revenue, and quality measure is foundational to any consideration of this directive given that as much as 93% of the objective data in the clinical record is contributed by the laboratory.² In addition, it is estimated that 50%-60% of all laboratory orders may be inappropriate³ and most (68%-87%) of laboratory errors are non-analytical.⁴ Inefficiencies involving the generation of orders (pre-analytical processing) and utilization of laboratory data (post-analytical processing) further increase the possibility of inappropriate resource utilization. Accreditors of clinical laboratories have taken up the challenge and are actively reviewing progress toward this “new quality” of appropriate use of clinical laboratory information relative to an increase in patient safety and decrease in medical errors (JCAHO, http://www.jointcommission.org/).

The responsibility of quality oversight will require education of clinical laboratory scientists at the doctoral level resulting in the conferral of either the doctor of CLS (clinical practice and clinical project) or the doctor of philosophy in CLS (clinical practice and dissertation). The curriculum of the DCLS will provide the CLS profession with the heuristics, based on the CLS generalist scope of practice, to deliver quality healthcare required in today’s workplace as summarized in the ASCLS position statement. Supporting this position are reports that healthcare practitioners with advanced, post-baccalaureate education (to include doctorate-prepared laboratory professionals) improved the quality of patient outcomes and medical care, reduced medical errors, and helped to contain costs.⁵⁶

This generalist DCLS’ knowledge will supplement and support the focused knowledge of clinical laboratory PhD specialty scientists as well as the practice of medical doctors in fulfilling quality responsibilities in the clinical laboratory. Most likely, rules regulating the practice of specialty scientists

Elizabeth Kenimer Leibach is chair and associate professor in the Department of Biomedical and Radiological Technologies, Medical College of Georgia, Augusta GA.

Address for correspondence: Elizabeth Kenimer Leibach EdD MS CLS MT(SBB), chair and associate professor, Department of Biomedical and Radiological Technologies, EC 2437 Medical College of Georgia, Augusta GA 30912-0500. (706) 721-3046, (706) 721-7631 (fax), ekenimer@mcg.edu.
in the clinical laboratory (e.g., CLIA, state-specific licensure laws) will apply to these new DCLS degrees. Additionally, a more non-traditional role of consultation is envisioned and supported in the literature. There is growing evidence of physicians’ need for advice on laboratory test selection and interpretation of complex and diverse laboratory test options and results. The DCLS will be formally educated as a key resource in disease prevention and management, thus reducing the burden of practice related to CLS among physicians.

Work continues on curriculum development and doctoral program implementation. A group of educators planning to implement DCLS degrees at their institutions will meet after the Clinical Laboratory Educators’ Conference in Savannah, Georgia, February 23-24, 2008. Continue to monitor our professional literature and the ASCLS website (www.ascls.org) for progress updates on the latest developments emerging from this meeting. Please post general comments to the ASCLS Forums. (You can find the Forums from the “About” link on the title bar of the ASCLS Homepage.) Your opinions, interest, and support are vital!

REFERENCES
Transfusion Therapy for Autoimmune Hemolytic Anemia Patients: A Laboratory Perspective

DARRELL D DROUILLARD

Patients presenting with autoimmune hemolytic anemias create inherent challenges to those tasked with providing compatible blood for transfusion therapy. These patients have developed autoantibodies against their own red cell surface antigens. Because these antigens are usually high-incidence, these patients will typically demonstrate panagglutination when their serum is exposed to most commercially procured screening red blood cells. This makes the identification of clinically significant alloantibodies difficult for laboratory personnel. Transfusion history, patient phenotype availability, and previous antibody records all impact the testing methods. The end goal is to identify clinically significant alloantibodies in order to provide antigen negative, compatible red blood cells, which reduces the risk of transfusion related reactions. It is imperative to understand the laboratory results and the techniques available that guide the investigative process.

ABBREVIATIONS: AHG = anti-human globulin; AIHA = autoimmune hemolytic anemia; CAS = cold agglutinin syndrome; DAT = direct antiglobulin test; HDN = hemolytic disease of the newborn; IAT = indirect antiglobulin test; IHA = immune hemolytic anemia; LISS = low ionic strength solution; PAM = prophylactic antigen-matched; PCH = paroxysmal cold hemoglobinuria; PEG = polyethylene glycol; RBC = red blood cell; WAIHA = warm autoimmune hemolytic anemia.

INDEX TERMS: anemia; autoimmune; hemolytic.

In order to effectively manage the technological methodologies employed in the attainment of compatible RBCs for these patients, it is essential for the transfusion service personnel to thoroughly understand the various types of IHAs. Moreover, in order to create an environment which makes the associated project management of these complex work-ups effective, supervisors must understand the background of IHAs, current scientific methods, and decision trigger points. Likewise, it is equally critical to embrace, rather than fear, new and emerging technological methodologies which will decrease processing time and increase efficiency, while simultaneously maintaining testing sensitivity and specificity.

IMMUNE HEMOLYTIC ANEMIAS

Autoimmune hemolytic anemias (AIHA) AIHAs are generally classified as warm, cold, or mixed. Warm reacting autoantibodies are generally an IgG class of antibody that is reacting with all patient RBCs. The reactions are typically stronger at their optimal temperature of 37°C and have a weakened expression at cooler temperatures. They are typically identified by their panreactive characteristics, when a patient's serum is incubated with commercially procured screening and panel RBCs. The resulting panagglutination is often noted when testing free antibodies found in a patient's serum and also when testing the antibodies that are eluted from a patient's RBCs, during in vitro identification techniques.

Cold reacting autoantibodies typically consists of IgM classes of antibodies, which are most reactive at 4°C and cause hemolysis, through the fixation of complement. Most of these antibodies are not clinically significant and are only observed because of their interfering characteristics with

Clin Lab Sci 2008;(21)1:7

Darrell D Drouillard MS MT(ASCP) is medical technologist, North Central Federal Clinic, San Antonio TX.

Address for correspondence: Darrell D. Drouillard, MS, MT(ASCP), Medical Technologist, North Central Federal Clinic, 17440 Henderson Pass, San Antonio TX 78232. (210) 483-2903, (210) 483-2943 (fax). darrell.drouillard@va.gov.

Immune hemolytic anemia (IHA) results from an immune mediated response to red blood cell (RBC) surface antigens. Based on the class of antibody, predominantly immunoglobulin G (IgG) and immunoglobulin M (IgM), patients may experience varying degrees of hemolysis. The immunological response may result in complement fixation or subsequent RBC destruction by the splenic macrophages. Though various classifications and sub-classifications exist, the AABB has divided IHAs into three main classes: autoimmune hemolytic anemias (AIHA), drug-induced hemolytic anemias, and alloimmune hemolytic anemias. Regardless of the type of anemia, most patients present with diverse, non-specific symptoms that may include dyspnea, pallor, weakness, fatigue, dizziness, abdominal pain, weight loss, and jaundice.
room temperature in vitro identification techniques. The most common cold-reactive antibody causes cold agglutinin syndrome (CAS).¹ Though relatively benign, this condition can cause hemolysis in the extremities when exposed to colder temperatures. Moreover, autoantibody agglutination can occur in the vasculature of distal extremities causing a numbing pain and bluish color referred to as acrocyanosis.²

A rarer, cold reacting antibody that is actually a biphasic, IgG class is the causative agent of paroxysmal cold hemoglobinuria (PCH). PCH was first identified in the early 1900s in association with syphilis, but has gained more recent notability as a secondary condition associated with viral and bacterial infections in children.³⁴⁶ In PCH, the antibody attaches to the RBC, fixes complement, and then dissociates as it circulates back to the warmer body core. The unique biphasic nature of this condition can be demonstrated in vitro using the Donath-Landsteiner test. This test allows for the macroscopic visualization of hemolysis in specimens that are cooled and then heated to 37°C, as detailed in the AABB technical manual.¹

In 1981, mixed type AIHA was proposed, as a new classification, by Sokol and others to categorize patients that appear to have a mixture of autoantibody immunoglobulin classes (IgG and IgM).⁷

These patients typically present with notable autoantibodies that appear reactive at both 37°C and 4°C. The IgM class of the group will also exhibit a larger than normal thermal amplitude, with reactivity from 4°C to > 30°C.³⁷⁸ In a 1985 study of 144 patients to investigate mixed AIHAs, it was noted that this type of hemolytic anemia constitute only 8.3% of the total number of cases.⁸

Drug-induced hemolytic anemias
Drug-induced hemolytic anemias involve various theoretical mechanisms of activity and account for 12%-18% of AIHA cases.¹⁴ Classifications have involved immune versus non-immune or have centered on the proposed activity thought to cause the ultimate hemolysis. However, the AABB has also presented referenced theories that the antibodies may form against the drug entirely, a combination of the RBC membrane and drug membrane components, or mainly against the RBC membrane.¹ Regardless of the mechanism of activity and the presence of a positive direct antiglobulin test (DAT), hemolytic anemias caused by drug therapies are rare.⁹

Alloimmune hemolytic anemias
In most instances, alloimmune hemolytic anemias occur from alloantibodies that were immunologically derived secondary to a sensitizing event. ABO antibodies, however, are naturally occurring and can provide the most severe acute hemolytic episode, if matched with the wrong donor type. For other antibody types, a sensitizing event is one in which a patient has been exposed to RBC antigens that they lack. This event has a propensity to cause an immunogenic response that may lead to the formation of alloantibodies. Sensitizing events can include blood exposure through transfusion, pregnancy, and intravenous drug use.

However, the sensitizing event does not necessarily cause antibody formation. In a published eight year study of 159,262 patients, it was noted that the mean number of red cell transfusions that elicited the formation of a single specificity antibody was 4.79.¹⁰ Moreover, the formation of multiple antibodies was found to be related to an increase in donor exposures, with all individuals forming >6 antibodies having a mean of 21.73 – 56.00 RBC transfusions.¹⁰ When these alloantibodies form, they must be identified to mitigate the risk of a transfusion reaction from a subsequent antigenic exposure. This is the main reason that the transfusion service must have a mechanism of identifying these alloantibodies, even in patients that have panreactive autoantibodies.

Another form of alloimmune hemolytic anemia is hemolytic disease of the newborn (HDN), caused when the IgG antibodies of the mother cross the placenta. If the baby has antigenic structures corresponding to the mother’s antibodies, these antibodies will react with the baby’s RBCs. This can occur with a mother’s non-ABO alloantibodies or with IgG ABO antibodies for Group O mothers that have group A, B, or AB babies. The severity of the problem can vary from mild to severe. At a facility in San Antonio, Texas, a mother required numerous intrauterine transfusions due to multiple alloantibodies, which were causing fetal hemolysis.

LABORATORY INVESTIGATION
All hemolytic anemias result from an immunological or non-immunological response that decreases the RBC survival rate, but, all patients with IHA will also show varying degrees of reactivity with commercially procured screening RBCs. The degree of reactivity demonstrated will vary based on the IHA classification type, the immunoglobulin type, the antibody titer, the drug history, and the immunological state of the patient.
Indirect antiglobulin testing

Initial transfusion testing typically includes blood typing and performing an indirect antiglobulin test (IAT). The IAT is necessary to identify clinically significant alloantibodies in the patient's serum. When a patient is showing reactivity to one or more screen cells, the antibody or antibodies that are causing the in vitro agglutination must be identified. Identification involves expanding testing, to include reactions with panel cells of a known phenotypic make-up. Laboratory testing normally identifies the antibody or antibodies present. This facilitates the follow-on investigation to find RBCs that lack the antigen which is eliciting the immunological response, so that crossmatch compatible blood can be provided. However, when initial IAT testing provides only inconclusive, panagglutination with all cells, the investigation continues. Causes of panreactivity include: multiple alloantibodies; antibodies to high-incidence antigens; drug-induced IHA; autoantibodies; or, a combination of these.

Direct antiglobulin testing

One of the key tests in helping to distinguish classes of hemolytic anemia is the direct antiglobulin test (DAT). The DAT is typically performed when the IAT is positive and is used to identify whether or not the patient has RBCs coated with either antibodies or complement. A positive DAT is usually suspect for the presence of alloantibodies. These can be formed by the patient as seen in transfusion reactions or passively acquired as seen in HDN. Unfortunately, most AIHAs will cause both the IAT and DAT to be positive, even if the patient does not have clinically significant alloantibodies.

The DAT is typically performed with a polyclonal, anti-human globulin (AHG), as a screening tool to identify RBCs that are coated, in vivo, from an immunological response. If the test is positive, follow-up testing includes monospecific reagents to distinguish complement fixation from an IgG class of antibody. If patient RBCs are only reacting with anti-C3 AHG, it typically signifies a cold reacting IgM class AIHA, a drug-induced hemolytic anemia, or PCH. However, if the reaction is occurring with only anti-IgG AHG or a combination of both anti-IgG and anti-C3 AHG, then the classification is most likely a warm autoimmune hemolytic anemia (WAIAH), mixed AIHA, drug-induced AIHA, a transfusion reaction or HDN as seen in some neonates. DATs that are positive with anti-IgG AHG will have an elution performed to identify the antibody present on the patient's RBC. Elutions are not performed on DATs that are positive for anti-C3 only, because there is no antibody present to identify. The follow-on testing after a positive IAT is determined by the DAT results (Figure 1).

Either way, the possibility of one or more alloantibodies being present must always be investigated thoroughly. Numerous studies, on the frequency of underlying alloantibodies being present in conjunction with autoantibodies, have provided statistical evidence that the range is between 31%-53%. These alloantibodies can only be identified when the autoantibodies, which are masking them, are removed.

Elution

An elution for antibody identification involves thoroughly washing the RBCs to remove unbound antibodies, prior to treating with an acidic solution. The removal of unbound antibodies is done to ensure the eluate contains only those antibodies which are coating a patient's RBCs. The bound antibodies are typically dissociated from the RBCs utilizing an acidic solution and then buffered back to a pH of approximately 7.0. The result is an eluate of freed antibodies that can be tested against phenotypically known RBCs. Reactivity that demonstrates
panagglutination is typical of WAIHA. Cold AIHA and drug-induced anemias will usually be non-reactive. If an identifiable pattern is noted, then the thought process should shift to an alloimmune response such as is found in certain transfusion reactions or in babies suffering from passively acquired maternal antibodies.

Caution must be taken, however, when identifying eluted antibodies. Several cases have been presented of warm autoantibodies mimicking certain classes of alloantibodies. In one study, it was found that an apparent 43% of the cases of underlying alloantibodies actually involved mimicking autoantibodies, which reduced the real alloimmunization rate of this patient population to 23%. The mimicking specificities typically fall in the Rh system. In a 1977 publication, a case was presented of an autoantibody mimicking the specificity of both anti-E and anti-c alloantibodies. In this case, the apparent alloantibodies were adsorbed by RBCs that were antigen negative for both E and c. This is unlikely if the specificities had been actual alloantibodies. In another case, an apparent anti-E was noted in both a patient’s plasma and when eluted from the patient’s RBCs, following a positive DAT. Once again, adsorption was possible with both E-antigen positive cells and E-antigen negative cells.

Adsorptions and complex testing

When the IAT and eluate are all demonstrating panreactivity, this is usually conclusive for a WAIHA. But, in order to provide RBCs for transfusion, it is important to identify any alloantibodies present. If the patient has not been recently transfused, then autologous adsorption techniques can be employed to remove the circulating autoantibody from the patient serum. In this technique, the patient cells are treated to remove the bound autoantibodies, which frees up the antigenic binding sites. These cells are then re-exposed to the patient serum to allow for attachment of more autoantibodies. Multiple adsorption techniques may need to be employed depending on the strength of the reactions. When the autoantibodies have been adequately removed from the sample, the remaining serum can be tested against panel cells for the presence of any clinically significant alloantibodies.

Many hospitals will not perform autologous adsorptions if a patient has been transfused within the preceding three months, because RBCs have a normal survival rate of approximately 110-120 days. This survival rate will create a transient, dual RBC population of patient and donor cells. Because these recently transfused patients have a chimera of donor and recipient cells, an autologous adsorption may actually remove a clinically significant alloantibody which may be reacting only with donor cells. It is important to note that the decreased red cell survival in patients with WAIHA affects all cells, donor and recipient, and therefore, some hospitals may perform the technique on recently transfused patients after a 90 day period.

Patients that have been recently transfused will require allogeneic adsorptions. This involves utilizing RBCs of various phenotypic make-ups to perform adsorption techniques. Since all of these cells will remove the autoantibodies, the result is several aliquots of patient serum that may or may not have alloantibodies remaining, depending on the phenotype of the cells utilized. This adsorbed serum is then reacted with screen cells to identify any specificity patterns. The process for allogeneic adsorptions is very complex and time consuming.

TRANSFUSION TESTING FOR WAIHA

An option employed by some hospitals involves the initial phenotyping of all patients that present with WAIHA. The phenotype can be obtained utilizing immediate spin or room temperature incubation anti-sera, as long as an auto-control is performed in tandem. For anti-sera that are taken to the AHG phase of testing, the patient RBCs will have to be treated, to remove the autoantibody, before performing antigenic testing. A treated aliquot of phenotypically matched donor RBCs can be used in lieu of patient RBCs, for an autologous adsorption technique.

Taking the concept of initial phenotyping further, the idea of utilizing prophylactic antigen-matched (PAM) donor blood for on-going transfusion therapy of WAIHA patients is definitely worth further investigation. One study supported the effectiveness of PAM blood in meeting the transfusion needs of this population while reducing normal testing time requirements. However, this option may not be the best if the rarity of the patient phenotype makes PAM blood more difficult and time-consuming to obtain than normal adsorption procedures. Moreover, the extent of the phenotyping must not be limited to the Rh and Kell specificities. In a recent study of underlying alloantibodies, it was found that 11% of these patients had antibodies found in other blood group systems, including the Duffy and Kidd systems.

When standard adsorption studies are required, numerous technical procedures are employed nationwide, which include untreated RBCs without antigen-antibody reaction potentiators, untreated RBCs with potentiators such as low ionic strength solutions (LISS) or polyethylene glycol (PEG),
enzymatic treatment of RBCs without potentiators, and enzyme treated RBCs in conjunction with various potentiators. In determining the method of choice for a transfusion service, it is vital to focus on efficiency in reducing the time to provide blood products without sacrificing sensitivity and specificity.

One study, which compared the use of papain-treated RBCs to procedures involving LISS alone or LISS-papain combinations, found that the use of a potentiator in adsorption procedures decreased the mean processing time from 180 minutes to 57.6 and 58 minutes respectively. Moreover, the mean number of adsorptions required per specimen dropped from six to under three without an apparent loss of sensitivity or specificity. Another method that further reduces the total processing time, the number of adsorptions required, and the need for enzyme treating RBCs is the PEG adsorption technique. Two PEG adsorption studies, which detailed procedures involving the use of one part untreated RBCs, one part patient serum (plasma), and one part PEG, reported mean processing times of 22.5 minutes and 28 minutes. In both PEG studies, no dilutional effect was noted and both sensitivity and specificity remained comparable to other methods.

SUMMARY
IHAs present some of the most difficult challenges for transfusion services. In order to provide compatible blood for these patients, it is important for clinical scientists to understand that each case is different and the cumulative, investigative process is step-driven, based on previous findings. Moreover, it is essential that clinicians understand the complexity involved with the testing and the time requirements of both the testing phases and the incubation steps. With close monitoring of patient hematological levels, adequate forecasting of requirements and a thorough understanding of the investigative process, the clinical team of clinicians and scientists will be better prepared to ensure that supportive transfusion therapy requirements are met.

It is also important for laboratories to embrace changes that will improve processes to streamline testing and ensure optimal efficiency. By understanding the various methodologies that are available for performing the required adsorption procedures, for WAIHAs, laboratories can adjust procedures as long as they are validated, maintain acceptable specificities, and do not sacrifice sensitivity.

Clin Lab Sci encourages readers to respond with thoughts, questions, or comments regarding this article. Email responses to ic.ink@mchsi.com. In the subject line, please type “CLIN

REFERENCES


Wake Up! Your PDQ is Due!

LORI WOESTE, BEVERLY BARHAM

ABBREVIATIONS: CLS = clinical laboratory science; PDQ = pre discussion quiz.

INDEX TERMS: active learning; clinical laboratory science; instructional design; student engagement.

Clin Lab Sci 2008;(21)1:12

Lori A Woeste EdD MT (ASCP) is assistant professor, Clinical Laboratory Science Program, Illinois State University

Beverly J Barham PhD MPH MT(ASCP) is associate professor, Clinical Laboratory Science Program, Illinois State University.

Address for correspondence: Lori A Woeste EdD MT (ASCP), assistant professor, Clinical Laboratory Science Program, Department of Health Sciences, 332 Felmley Hall Campus Box 5220, Illinois State University, Normal IL 61790-5220 (309) 438-8810, (309) 438-2450 (fax). lawoest@ilstu.edu.

This information was presented as a poster presentation at CLEC 2007 in Louisville KY.

BACKGROUND
Student engagement in the classroom can often be an elusive goal. We as faculty in a four-year university-based clinical laboratory science program were noticing a trend of more students coming to class unprepared. In an effort to increase student engagement in two different pre-professional practice clinical laboratory science (CLS) courses, the pre-discussion quiz (PDQ) was implemented as a curricular component for enhancing student engagement. This was done as an active learning strategy to motivate students to read the material and respond to a series of questions in preparation for discussion before they came to class. A review of educational literature suggests intrinsically motivated learning enhances the learning process. It is suggested this intrinsic motivation is linked to such factors as the perception of personal control, self-efficacy, and the perception of relevance. These instructional strategies should give the learner some control over sequence of instruction and pace, and some even believe they should not be optional. The use of incentive-based preparation exercises has been found to significantly improve student engagement and provide an effective means of assessment.

OVERVIEW
The pre discussion quizzes (PDQs) were delivered via WebCT® in undergraduate CLS immunology and chemistry courses. Each course was 16 weeks long, met twice a week at 8:00 AM during the fall semester, and included 24 in the student cohort. Most students were at junior status with a few seniors and an occasional sophomore. The cohort included both native students, e.g., those students who began their post secondary experience at this institution, and transfer students from other two-year and four-year institutions. Each PDQ was made available to students as early as 48 hours before and up to 15 minutes before class began. Once the deadline for submission of the PDQ had passed, students were able to print the PDQ including both questions and answers to use as a resource when studying for the subsequent exam.

In general, the PDQs covered one, two, or three chapters in the text with four to five key points per chapter used as the foundation for the questions. Most of the questions included in the PDQ were basic recall questions. Often the information included in the PDQ would later be used in an exam question which was usually delivered as an application, synthesis, or evaluation question. Students were required to answer each PDQ question within one minute of accessing the questions in WebCT®. Most questions were multiple choice with a range of 8 to 15 questions per PDQ. Students were allowed to take the timed PDQ only once. The PDQ was not proctored and students had been made aware of the penalties for dishonesty including collusion. The points a student achieved on the individual PDQs were added to the total points for the course. By using WebCT® for the delivery of the PDQ, the timing factors were never an issue. The quiz opened and closed at a specific time and students could view the time frame on a continual basis.

RESULTS
The majority of students took their PDQ within 12 hours of the individual class discussion but before the 60 minute interval (Figure 1). In the immunology course this meant students were taking the PDQ sometime between 8:00 PM Sunday evening and 6:45 AM on Monday morning. For the chemistry course, students were taking the PDQ sometime between 8:00 PM on Wednesday evening and 6:45 AM on Sunday evening and 6:45 AM on Monday morning.
Thursday morning. Only 70% of students completed the PDQ during the first week in the immunology course and 75% in the chemistry course. Once students realized the value in both content and points, the participation level increased to 100% after the first three weeks in both courses.

Additionally, the mean scores on the subsequent exams increased for students using PDQs compared to the previous cohort of students prior to PDQ implementation (Figures 2 and 3). The mean score increased on all but one of the immunology exams and increased on all three of the chemistry exams. The content on each exam and the type of questions did not change from year to year. The exams were never made available to either cohort of students other than in the instructor’s office with both the student and the instructor present for a meaningful discussion about the individual student’s responses on the exam. While increasing exam scores was not the primary objective, it was a value added outcome.

DISCUSSION

Through implementation of the PDQ, students in both pre-professional practice immunology and chemistry CLS courses made the choice to read the material before the beginning of class and come better prepared to discuss the material. The concept of opening the book before class and not relying solely on the lecture material during class was not a popular one with the cohort of CLS students when it was first implemented. Perhaps put more accurately, in the beginning students approached the PDQ challenge “kicking and screaming all the way”. However, it was our observation students came to rely on the PDQs as yet another resource in narrowing a large amount of content into a more manageable unit of information. Comments from student evaluations in other courses that did not use the PDQ as an active learning strategy included:

- “I really miss the PDQs, they helped me focus.”
- “Why doesn’t every course have these (PDQs) available?”
- “Suggestion for next year: Make PDQs for Blood Bank too.”

Once students realized the content and points were valuable to their overall success in the course, many students became part of the solution to achieving student engagement instead of part of the problem of taking up space and never contributing. If students were not going to be in class the morning the PDQ was to be completed, they were required to contact the instructor before class either via email or telephone regarding the reason for their absence in order to protect the points earned on the most recent PDQ. If students completed their PDQ before the deadline but failed to come to class that day without contacting their instructor, the PDQ points were forfeited. This practice also addressed a professional behaviors component for pre-professional practice CLS students.

Each instructor noted increased student engagement in their respective course. Both instructors felt the students were asking better questions and commenting on content whereas before the instructors were basically lecturing to an often unresponsive group of students. With this positive outcome, instructors could then present application scenarios where students could apply theory to real-life situations in either a group setting or individually rather than spend time discussing basic information. Students enjoyed working through the scenarios especially as part of a group dynamic where they were engaged as full partners.

In these two content-heavy courses, the PDQ did help to increase student engagement on a weekly basis which met the primary objective for implementing the PDQ. The entire PDQ experience can perhaps best be summed up by the student quote: “I had to read that whole chapter to answer that little PDQ.”

CONCLUSION

Many active learning strategies have been suggested for increasing student...
engagement. The PDQ is one strategy that can be used in content-heavy courses with students who are reluctant to take on the task of preparing before the class discussion. In comparison to other student engagement strategies, from the instructor perspective, creating and implementing the PDQ was a fairly simple process which required minimal time with maximum benefits. The use of technology via WebCT enhanced the process and provided the student a dual advantage of immediate feedback and future use of the information as a study tool.

While these results are from very discipline-specific courses, we feel there is a broad application for the PDQ in most courses throughout any curriculum. Adaptations to this instructional design might include variations in timing such as decreased or increased frequency and time allotted for each question. Future inquiry into the correlation of PDQ question to associated exam question could provide insight into challenging curricular material that might need useful repetition. While this instructional design delivery used WebCT, other web-based instructional courseware could be used as the instructional delivery format.

Clin Lab Sci encourages readers to respond with thoughts, questions, or comments regarding this article. Email responses to ic.ink@mchsi.com. In the subject line, please type “CLIN LAB SCI 20(4) CP WOESTE”. Selected responses will appear in the Dialogue and Discussion section in a future issue. Responses may be edited for length and clarity. We look forward to hearing from you.

REFERENCES
For many years, laboratory diagnosis of rheumatoid arthritis has relied on the detection of rheumatoid factor. A new assay that detects antibodies to citrullinated peptides, called the anti-CCP assay, has demonstrated a comparable sensitivity but a much higher specificity than the RF test. This paper reviews RF and anti-CCP in rheumatoid arthritis and examines the usefulness of each autoantibody in RA testing.

**ABBREVIATIONS:** AFA = antiflaggrin autoantibodies; AKA = antikeratin antibodies; APF = antiperinuclear factor; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; DMARDS = disease-modifying anti-rheumatic drugs; ELISA = enzyme-linked immunosorbent assay; ESR = erythrocyte sedimentation rate; Ig = immunoglobulin; MTX = methotrexate; NSAIDS = non-steroidal anti-inflammatory drugs; PAD = peptidylarginine deiminase; RA = rheumatoid arthritis; RF = rheumatoid factor.

**INDEX TERMS:** anti-CCP; rheumatoid arthritis; rheumatoid factor.

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown etiology that is characterized by chronically inflamed synovial joints and subsequent destruction of cartilage and bone. RA is found in about one percent of the population, making it one of the most common autoimmune diseases in the United States. RA is marked by several key characteristics, including synovitis occurring in a symmetrical fashion, polyarthritis, morning stiffness lasting over an hour, periods of disease flare-ups followed by periods of disease remission, and the development of subcutaneous rheumatoid nodules. The disease does not affect all patients the same way, and may range from a mild form to one that is very debilitating. RA can present with many symptoms, including pain, swelling, stiffness, joint deformity, and loss of movement. It can have a serious impact on a patient's quality of life, and early intervention is key to minimizing the damaging effects of the disease. The standard therapies for RA include analgesic drugs, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids or prednisone, and disease-modifying anti-rheumatic drugs (DMARDs).

RA can be difficult to diagnose, especially in the early stages of the disease. In 1987, the American College of Rheumatology established seven criteria for the diagnosis of RA, four of which must be met for diagnosis. The only criterion based upon laboratory testing is the detection of abnormal amounts of serum rheumatoid factor (RF). Testing for RF in the diagnosis of RA has been performed for over fifty years. Unfortunately, the RF test does not yield a high specificity for RA. Research over the past several years has focused on developing other tests that have increased diagnostic specificity over the RF test. Such research led to the development of the anti-cyclic citrullinated peptide (anti-CCP) assay, which detects the presence of anti-citrullinated peptide autoantibodies found in the serum of many patients with RA. The anti-CCP assay has proven to be as sensitive as the RF test with a much higher specificity. Studies have also indicated that the anti-CCP assay has higher disease predictability and prognostic value than the RF test, while RF appears to be a better marker for patient response to treatment than anti-CCP.
BACKGROUND

Rheumatoid factor

The first autoantibody detected in patients with RA was RF. It was discovered in the early twentieth century when researchers noticed that sera from patients with RA agglutinated sheep red blood cells that had been sensitized with rabbit antibody. In the 1940s, the term “rheumatoid factor” was coined after researchers confirmed that the factor inducing agglutination correlated with the presence of RA. RF antibodies may be of the IgM, IgG, or IgA classes, and they target patient IgG. Following the discovery of RF, the RF test became the primary laboratory test used in the diagnosis of RA.11

Many methods of RF detection have been developed. Particle agglutination tests employ latex, charcoal, or human erythrocytes as carrier molecules to which human or rabbit IgG is bound.12 Agglutination tests detecting IgM-RF are the most common methods used in laboratory diagnosis of RA.11 Nephelometry is another method used for detecting RF. In nephelometry, latex particles are coated with human IgG that captures RF. Complexes formed between the IgG and RF are detected by light scattering. The degree of light scatter is dependent upon the concentration of immune complexes formed, making this a quantitative test.12 A third method of RF detection is an enzyme-linked immunosorbent assay (ELISA). It is a solid phase assay that detects IgM- and IgA-RF using human IgG Fc as the substrate, and detects IgM-, IgG-, and IgA-RF if rabbit IgG is used as the substrate.11

Anti-CCP

In 1964, researchers described antibodies to perinuclear granules in the cytoplasm of human buccal cells, called antiperinuclear factor (APF), that had high specificity for RA. In 1979, antibodies to cytokeratin of stratum corneum of rat esophagus epithelium, called antikeratin antibodies (AKA), were discovered and also found to be highly specific for RA. Years later, APF and AKA were both found to be directed against filaggrin or its precursor, profilaggrin, and were grouped into a family of antibodies called antifilaggrin autoantibodies (AFA). Researchers discovered that AFA recognize epitopes that are created by citrullination of the targeted proteins.13 Citrullination is the posttranslational deamination of arginine residues by peptidylarginine deiminase (PAD), which hydrolyzes the NH₂ group of arginine to a neutral oxygen group and results in the formation of an atypical amino acid called citrulline. The neutral oxygen group of the citrulline residue is the part that is recognized by the autoantibodies.4 Research has demonstrated that AFA do not target filaggrin or profilaggrin in patients with RA, but instead are directed towards other citrullinated proteins. Vincent and others recently discovered that filaggrin variants are not found in the synovial tissue and proposed that (pro)filaggrin is recognized by AFA due to cross-reactivity. AFA are actually directed against citrullinated forms of the α- and β-chains of fibrin, and represent only one group of autoantibodies to citrullinated proteins. Fibrin deposits are a characteristic of rheumatoid synovial tissues, and autoantibodies to citrullinated human fibrin are secreted locally in the synovial tissue interstitium.13

Original tests for the detection of autoantibodies to citrullinated proteins detected APF or AKA in patient sera by utilizing filaggrin antigens and indirect immunofluorescence. The tests did not become widely used, likely due to technical difficulties associated with the assays. The development of citrullinated peptides paved the way for a new laboratory test for RA – the first-generation anti-CCP (CCP1) assay. The anti-CCP assay utilizes synthetic peptides containing citrulline and detects the presence of autoantibodies to citrullinated peptides.14 The peptides were made cyclic because the three-dimensional structure optimizes the sensitivity of the test and allows the antigenic group of the peptides to be recognized by a heterogeneous population of RA autoantibodies. The CCP1 assay yielded an excellent specificity (97%) and a decent sensitivity (68%). A second-generation anti-CCP (CCP2) assay was soon developed that employed other citrullinated peptides and yielded a better sensitivity (75%-80%) than the CCP1 assay.6 Recently, a third-generation anti-CCP (CCP3) assay was developed that demonstrated a sensitivity about five percent greater than that of the CCP2 assay.15

COMPARISON OF RF AND ANTI-CCP

Sensitivity and specificity

Since its discovery, RF has become the primary laboratory test used in the diagnosis of RA. RF is found in the sera of up to 85% of patients with RA;16 however, it is also found in many other diseases, including Sjögren’s syndrome, systemic lupus erythematosus, and mixed connective tissue disease.11 In addition, RF is found in the sera of five percent to ten percent of apparently healthy individuals.14 The presence of RF in so many other conditions decreases the diagnostic specificity of the RF test, resulting in the search for a more specific test for the diagnosis of RA. The CCP2 assay was found to have a sensitivity comparable to that of
the RF test; however, the specificity proved to be superior. Riedemann and others performed a comprehensive review of CCP2 studies and found that the specificity ranges from 88.9 – 100%, depending upon the diseases included in each study. Anti-CCP autoantibodies are also found in diseases other than RA, although at a lower frequency than RF.

Predictive value
Early treatment of RA is important for providing the patient with the best outcome and quality of life. It is therefore essential that a diagnosis be made as early into the course of the disease as possible. Anti-CCP and RF autoantibodies can both be used as predictors of RA in some patients. Studies have shown that autoantibodies can be detected as early as ten years prior to the onset of RA. In a study by Nielen and others, frozen serum from RA patients who had donated blood prior to developing RA was tested for the presence of anti-CCP antibodies and IgM-RF. Of the 79 patients who were included in the study, 39 patients, or 49%, were positive for anti-CCP antibodies, IgM-RF, or both. These patients were positive for autoantibodies a median of 4.5 years prior to the onset of symptoms. Of 2,138 matched healthy control subjects, 0.6% tested positive for anti-CCP antibodies and 1.1% tested positive for IgM-RF. The researchers determined that the chance of developing RA five years after the detection of autoantibodies was 69.4% with anti-CCP and 37.7% with RF. Therefore, anti-CCP shows higher disease predictability than RF. The presence of both markers increases the risk to 100%. This study demonstrates that autoantibody testing may be useful for predicting RA development in individuals in high-risk populations, such as those possessing the genetic marker HLA-DR4. Patients with autoantibodies prior to developing RA also tended to be younger and suffered a more aggressive disease than those who tested negative for autoantibodies before the onset of RA. Rantapää-Dahlqvist and others found similar results in two Swedish cohorts of 83 patients. The prevalence of antibodies more than 1.5 years prior to disease onset was 33.7% with anti-CCP, 19.3% with IgM-RF, 33.7% with IgA-RF, and 16.9% with IgG-RF. These results were all highly significant compared to matched controls. The prevalence of each autoantibody was even higher when measured less than 1.5 years prior to disease onset, with anti-CCP demonstrating the highest prevalence (52%), followed by IgA-RF (39%). This study demonstrated that anti-CCP and IgA-RF are significant predictors of RA, with anti-CCP exhibiting a higher predictive value.

Prognostic value
The presence of anti-CCP and RF autoantibodies has been associated with a less favorable prognosis than the absence of them. Meyer and others reported that the percentage of patients with significant progression of joint destruction five years after the onset of disease was higher in patients who were positive for anti-CCP antibodies (67%) than patients who were negative (44%). The presence of anti-CCP in RF negative patients was also associated with more severe joint damage than in patients positive for RF and negative for anti-CCP. In a study by Vallbracht and others, the presence of anti-CCP autoantibodies was the most predictive marker for severe joint damage when compared with all RF isotypes. Of 295 patients with RA, 109 presented with minimal joint damage, 115 with moderate joint damage, and 71 with severe joint damage. The prevalence of each autoantibody in patients with severe damage was 80.3% with anti-CCP, 67.6% with IgM-RF, 48.3% with IgA-RF, and 47.9% with IgG-RF. By comparison, the prevalence of each autoantibody in patients with minimal damage was 54.1% with anti-CCP, 67.0% with IgM-RF, 45.3% with IgA-RF, and 40.4% with IgG-RF. These results demonstrate a higher incidence of anti-CCP in RA with severe damage than any RF isotype, and a higher incidence of IgM-RF than anti-CCP in RA with minimal damage. Patients with severe joint damage were also more likely to present as negative for RF and positive for anti-CCP than patients with minimal joint damage.

Effects of drug therapy
Many studies have researched the effects of DMARDs, especially methotrexate (MTX) with or without infliximab, on autoantibodies in RA. Most researchers have found that the titers of RF decrease when patients use DMARDs, while the drugs induce no significant changes in the titers of anti-CCP. De Rycke and others studied the effects of treatment with DMARDs on levels of autoantibodies in patients with RA. Among the 62 patients in the study, treatment with MTX and infliximab resulted in a significant decrease in the titer of RF after 30 weeks of treatment. In contrast, titers of anti-CCP showed no significant changes. The researchers also tested the predictability of the autoantibodies with regard to patient response to treatment. Baseline IgM-RF correlated inversely with changes in the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels during treatment, with higher baseline IgM-RF demonstrating a smaller decrease in ESR and CRP levels than lower baseline IgM-RF. These results show that IgM-RF levels may be used to predict the response of the patient
to therapy with MTX and infliximab. Baseline anti-CCP titers did not demonstrate any significant changes in acute phase reactants, and therefore would not be a good predictor of patient response to the chosen drug therapy. Though most studies found similar results, one study did find a significant decrease in anti-CCP titers after treatment with MTX and infliximab.18

CONCLUSION
Although the diagnosis of RA relies primarily upon clinical symptoms,2 laboratory tests that detect autoantibodies, such as RF and anti-CCP, are helpful aids in diagnosis. The usefulness of these autoantibodies in established RA has been demonstrated, but more research is needed to determine the value of these tests in detection of early RA, disease prognosis, and disease monitoring. In addition, the ability of these tests to predict disease development may allow for their use as screening tools in at-risk populations. Because early treatment is essential to reduce or reverse morbidity in patients with RA,6 it is important to distinguish between RA and other rheumatic diseases. This can be achieved for many patients via detection of anti-CCP autoantibodies. An advantage of RF is that the different isotypes can give a better idea of how the disease will progress. Patients with IgM-RF tend to have a more severe disease, those with IgG-RF tend to have vasculitis, and those with IgA-RF tend to have a more erosive disease with extra-articular manifestations. There are advantages and disadvantages to the RF and anti-CCP tests, but both tests together may provide a very useful tool in early and accurate diagnosis of RA.11

Clin Lab Sci encourages readers to respond with thoughts, questions, or comments regarding this article. Email responses to ic.ink@mchsi.com. In the subject line, please type “CLIN LAB SCI 21(1) CP LEE”. Selected responses will appear in the Dialogue and Discussion section in a future issue. Responses may be edited for length and clarity. We look forward to hearing from you.

REFERENCES
Teaching Method Validation in the Clinical Laboratory Science Curriculum

TARA C MOON, VICKY A LÉGRYS

With the Clinical Laboratory Improvement Amendment’s (CLIA) final rule, the ability of the Clinical Laboratory Scientist (CLS) to perform method validation has become increasingly important. Knowledge of the statistical methods and procedures used in method validation is imperative for clinical laboratory scientists. However, incorporating these concepts in a CLS curriculum can be challenging, especially at a time of limited resources. This paper provides an outline of one approach to addressing these topics in lecture courses and integrating them in the student laboratory and the clinical practicum for direct application.

ABBREVIATIONS: ASCLS = American Society for Clinical Laboratory Science; CLIA = Clinical Laboratory Improvement Amendment; CLS = Clinical Laboratory Science; JCAHO = Joint Commission on Accreditation of Healthcare Organizations; NAACLS = National Accrediting Agency for Clinical Laboratory Science.

INDEX TERMS: clinical laboratory science; education methods; methods; statistics; teaching techniques.

Despite the attention that quality in the laboratory has received as of late and the new regulations and policies that have resulted, it remains an area that can be improved. Many method validation procedures are still carried out inappropriately or are interpreted incorrectly. In the past, when the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has inspected laboratories, the most frequently cited deficiency involved quality control problems. Reasons for these deficiencies in spite of improved regulations and awareness are unknown. It is clear, however, that correcting problems with laboratory methods is difficult and requires higher cognitive processes of analysis coupled with a strong command of the method evaluation process. Giving CLS students a more solid foundation in this area could prove to diminish these inadequacies in future laboratories.

In addition to ASCLS, the National Accrediting Agency for Clinical Laboratory Science (NAACLS) also includes method validation in their description of the profession. To many, these skills seem abstract and are often more difficult to
integrate in a CLS curriculum. Educators are very comfortable teaching technical practices, but the situations and analytical processes that are required for method evaluation can be more difficult to simulate in an educational setting. Barriers to teaching method validation in the CLS curriculum can include limited time, reagents, and automation.

Due to the dynamic nature of the field, faculty struggle when choosing the amount of content to include in CLS educational programs. It can be easy to dismiss an emphasis on method validation in a CLS curriculum for entry-level positions because it is often viewed as a skill that is only needed by the experienced CLS. However, in Beck and Doig’s 2005 survey of managers, practitioners, and educators, respondents indicated that they expected a CLS to be competent in the procedures of method validation at entry-level. About half of those surveyed stated that they expected the CLS to be able to assess and evaluate methods, adopt new methods, and perform method evaluation studies with no additional education. Practitioners expect that these skills are acquired in educational programs and are not learned on the job or with additional training.

Clearly, technology in the laboratory is changing every day. With some assays, it is becoming easier to operate the instrument that performs the assay on a routine basis. However, the cognitive skills that are required to perform the quality control, validate the assay, and ensure that the test results are valid are much greater. Additionally, expansions in the area of molecular diagnostics have required more complex method validation for those assays that are developed in-house. It is easy to imagine that the role of the CLS in method validation will only increase in the future. No matter what the technology is, how it evolves, or what level of practitioner is performing the testing, method validation will always be an integral part of the clinical laboratory and an essential skill for students to obtain in their educational programs.

The following is a review of how one educational program has incorporated the concepts of method validation into the CLS curriculum. This overview focuses on the course materials and methods that are used to teach the concepts of method validation and prepare CLS students for entry-level responsibilities. Instruction for these methods comes intermittently throughout the two year curriculum using a variety of instructional techniques. Didactic lectures are used to present information in the students’ first semester, while laboratory exercises are used for active learning and simulation in the second semester. The method validation course work culminates with the clinical practicum in which the students investigate data and problems from actual laboratory scenarios. Other statistical and research design methods, such as odds ratios, type I and type II errors, and analysis of variance, are not included in this discussion as they are covered in a separate research course that is offered during the fall semester of the second year of the CLS curriculum.

RESOURCES FOR METHOD VALIDATION INFORMATION

There are a variety of Internet resources available for both the student and instructor on the topic of method validation. The Centers for Medicare and Medicaid Services has an overview of the Clinical Laboratory Improvement Amendment (CLIA) at http://www.cms.hhs.gov/CLIA and the specific requirements for method validation for nonwaived and modified tests from Subpart K can be found at http://www.cms.hhs.gov/CLIA/downloads/apcsubk1.pdf (Table 1). Other governmental websites with information about CLIA include the Centers for Disease Control (www.phppo.cdc.gov/clia/default.aspx) and the Food and Drug Administration (www.fda.gov/cdrh/CLIA/index.html). The College of American Pathologists Laboratory Accreditation Program Inspection Checklist for Chemistry, available from http://www.cap.org/apps/docs/laboratory_accreditation/checklists/chemistry_and_toxicology_april2006.pdf, contains

<table>
<thead>
<tr>
<th>Test type</th>
<th>Required verifications of manufacturer’s performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>New, unmodified, nonwaived tests</td>
<td>Accuracy, Precision, Reportable range, Reference ranges</td>
</tr>
<tr>
<td>Test system that has been modified or developed in-house</td>
<td>Accuracy, Precision, Analytic sensitivity, Analytic specificity to include interfering substances, Reportable range, Reference intervals</td>
</tr>
</tbody>
</table>

Table 1. CLIA requirements for method validation²
items and commentary defining and describing the practice and appropriate documentation for method validation. The Clinical Laboratory Standards Institute (CLSI) Evaluation Protocol documents (EP series) contain useful procedures for implementing method validation studies and analyzing the results (www.clsi.org).

Dr. James Westgard’s website (www.westgard.com) contains an extensive set of lessons on method validation that are very useful for students. Each lesson contains the purpose of the given experiment, factors to consider, examples of data calculations, criteria for acceptance, and selected references. In addition, the website contains data calculation tools that can be used by the student in assignments to generate standard deviation, linear plots, and reportable range. Other commercially available sources of method validation software include EP Evaluator (http://www.dgrhoads.com) and Analyze It (http://www.analyse-it.com/products/clinical/overview.htm). Some of these products can be purchased for limited use for student assignments.

IMPLEMENTATION IN THE CLS CURRICULUM

Didactic lectures

Because the lecture method is effective in disseminating a large amount of information, we initially present the information concerning method validation in the students’ first semester Laboratory Mathematics and Quality Assurance course. The topics covered in the lectures are listed in Table 2 and begin with a description of the importance of method validation. They move from the simplest assays (precision studies) to the more complex (interference and lower limit of detection), ending with a conclusion reviewing all the parts of method validation and summarizing the key points. The lectures are supplemented with problem sets, requiring the student to calculate parameters such as imprecision, linearity, and bias, and to apply appropriate criteria to evaluate the results for acceptability. Students are evaluated on the material based on their answers to the problem sets and scores on several quizzes.

A limitation of the lecture format is that the student is not involved in the generation of data and the ideas and application can seem abstract, especially if the material is presented to the student early in their curriculum before they have had the opportunity to become familiar with clinical assays. The instructor may need to provide additional clinical details and ensure that the student has later opportunities in the curriculum to apply the concepts presented in the lecture to actual practice of method evaluation.

Some students struggle with the calculations and theory associated with method validation, often due to differences in their backgrounds and abilities in mathematics and basic statistics. To help the students master the material, tutoring sessions are available from a second year student in the late afternoons, twice a week. The student tutor prepares and evaluates additional problems in method validation, working closely with the instructor to monitor performance. The tutoring sessions have been very beneficial as they allow the student additional opportunities to integrate the information and master the material.

Laboratory course

The application of method validation procedures is implemented in the second semester of the program’s first year in the clinical chemistry laboratory. It is included in the chemistry laboratory for several reasons: 1) there is little automation in the student laboratory, 2) manual methods are used primarily in the first year laboratory courses, and 3) many of the reagent kits on which we have long depended have been discontinued. The inability to obtain certain reagent kits left some vacant time in the chemistry laboratory schedule which was not available in any other course. The reagent kits that are available are simple to use and require very little applica-

<table>
<thead>
<tr>
<th>Unit</th>
<th>Topics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Purpose of MV</td>
</tr>
<tr>
<td>2</td>
<td>CLIA requirements for MV</td>
</tr>
<tr>
<td>3</td>
<td>Types of analytical errors</td>
</tr>
<tr>
<td>4</td>
<td>Precision studies</td>
</tr>
<tr>
<td>5</td>
<td>Linearity/analytic measurement range</td>
</tr>
<tr>
<td>6</td>
<td>Method comparison studies</td>
</tr>
<tr>
<td>7</td>
<td>Verifying/establishing reference intervals</td>
</tr>
<tr>
<td>8</td>
<td>Comparing analytical sensitivity and specificity to clinical sensitivity and specificity</td>
</tr>
<tr>
<td>9</td>
<td>Recovery studies</td>
</tr>
<tr>
<td>10</td>
<td>Interference studies</td>
</tr>
<tr>
<td>11</td>
<td>Detection limits</td>
</tr>
<tr>
<td>12</td>
<td>Drawing conclusions: Is the method acceptable?</td>
</tr>
</tbody>
</table>

• Appropriate criteria
• Factors influencing decision making
tion of chemistry theory. However, by adding the method validation concepts to the procedures, students can become proficient at some basic skills as well as incorporate a more complex cognitive level to the laboratory exercise.

Method validation is performed by comparing the two manual methods, glucose oxidase and glucose hexokinase. Glucose was chosen because it is inexpensive, it is a very common analyte, and the manual methods for glucose determination are not time consuming. These factors allow more ground to be covered in the student laboratory.

The method validation studies span four sessions of the clinical chemistry laboratory course. Students begin by performing the procedure to develop technical competency and then move on to the specific method validation procedures listed in Table 3. In the interest of time, students are divided into two groups for the laboratory exercises. Half of the class performs the glucose oxidase procedure and the other half performs the glucose hexokinase procedure. At the end of each laboratory session, the groups share their data and have time to compare the results of the two methods. While allowing students to share data compromises error reduction, it also allows for exposure to more experiments and overall, a more robust laboratory experience. With explanation, the students are able to understand this tactic and it does not detract from their understanding of the principles. In addition to the laboratory exercises, two assignments are given: a data analysis exercise and a method evaluation paper.

Because learning the concepts and mathematical operations is imperative to the students’ understanding of the procedures, calculations and graphs are done by hand in the student laboratory. However, the potential for human error in the manual calculations and hand-drawn graphs is contrasted with the benefits of using a computer when the students use statistical software for the data analysis assignment and method evaluation paper. In addition to their printed results and graphs, students also submit a written interpretation of the statistical results. To make interpretations, students are

<table>
<thead>
<tr>
<th>Table 3. Laboratory schedule and activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory exercises</strong></td>
</tr>
<tr>
<td><strong>Session</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td><strong>Additional assignments</strong></td>
</tr>
<tr>
<td><strong>Session</strong></td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

Describe the effects of the implementation of a new method on clinical practice.
required to research CLIA guidelines and use online resources to determine acceptable limits. They are asked to make decisions regarding their data and its acceptability in the clinical laboratory, as well as relate this information to the clinical setting and explain what this means for patient results.

The overall goal for the method evaluation paper is for the student to take all of the concepts and methods that have been performed over the previous laboratory sessions, provide an interpretation of the entire picture, and give a recommendation for the use of one of the methods. Prior to this, the students’ analyses have included one procedure at a time. For the method evaluation paper, they are given additional data and some summary statistics to analyze. This data complements the data that they collected in their laboratory exercises. They are asked to address specific questions regarding t-test statistics, the linear regression line, and correlation coefficient. In this final assignment, a complete analysis of all of the studies and a summary is expected. The students are required to integrate the concepts from their lecture course and the application of those concepts in the laboratory, then apply them to make a decision regarding the clinical utility of a new method.

Writing the method evaluation paper is where the students struggle the most. They are able to analyze individual pieces of information during each laboratory exercise, but they have trouble putting those pieces together to give a complete analysis. They are hesitant to recommend one method over the other as they are still trying to develop some confidence in their skills and become nervous about making an incorrect decision. Another area they struggle with is relating these studies to the clinical situation. They understand what error is present and they can explain it, but they have some difficulty applying that knowledge to patient values, understanding how it may influence an interpretation of a value, and what implications adopting a new method may have for clinicians and their patients. These issues are often resolved during the clinical practicum when students perform additional method evaluations and are able to consult with practitioners about real laboratory cases.

Clinical practicum
Method validation occurs in all areas of the clinical laboratory and is well suited to some degree of student involvement. Depending on the design and scheduling of clinical rotations in the CLS curriculum, students may be able to perform the validation assays with supervision. Some curricula are designed to allow students to complete specialized rotations and projects in method validation. Other programs may not have the time to allow students to actually perform the assays, however, in these situations, students can use the data generated by others and apply their own data analysis and interpretation using commercially available evaluation software. Often it is not until students are involved in the performance of “real lab” method validation do they begin to understand the principles and appreciate the importance of error detection as it relates to patient care.

SUMMARY
By including method validation as an integral part of the CLS curriculum, we emphasize quality and give students the background they need to feel competent in applying this knowledge on the job. The approach described in this review has lessened issues of student difficulties with calculations and their struggles to integrate the many concepts of method validation. This was accomplished primarily by the addition of activities such as organized student tutoring, student preparation of a written synopsis with an interpretation of results, and the use of real cases in the clinical practicum.

CLS students need to have a solid background in method validation, because performing method validation in a real world setting can be tedious and time consuming, especially if it is done incorrectly. We try to give our students the necessary skills for this process when they face it in the real world, recognizing that most College of American Pathologists (CAP) checklists ask for a plan in place for validating methods, without indicating how to validate methods. Teaching CLS students to perform these procedures properly is important to save time, money, and resources when they are functioning in a clinical setting in their future roles.

Instilling in students an appreciation for quality and quality standards and regulations throughout the CLS program is imperative. The studies of method validation provide a unique opportunity to discuss quality from a slightly different perspective. In addition, expertise in method validation is a skill that is very specific to CLS practice. While another healthcare professional may be able to perform a point-of-care test, he or she will not be able to perform the method validation for that instrument. Some of the procedures that are included in our scope of practice can overlap with other healthcare professionals, but method validation does not. This is something that only the CLS is educated to do and we should continue to strive for excellence in this arena.
Clin Lab Sci encourages readers to respond with thoughts, questions, or comments regarding this article. Email responses to ic.ink@mchsi.com. In the subject line, please type “CLIN LAB SCI 21(1) CP MOON”. Selected responses will appear in the Dialogue and Discussion section in a future issue. Responses may be edited for length and clarity. We look forward to hearing from you.

REFERENCES

A THANK YOU TO
SUSAN J. LECLAIR
FOR HER DEDICATION AND COMMITMENT
TO CLINICAL LABORATORY SCIENCE
EDITOR-IN-CHIEF, 2000 – 2007
CLINICAL PRACTICE EDITOR, 1993 – 1999
CONSULTING EDITOR (HEMATOLOGY/HEMOSTASIS), 1990 – 1993

From the Clinical Laboratory Science Editorial Board
A Survey of Quality Indicator Use in the Clinical Laboratory

LESLEY JANE PRESTON

OBJECTIVE: A survey of clinical laboratories was conducted to capture information about quality indicators in use within the state of Arizona. This information was then used to determine which quality indicators are applicable across the spectrum of clinical laboratories making them suitable for benchmarking laboratory performance. The objectives of this study were also to heighten awareness of benchmarking practices for clinical laboratory managers and laboratory quality assurance personnel, to develop objective methods of quality monitoring for performance improvement, and to encourage collaboration between laboratories and accreditation agencies.

METHODS: A review of the current literature was conducted to assess the status of benchmarking within the clinical laboratory. Data were also obtained from the Centers for Medicare & Medicaid Services (CMS) about all licensed clinical laboratories in Arizona. A mail survey was then created and conducted to investigate the use of clinical laboratory quality indicators in Arizona.

SETTING AND PARTICIPANTS: A paper survey was mailed to a representative sample of clinical laboratory managers included in the CMS licensed laboratories listing for the state of Arizona.

MAIN OUTCOME MEASURES: The selected sample was surveyed by mail and validation testing of the survey was conducted using the t-test. The compiled survey data is also presented in the form of histograms.

RESULTS: Applying the t-test to the sample vs. population data proved that the sample was not a very good representation of the population and a better selection method should be used in future studies. Of the 319 of 3198 clinical laboratories randomly selected to receive the survey, 21 (6.58% of the sample or 0.66% of the population) responded with completed surveys. The information received from the respondents revealed a relationship between test volume and the number of indicators being monitored by clinical laboratories, the preference of indicators being monitored by those laboratories, the size of the laboratories where the majority of benchmarking is occurring, and a link between accrediting agencies and benchmarking activities.

CONCLUSION: The survey proved that quality indicators are used for quality improvement purposes within the clinical laboratory; although it also showed that the industry still does not have a standardized approach to the use of quality indicators for benchmarking performance against other laboratories.

ABBREVIATIONS: CAP = College of American Pathologists; CDC = US Centers for Disease Control and Prevention; CLIA = Clinical Laboratory Improvement Act of 1988; CMS = Centers for Medicare & Medicaid Services; JCAHO = Joint Commission on Accreditation of Healthcare Organizations; NQF = National Quality Forum; PPM = provider performed microscopy; TAT = turnaround time.

INDEX TERMS: clinical laboratory science; healthcare quality indicators; healthcare benchmarking.


Lesley Jane Preston MS MT(ASCP) is Lieutenant Commander (LCDR), US Public Health Service (PHS) Indian Health Service, Hopi Health Care Center, Keams Canyon AZ.

Address for correspondence: Lesley Jane Preston MS MT(ASCP), Lieutenant Commander (LCDR), US Public Health Service (PHS) Indian Health Service, Hopi Health Care Center, 69 Low Street (P.O. Box 432), Keams Canyon AZ 8603. (928) 738-2389, (928) 737-6047 (fax). ljpreston@hopitelecom.net.
This paper was completed in partial fulfillment of the requirements for the Master of Science in Quality Assurance.

Very little has been written about the use of quality indicators within the clinical laboratory, although the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has worked hard to initiate quality processes in healthcare and use them as a basis for accreditation. To achieve this they have moved toward a holistic approach for their inspections by reviewing both patient outcomes and patient safety. A large part of their inspections also involves a process audit. In the case of a laboratory inspection, the inspector will review the laboratory testing that was ordered, what the results were, how the quality control testing performed at the time of patient testing, who performed the testing and their credentials, training and competency assessment, and finally the patient’s outcome.

This approach is more in line with today’s quality systems approach than any of the other accreditation organizations, but it fails to review other quality processes such as the use of quality monitors and other improvement activities. To ensure these areas are reviewed, JCAHO requires accredited laboratories to monitor certain National Patient Safety Goals to:

- improve the accuracy of patient identification,
- improve the effectiveness of communication among caregivers,
- reduce the risk of healthcare-associated infections, and
- encourage the active involvement of patients and their families in the patient’s care as a patient safety strategy.

Although JCAHO gives some guidelines of how these monitors are to be measured, such as “Comply with current US Centers for Disease Control and Prevention (CDC) hand hygiene guidelines” for the reduction of risk of healthcare-associated infections, they are not specific and therefore don’t allow for accurate comparison. Since they are not laboratory specific they do not reflect the laboratories’ testing abilities.

As opposed to JCAHO, the College of American Pathologists (CAP) is a laboratory-based organization and their accreditation process focuses solely on the laboratory. For this reason, their development of quality indicators are laboratory specific, and focused on the clinical laboratory testing processes, from order entry to result reporting.

The College of American Pathologists’ current list of suggested quality monitors is selected from data gathered during their performance of Q-Probes studies. So as not to create a conflict of interest between their accreditation of a facility and their Q-Tracks program (which is a separate fee-for-service program), CAP only gives “Examples of key indicators [which] include, but are not limited to”:

- Patient/Specimen Identification
- Test Order Accuracy
- Stat Test Turnaround Time
- Critical Value Reporting
- Customer Satisfaction
- Specimen Acceptability
- Corrected Reports – General Laboratory
- Corrected Reports – Anatomic Pathology
- Surgical Pathology/Cytology Specimen Labeling
- Blood Product Wastage
- Blood Culture Contamination

The College of American Pathologists’ Q-Probes studies were designed to study individual laboratories’ current problems for potential improvement. The selection of areas of study was therefore based on laboratories notifying CAP of areas where problems were occurring and paying CAP to review these areas in a performance improvement format. CAP’s subsequent development of Q-Tracks uses the information gathered from the Q-Probes studies in a benchmarking format to allow all laboratories that wish to participate a way of monitoring these selected indicators over time.

A review of the current literature of the Q-Tracks program indicates that the organizations that initially subscribed to Q-Probes and Q-Tracks were larger organizations. This assumption is based on the types of monitors selected being those that are applicable only to larger facilities; such as wristband monitoring for patient identification accuracy and blood culture contamination rates. Smaller facilities such as acute care hospitals and outpatient clinics may have very few to no in-patients with wristbands, or the need for blood culturing, so data from such indicators would be unavailable or only available in such small quantities as to be unusable as a continuous monitor of statistical significance. CAP’s use of data from larger facilities may be due to larger organizations having more funding available to subscribe to outside monitoring rather than having to rely solely on in-house methods.

To date Q-Tracks has monitors for:

- Patient Identification Accuracy
- Blood Culture Contamination
- Laboratory Specimen Acceptability
- In-Date Blood Product Wastage
- Satisfaction with Outpatient Specimen Collection
- Stat Test Turnaround Time Outliers
RESEARCH AND REPORTS

- Morning Rounds Inpatient Test Availability
- Critical Values Reporting
- Type and Screen Completion for Scheduled Surgery
- Turnaround Time (TAT) of Troponin
- Gynecologic Cytology Outcomes: Biopsy Correlation Performance
- Physician Satisfaction with Surgical Pathology Reports

The only research studies published about clinical laboratory indicator use to date and their ability to improve performance are those associated with the Q-Probes and Q-Tracks programs.

The CDC is currently working with the National Quality Forum (NQF), a consortium of public and private members, to create clinical laboratory monitors that are nationally

Figure 1. Mail survey

A SURVEY OF QUALITY INDICATOR USE AND BENCHMARKING PRACTICES WITHIN THE STATE OF ARIZONA

Please take a few moments to complete this survey about the collection of clinical laboratory indicators data. The information collected will determine indicators currently in use and identify those that are applicable across the spectrum of clinical labs for benchmarking suitability. This survey is one part of a thesis presentation to the faculty of California State University Dominguez Hills. Please return the survey in the envelope provided within 30 days of receipt.

1. What is your laboratory's annual test volume?
   - <10,000
   - 10,001 - 50,000
   - 50,001 - 100,000
   - 100,001 - 1,000,000
   - >1,000,000

2. What services does your laboratory provide? Please check all that apply.
   - Phlebotomy
   - Chemistry
   - Microbiology
   - Hematology
   - Coagulation
   - Urinalysis
   - Blood Bank
   - Immunology
   - Molecular Biology
   - Virology
   - Toxicology
   - Histology/Cytology

3. Which of the following quality indicators does your laboratory routinely (monthly/quarterly) monitor?
   - Patient Specimen Identification Accuracy
   - Test Order Accuracy
   - STAT
   - All
   - Critical Value Reporting
   - Customer Satisfaction
   - Patient Satisfaction
   - Physician/Provider Satisfaction
   - Other
   - Specimen Acceptability
   - Corrected Reports
   - Blood Product Wastage
   - Blood Culture Contamination
   - Type and Screen Completion for Scheduled Surgery
   - Cytopathology/Biopsy Correlation
   - Point-of-Care Testing Accuracy
   - Workload/Full Time Employees
   - Reference Laboratory Expenses
   - Other
   - Other
   - Other
   - Other
   - Other

4. Does your laboratory benchmark/compare quality data with other laboratories?
   - Yes
   - No

If yes, who do you benchmark/compare quality data with?
   - Private Data Collection Agency
   - Governmental Agency
   - Accreditation Agency (CAP, COLA, JCAHO, etc.)
   - Clinical Laboratory Network (such as an organization’s internal network)

5. Who accredits your laboratory?
   - CAP
   - CLIA
   - COLA
   - JCAHO
   - Other

VOL 21, NO 1 WINTER 2008  CLINICAL LABORATORY SCIENCE 27
but as Lusky states, “Some things aren’t a matter of whether but of when. And national quality measures for [clinical] laboratories that can be linked to payment incentives or inspection penalties or both are likely to be one of them.”

The goal of this study was to survey clinical laboratories of all sizes and scopes within the state of Arizona to identify quality indicators currently being monitored. This would allow for a comparison of monitors recommended by CAP, JCAHO, and the NQF. It would also allow for the segmentation of monitors based on laboratory size and scope, to determine whether monitors for different facility types are necessary.

**MATERIALS AND METHODS**

To obtain data that may be generalized for any state throughout the United States an arbitrary single state, the state of Arizona, was selected as the survey sample.

Relevant data about all licensed clinical laboratories currently operating within the state of Arizona were obtained from the CMS of the Department of Health and Human Services. These data included Clinical Laboratory Improvement Amendment (CLIA) Act licensure numbers, names of laboratories, laboratory addresses and contact information, the type of certificate of licensure held (compliance, waived, provider performed microscopy, or accredited), type of control (ownership), and facility type (ambulatory surgery center, community clinic, ancillary test site, etc.) The list contained 3198 licensed laboratories within the state of Arizona printed in order of licensure number; of this list, a sample of 319 (10%) laboratories were selected to receive a mailed survey. The sample selection was made using a systematic approach with a random number start, as described by Hayes.

The survey (Figure 1) contained questions regarding laboratory demographics that were not available on the CMS list, such as the laboratory’s annual test volume (an indicator of laboratory size), the services provided (an indicator of laboratory type), and the accrediting organization by which the laboratories were inspected (for comparison of indicator use and accreditation agency). The intention of the survey was to capture data about all clinical laboratory types and sizes, so that the information obtained was a fair representation of quality indicators in the clinical laboratory industry.

The actual sample size used for the final investigation was determined by the survey response rate.

**RESULTS**

The data collected from the list of laboratories obtained from the CMS, was used to calculate a possible correlation ($r$) between the population data and the sample, using t-tests (with a $p = 0.05$) as described by Crossley. This was performed to determine whether the sample surveyed was representative of the Arizona laboratory population.

<table>
<thead>
<tr>
<th>Table 1. Correlation and t-test comparisons of surveyed sample vs. population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Type of certificate of licensure</td>
</tr>
<tr>
<td>Type of control</td>
</tr>
<tr>
<td>Facility type</td>
</tr>
</tbody>
</table>

$r^2$ = correlation coefficient squared; $r$ = correlation coefficient; $t$ = t-test result; $t_{crit}$ = critical value that the t-test result must be less than for results to be comparable.
(Table 1). Upon initial review, the data in Table 1 appear to indicate that the sample data correlate well with the population but when the t-test is applied, one can see that the two sets of data (population vs. sample) are not the same, indicating that the selected sample was not a very good representation of the population being surveyed. Even with this limitation, the survey results produced some important information that could provide a basis for future research.

There was no current literature on the use of surveys to obtain information about quality indicator use within the medical field; therefore, the survey was constructed following the guideline of Hayes for customer satisfaction surveys. A direct comparison (correlation analysis or t-test) could not be made between the respondents and the initially selected sample or population because the survey did not ask questions about type of licensure held, type of ownership, or facility type. This would have made a direct comparison and complete survey validity testing possible.

Of the 319 clinical laboratories selected to receive a survey, 21 responded with completed surveys. This represented 6.58% of the sample or 0.66% of the total population of licensed clinical laboratories within the state of Arizona.

The survey data collected was used to make a comparison between the laboratory’s test volume and the average number of quality indicators monitored (Figure 2). Although the correlation coefficient of 0.6193 is not high, these data do indicate that larger sized laboratories are performing more indicator monitoring compared to smaller facilities. The low correlation coefficient may be due to the low sample size and could improve if the sample size were increased.

There are only three indicators that are required or suggested for monitoring by JCAHO, CAP, and NSF; these are patient specimen identification accuracy, critical value reporting, and physician/provider satisfaction (Table 2). Therefore, it is not surprising that these three indicators were monitored by more laboratories than most of the other indicators. Two other quality indicators that were monitored as much as the above-mentioned three were specimen acceptability (suggested by CAP) and test order accuracy (suggested by both CAP and NQF).

The two quality indicators that were monitored the least were type and screen completion for scheduled surgery and cytology/biopsy correlation, two indicators that are highly specific for specialized laboratories (blood banks and anatomic pathology laboratories, respectively).

Patient/specimen identification, critical value reporting, and patient satisfaction were also the only three indicators that were monitored by all laboratory sizes surveyed (<10,000; 10,001-50,000; 50,001-100,000; 100,001-1,000,000; >1,000,000) which may be an important factor when considering indicators that are applicable to most if not all clinical laboratories. STAT turnaround times, specimen acceptability, and blood culture contamination were only monitored by the larger facilities.

Most of the responding laboratories that had a test volume of >10,000 were performing some type of benchmarking activities (Figure 3). The smallest facilities, with a test volume of 0-10,000, seem least likely to perform benchmarking activities.

Of the facilities that were benchmarking quality indicator data, private data collection agencies and private clinical laboratory networks appeared to be the favored methods of quality data comparison. A few laboratories included private industry, such as reagent manufacturers, as a means for benchmarking quality assurance data. This response may be a misunderstanding of the dif-

Figure 2. Test volume vs. number of indicators monitored
Table 2. List of monitors surveyed with associated accrediting organizations

<table>
<thead>
<tr>
<th>Monitors surveyed</th>
<th>Accreditation/quality organization</th>
<th>Percentage of laboratories monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Specimen Identification Accuracy</td>
<td>JCAHO/CAP/NQF</td>
<td>57</td>
</tr>
<tr>
<td>Test Order Accuracy</td>
<td>CAP/NQF</td>
<td>43</td>
</tr>
<tr>
<td>Turnaround Time – STAT</td>
<td>CAP</td>
<td>33</td>
</tr>
<tr>
<td>Turnaround Time – All</td>
<td>NQF</td>
<td>33</td>
</tr>
<tr>
<td>Critical Value Reporting</td>
<td>JCAHO/CAP/NQF</td>
<td>62</td>
</tr>
<tr>
<td>Patient Satisfaction</td>
<td>JCAHO/CAP</td>
<td>38</td>
</tr>
<tr>
<td>Physician/Provider Satisfaction</td>
<td>JCAHO/CAP/NQF</td>
<td>43</td>
</tr>
<tr>
<td>Specimen Acceptability</td>
<td>CAP</td>
<td>57</td>
</tr>
<tr>
<td>Corrected Reports</td>
<td>CAP</td>
<td>33</td>
</tr>
<tr>
<td>Blood Product Wastage</td>
<td>CAP</td>
<td>29</td>
</tr>
<tr>
<td>Blood Culture Contamination</td>
<td>CAP/NQF</td>
<td>29</td>
</tr>
<tr>
<td>Type and Screen Completion for Scheduled Surgery</td>
<td>NQF</td>
<td>0</td>
</tr>
<tr>
<td>Cytology/Biopsy Correlation</td>
<td>NQF</td>
<td>5</td>
</tr>
<tr>
<td>Point-of-Care Testing Accuracy</td>
<td>NQF</td>
<td>24</td>
</tr>
<tr>
<td>Workload/Full-time Employees</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Reference Laboratory Expenses</td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

ference between quality control and quality assurance on the part of the respondents, as quality control data, not quality assurance data, is regularly collected by reagent/instrument manufacturers for comparison. Eleven of the 21 respondents indicated that they “benchmark/compare quality data”.

Thirteen of the 21 respondents also indicated that they were accredited through CLIA as opposed to other clinical laboratory accreditation agencies (Figure 4). CLIA usually accredits facilities that are performing waived and/or provider performed microscopy (PPM), whereas larger facilities performing more complex testing with higher regulatory requirements are usually accredited by CAP or JCAHO. Therefore, the survey findings were largely affected by the number of smaller facilities that responded to the survey and could be more accurate if each licensure group were surveyed separately. The data in Figure 4 also shows that less than half of the laboratories accredited through CLIA are benchmarking.

DISCUSSION

Clinical laboratories have collected quality indicator data to monitor performance and initiate improvement for approximately 10 to 20 years, but they may not fully recognize the value of using these data to perform comparisons (benchmarking) with other clinical laboratories on a large scale, and large-scale comparisons may provide a more objective picture of their laboratory’s performance. Many laboratories have collected quality data based on their own laboratory’s experiences and needs; this has led to the development of a variety of monitors that are hard to compare directly.

The two largest clinical laboratory accreditation agencies, CAP and
JCAHO, have studied the use of quality monitors within the clinical laboratory. Both agencies began by selecting monitors that were already in existence. CAP used the information it collected to develop a voluntary benchmarking tool called Q-Tracks, while JCAHO is progressing toward standardization of clinical laboratory quality monitors to encourage collaboration between clinical laboratories.

Before any form of collaborative comparisons can take place, clinical laboratory scientists must define the indicators that are needed to monitor performance and exactly how they should be monitored, a goal of the NQF. These monitors should be based on the size and/or scope of the laboratory.

This survey was conducted to capture information about the status of clinical laboratory quality monitoring, and benchmarking practices, with the expectation of identifying indicators that are comparable across a spectrum of laboratories.

A review of the literature failed to locate any previous clinical laboratory surveys conducted to collect information about the use of quality monitors. Therefore, the survey was created using guidelines from customer satisfaction surveys described by Hayes and the lists of quality monitors described by CAP, JCAHO, and the NQF.

Information obtained from on the CMS list was used to determine the validity of the selected sample by obtaining the t values for the population data vs. the sample data. Unfortunately, this data analysis showed that the surveyed sample was not a fair representation of the population and therefore weakens the validity of conclusions made regarding the data collected. Final survey validation would best be determined by performing comparisons of the population data vs. the survey respondent data. This survey did not capture the relevant information to perform these calculations, as it did not address questions about the facilities’ certification, control, and type from the actual respondents.

Of the 319 laboratories initially surveyed, 21 laboratories responded, allowing some conclusions to be drawn from the information received.
Larger facilities appear to be performing more quality indicator monitoring than smaller facilities. This is not surprising because larger facilities are the moderate to high complexity testing laboratories as defined by the CMS\textsuperscript{12} that have more stringent regulatory requirements than smaller laboratories.

When laboratories do select quality indicators to monitor, they generally select monitors that represent the entire process for all laboratory testing. To do this, at least one monitor is usually selected to represent pre-analytical testing, analytical testing (the actual measuring phase), and post-analytical testing. The results of the survey indicate that the top six monitored indicators are:

- Critical Value Reporting (post-analytical)
- Patient Specimen Identification Accuracy (pre-analytical)
- Specimen Acceptability (pre-analytical)
- Test Order Accuracy (pre-analytical)
- Customer Satisfaction – Physician/Provider (system)
- Customer Satisfaction – Patient (system)

These monitors do appear to be a good representation of the entire process (as long as system monitors are considered equivalent to analytical monitors) and are applicable to most laboratory sizes and scopes. This would make them easily comparable and an attractive selection for benchmarking purposes.

Many laboratories monitor three to six quality indicators, which seems to be a reasonable amount for monthly monitoring. Benchmarking too many monitors may become prohibitive and probably counterproductive, especially when laboratories also have to address their own unique problems for monthly monitoring and performance improvement. Some larger facilities with more specialized testing may want to benchmark other monitors that are more specific to their needs, such as cytology/biopsy correlation accuracy or type and screen completion for scheduled surgery, so this option must also be available.

The data collected indicate that benchmarking is occurring at a high rate in the facilities that are performing >10,000 tests per year. This was a surprising finding and it may be due to survey self-exclusion by laboratories not performing any monitoring activities. One of the problems with using a voluntary survey to collect data is that facilities that may not feel comfortable with their performance (don’t monitor quality indicators and/or benchmark) may decide not to answer the survey. This would skew the data, making it seem that there are more laboratories performing monitoring and benchmarking than actually are.

Further research needs to be performed in this area before successful benchmarking programs can be produced that will be applicable to most, if not all, clinical laboratories. If future surveys are performed, the support of at least one of the nationally recognized accreditation organizations would probably encourage a larger survey response. Another suggestion is to survey laboratories that hold different types of licensure separately, so that the information collected could be analyzed based on laboratory size/or scope. Additionally, construction of a survey that can directly compare sample and population data against response data would allow for the appropriate validity testing of the survey tool.

REFERENCES

FOCUS: INFORMATION LITERACY

Finding the Knowledge in Information

BURTON WILCKE

In 1934, when T.S Eliot wrote the following in his poem, “The Rock”, it is doubtful he envisioned his words being applied to the field of clinical laboratory science some 74 years later.

“Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?”

Perhaps more than any other group of healthcare professionals, clinical laboratory scientists can easily become lost in data and information. Indeed, the primary focus of the field of clinical laboratory science is the generation of data for clinical decision making. Through production of this data, laboratorians contribute critical information for use by physicians and others for the diagnosis, treatment, and monitoring of disease.

Today, the clinical laboratory depends heavily upon computers for processing and handling the large volumes of data it generates. In fact, in the early stages of their development, computers were referred to as “data processing machines”.1 Having a solid understanding of the function of computers has become an essential part of becoming a clinical laboratory scientist. A working knowledge of the use of computers and common software applications is now an essential prerequisite for students entering into clinical laboratory science programs such as that at the University of Vermont. Accrediting bodies that oversee clinical laboratory science programs now expect and require evidence of this in our curricula. But merely knowing how to use computers and computer software is no longer sufficient in today’s world.

Throughout its history, the focus of the field of informatics has gradually evolved from information technology (IT) to the broader discipline of information science (IS). In many ways this parallels changes that have occurred in the field of clinical laboratory science, for this field too had its origins in technology but is now legitimately identified as a science. Reflecting the maturation that has occurred in both fields, it is not enough for clinical laboratory scientists to simply be knowledgeable about the mechanics of information systems. Today, they must be truly “information literate”.

Information literacy is defined as “the ability to recognize a need for information, find, evaluate, and use that information in whatever format … it appears.”2 As academics, we must educate our students to a level of expertise that goes far beyond the basics of information technology and addresses these higher functions. In addition to being able to operate sophisticated instruments to generate data, we need to ensure that our students have the ability to translate data into information, and information into knowledge.

In practice, clinical laboratory scientists are called upon to transform information into knowledge on a regular basis. Whether it is to write or update technical protocols, document best practices, design methods for new assay evaluation, or write grant and project proposals, all require the ability to access and use information effectively.

Yet to be truly information literate, the clinical laboratory scientist cannot rely on information found in hard-bound references and textbooks. Given the rapid changes in the field, such sources quickly become outdated and the information contained therein either incomplete, incorrect, or both. With the volume of published literature growing exponentially and new publication formats continuously being developed, clinical laboratory science students and practitioners need a toolbox filled with a variety of resources upon which to draw. These will include online literature databases, citation indexes, Internet search engines, and clinical decision-making resources.

This series of articles will help clinical laboratory scientists become more facile with using contemporary information...
retrieval techniques and tools. As we continue to modify and improve the way in which we educate our future clinical laboratory scientists, we should be certain that informatics and information literacy are a standard part of their primary as well as continuing educational experiences. In answer to Eliot’s question, “Where is the knowledge we have lost in information?” we respond that “knowledge is found in education”.

Burton W Wilcke Jr PhD is associate professor and chair of the Department of Medical Laboratory and Radiation Sciences at the University of Vermont, Burlington VT.

Frances Delwiche MLIS MT(ASCP) is the Focus: Information Literacy guest editor.

REFERENCES
As the volume of biomedical literature has increased, so have the number and complexity of databases that index it. Learning to conduct an efficient literature search in an online database is an essential skill for today’s clinical laboratory scientist. This article describes basic and advanced strategies for searching PubMed and the use of specialized features including MyNCBI.

**ABBREVIATIONS:** MeSH = Medical subject headings.

**INDEX TERMS:** abstracting and indexing; bibliographic databases; controlled vocabulary; Internet; medical technology; medical subject headings; MEDLINE; periodicals; PubMed.

**Clin Lab Sci 2008;21(1):35**

**LEARNING OBJECTIVES**
1. Identify the search feature that reveals how PubMed translated a search query.
2. Define “MeSH terms” and describe their usage.
3. Describe the order in which PubMed results are displayed by default.
4. Illustrate how a search that brought up either too many results or too few results could be modified.
5. Compare the effects of the use of the Boolean operators AND and OR.

*Frances A Delwiche MLIS MT(ASCP) is library assistant professor at Dana Medical Library at the University of Vermont, Burlington VT.*

**Address for correspondence:** Frances A. Delwiche MLIS MT(ASCP), library assistant professor, Dana Medical Library, University of Vermont, Medical Education Center, Burlington VT 05405. (802) 656-4423, (802) 656-0762 (fax). frances.delwiche@uvm.edu.

*Frances Delwiche MLIS MT(ASCP) is the Focus: Information Literacy guest editor.*

Nearly thirty years ago, William D. Garvey wrote in his seminal work that “communication is the essence of science”.¹ In medicine and the biological sciences, the cornerstone of scientific communication is the scholarly journal article. Although monographs, textbooks, and handbooks are crucial for answering basic background questions and providing a solid foundation in the field, the journal article serves as the primary vehicle for the dissemination of new knowledge. “Publication in a refereed scientific journal marks the completion of a project; that the project's findings have been reviewed and accepted by professional peers signifies acceptance by the scientific community and also certifies a claim on any reported discoveries.”²

The importance of the journal article in science and medicine is borne out in sheer numbers. In 2001, it was reported that over 30,000 biomedical journals are published annually.³ “The total body of medical information doubles every 5 years”,⁴ and with the increasing use of electronic publishing, the pace is accelerating with dizzying speed. There is so much literature published in the health sciences that it’s become increasingly impossible to keep up. It is even difficult to keep up with a few personal journal subscriptions. As Gehlbach notes in his popular text:

> “Confronted with a burgeoning pile of journals, we cannot bear the thought that any of the information packed within those glossy pages should go unabsorbed. We wait for that magical time when we can sit down and plow through it. That day never arrives, and our guilt grows proportionally with the stack, diminishing only...when a housekeeping purge assigns it all irrevocably to the attic or trash bin.”

A 2003 study of the literature of clinical laboratory science revealed that approximately one third of references used by authors writing in three popular journals over a three-year period came from just thirteen journal titles. The remaining two thirds of the references were drawn from over 900 different journal titles, many of which were cited only once.⁶ Clearly, browsing a handful of favorite titles or reading the tables of contents from selected prestigious journals would never be sufficient to retrieve all the useful articles published on a given topic.

A better way of identifying useful articles on topics of interest (and maintaining one’s sanity) is to cultivate the necessary

---

⁶ A 2003 study of the literature of clinical laboratory science revealed that approximately one third of references used by authors writing in three popular journals over a three-year period came from just thirteen journal titles. The remaining two thirds of the references were drawn from over 900 different journal titles, many of which were cited only once.
knowledge and skills to be a competent searcher of electronic information resources, especially bibliographic databases. Owing to their convenience and superior search capabilities, the popularity of online databases has far exceeded that of their print predecessors. Academic, hospital, and public libraries offer access to these resources, and some of them are available free to anyone with an Internet connection.

As the volume of journal literature has increased, so has the number, complexity, and capability of the databases that index it. Learning to manipulate the features of online databases to find all the articles on a given topic is a skill that is essential to today's healthcare professional. This article will focus on the use of a specific database, but many of the search techniques described are readily transferable to other systems.

**MEDLINE/PUBMED**

One of the primary databases for searching the biomedical journal literature is MEDLINE, produced by the United States National Library of Medicine in Bethesda, Maryland. Originating from the print *Index Medicus* first published in 1879, today MEDLINE contains over 17 million records dating from the 1950s to present. MEDLINE covers the fields of medicine, nursing, dentistry, health sciences, healthcare administration, and veterinary medicine, as well as preclinical sciences such as biochemistry, immunology, microbiology, and molecular genetics. MEDLINE indexes over 5,000 journals published in the United States and 80 other countries, providing citations and abstracts for the articles indexed and, increasingly, links to the full text.

The MEDLINE database is a compilation of records, one for each article indexed. These records provide citation and abstract (when available), plus additional details such as language, publication type, institution of primary author, country of publication, chemical names, pharmacologic action, and subject headings. The subject headings, referred to as “MeSH” terms (Medical Subject Headings), serve to describe the key concepts discussed in the article. They constitute a standardized vocabulary that is used to find articles on any given term without having to search for every possible spelling variation, acronym, and synonym. Because they are manually assigned by expert indexers and are fully searchable, the subject headings contribute substantially to the power and search capability of MEDLINE.

MEDLINE is available in multiple forms, both free and by license through commercial vendors such as Ovid Technologies. Among the most popular ways to access MEDLINE is through PubMed, a free web-based search engine developed by the National Center for Biotechnology (NCBI) at the National Library of Medicine. As a component of NCBI’s Entrez retrieval system, PubMed provides a vital link between the biomedical literature and its molecular biology and genetics databases.

Although MEDLINE makes up the largest component of PubMed, PubMed contains several small subsets that exist outside of MEDLINE. These include publisher-submitted citations that precede the date a journal was selected for indexing by MEDLINE; citations from general science journals on topics that are considered out-of-scope for MEDLINE, such as astrophysics or plate tectonics; and citations submitted directly by publishers for articles in the latest issues of their journals. Once the records for the newly submitted citations are fully annotated, they will either be added to the MEDLINE database or converted to out-of-scope status, depending upon the topic.

PubMed offers a wide range of options designed to meet the needs of searchers at all skill levels, including healthcare professionals, scientists, professional librarians, and the general public. Despite its size and complexity, even the most novice searcher will often be successful in finding at least a few useful articles. However, to use PubMed effectively and efficiently, and to find the most relevant articles on your topic, you'll need to have a solid understanding of the search tools and strategies available.

**BASIC PUBMED SEARCHING**

PubMed can be accessed directly at [http://www.pubmed.gov](http://www.pubmed.gov). Access to PubMed is also often available through the website of academic, health sciences, or hospital libraries. If that library is registered as a PubMed “LinkOut Provider”, accessing PubMed through their web page may enable you to connect directly to its online journal subscriptions from PubMed records.

Begin the search process by formulating your search question, using the most precise terms possible. Identify the searchable terms, and enter them into the search box as a word string. Click Go, or press Enter. By default, PubMed automatically combines the terms using the Boolean operator AND to bring up articles that include all the terms entered. Thus, use of the connector AND in your search statement is not necessary. PubMed also supports use of the Boolean operators OR and NOT when entered in a nested search statement. OR will bring up results that include at least one, but not necessarily all, of the terms, and NOT will eliminate results containing specified terms. Quotes can be used to search for exact phrases,
but their use is not advised because it disables the automatic MeSH term search (described below). Use of truncation is generally not recommended for the same reason.

Suppose you wish to conduct a search on methods of laboratory screening for gestational diabetes. Enter “gestational diabetes screening” into PubMed’s search box, and click Go (Figure 1). The first page of results will be displayed, but before looking at them, click on the Details tab to see how PubMed translated your search query (Figure 2). Processing the word string from left to right, PubMed searched on the subject heading (MeSH term) that most closely matched each word or phrase entered, plus performed a text word search for every occurrence of the word(s) in the database. In this case, the word string “gestational diabetes” was translated as the MeSH term “diabetes, gestational” and was also searched as a text word. The word “screening” was translated as the subheading “diagnosis”, as the phrase “mass screening” anywhere in the title or abstract of the non-MEDLINE subset of PubMed, as the MeSH term “mass screening”, and as a text word. By clicking on the Details tab every time you run a PubMed search, you can see exactly how the search was executed and modify your choice of search terms accordingly.

As frequently happens, the initial set of results in our sample search is very large, with over 1900 hits (Figure 3). To reduce the number of results and identify those that are most relevant to your topic, apply limits to your search. Click on the Limits tab and scan the options available, including language, sex, human or animal, animal species, journal subset, publication date, research study design, and age group (Figure 4). Use of the Abstracts limit is not usually recommended, as many valuable articles, including review articles, do not have abstracts. In this case, select Published in the Last 5 Years, Humans, English language, and the Core Clinical Journals subset. Click Go. The resulting set of 88 citations is much more manageable and focused (Figure 5). The limits selected will remain in effect for all subsequent searches until the option is de-selected.

PubMed results are displayed in reverse chronological order (most recent first), rather than in relevancy-ranked order as is the case with most Internet search engines. The default Summary display provides the authors, title, journal name, date, volume, issue, and page numbers, and PubMed status. To view the abstract for one article, click on the author line or abstract icon for that article. To view the abstracts for all the records on that page, click on the Display drop-down box and select Abstract. To view the MeSH terms assigned to the articles, change the Display drop-down
box to Citation (Figure 6). By reading the abstract and noting the range of topics covered by the MeSH terms, you can gain a fairly accurate sense of the content of the article.

Often, in the Abstract or Citation display, you may notice one or more icons for online access of the full article. These may include an icon for the publisher’s website, PubMed Central, or for participating LinkOut libraries and institutions (Figure 6). Except for PubMed Central, the presence of an icon does not imply that the article is necessarily available free to the general public. Most publishers require either an individual or institutional subscription to their journals, but frequently they will offer non-subscribers the option to pay per article. Icons for individual libraries indicate that the library has obtained a subscription to that journal. Unaffiliated patrons are generally not able to access the full article through these links unless logged in onsite. Many academic, health sciences, and hospital libraries welcome walk-in traffic from members of the community, and have professional librarians available to assist patrons regardless of affiliation.

After applying limits, browse the results, and check the boxes next to those you wish to keep. Then click the Send To drop-down box and choose from the available options. The Text option will convert the citations to plain text, removing all PubMed graphics. The File option can be used to save citations to your computer or travel drive. For printing or emailing, select the appropriate option and complete the dialog box. The Clipboard option can be used to temporarily save your selected citations, up to a maximum of 500, for later action.

REFINING A PUBMED SEARCH

Often an initial search will bring up only a small number of useful (“relevant”) articles. An easy method of expanding your search is to click the Related Articles link located on the right margin for each citation. This will launch a pre-fabricated search, generating a set of relevancy-ranked citations based on an algorithm applied to the original citation. Each of those citations will have a Related Articles link that will bring up its own unique set of related articles. Using your browser’s Back button to navigate, click on the Related Articles link for each of the relevant citations, making your selections and sending them to Clipboard, thus creating a composite set of highly relevant citations.

Frequently you may have one “known” article and wish to find others like it. Click on the Single Citation Matcher link on the blue sidebar, and complete at least one field. When you bring up the record for the original article, you can click on the Related Articles link for that article to expand your search. A more sophisticated method of expanding a search is to take advantage of the MeSH terms assigned to each article (viewed in the Citation display). For example, in the results

---

**Figure 4. PubMed limits**

![PubMed limits](image1)

National Library of Medicine. Used with permission.

**Figure 5. Results of PubMed search after applying limits**

![Results of PubMed search after applying limits](image2)

National Library of Medicine. Used with permission.

---
for the gestational diabetes screening search, you may have noted that some articles were assigned numerous MeSH terms in addition to “diabetes, gestational” and “mass screening”. These may include closely related MeSH terms such as “prenatal diagnosis”, “early diagnosis”, or “glucose tolerance test”. A search on any of these terms, alone or in combination, could potentially bring up useful citations that were not found with the original search strategy.

To perform a search using MeSH terms in the PubMed record, begin by going to the Citation display for the desired record. Clear the search box and remove any limits. Click on the desired MeSH term and select PubMed from the drop-down box. Now click on the History tab to view a list of searches you have run in this session. Using the syntax, #1 AND #2, combine the appropriate searches using the Boolean operators AND, OR, or NOT. By experimenting with different combinations of terms, you can determine which produces the most relevant results for your particular search question.

The full power of MEDLINE can best be utilized by searching via the MeSH Database. With this method, you must search on each concept separately. Click on the link on the blue sidebar, and enter a word or phrase representing the first concept. From the list provided, select the MeSH heading that most closely matches your term. Read the Scope Note (a definition of the term as used by MEDLINE) and the available subheadings. Scroll down to view the hierarchical arrangement of MeSH terms, observing that with each indention to the right, the terms become progressively more specific (Figure 7). By default, all MeSH term searches in PubMed automatically include not only the term selected, but also all more specific terms nested beneath it, a process referred to as “exploding”. If you do not wish to capture articles indexed under these more specific terms, check the box to turn off the Explode feature.

Figure 6. PubMed’s citation display showing MeSH terms

Note publisher’s icon and icons for the University of Vermont library’s journal holdings. Also note MyNCBI highlighting of search items. National Library of Medicine. Used with permission. Abstract used with permission from Elsevier.
Also, note the check box to restrict the search to major topic headings only. Both functions have the net effect of reducing the total numbers of results, albeit through different mechanisms.

Make your selections, then in the “Send To” drop-down box, choose “Search Box with And”. Then click PubMed Search. Repeat for the next concept. Finally, click on the History tab and combine sets as described above (Figure 8). In Figure 8, compare sets #2 and #16, noting the dramatic reduction in number of results obtained by restricting the search to MeSH terms. By using this more sophisticated method of searching, you can increase your chances of finding relevant articles in the database while effectively screening out most of the irrelevant articles.

One important caveat to keep in mind when searching via MeSH terms is that new records for citations supplied directly by publishers do not initially contain MeSH terms. During the one to four weeks that it takes to complete the annotation process, these articles would be missed by restricting the search to MeSH terms only, but would be found with a basic text word search.

In addition to the search strategies described in this article, searches can also be conducted using the Preview/Index tab, traditional command line language, or by running a Clinical Queries search via the tab on the blue sidebar. The Clinical Queries feature is designed for busy clinicians to bring up rigorous, high-quality, clinically-relevant articles, while eliminating non-research articles and weaker forms of research. For more information on these specialized methods of searching, consult the PubMed Help pages or tutorials, or ask a professional librarian for help.

**MyNCBI**
PubMed offers a wide range of customization options through use of a MyNCBI account. For example, under MyNCBI User Preferences, you can enable the highlighting feature to help you spot the search terms at a glance. Under MyNCBI Filters, you can choose LinkOut institutions and organizations, and set a filter for their journal holdings. You can set filters to group records according to various properties, such as publication type, age groups, or language. In this example (Figure 6), the author set a filter
FOCUS: INFORMATION LITERACY

for her home library, as well as one for review articles. Your MyNCBI account permits you to save search strategies and request automatic email updates to be sent on a weekly or monthly basis. Registration for a MyNCBI account is free, and cookies must be enabled on your browser.

CONCLUSION
Having obtained a list of citations and abstracts from your PubMed search, the final step is to obtain the actual articles. In some cases, the full text of the articles may be available for free online in PubMed Central or directly from the publisher. More often, journals are sold by subscription to individuals or libraries in print, online, or both. Access to online journals subscribed to by libraries is typically restricted to their patrons, although many libraries permit walk-in users to access their collection.

Some journal articles are now being published in their full form online, with the print version being abridged. However, in most cases, the content is identical regardless of format. Therefore, when online access is denied, a photocopy from the print journal may be a satisfactory substitute. For articles in journals not subscribed to by your library, a copy may be requested via interlibrary loan. Whereas interlibrary loan requests once required as long as a week to arrive, today they are frequently filled with very short turnaround times, sometimes the same day.

As one of the premier databases in the biological and health sciences, PubMed serves as an excellent starting point for searching the journal literature. Depending on the topic and level of comprehensiveness required, a PubMed search may be augmented with a search in one of many other bibliographic databases, such as BIOSIS, CINAHL, Cochrane Database of Systematic Reviews, EMBASE, or Web of Science. Each of these resources fills a unique niche and indexes publications not covered by the others. Google, Google Scholar, Sirius, or other Internet search engines may contain preprints, technical reports, meeting abstracts, and other forms of “grey” literature not found elsewhere. The professional staff at your academic, health sciences, or hospital library can help you search these and other useful resources.

It takes time and practice to learn to conduct an efficient and productive literature search, but it is an endeavor well worth the effort. Many of the PubMed features and search techniques described in this article can readily be applied to other software platforms. As you become more adept at navigating online databases and other electronic resources, you’ll discover that you have cultivated a knowledge base and skill set that will serve you well throughout your career.

 Clin Lab Sci encourages readers to respond with thoughts, questions, or comments regarding this article. Email responses to ic.ink@mchsi.com. In the subject line, please type “CLIN LAB SCI 21(1) FO DELWICHE”. Selected responses will appear in the Dialogue and Discussion section in a future issue. Responses may be edited for length and clarity. We look forward to hearing from you.

REFERENCES
FOCUS: INFORMATION LITERACY

Searching the Biomedical Literature: Research Study Designs and Critical Appraisal

PETER W CALLAS

Two essential issues to consider when assessing the validity of research studies are the strengths and weaknesses of the study design and quality of methodology. This paper reviews study designs commonly used in clinical research, including case reports, cross-sectional studies, case-control studies, cohort studies, randomized controlled trials, reviews, and meta-analyses. It concludes with an outline for assessing study quality.

ABBREVIATIONS: AIDS = acquired immunodeficiency syndrome.

INDEX TERMS: case-control studies; cohort studies; cross-sectional studies; epidemiologic studies; randomized controlled trials.

Clin Lab Sci 2008;21(1):42

Peter W Callas PhD is research associate professor in the Department of Medical Biostatistics at the University of Vermont, Burlington VT.

Address for correspondence: Peter W Callas PhD, research associate professor, Medical Biostatistics, University of Vermont College of Medicine, Hills Building, 105 Carrigan Drive, Burlington VT 05405. (802) 656-3195, (802) 656-0632 (fax). pcallas@uvm.edu.

Frances Delwiche MLIS MT(ASCP) is the Focus: Information Literacy guest editor.

LEARNING OBJECTIVES
1. Describe what is meant by “strength of evidence” when referring to research study designs.
2. Describe each of the following study designs: case report/case series, cross-sectional study, case-control study, cohort study (prospective and retrospective), and randomized controlled trials.
3. Discuss the strengths and weaknesses of each of the above study designs.
4. Define selection bias, recall bias, interviewer bias, and information bias.
5. Explain the major issues that should be considered when conducting a critical appraisal of a research study.

A search of the primary biomedical literature frequently brings up a number of research studies on the topic of interest. Much to the searcher’s consternation, there will often be multiple studies that arrive at very different conclusions. Which is correct? Could two conflicting studies both be correct?

To answer these questions, the reader needs a sound basis on which to judge the quality of each study, for in reality, all published research studies are not equally valid. Some may be very strong, while others may have methodological weaknesses that render their findings questionable or even useless. In evaluating a research study, two essential issues must be considered: the particular study design used and its inherent strengths and weaknesses, and the quality of the methodology employed. This paper will review the various study designs commonly used in clinical research, and conclude with an outline for assessing the quality of individual studies.

STUDY DESIGNS
Most papers encountered in the biomedical literature can be classified as one of three types: clinical research, basic science research, or non-research. Clinical research is any research involving human subjects. Basic science research consists of laboratory (“bench” or “test tube”) studies and animal studies. Basic science research is valuable because it can safely and ethically study topics not yet understood to the level where they can be applied to humans, but because it is not yet applicable to humans, basic science research is sometimes of
FOCUS: INFORMATION LITERACY

questionable relevance. Non-research papers include commentaries, news, and correspondence. These forms of publication, too, play an important role. For example, letters to the editor can be helpful in elucidating methodological issues with published research studies. This article will focus primarily on clinical research, since this is most relevant for clinical practice.

Table 1. Study designs used in clinical research

<table>
<thead>
<tr>
<th>Design</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case report/ case series</td>
<td>Useful for generating hypotheses</td>
<td>No comparison group</td>
</tr>
<tr>
<td></td>
<td>Relatively quick and inexpensive</td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>Relatively quick and inexpensive</td>
<td>Causal direction unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Affected by duration of outcome</td>
</tr>
<tr>
<td>Case-control</td>
<td>Useful for rare outcomes</td>
<td>Difficult to select unbiased control group</td>
</tr>
<tr>
<td></td>
<td>Relatively quick and inexpensive</td>
<td>Possible information bias since outcome has already occurred</td>
</tr>
<tr>
<td>Cohort</td>
<td>Directly measures incidence of outcome</td>
<td>Loss to follow-up</td>
</tr>
<tr>
<td></td>
<td>Risk factors measured prior to outcome</td>
<td>Can be very time-consuming and expensive</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>Groups differ only on randomization variable</td>
<td>Ethical concerns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of compliance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sometimes less generalizable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can be very time-consuming and expensive</td>
</tr>
</tbody>
</table>

Most clinical studies are conducted to examine the relationship between one or more independent variables (risk factors, exposures, treatments, therapies, interventions) and one or more dependent variables (outcomes such as illness, death from a specific cause, death due to all causes, recovery, cure, or quality of life). Depending upon the rigor of the research study design, the relationship found between the independent and dependant variables is considered more or less valid. A study with high validity means that the reported relationships are likely to be true, while studies of questionable validity may have other explanations for the reported findings. Table 1 presents the most common types of clinical research, ordered from weakest to strongest in terms of the strength of evidence they provide.

Case-report/case series
The simplest studies are descriptions of a single case (case report) or a number of cases (case series) that were encountered in clinical practice or routine disease surveillance. Often the cases are presented in the literature because there is some aspect about them that is unusual.

Example: The June 5, 1981 issue of the Morbidity and Mortality Weekly Report reported that five young homosexual men in Los Angeles had been diagnosed with Pneumocystis carinii pneumonia.1 This was noteworthy because this disease is extremely uncommon in young people who are otherwise healthy. The report led others to look for similar cases, and eventually led to the identification of acquired immunodeficiency syndrome (AIDS) as a newly discovered disease.

The major weakness of case reports and case series is that without any frame of comparison for the cases, the meaning
of any observed associations is unclear. Early case reports of what became known as AIDS mentioned that many of the patients had used recreational drugs, particularly amyl nitrite. Without a comparison group of similar people without AIDS, it was impossible to know if amyl nitrite use was more common in AIDS patients, let alone causally related.

Though they rank low in terms of strength of evidence, case reports and case series are often the genesis of analytical studies using one of the more sophisticated study designs.

**Cross-sectional studies**

In cross-sectional studies (also know as “prevalence” or “survey” studies), the independent variable of interest (often a particular exposure) and the outcome are measured at the same point in time. A typical methodology may involve performing a diagnostic test, followed by completion of a questionnaire. The association between different amounts of the exposure and the likelihood of having the outcome is then computed.

**Example:** Wells and others found that injection drug users had a higher prevalence of hepatitis antibodies than did subjects who were not injection drug users. This study is cross-sectional because the risk factor (injection drug use) and outcome (hepatitis A seropositivity) were determined at the same point in time.

There are two major drawbacks to cross-sectional studies. First, since exposure and outcome are measured at the same time, it is unknown which came first. In the above example, it was impossible to tell if injection drug use was preceded by or followed hepatitis A infection. Thus, it cannot be determined if the exposure caused the outcome or vice versa. Or the association could be noncausal, with the exposure and outcome related only because both are associated with some other factor, such as high risk sexual activity.

The second drawback to cross-sectional studies is that because they detect outcomes that exist at a particular time in the surveyed population (i.e., the prevalence of the outcome), they cannot tell if an exposure leads to increased risk or increased duration of the outcome. For example, insulin use is associated with being diabetic, not because insulin use increases the risk of diabetes but because it increases survival with diabetes.

**Case-control studies**

Case-control studies start with a group of people known to have the outcome of interest (“cases”). A comparison group of people without the outcome is then assembled (“controls”). Finally, the exposure history of both groups is compared and the results analyzed for any association between the exposure and the outcome. Past exposure is determined through interviews, questionnaires, medical record reviews, laboratory tests for biomarkers, or similar methods.

**Example:** A case-control study was conducted to compare several serum markers on their ability to detect gestational diabetes at several points during pregnancy. The cases were 35 women with confirmed gestational diabetes. Two control groups were used. The first consisted of 37 women who had abnormal one-hour post-glucose loading test glucose levels but no gestational diabetes, and the second was 73 pregnant women with normal one hour post-glucose loading test results. Comparison of the three groups showed that decreased first trimester levels of sex hormone-binding globulin were most strongly associated with being a case. The authors remark that future research using a prospective cohort design (described below) could investigate how well first trimester levels of sex hormone-binding globulin predict the development of gestational diabetes.

Case-control studies are well suited for rare outcomes. Unlike studies that need to follow very large numbers of subjects to obtain a few cases with the outcome, case-control studies can continue to enroll cases until they have enough to ensure adequate statistical power for the study objectives.

A difficulty with case-control studies is that it can be very challenging to create a valid control group. The controls should represent the population from which the cases arose with regard to past exposure history, but in practice they are often not entirely representative. Selecting an appropriate control group has been called “one of the most difficult problems in epidemiology”. If an unrepresentative control group leads to incorrect study findings, this is considered a form of selection bias, wherein “bias” means results that differ systematically from the truth.

Another concern is that since the outcome is already known at the time the study begins, determining past exposures in an unbiased manner can be difficult. Cases may recall past exposures differently than controls (“recall bias”), interviewers may ask cases and controls about past exposures in a different way (“interviewer bias”), or researchers extracting information from medical records may search for or document information differently for cases and controls. If information obtained differently for cases and controls leads to incorrect study findings, this is called information bias.
In spite of these potential sources of error, a well-conducted case-control study can be a very efficient way to investigate relationships between risk factors and outcomes, especially for rare outcomes.

Cohort studies
Cohort studies start with either separate exposed and unexposed groups of subjects or a single group of subjects (a “cohort”) which is then divided into groups based on exposure status. In either approach, the subjects are followed over time, and the incidence of the outcome is compared for the exposed and unexposed groups. Sometimes cohort studies are referred to as prospective or longitudinal studies.

Example: The Nurses’ Health Study began in 1976, when 121,700 female nurses in the US provided baseline information on health status and numerous potential disease risk factors. This study has examined many possible risk factor/outcome associations, including oral contraceptive use and breast cancer, vitamin D intake and hypertension, genetic polymorphisms and endometrial cancer, and phobic anxiety and coronary heart disease. A recent analysis focused on the relationship between plasma C peptide concentration and cognitive function among a subset of the nurses (n = 718) who had plasma C peptide levels measured and did not have diabetes. Cognitive function was measured at baseline and again after two years of follow-up. Women with higher levels of C peptide were found to have lower cognitive function at baseline (a cross-sectional analysis) and greater cognitive decline over follow-up (a cohort analysis), suggesting that increased C peptide levels may be related to cognitive impairment in nondiabetics.

Because incidence rates of the outcome for exposed and unexposed subjects are directly computed in cohort studies, and because exposure is measured before the outcome has occurred, cohort studies can provide stronger evidence that an observed association is truly causal. However, cohort studies also have some potential difficulties. Since subjects are followed over time, some may be lost before the end of the study. If those lost differ from those not lost for both exposure and outcome status, study findings may be biased. Another problem is that these studies can be very expensive and time-consuming to conduct, particularly for chronic diseases that may require many years to develop or rare conditions that require a large number of subjects to obtain enough cases of the outcome to be able to compare the exposed and unexposed groups.

A variation on the prospective cohort design described above is the historical or retrospective cohort study, in which the exposed and unexposed groups are assembled based on information available about past exposures and then “followed” to the present. For instance, industrial hygiene records may allow estimation of worker exposure to asbestos many years ago, and health records may be used to determine who developed lung cancer since then. Such studies are less time-consuming than prospective cohort studies, but are dependent upon accurate exposure records being available. Additionally, data are often lacking other information that may help explain observed associations (e.g., were the workers who were exposed to asbestos also more likely to smoke cigarettes?).

All of the study designs discussed thus far are known as observational studies because the researchers are simply observing and measuring what occurs naturally. Clinical research can also use an experimental design, in which there is an intentional manipulation of the independent variables.

Randomized controlled trials
Randomized controlled trials are conducted by randomly assigning study participants to one of two or more exposures, and then following the subjects over time to determine the outcome of interest.

Example: A randomized controlled trial was conducted to study if all pregnant women should be screened for gestational diabetes, or only those judged to be at high risk. All consenting women at a particular obstetrics clinic were randomized at the first visit to one of two groups: selective screening, in which screening was only performed if the women had one or more known risk factors for gestational diabetes, or universal screening. All women were followed to the end of pregnancy. For the universal screening group, significantly more cases of gestational diabetes were detected, diagnosis of gestational diabetes was significantly earlier, and pregnancy outcomes were better, leading the authors to conclude that universal screening for gestational diabetes is superior to screening based on the presence of risk factors.

Randomized controlled trials most closely follow the model of basic science research in which everything is controlled except the exposure of interest. Thus they provide the strongest evidence that any observed relationship is true. So why aren’t randomized controlled trials always used for clinical research?
First, there are ethical concerns. It is unethical to randomize people to exposures known to be harmful. Observational designs must therefore be used for examining known risk factors such as cigarette smoking, pesticide exposure, poverty, lack of exercise, exposure to lead paint, and poor air quality. Randomized controlled trials, however, are ideal for studying potential prevention or therapeutic interventions. Here the key word is “potential.” If the intervention is not thought to at least be possibly beneficial, it may be unethical to randomize subjects to receive it. But, if an intervention is known to be beneficial, it is not ethical to randomize subjects to not receive it. So, careful ethical consideration of the proposed intervention and alternatives is necessary when proposing a randomized controlled trial.

Next, the ability to detect differences in subjects randomized to different conditions depends on subjects complying with the condition to which they were randomized. For example, if subjects are randomized to be on a low fat diet for the next seven years, any effect of a low fat diet on health outcomes will be difficult to detect unless those subjects actually follow such a diet for the duration of the study. To increase the likelihood of compliance, there are often strict inclusion and exclusion criteria for enrollment into a randomized trial, which can then adversely affect the generalizability of findings from these select subjects.

Additionally, like prospective cohort studies, randomized controlled trials can be quite time-consuming and expensive to carry out, frequently requiring a very large sample size and lengthy follow-up to have any potential for definitively answering the question being studied.

So although randomized controlled trials are in theory the ideal study design for answering clinical questions, in practice they are not always feasible due to ethical, generalizability, or logistical constraints.

A variation on the randomized controlled trial is a study that is experimental but not randomized. For example, an educational intervention might be implemented for patients at one health clinic, with outcomes compared to patients at a health clinic which did not receive the intervention. This study is experimental because the researchers have intervened, but it is not randomized since patients are not randomly assigned to clinic, and clinics are not randomly assigned to receive or not receive the intervention. This design is not as strong as a randomized controlled trial since patients at different clinics may differ in ways other than just the educational intervention. This study design is sometimes referred to as quasi-experimental or nonrandomized experimental.

Almost all clinical studies use one of the designs outlined above. Strengths and limitations of these designs are summarized in Table 1.

**Reviews and meta-analyses**

Once a number of studies on a particular topic have been done, it can be quite informative to do a study of studies, looking for consistency of results across studies. This can be done qualitatively (reviews) or quantitatively (meta-analyses).

In a review, similarities and differences in findings are evaluated. Potential explanations for differences, such as different populations or measurement of variables, are explored. Consistent findings across several studies can increase confidence that these findings are true.

In a meta-analysis, results for different studies are statistically combined. If Study A found the risk of the outcome increased 2.5 times among those exposed to the risk factor as compared to those unexposed, and Study B found an increase of 3.5 times, an average of these two increases (weighted to account for different sample sizes for the studies) can be computed. Because the average is based on a combination of all the studies, it is a more precise estimate of the association. Care must be taken in such analyses since misleading results may be obtained if the studies being combined differ in significant ways.

**ASSESSING STUDY QUALITY**

The primary question when reading a study is whether the observed findings are likely to be true or due to some other explanation. As noted, all studies are not equally strong. Some designs are inherently more likely to provide results with alternate explanations, and some use less valid methods for selection of subjects and measurement of variables.

Briefly, the following items should be considered:

- Are the study objectives clearly stated? If the hypotheses being examined are unclear, the meaning of the findings will probably also be unclear.
- What study design was used? This will help in assessing the possible threats to validity (for instance, recall bias can occur in a case-control study but not a cohort study or randomized controlled trial).
- From what population were the study subjects selected? To whom might the results be generalized?
- How were the subjects selected from the population? If there is a comparison group (e.g., controls in a case-control study), might they differ in ways that could compromise the validity of the comparisons (that is, could there be selection bias)?
- How were the study variables measured? Were objective methods used? How probable is information bias (differences in outcome measurement for exposed and unexposed subjects or differences in exposure measurement for subjects with and without the outcome)?
- Is the sample size large enough to answer the study questions? Occasionally authors provide the rationale for the number of subjects used, but often they do not. Unfortunately, sometimes advanced knowledge of statistics is needed to evaluate sample size adequacy.
- Were the methods for statistical analyses clearly described and appropriate? Training in statistics can also be helpful for determining this, but no matter how complicated the analysis, the authors should provide a clear explanation of what was done.
- Were there any problems with low participation (due, for example, to high refusal rates or high loss during follow-up)? The higher the level of nonparticipation, the greater the possibility that those who did not participate differ in ways that affect the study validity.
- Could there be differences between the study groups that might explain any observed associations? To follow up on an earlier example, a case-control study did find an association between amyl nitrite use and AIDS. Later research found that amyl nitrite use was strongly associated with amount of sexual activity, which was the actual risk factor for AIDS. A difference such as this in some other explanatory variable is called confounding, with the other variable (amount of sexual activity in this instance) known as a confounder. If there are potential confounders, the authors should discuss how they controlled for them in the design or analysis of the study.

Consideration of the above points, which are summarized in Table 2, will help in answering the two most important questions. What is your overall evaluation of the validity of the findings? Do the results appear to be true, or could they be due to bias in selection of study subjects, bias in measurement of study variables, or uncontrolled confounding? An additional point that can strengthen the evidence that the findings are correct is consistency with findings from other studies. One clinical study is rarely definitive, but consistency across studies that use different designs with different measurements in different populations will help lead to the conclusion that the findings are valid.

Warning! With a little practice, it becomes easy to criticize any study (e.g., “The findings might be due to uncontrolled confounding”). The critical issues are the likelihood that such flaws occurred and, if likely, the likelihood that these flaws will affect the findings enough to change the conclusions. Determining these requires a clear understanding of the principles of conducting research and of the subject matter being studied.

Table 2. Summary of issues for assessing study quality

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are the study objectives clearly stated?</td>
<td></td>
</tr>
<tr>
<td>What study design was used?</td>
<td></td>
</tr>
<tr>
<td>From what population were the study subjects selected?</td>
<td></td>
</tr>
<tr>
<td>How were subjects selected from the population?</td>
<td></td>
</tr>
<tr>
<td>How were the study variables measured?</td>
<td></td>
</tr>
<tr>
<td>Is the sample size large enough to answer the study questions?</td>
<td></td>
</tr>
<tr>
<td>Were the methods for statistical analysis clearly described and app-</td>
<td></td>
</tr>
<tr>
<td>propriate?</td>
<td></td>
</tr>
<tr>
<td>Were there any problems with low participation?</td>
<td></td>
</tr>
<tr>
<td>Could there be differences between the study groups that might</td>
<td></td>
</tr>
<tr>
<td>explain any observed associations?</td>
<td></td>
</tr>
</tbody>
</table>
Clin Lab Sci encourages readers to respond with thoughts, questions, or comments regarding this article. Email responses to ic.ink@mchsi.com. In the subject line, please type “CLIN LAB SCI 21(1) FO CALLAS”. Selected responses will appear in the Dialogue and Discussion section in a future issue. Responses may be edited for length and clarity. We look forward to hearing from you.

REFERENCES

This article reviews the use of journal literature databases including CINAHL, EMBASE, and Web of Science; summarizing databases including Cochrane Database of Systematic Reviews, online textbooks, and clinical decision-support tools; and the Internet search engines Google and Google Scholar. The series closes with a practical example employing a cross-section of the knowledge and skills gained from all three articles.

ABBREVIATIONS: CDSR = Cochrane Database of Systematic Reviews; CINAHL = Cumulative Index to Nursing and Allied Health Literature; GDM = gestational diabetes; SCI = Science Citation Index.

INDEX TERMS: algorithms; bibliographic databases; information storage and retrieval; Internet; medical technology; online systems.

Clin Lab Sci 2008;21(1):49

Donna L O’Malley MLS is library associate professor at the Dana Medical Library at the University of Vermont, Burlington VT.

Address for correspondence: Donna L O’Malley MLS, library associate professor, Dana Medical Library, University of Vermont, Medical Education Center, Burlington VT 05405. (802) 656-4415, (802) 656-0762 (fax). donna.omalley@uvm.edu.

Frances Delwiche MLIS MT(ASCP) is the Focus: Information Literacy guest editor.

The primary literature in the health sciences consists of reports of original research generally published in the form of articles in scholarly/academic journals. The articles in these journals are indexed by searchable databases such as MEDLINE, CINAHL, and EMBASE, which function as an aid to finding articles on a desired topic. The primary literature has the advantage of being a direct communication from the researchers who performed the investigations. By studying the methodology used, the results of the research, and the investigators’ reasoning, readers are able to reach their own conclusions regarding the validity of the research findings. However, until they have stood the test of time, the findings of original research must be interpreted with caution.

Since the primary literature is such an enormous body of work, much of which will later be disproved or substantially revised, many scientists and health professionals rely on secondary and tertiary forms of literature to summarize original research. These forms of literature provide the essential background knowledge required to understand and interpret the primary literature and for making professional and clinical decisions. Examples of such literature include review articles, yearbooks, print and online textbooks, and clinical decision-making tools.

This final article in the FOCUS series will examine several databases of the primary literature, as well as several secondary and tertiary resources commonly used by health professionals. It will also examine the use of popular Internet search engines for finding forms of literature not usually included in proprietary databases. Finally, the article will close with a practical example utilizing a cross-section of the concepts, techniques, and skills described in the entire series.
PRIMARY LITERATURE DATABASES
Though MEDLINE is the premier database for the professional health sciences literature, research shows that it does not provide complete coverage of all the journals relevant to clinical laboratory science. To cover a topic comprehensively, other literature databases such as CINAHL, EMBASE, or Web of Science may need to be searched in addition to or instead of MEDLINE. These databases may cover a different mix of journal titles representing a slightly to markedly different subject area coverage; their records may contain unique elements of information not found in the other databases; or they may utilize alternative mechanisms for identifying related records. As a result, a search in one of these databases will frequently bring up articles not found in MEDLINE.

CINAHL
The focus of the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database is evident from its title. CINAHL includes over one million records for journal articles, book chapters, doctoral dissertations, conference proceedings, websites, and other types of publications. CINAHL covers publications from 1982 to the present. Although there is considerable overlap with MEDLINE, CINAHL indexes many publications important to health sciences professions that are not covered by MEDLINE. Access to CINAHL is available through EBSCO Information Services and Ovid Technologies. Like the MEDLINE records described in the first article, CINAHL records include standard bibliographic elements, such as author, title, journal name, volume, issue, page numbers, and publication date, plus abstracts and CINAHL subject headings. CINAHL records also include several unique fields, such as the Cited References field and Journal Subset (Table 1).

The search algorithm used by CINAHL depends largely on which vendor's version is being searched. Ovid Technologies' advanced search actively encourages the searcher to utilize CINAHL subject headings rather than relying solely on key-

<table>
<thead>
<tr>
<th>Field</th>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>The personal name or names of the authors of this document</td>
</tr>
<tr>
<td>Institution</td>
<td>Contact information for the author to whom correspondence should be addressed</td>
</tr>
<tr>
<td>Title</td>
<td>The title of the article</td>
</tr>
<tr>
<td>Source</td>
<td>The information necessary to locate the document. In the case of a journal article it is the journal name, volume, issue and page numbers.</td>
</tr>
<tr>
<td>Journal subset</td>
<td>CINAHL allows searchers to limit their searches to subsets of the database. Subsets include subject areas, country of publication, and peer review status.</td>
</tr>
<tr>
<td>CINAHL subject headings</td>
<td>Just as Medline uses the MeSH vocabulary, CINAHL uses an approved list of subject headings. These subject headings overlap with MeSH, but include specialized terms related to allied health and nursing.</td>
</tr>
<tr>
<td>Abstract</td>
<td>A summary of the document</td>
</tr>
<tr>
<td>Publication type</td>
<td>Journal article, book, audiovisual, pamphlet, software, dissertation, research instrument, etc.</td>
</tr>
<tr>
<td>Language</td>
<td>Most documents referred to in CINAHL are in English.</td>
</tr>
<tr>
<td>Citations</td>
<td>The references in the document's bibliography</td>
</tr>
</tbody>
</table>
EMBASE

EMBASE is a biomedical literature database published by Elsevier, headquartered in Amsterdam, The Netherlands. EMBASE contains records for over 11 million journal articles from over 5,000 biomedical journals published in 70 countries. EMBASE excels in coverage of European and non-English language publications, as well as in the subject areas of pharmaceuticals, psychiatry, toxicology, and alternative medicine. EMBASE’s earliest articles are from 1974 and new records are entered on a weekly basis. EMBASE is available through various vendors, including Dialog/Datastar, DIMDI, Lexis/Nexis, NERAC, OVID Technologies, and STN. Elsevier also offers its own version of EMBASE through EMBASE.com.

EMBASE records contain the usual citation details, plus abstract, subject headings, drug descriptors, medical descriptors, medical devices, brand names, and manufacturer names. EMBASE uses a list of approved subject headings comparable to MEDLINE’s MeSH headings called the EMTREE thesaurus. EMTREE allows searchers to include all narrower terms under broader terms, much like MEDLINE’s “explode” feature. Though EMTREE makes no effort to use the same subject headings as MeSH, the EMBASE.com version of EMBASE includes MeSH terms in its records in addition to its own subject headings.

To search EMBASE, begin with a keyword search. Then, from the complete record of relevant articles, identify searchable terms that can be used to narrow, expand, or otherwise revise the search. In addition to a search box to enter terms, a link to the EMTREE thesaurus is provided to enable browsing for subject headings. An EMBASE search is especially useful for identifying articles in European journals that are covered less comprehensively by MEDLINE, and for searches in subject areas in which EMBASE is particularly strong.

Web of Science/Science Citation Index

Web of Science is produced by Thompson Scientific, an international information company with a wide range of products for academia, business, and government. Web of Science contains over 38 million records and consists of three databases: Science Citation Index, Social Sciences Citation Index, and Arts & Humanities Citation Index, each of which may be searched separately or in combination with the others. Science Citation Index (SCI) contains references to over 6,300 peer-reviewed journals in science, medicine, and engineering. SCI provides data from as far back as 1900, with weekly updates.

Although SCI has a general search function, its real strength is in cited reference searching. In addition to basic bibliographic information (author, article title, journal name, publication date, etc.), SCI records contain the full list of references cited by the articles indexed (Table 2). The cited and citing articles are connected by the database software in such a way that a concept can be tracked backward and forward in time through the articles’ bibliographies. Suppose a searcher has located a useful but older article, and wants to identify more recent articles that have been published on that topic. By bringing up the SCI record for the original article and clicking on the “Times Cited” link, one can easily obtain a list of articles that used the original article in their bibliographies. Presumably, more recent articles that cited the original article will be on the same or a similar topic. Although other literature databases, including CINAHL, have a similar feature, because SCI indexes such a large number of journals crossing many disciplines, its cited reference searching is far more useful.

Like PubMed, SCI has a “related articles” feature, but it is structured on a completely different algorithm. In PubMed, related articles are identified on the basis of their shared subject headings. In contrast, related articles in SCI are identified based on shared references in their bibliographies. Articles that share many of the same references with the original record will appear higher in the list than those that share just a few references.
Lacking a formal thesaurus of subject headings, SCI relies on keywords for general subject searching. As a search mechanism, this is not nearly as powerful as the subject heading searches available in MEDLINE, CINAHL, or EMBASE. Hence, general subject searches are best performed in these other databases, at least initially. However, SCI’s cited reference search is an excellent tool for expanding a search, especially when only a small number of articles can be found.

DATABASES THAT SUMMARIZE

Literature that summarizes the primary research of a given field serves a vital role in the communication of knowledge. It saves the time of the reader and highlights important points that someone less familiar with a topic might not appreciate. It is especially useful for gaining background information on topics outside one’s area of expertise. In the clinical arena, secondary literature serves as a valuable source of ready information regarding diagnostic indicators and treatment guidelines. However, since they are removed from the original documents, summarizing publications run the risk of introducing misinterpretations, biases, and omissions. With this caveat in mind, databases of secondary literature can be highly useful.

Journal articles that summarize research regularly appear in MEDLINE, CINAHL, EMBASE, and Web of Science as review articles. Review articles may take the form of literature reviews, often with hundreds of references, or they may be in the form of academic tutorials, such as this article. Most literature databases have an option to limit searches to review articles only. Other databases, such as the Cochrane Database of Systematic Reviews, electronic textbooks, and clinical decision-making tools, contain only summaries.

Cochrane Database of Systematic Reviews

The Cochrane Database of Systematic Reviews (CDSR) is a full text database of a specialized type of review article designed to summarize all relevant research on a specific healthcare intervention. High quality research studies, primarily randomized controlled trials, are identified through an exhaustive search of the literature, coupled with a hand search of selected journals, and their findings compared following a standardized protocol. The completed systematic review analyzes the results of all the studies and derives an overall conclusion regarding the intervention. Each review concludes with implications for clinical practice and suggestions for future research. As a summary of the most rigorous research studies available, the Cochrane systematic review represents the highest level of evidence available for that particular intervention. Of course, not all possible interventions or treatments will have been studied, so not all topics will have a review in CDSR. Approximately 4,800 systematic reviews have been published.

<table>
<thead>
<tr>
<th>Table 2. Important fields in a Science Citation Index record</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Field</strong></td>
</tr>
<tr>
<td>Title</td>
</tr>
<tr>
<td>Authors</td>
</tr>
<tr>
<td>Source</td>
</tr>
<tr>
<td>DOI</td>
</tr>
<tr>
<td>Language source</td>
</tr>
<tr>
<td>Abstract</td>
</tr>
<tr>
<td>Document type</td>
</tr>
<tr>
<td>Author keywords</td>
</tr>
<tr>
<td>Keywords plus</td>
</tr>
<tr>
<td>Subject category</td>
</tr>
<tr>
<td>Bibliography</td>
</tr>
</tbody>
</table>
The CDSR is updated quarterly, and is available from Wiley Interscience and Ovid Technologies. Abstracts of the reviews are available free online from the Cochrane Collaboration at http://www.cochrane.org/reviews/. The CDSR is searched using either keywords or MeSH headings. As a full text database, the entire records are searchable. This is a mixed blessing, as keyword searches often bring up articles missed by subject heading searches, but they may also retrieve more irrelevant articles simply because they pick up every occurrence of the term(s) anywhere in the full-text of the documents.

Since CDSR is indexed by MEDLINE, the reviews can be found by conducting a topic search in MEDLINE, combined with a search on CDSR as a journal title.

Online textbooks
The content and structure of textbooks is familiar to any current or past student in the sciences. Online, these textbooks have tables of contents, chapters, page numbers, and indexes just like their print counterparts. Upon their initial publication, the online textbooks are identical to the print versions, but they have the advantage of being able to be updated far more frequently and economically. Vendors of online textbooks in the health sciences include Ovid Technologies, AccessMedicine, MD Consult and the (free) NCBI Bookshelf. These companies typically attempt to include a textbook representing most of the major medical specialty areas, thus enhancing their usefulness to busy clinicians and hospital staff. Usually only the most current edition of a textbook is available online.

The full-text of online textbooks is usually searchable. If the search is specific enough it can target a narrow topic, but quite often it will generate a long list of irrelevant hits due to incidental occurrences of the search terms. When available, searching within specific chapters or using the index can help to focus a search.

Clinical decision-support databases
In contrast to the seemingly anachronistic online textbooks, with their quaint tables of contents, indexes, and even page numbers, new formats for online information have emerged. These are clinical decision-making tools designed to provide health professionals with rapid, authoritative access to clinical information. Examples of these databases include Clin- eguide, DynaMed, eMedicine, FIRSTConsult, InfoRetriever, and UpToDate. Each of these competing resources fill a unique niche, some providing lengthy, evidence-based topic reviews, and others very brief summaries that can be accessed via handheld devices.

The information in these databases is more clinically oriented than textbooks. DynaMed records, for example, include fields for ICD-9/10 Codes, Causes and Risk Factors, Combinations and Associated Conditions, History, Physical, Diagnosis, Prognosis, Treatment, Prevention, Screening, References, and Patient Education information.

Clinical decision-support databases are updated on a quarterly, monthly, or weekly basis. These databases don’t have editions as textbooks do. When a change is made in the database, the old information is not retained.

Researchers have estimated that healthcare professionals will spend no more than two minutes researching a clinical question, so database developers have experimented with a variety of interfaces to make these databases operate more quickly. Each database is different and can change its interface without warning. Users should observe the display carefully for instructions on how to conduct a search, knowing that programmers are continuously making improvements.

The bibliographies of records in these databases are an excellent source of high quality references. References may link to journal articles through PubMed or to guidelines available from professional organizations or government bodies.

THE INTERNET
Some of the most heavily used literature databases were converted to electronic form on mainframe computers decades before the rise of the popular Internet. MEDLINE, for example, was searchable electronically through the MEDLARS system as far back as 1964. Cancer.gov went online in 1982 as the National Cancer Institute’s Physician Data Query (PDQ®) database. Today, both of these databases are available free to the general public through the Internet. While some may think of the Internet as an alternative to databases of professional literature, in fact it merely serves as a conduit through which to access this and other types of information.

The difficulty with the Internet is that the high-quality, reliable, and authoritative information is so thoroughly intermixed with everything else that it is sometimes virtually impossible to find. It requires a sophisticated searcher and a refined skill set to effectively extract high-quality scholarly and professional documents. Using the popular Internet search engine Google as an example, some of these techniques will be examined.
Google

Google, also known as Google Web, is a database with unlimited scope. The authors of pages in Google range from experts in every field to charlatans deliberately promoting false information. The Google database consists of a copy of every page on the Internet that it has been able to access, now numbering in the billions. Each page becomes a record, with the words on the page sorted into fields, including page title, headings, links, and images.

Google rose to prominence among Internet search engines in part due to its innovative Page Rank system. The Page Rank for a Google record is based on how often other web pages cite the page and the rank of the citing pages. It is this feature that allows Google searches to produce more relevant results than other Internet search engines. Google's ability to outperform other search engines is also due to the approaches it uses to translate and execute search queries. Google is understandably reluctant to share the specifics of its search algorithm, but generally speaking, it displays the results of a search in order of relevance and Page Rank, with the most relevant and highest-ranked pages displayed first. This presents a distinct drawback for scientists who are often looking for the most recent information. Since recent articles have not had the benefit of years of exposure that would allow other web pages to link to them, they are often not among the most highly ranked by Google, and therefore may not appear in the top pages of a Google search.

Google is a powerful search engine and an enormous database. Research has shown that, unfortunately, the larger a database is the harder it is to locate information in it, no matter how good the search engine or how expert the searcher. However, there are several effective strategies that will maximize success when searching Google. One of the most useful is the use of quotation marks for phrase searching. If a search on a phrase produces records that don’t use the words in the order expected, it may be placed in double quotation marks to ensure that Google will search exactly those words in exactly that order. Another strategy is to search on the most specific and unique terms possible.

Rather than searching on a specific topic directly, relevant results can often be found by searching for the name of the organization, society, or government body that would most likely provide the information. Access that organization's home page, and conduct an internal search. The strategy of searching for an organization rather than the exact topic can be very helpful because of Google's limitations. Google cannot transfer a search from its search box to the search box on another website. Although Google can see all of PubMed's records, for example, it can't search like PubMed, mapping to MeSH headings and combining terms in the way PubMed does. Nor can Google generate results from a dynamic database. The Centers for Disease Control and Prevention (http://www.cdc.gov), for example, links to many databases that will produce reports based on CDC statistics. Because these reports are generated dynamically, they only exist when someone requests them, so Google can't include them in its database.

Some well-known publicly available databases are not available through Google at all. Examples include the National Cancer Institute Clinical Trials Database, the US Patent and Trademark Database, and US Census Bureau data. The information in those databases is available through the Internet, but is not searchable by Google. Private, fee-based databases, such as CINAHL, EMBASE, Web of Science, most medical textbooks, and clinical decision support systems, are also not searchable through Google.

Google Scholar

Google attempts to address the needs of scientists and professionals through its Google Scholar database. Google Scholar includes journal articles, theses, books, meeting abstracts, and certain unique documents not found elsewhere. Unlike most licensed literature databases, Google has agreements with many publishers that grant it permission to search the full text of each article.

Like Google Web, Google Scholar displays the most relevant, highest ranked pages first, but Google Scholar uses cited references from bibliographies, not Page Rank, to determine rank. Publications that have been cited more frequently by other publications will be ranked higher. Again, this can impact the retrieval of recent articles. In order to address this problem, Google Scholar offers a Recent Articles link at the top of the results page. When this link is clicked, a drop-down box for publication date appears, allowing searchers to limit the search to a specified year, forward.

Google Scholar has several unique features that further distinguish it from its parent. When multiple versions of a given article exist in the database, it groups them together via a link attached to the original record. For example, there may be an official version of an article on the publisher's website, a link to the preprint of the article on the author's website, and a link to the PubMed record. By clicking on
the All Versions link, Google automatically displays these records as a separate set.

Secondly, articles in Google Scholar that have been cited by other articles in Google Scholar indicate this connection through a “Cited By” link. Clicking on this link will produce a list of articles that cited the original article (Figure 1). Thus, Google Scholar provides a form of cited reference searching similar to that provided by Web of Science.

Finally, Google Scholar employs an undisclosed mechanism for finding related articles, using the Related Articles link found at the bottom of each record.

Since Google Scholar includes articles that are not available free on the Internet, many records include a link to obtain a copy through other means. If the article is not available for free or through an institutional subscription, the publisher may offer the option to purchase the article outright. There may be a link through Library Search to WorldCat, a service that lists libraries that subscribe to the journal in question. Or, the BL Direct link offers the option to purchase a copy of the article through the British Library, although it is often more expensive than purchasing a copy directly from the publisher.

Google Scholar can be useful for cross-disciplinary searches. Topics in public health, healthcare administration, and education are not always well covered in databases like MEDLINE, EMBASE, and CINAHL. On the other hand, owing to the enormity of Google Scholar, if a topic is well-represented in a smaller, subject-specific database, a search of that database may be more productive.

USING THE LITERATURE IN CLINICAL LABORATORY PRACTICE

Suppose your laboratory is interested in exploring the various methods and protocols for screening for gestational diabetes (GDM), and you want to find what has been published to date on the topic. You begin by reviewing the basic facts of the disease, such as its clinical importance, incidence and prevalence, early detection, methodologies used for screening, current screening recommendations, and the effectiveness of treatment.

These background questions can best be addressed by literature that summarizes the current state of knowledge. From the array of clinical decision-making resources available, you choose UpToDate as a starting point. Searching on “gestational diabetes”, you find the topic review entitled “Screening and diagnosis of gestational diabetes mellitus”. The article discusses the prevalence of the disease, possible adverse outcomes for mother and infant, and therapeutic outcomes. It summarizes guidelines for screening and diagnosis of gestational diabetes mellitus from the American Diabetes Association, the American College of Obstetricians and Gynecologists, the United States Preventive Services Task Force, the Canadian Task Force on Preventive Health Care and the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. You note that these guidelines are not in complete agreement with one another. The review concludes with a summary and its own recommendations. The bibliography for this article includes 67 references, most with links to the MEDLINE abstract.
Having obtained the clinical background of the disease, you next seek laboratory-specific information from a current textbook or manual. MDConsult's book collection contains the 21st edition of *Henry's Clinical Diagnosis and Management by Laboratory Methods*, wherein the chapter on carbohydrates offers a lengthy discussion on glucose measurements and GDM screening protocols, including references to the American Diabetes Association guidelines. Ovid Technologies provides access to *A Manual of Laboratory & Diagnostic Tests*, which describes the test procedure, patient preparation and aftercare, and limitations of the test. While the recommendations included are not referenced, they do follow WHO guidelines. Conflicting guidelines are not mentioned.

Additional information may be sought from the websites of professional societies and organizations. A quick Google search leads you to the website of the American Association for Clinical Chemistry. This site lists a number of standards, including the 2002 *Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus*. This guideline does acknowledge the controversy. The authors recommend following the American Diabetes Association guideline, but do not provide their rationale.

Realizing there is no consensus on issues surrounding screening for GDM, you begin to wonder if there is another methodology for testing that might prove more effective than the traditional glucose tolerance test. You decide to search the journal literature indexed in MEDLINE, which covers much of clinical chemistry. You quickly access PubMed via your hospital library's website. Recalling that PubMed executes a simultaneous MeSH term and textword search, you enter the word string “gestational diabetes screening” into PubMed's search box. You limit your search to human studies, English language, and Core Clinical Journals. A quick scan of the results brings up a case-control study from 2007 describing the use of various serum markers for predicting gestational diabetes in the first and second trimesters of pregnancy. You are intrigued, and decide to expand your search. Checking the MeSH headings assigned to this article, you re-run the search utilizing additional relevant terms. Additionally, you follow the Related Articles link for the most relevant results to bring up additional useful articles.

In an effort to search the literature thoroughly, you repeat the search in Ovid CINAHL, which indexes some publications not covered by MEDLINE. Searching on each concept separately, you generate separate sets of results for “diabetes mellitus, gestational”, “glucose tolerance test”, and “health screening”. You also generate a set of articles indexed under the subject heading “diabetes mellitus, gestational” combined with the subheading “diagnosis”. Finally you combine the

---

**Figure 2.** CINAHL search strategy

**Figure 3.** Web of Science Cited Reference Search
sets, using the Boolean AND and OR. To help eliminate duplicates from the previous PubMed search, you limit your final set to Allied Health Journals (Figure 2). From this set, you discover several unique hits to add to your collection.

Rounding out your search, you conduct a Cited Reference Search in Science Citation Index to see if any research has been published following up on the 2007 study (Figure 3). No references are brought up, probably because the study is so recent. Would Google Scholar have any unique hits? Since PubMed, CINAHL, and Web of Science only allow searches to match words in a limited number of fields such as the title, abstract, and subject headings, being able to search the full text of articles might be advantageous. Furthermore, Google Scholar may contain some forms of “grey” literature such as pre-prints and technical reports that are not generally included in the traditional databases. Clicking on the Recent Articles link and limiting to 2002 forward, you scan for any unique documents.

CONCLUSION

The research question on screening for gestational diabetes resulted in a search of eight different databases. Fortunately, most research topics in clinical laboratory science do not require such an exhaustive (and exhausting) search. However, when a comprehensive search is needed, you’ll want to take advantage of all the resources at your disposal and draw on a variety of search techniques. By learning the characteristics of the various information resources available, cultivating the skills to search them competently, and knowing how to evaluate the quality of the studies you find, you’ll be well on your way to becoming truly “information literate”.

Clin Lab Sci encourages readers to respond with thoughts, questions, or comments regarding this article. Email responses to ic.ink@mchsi.com. In the subject line, please type “CLIN LAB SCI 21(1) FO O’MALLEY”. Selected responses will appear in the Dialogue and Discussion section in a future issue. Responses may be edited for length and clarity. We look forward to hearing from you.

REFERENCES

2. CINAHL. Ipswich, MA: EBSCO Publishing.
To receive 3.0 contact hours of basic level P.A.C.E.* credit for the Focus: Information Literacy questions, insert your answers in the appropriate spots on the continuing education registration form that follows, then mail a photocopy of the form as directed.

LEARNING OBJECTIVES
1. Identify the search feature that reveals how PubMed translated a search query.
2. Define “MeSH terms” and describe their usage.
3. Describe the order in which PubMed results are displayed by default.
4. Illustrate how a search that brought up either too many results or too few results could be modified.
5. Compare the effects of the use of the Boolean operators AND and OR.
6. Describe what is meant by “strength of evidence” when referring to research study designs.
7. Describe each of the following study designs: case report/case series, cross-sectional study, case-control study, cohort study (prospective and retrospective), and randomized controlled trials.
8. Discuss the strengths and weaknesses of each of the above study designs.
9. Define selection bias, recall bias, interviewer bias, and information bias.
10. Explain the major issues that should be considered when conducting a critical appraisal of a research study.
11. Describe what is meant by “primary literature” in the health sciences.
12. Discuss the characteristics of the major primary and summarizing databases used by health professionals.
13. Discuss the advantages and disadvantages of searching the Internet for professional health information.
14. Illustrate how popular Internet search engines can be used to find unique information in the health sciences.

CONTINUING EDUCATION QUESTIONS

SEARCHING MEDLINE VIA PUBMED

1. Which feature reveals how PubMed translated a search query?
   a. Clipboard  
   b. Limits  
   c. History  
   d. Details

2. What are “MeSH terms”?
   a. Major sections of an original research article  
   b. Subject headings used to describe an article’s content  
   c. Algorithms used to retrieve related articles  
   d. Filters for LinkOut Providers

3. What important group of articles would be missed by a search using exclusively MeSH terms?
   a. Articles from the Complementary & Alternative Medicine subset  
   b. Foreign language articles  
   c. Articles on dentistry, nursing, or veterinary medicine  
   d. Newly submitted articles that have not yet had MeSH terms assigned

4. How are PubMed results sorted in the default display?
   a. Alphabetically by author  
   b. Relevancy-ranked  
   c. Reverse chronological order  
   d. Alphabetically by title

5. Suppose you ran a basic search in PubMed, and the system brought up only two records. What would be a good strategy to increase the number of hits?
   a. Search on a related MeSH term  
   b. Limit the search to Core Clinical Journals  
   c. Click on the Free Full Text tab  
   d. Search using one or more subheadings
6. Suppose you ran a basic search in PubMed, and the system brought up over 1900 records. What would be a good strategy to reduce the number of hits and simultaneously increase the focus of the resulting set?
   a. Enclose phrases in quotation marks
   b. Search on a more general MeSH term
   c. Add limits for publication type and age group
   d. Search on any variant spellings, acronyms, and synonyms

7. Suppose you want to find all the articles in the database about mass screening for gestational diabetes. Which of the following search statements would likely produce the best results?
   a. Diabetes, gestational OR mass screening
   b. Diabetes, gestational AND mass screening
   c. Diabetes, gestational NOT mass screening
   d. Diabetes, gestational ADJ mass screening

8. Suppose you want to find articles about any aspect of prenatal screening for gestational diabetes. Which of the following search statements would likely produce the best results?
   a. Diabetes, gestational AND (prenatal diagnosis OR mass screening OR early diagnosis)
   b. Diabetes, gestational AND prenatal diagnosis AND mass screening AND early diagnosis
   c. ((Diabetes, gestational AND (prenatal diagnosis NOT mass screening) OR early diagnosis)
   d. ( (Diabetes, gestational AND (prenatal diagnosis OR mass screening) NOT early diagnosis)

SEARCHING THE BIOMEDICAL LITERATURE: RESEARCH STUDY DESIGNS AND CRITICAL APPRAISAL

9. Which of the following study designs has the highest strength of evidence?
   a. Prospective cohort study
   b. Case-control study
   c. Randomized controlled trial
   d. Cross-sectional study

10. Which of the following is true for case-control studies?
    a. Exposure and outcome are measured at the same time.
    b. Outcome is known initially, then look for possible exposures to explain outcome
    c. Exposure is determined first, then follow forward in time and look for development of outcome
    d. Exposure is considered irrelevant because outcome is already known

11. Suppose you gather a group of healthy subjects, and follow them for the next twenty years for the occurrence of Alzheimer disease. What type of study is this?
    a. Cross-sectional study
    b. Retrospective cohort study
    c. Case-control study
    d. Prospective cohort study

12. All patients visiting an ophthalmology clinic during a specified period of time are given a visual acuity test, followed by a questionnaire about carrots in their diet. What type of study is this?
    a. Case series
    b. Prospective cohort study
    c. Retrospective cohort study
    d. Cross-sectional study

13. Which of the following is a limitation to retrospective cohort studies?
    a. Unable to determine if exposure preceded outcome
    b. Dependent upon accurate records being available
    c. Subject to recall bias
    d. Unable to select an unbiased control group

14. Which of the following is a strength of the randomized controlled trial?
    a. Randomization results in minimal selection bias
    b. Relatively quick and inexpensive to conduct
    c. Reduced generalizability due to strict inclusion/exclusion criteria
    d. Subject to compliance issues

15. In which of the following instances would it be appropriate to consider doing a randomized controlled trial?
    a. The treatment under study is known to be highly effective.
    b. Subjects in the study are unlikely to be compliant with the condition to which they were randomized.
    c. It is hopeful, but not proven, that a new therapy is more effective than the traditional therapy.
    d. The “exposure” is a well known carcinogen.

16. What is it called when an unrepresentative control group leads to incorrect study findings?
    a. Recall bias
    b. Selection bias
    c. Information bias
    d. Interviewer bias
17. Which of the following should be considered when evaluating the validity of a study’s findings?
   a. The first author’s institution
   b. The journal it’s published in
   c. The length of the article
   d. The methodology employed

A SURVEY OF SCHOLARLY LITERATURE DATABASES FOR CLINICAL LABORATORY SCIENCE

18. What is an advantage of reading the primary literature?
   a. The results can be directly applied to clinical practice.
   b. It saves time by summarizing findings from multiple studies.
   c. You can make your own conclusions regarding the validity of the findings.
   d. It is useful for gaining background knowledge on a topic.

19. Which of the following databases indexes the primary journal literature?
   a. Web of Science
   b. Cochrane Database of Systematic Reviews
   c. Online textbooks
   d. FIRSTConsult

20. Which of the following is considered a summarizing database?
   a. EMBASE
   b. CINAHL
   c. Google Scholar
   d. UpToDate

21. Which of the following describes the Cochrane systematic review?
   a. It enables you to track use of an article forward in time.
   b. It summarizes results of high-quality studies, especially randomized controlled trials.
   c. It provides a set of results sorted by relevancy and Page Rank.
   d. It permits automatic searching on all narrower terms listed under a more general term.

22. What is an advantage of an online textbook over its print counterpart?
   a. Easily and quickly updated
   b. May be sold only by license through various vendors
   c. Requires a targeted search to avoid bringing up an excessive number of irrelevant hits
   d. Usually only the table of contents and chapter headings are searchable

23. Which of the following is true for Google?
   a. It effectively filters out low quality studies, commercial pages, and personal opinion articles.
   b. It searches databases such as CINAHL and EMBASE seamlessly.
   c. It is able to search both dynamic and static databases.
   d. It may contain publications not included in journal literature databases.

24. What determines the order in which Google displays results?
   a. Publication date
   b. Multiple versions grouped together
   c. Relevancy and Page Rank
   d. Most cited first
Continuing Education Registration Form

To earn continuing education (PACE) credit, (1) complete the form below, (2) record your answers, and (3) mail a photocopy with a check or money order ($18 for ASCLS members, $28 for non-members) to:

American Society for Clinical Laboratory Science
P.O. Box 79154, Baltimore MD 21279-0154

A certificate of completion will be awarded to participants who achieve a passing grade of 70% or better. Participants should allow eight weeks for notification of scores and receipt of certificates.

**Focus: Information Literacy** carries 3.0 hours of basic level P.A.C.E.® credit. This form can be submitted for credit for up to one year from the date of issue.

Print or type carefully.

**Part 1: Participant Information**

(01) NAME ______________________________________________________________________________________________

(02) ADDRESS __________________________________________________________________________________________

(03) CITY________________________ (04) STATE/COUNTRY _____________ (05) ZIP/POSTAL CODE_________________

(06) DAYTIME PHONE ( ______ )__________________________ (07) E-MAIL:_______________________________________

(08) CREDIT CARD # ______________________________ TYPE (CIRCLE) AE MC VIS EXP. DATE_____________

ASCLS membership number ___________________________ Licensure number ___________________________

Check all that apply

- Send my certificate of completion via email
- I would like to receive ASCLS membership information
- I would like information on other continuing education sources

**Participant Information**

Please circle the most appropriate answers.

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?

**Answers**

Circle correct answer.

1. a b c d
   13. a b c d

2. a b c d
   14. a b c d

3. a b c d
   15. a b c d

4. a b c d
   16. a b c d

5. a b c d
   17. a b c d

6. a b c d
   18. a b c d

7. a b c d
   19. a b c d

8. a b c d
   20. a b c d

9. a b c d
   21. a b c d

10. a b c d
    22. a b c d

11. a b c d
    23. a b c d

12. a b c d
    24. a b c d
CONTINUING EDUCATION

Answers to 2006 FOCUS
Continuing Education Questions

19(1) Winter 2006

GENE-BASED DIAGNOSTICS II

Introduction to Molecular Cystic Fibrosis Testing

1. Cystic fibrosis is most common among which of the following ethnic groups in the United States?
   c. European Caucasians

2. The CFTR gene encodes a protein that functions as a(n) ___________ transporting channel.
   b. chloride

3. The most common cystic fibrosis-causing mutation in the United States population is:
   d. F508del.

4. The risk for two cystic fibrosis carriers to have child who is a carrier of the disease is one in:
   a. two.

5. The complex allele combination that would most likely lead to a pancreatic sufficient cystic fibrosis phenotype is:
   d. R117H in cis to a 5T allele.

6. Which of the following commercial cystic fibrosis test kits does not attempt to identify a limited number of specific mutations but instead detects mutations without regard to specificity for individual mutations?
   c. SNP Capture™ Mutation Screening

7. Of the following choices, when would molecular testing normally be most appropriate in a newborn screening program for cystic fibrosis?
   d. After immunoreactive trypsinogen testing and before sweat testing

8. The median lifespan for cystic fibrosis patients is currently about:
   d. 33 years.

9. Validation studies required to be performed by clinical laboratories using ASRs include all of the following except:
   a. allele frequency studies.

10. Which of the following is not typically included in a molecular cystic fibrosis test report?
    b. Individual allele frequencies

11. Of the following, the biggest difference between molecular cystic fibrosis tests and more traditional laboratory tests is:
    c. the increased education of healthcare providers required to understand the result of a molecular cystic fibrosis test.

Molecular Diagnostics of Hematological Malignancies

12. Acute promyelocytic leukemia is initially treated with:
    b. all-trans retinoic acid.

13. Southern hybridization involves all of the following steps except:
    b. amplification of DNA.

14. The immunoglobulin locus is rearranged in which of these entities:
    a. Lymphoma

15. Oligonucleotide primers are used in RT-PCR for translocated oncogene detection. Given a hypothetical translocation between two oncogenes on chromosomes 6 and 12, the primers would typically be located:
    d. one on chromosome 6 and one on chromosome 12, facing toward the breakpoint.

16. Which of the following genes is not associated with leukemia or lymphoma development?
    b. EWS

17. Molecular diagnostics of hematological malignancies has made important contributions to which of the following?
    c. Residual disease detection
GOVERNMENT REGULATIONS

Regulatory Agencies Involved with the Clinical Laboratory
1. Which of the following agencies has primary oversight in standards for instrumentation for the clinical laboratory?
   c. FDA
2. By using the “neg reg” process, one hopes to avoid:
   b. contentious and lengthy hearings and potential battles.
3. The regulations created as a result of CLIA ’88 resulted in:
   b. a lowered standard for personnel than was originally hoped.
4. CMS is the agency responsible for:
   a. financial oversight of Medicare and Medicaid funding.

Government 101: How An Idea Becomes Law
5. The convening of a conference committee to evaluate a possible bill occurs:
   a. when the House version of the bill is different from the Senate version.
6. An “Act Relative to the Special Awarding of a Disability for a Permanently Injured Firefighter” is an example of a:
   c. private law.
7. The notation “42 CFR 405-494” describes:
   c. the chapter and page of Federal Regulations that locate a specific law.

Government 103: What Happened to the Great Idea?
8. Which of the following would not be considered a potential significant influence after the passage of a law?
   d. Review by conference committee
9. The Older American Act Amendments of 1987 was weakened by:
   b. inadequate funding.
10. Which of the following has current direct impact on clinical laboratory personnel?
    c. P 100-578

19(2) Spring 2006
EDUCATIONAL TECHNOLOGY
Breezing Up – An Interdisciplinary Health Professions Course for High School Juniors and Seniors

1. The Medicine 100: Introduction to the Health Professions course was designed for:
   d. all of the above.
2. A software application used in the design and delivery of the Medicine 100 course is:
   d. all of the above.
3. The Medicine 100 course was marketed by:
   a. partnerships with stakeholders.
4. The Medicine 100 course was offered for:
   d. “a” and “b” of the above.

Student Laboratories as a Component of a Web-based Curriculum
5. The impact of traveling to campus for weekend labs was minimized for WEBCLS students by:
   b. minimizing time on-campus.
6. One reason that on-campus laboratory experiences were preferred over work-site mentoring for the WEBCLS students is that:
   a. faculty do not have patient care responsibilities.
7. All of the following are essential to the preparation and delivery of on-campus weekend student laboratories EXCEPT:
   a. having students provide their own specimens.
8. WEBCLS weekend laboratories provide:
   d. face-to-face discussions with the faculty.
9. The WEBCLS weekend laboratories characteristically:
   d. provide experiences that are equal to the on-site program.
10. What percentage of WEBCLS students earned grades of A or B in laboratory classes from 2003 to 2005?
    b. 66%
11. WEBCLS students’ averages on national certification examinations compared to those of traditional students were:
    b. higher.
12. In performing advanced techniques in weekend labs, instructors must be prepared to compensate for:
    c. students from rural settings having little exposure to advanced laboratory techniques.
Interactivity: Key to CLS Online Instruction

13. When a teacher posts a question on a discussion board and an online student answers the question as a thread in the discussion board:
   a. a message loop has occurred from the teacher’s perspective.

14. When two online students meet in the discussion board during a collaborative project and realize that they grew up in the same community and have mutual memories and acquaintances, this is an example of:
   b. affective benefits output.

15. To meet the “Content Leaning” output of instructional online interactivity, questions posted in an online discussion board must:
   a. be written at the same cognitive level as the course objectives.

Learning Objects: Resources for Instruction

1. Learning objects are:
   a. small, reusable, technology-based elements.

2. Learning objects may be used for all of the following instructional events except:
   d. as an example of the contextual.

3. Metatags facilitate:
   d. retrieval and storage of learning objects.

4. A learning object that requires student interaction is an example of a Level ______ learning object.
   c. 3

5. A learning object that is a photograph is an example of a Level ______ learning object.
   a. 1

6. A learning object that is a statement of process illustrated by a video clip is an example of a Level __ learning object.
   b. 2

7. Characteristics of learning objects include all of the following except:
   c. references to other learning objects.

8. Select the best example of CLS instructional material that would be appropriate to use as a learning object:
   c. animation of antigen-antibody agglutination

9. The creation of learning objects models the preparation of instructional material by an expert in:
   b. breaking instructional content into smaller and smaller concepts.

10. Learning object is to instructional context as:
    c. digital data is to algorithm.

Teaching and Learning New Method Verification Skills Using Interactive Simulations

11. New method verification simulations have educational advantages over actual laboratory validations because:
    a. performing the actual analytical testing
    b. breaking instructional content into smaller and smaller concepts.
    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. breaking instructional content into smaller and smaller concepts.

13. The verification tasks required of students performing new method verification simulations include all of the following with the exception of:
    d. determining whether or not observed difference in the new method compared to a reference method is 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. Send test data back to the student which matches the instructions.
    b. Send test data back to the student which matches the instructions.
    d. Answers “b” and “c” should both be done by the teacher.

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.
    d. Answers “b” and “c” should both be done by the teacher.

Human Immunodeficiency Virus

An Overview of the Human Immunodeficiency Virus Featuring Laboratory Testing for Drug Resistance

1. Which of the following is an accurate description of the genetic properties of HIV?
a. HIV is an RNA virus capable of converting its genetic material to DNA

2. Viral enzymes reverse transcriptase, protease, and integrase are transcribed from which of the following genes?
b. Pol

3. During the life cycle of HIV, the gp160 precursor protein is cleaved to form:
d. gp120 and gp41.

4. The primary role of the protease in the life cycle of HIV is to:
c. form the functional proteins of HIV by cleaving the inactive precursors.

5. The three main stages in the natural course of the HIV disease area are:
c. acute infection, clinical latency, AIDS.

6. Which of the following laboratory findings would lead to the diagnosis of AIDS according to the CDC criteria?
a. CD4 count 150 cells/μL, viral load 5,000,000 copies/mL

7. The four FDA-approved classes of antiretroviral drugs area are:
b. nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, fusion inhibitors.

8. Which of the following viral proteins is the primary target for the cytidine analogues – lamivudine, zalcitabine, and emtricitabine?
a. reverse transcriptase

9. All of the following are benefits of highly active antiretroviral therapy (HAART), EXCEPT:
d. absence of serious side effects and long term toxicities.

10. The two main biochemical mechanism leading to NRTI (nucleoside analogue reverse transcriptase inhibitor) resistance are:
a. sterical inhibition and primer unblocking.

11. K103N mutation is primarily associated with resistance to:
b. non-nucleoside reverse transcriptase inhibitors.

12. The two fundamental approaches to HIV drug resistance testing are:
c. genotypic testing and phenotypic testing.

13. HIV RNA extraction, reverse transcription, amplification, recombinant vector preparation, and quantitative assessment of viral replication in cell culture are steps of:
b. phenotypic resistance testing.

14. IC50 may be defined as:
a. the concentration of the drug that results in a 50% inhibition of viral growth.

15. If the IC50 of the wild-type virus is 2 mg/mL and the IC50 of the patient’s isolate is 6 mg/mL, then the X-fold reduction in susceptibility will be reported as:
a. 3-fold resistance.

16. HIV RNA extraction, reverse transcription, amplification, dideoxynucleotide sequencing, and algorithmic interpretation of the sequencing data are steps of:
b. genotypic resistance testing.

17. A double peak appears on the electrophoretogram during the process of dideoxynucleotide sequencing when:
a. a mixture of two nucleotides is detected at a specific position.

18. During the process of dideoxynucleotide sequencing, which of the following procedures is used to arrange the DNA strands in the order of increasing length?
b. Polyacrylamide gel electrophoresis

19. Resistance testing by reverse hybridization involves:
c. binding of the amplified biotinylated DNA material to codon-specific oligonucleotide probes.

20. The clinical utility of HIV drug resistance testing has been evaluated in a number of studies with the following results (select the correct answer):
c. Some studies demonstrated the benefit of resistance testing while other studies failed to demonstrate the benefit of resistance testing.
LABORATORY PROFESSIONALS
DELIVERING TODAY’S RESULTS FOR A HEALTHIER TOMORROW
NATIONAL MEDICAL LABORATORY PROFESSIONALS WEEK

April 20-26, 2008

During National Medical Laboratory Professionals Week, April 20-26, 2008, we’re celebrating the people and practices that keep the focus on quality care. It is a demonstration of commitment we’re carrying to communities across the nation—and a spotlight on the professionals who provide outstanding results every day of the year.

This April, we’re uniting under the theme “Delivering Today’s Results for a Healthier Tomorrow.” The 2008 logo is a symbol of a proud past and an even brighter future. Join with us in paying tribute to laboratory professionals and showcasing their continuing pursuit of excellence.

It’s easy to be part of this exciting event. Just go to www.labprofessionalsweek.com and explore a wonderful selection of recognition gifts, awards and promotional ideas that make this a celebration as special as the people we honor.

For your free Event Product Guide, call 866-52-ASCLS (27257)

For general information about National Medical Laboratory Professionals Week, visit www.ascls.org/conferences/2008NMLW/index.asp

© 2008 Belts International Inc.