Pharmacogenetics: Pro and Con

Multiplex Molecular Testing

Warfarin Pharmacogenetics: Pro and Con

Multiplex Molecular Testing
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Information about the interactions between human genetics and clinical disease is increasing exponentially. Open any issue of the ASCP e-mail newsletter Daily Diagnosis and there will be at least one story about research associating a gene with a disease state. Such news coverage has raised hopes for a new era in health care: that of personalized medicine. While we may be confident that we are on the pathway toward personalized medicine, we also know that there are many questions yet to be answered.

If a specific genetic profile becomes clearly associated with a particular disease, what is next? Is there a test to detect this trait? Who has access to the testing? What laboratories should be doing the testing, and how should the tests be regulated? Are there sufficient qualified laboratory professionals to perform these sophisticated tests? What should be done with patients who have positive results? Are there ways to prevent the disease from developing, or treating it once it has?

As pathologists and laboratory professionals, we must begin asking these questions now rather than later. This issue of Critical Values addresses these questions by weighing the pros and cons of gene-based warfarin dosing and considering the case of a woman who tested negative for cystic fibrosis but gave birth to a child with the condition.

In addition, this issue of Critical Values provides numerous resources for pathologists and laboratory professionals, including:

- Information about new multiplex molecular tests
- A source for genetic testing reference materials
- An overview of the World Health Organization update of Classification of Tumours of Haematopoietic and Lymphoid Tissues
- An ASCP report on the job market for hematopathology fellowships
- And a long list of ASCP molecular testing resources.

This issue continues the practice of printing messages from ASCP leaders: the President, the Chair of the Council of Laboratory Professionals, and the Chair of the Resident Council. The Arts in Culture section features the work of an artist who gives form to memory and neural activation in an effort to process her family history of Alzheimer’s disease.

Finally, Critical Values welcomes a new board of editorial advisors, whose names are listed on page 4. They have already made their mark on this issue, and we look forward to their continued guidance. We also thank the editorial advisors who recently completed their terms; their advice has been invaluable.

I welcome your thoughts—both positive and negative—about the topics addressed in this issue. Send your comments to ascp@ascp.org and put “Critical Values” in the subject line.

Dr. McKenna is president of ASCP.
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I love to hear a choir. I love the humanity... to see the faces of real people devoting themselves to a piece of music. I like the teamwork. It makes me feel optimistic about the human race when I see them cooperating like that.

Paul McCartney
Pathologists and laboratory professionals might experience a similar sense of optimism after walking through their own laboratory on a weekday morning and seeing common vignettes such as these:

- A cytopathologist leans on the door frame of the cytotechnology screening room while discussing a challenging case with the cytotechnologist who screened it. Together, they decide on the most appropriate diagnosis.

- In the frozen section suite, a histotechnologist and pathologist work in concert to manage a lineup of frozen sections that have arrived from three different operating rooms. They clearly have a system in place to manage the work efficiently, as each seems to anticipate the other’s actions.

- When an unusual pattern of antibiotic resistance appears in a patient’s bacterial isolate, the microbiology technologist and laboratory director review the frequency of this finding in other laboratory isolates. They then discuss the best way to communicate this finding to the clinical care team.

Just as any laboratory is a diverse collection of professionals who work in concert to achieve excellence in laboratory medicine, the American Society for Clinical Pathology (ASCP) is an organization that, from its inception, has recognized the importance of harmony in the laboratory.

A group of 40 physicians, who were among the early practitioners of laboratory medicine, formed the ASCP in 1922. Two of their primary objectives were to establish standards for the performance of laboratory tests and to enhance the recognition and status of the nascent profession. The next logical step was the 1928 formation of the Board of Registry, an organization formed to ensure laboratory tests are performed by qualified individuals. BOR certification has been the gold standard for the certification of laboratory professionals ever since, and more than 430,000 individuals have become certified since the organization’s inception.

However, the achievements did not stop there. Throughout its history, ASCP has balanced service to its pathologist members with attention to the importance of excellence throughout the profession and, today, can take credit for many firsts:

- The first compilation of standardized laboratory techniques
- The first journal devoted to laboratory medicine
- The first Curriculum for Schools of Medical Technology
- The first continuing education program offered specifically for medical technologists (It was conducted by Dr. Emma Moss, who later became the first female ASCP president as well as the first female president of any pathology society.)
Establishment of the Board of Schools and publication of the *Essentials of an Acceptable Medical Technology School* (The Board of Schools later became the National Accrediting Agency for Clinical Laboratory Sciences.)

The first regional workshops for directors of medical technology schools (They were cosponsored by ASCP and the American Society for Medical Technology, today’s American Society for Clinical Laboratory Science.)

First pathology organization to create Associate and Affiliate member categories

The first self-assessment tool for technologists (TechSample)

The first pathology organization to include technologists on its board of directors and executive committee

Establishment of laboratory professional certification programs in 28 countries.

ASCP is the only organization whose composition truly reflects your laboratory. Its membership comprises pathologists, medical technologists, histotechnologists, cyto technologists, pathology assistants, and phlebotomists. Pathology residents and technology students are also members.

At every level of the Society, the theme continues. The chairs of the Fellow Council, the Council of Laboratory Professionals, and the Resident Council all hold seats on the ASCP Board of Directors. Cytopathologists and cyto technologists work as an ensemble to create cytology assessment programs. The various committees overseen by the Commissions on Education and Assessment include representatives from every ASCP membership category—and they all work together to make sure ASCP programs meet members’ needs.

The Public Policy Commission and the ASCP Washington Office, meanwhile, strive to bring attention to issues that affect every area of laboratory medicine, from pathologist reimbursement and the clinical laboratory fee schedule to the laboratory workforce shortage and state licensure of laboratory professionals.

I could go on and on, but you already know the song. You and your colleagues are busy living it day in and day out. ASCP Board member Irina Lutinger, MPH, FACHE, MASC, H(ASCP)DLM, is senior administrative director for clinical laboratories at New York University Langone Medical Center. She is also a talented pianist. At a recent ASCP event, she explained her view of the laboratory. She said it is like a symphony orchestra with the various divisions playing together under a single conductor. It takes talented individuals with special skills to keep laboratory instruments calibrated, just as it does to keep musical instruments tuned. When the laboratory is working well, it produces accurate and elegantly sound test results, just as properly tuned woodwinds and strings make beautiful music.

Today, when you look around your laboratory, notice the choir of people working in harmony to produce those elegantly accurate and sound test results. You know this does not happen without training, practice, and ongoing education. You know laboratories could not properly serve patients without skilled individuals to draw their blood, analyze their specimens, handle and prepare their biopsies, and then determine what it all means. The fact is, we could not serve any patients without all of us. ASCP understands this.

Dr. McKenna is Associate Professor of Pathology, University of Michigan Medical School, Director, Surgical Pathology Fellowship Program, and attending physician, University of Michigan Hospitals, Ann Arbor, MI.
Leadership Messages
Message from the Chair of the Council of Laboratory Professionals

While the general public often assumes that health care is a recession-proof industry, I think most people who work in the clinical laboratory field would beg to differ. As director of a system laboratory with more than 200 staff members, I know our laboratory has felt the impact of the economic downturn—and we are certainly not alone.

Like other industries, clinical laboratories have been forced to tighten their belts during these difficult times. One of the first places this belt-tightening was felt is the availability of capital. The scarcity of capital can probably be traced to the banking crisis and the same types of financial woes plaguing automakers and other industries nationwide.

Feeling the Effects of the Economic Downturn

By Lynnette G. Chakkaphak, MS, MT(ASCP)
How does capital funding affect clinical laboratories and the care for patients? Consider the situation of a laboratory with plans to add new molecular testing during the coming fiscal year. The laboratory staff has done all its homework—talked with the vendors, made several site visits, evaluated the work flow impact, and calculated the cost per test. As a result, the staff has selected the system that is right for the laboratory. The laboratory director has submitted a sound proposal showing that molecular testing will provide more sensitive and specific results, lower turnaround times, and improve patient outcomes. In addition, by performing the molecular testing in-house rather than sending it to a reference laboratory, the laboratory will tap into a new revenue stream and cut its referral testing bill.

Although this proposal is convincing, many laboratories in this kind of situation could be disappointed this spring when their proposals are denied by the administration. The funding needed to purchase the necessary equipment simply will not be available. With most institutions having limited capital dollars to spend, the competition for funding will be fierce. New laboratory instrumentation will be forced to compete with high-priced equipment needed by the imaging department or the operating room. This is a competition the laboratory has difficulty winning.

Some laboratories may find a way to include new instrumentation in their operating budgets, in the form of either an operating lease or reagent rental. This option is no guarantee either, however, as some institutions are holding the line on spending by freezing operating budgets at 2008 levels. With possible decreases in both capital and operating budgets, the likelihood of adding new testing modalities is rather bleak. Even the prospect of replacing an essential analyzer in the chemistry or hematology sections could be difficult.

Another by-product of the recession for many clinical laboratories is a reduction in test volume. An American Hospital Association survey conducted in October 2008 showed a drop in patient census numbers at many hospitals. While some Americans have lost their health insurance, others are holding off on non-essential health care. As a result, fewer laboratory tests are being ordered.

Ordinarily, decreasing workloads would be expected to bring the threat of job losses. Fortunately, the nationwide shortage of clinical laboratory personnel will probably buffer the blow of the reduced work volume at most institutions. Many laboratories continue to hire technical personnel, while others are cutting costs by freezing staffing levels or eliminating empty positions rather than laying off staff members.

If there is a bright side to the problems facing laboratories, it could be that the economic crisis is attracting former laboratory professionals back to jobs within the laboratory. Clinical laboratory science program directors and laboratory managers are increasingly hearing from medical technologists, medical laboratory technicians, and others who left the laboratory for jobs in industry, real estate, and other fields. Displaced from their current jobs, they are hoping to get up to speed in order to re-enter the field of laboratory medicine.

If this trend continues, it may lessen the extent of workforce shortages expected in the years ahead.

Each laboratory faces its own unique challenges as a result of the current economic decline, and I am sure many of you have come up with unique ways of dealing with these challenges. If your laboratory could use some advice or if you have a suggestion that might help another laboratory, please contact me at MemberChair@ascp.org. The Council of Laboratory Professionals and our network of Local and Regional Representatives will do their best to connect you with others.

Ms. Chakkaphak is Laboratory Services Director, St. Vincent’s Medical Center, Jacksonville, FL.
Leadership Messages
Message from the Chair of the Resident Council

By Ahren C. Rittershaus, MD

In 1922, pathology was a new field of medicine that was attracting many talented young scientists and physicians to its ranks. But those entering the specialty were frustrated by the almost complete unavailability of continuing education geared to their particular needs. This frustration finally led a group of 40 pathologists to organize their own medical society, one that would better address their special needs. This was the beginning of ASCP.

More than 85 years later, the Society continues to work hard to meet the needs of its membership, which has expanded to represent the entire laboratory team. As already noted, a founding principle of ASCP is to provide high-quality continuing education. The goal is to equip pathologists and other laboratory professionals to deliver the best, most up-to-date patient care possible. That goal dovetails very nicely with the needs of residents, who strive to learn the art and science of diagnostic medicine.

In a profession characterized by almost constant and often dramatic change, medical education is a never-ending task—one complicated by today’s complex medical environment in which quality must be maintained while costs are controlled. In addition to understanding the science, we must develop our leadership skills and master the business and politics of pathology. We also need to hone our communication skills in order to interact effectively with a broad spectrum of people, including hospital administrators, various medical colleagues, clients, patients, payers, and policy makers.

ASCP offers a litany of products, grants, educational courses, and other resources to help residents on their journey to board examinations and beyond. Many of these resources are offered either free of charge or at significant discount to residents. This article highlights some of the most important ones:

- **Membership.** ASCP membership is free to pathology residents. This is a tremendous benefit because it qualifies residents for a number of special member services.

- **Publications.** Members can purchase the superb books published by ASCP Press at a discount. Membership also provides free online access to the American Journal of Clinical Pathology (AJCP), one of the most prestigious pathology journals in the world.

- **Educational Courses.** ASCP offers an array of high-quality educational courses in pathology and laboratory medicine, more than 400 events annually in a variety of venues. The ASCP Annual Meeting, Weekends of Pathology, and Educational Courses are held in different locations around the country, all at steep discounts for residents. One of the most successful and beneficial live events was the 2008 Annual Meeting Residents’
Day program, which featured an outstanding educational course on laboratory management and informatics given by speakers from the American Pathology Foundation. These topics are often lacking in residency programs and have been identified as a weakness by new pathologists as well as those currently hiring new pathologists.

- **Grants.** The Resident Council Grant Program is one of the biggest benefits of resident membership, yet many people are unaware of it. Each year the Council awards more than $20,000 in Subspecialty Grants to help make elective rotations at a different institution more affordable for residents who want more intensive exposure to a particular area of pathology. A Day on the Hill Grant awards recipients a paid trip to Washington, DC, for ASCP Capitol Hill Day. One day each year the ASCP Washington office arranges for members to meet with scores of key Congressional members and high-level staff members. This puts a face on pathology and laboratory medicine and gives us a chance to educate legislators about what we do and why we are important. Advocacy is one of the primary focuses of the ASCP and, I believe, of critical importance to the profession.

- **Volunteer Opportunities.** Believe it or not, this is probably the greatest benefit of ASCP membership. First, it gives residents an opportunity to learn about both the science and the business of pathology. Second, residents become more familiar with important public policy issues affecting the profession. Third, volunteering helps improve communication and leadership skills. There are positions for residents on almost all ASCP committees, as well as opportunities to serve as a residency program liaison and on the Resident Council itself. Finally, volunteers work side-by-side with some of the country’s best pathologists and other laboratory professionals, allowing them to develop a valuable professional network that benefits their entire career.

These are just a few of the ways ASCP is meeting the needs of its resident members. I am always interested in hearing from my fellow resident members. If you have needs that you think are not being met, please let me know what they are so they can be addressed. I would also like to hear from anyone who would like to volunteer. Send me an e-mail at ResidentChair@ascp.org. You can also visit the ASCP Web site at www.ascp.org, and click on Residents at the top of the page for links to information, application dates, and forms.

Dr. Rittershaus is a fourth-year resident in anatomic and clinical pathology at the Medical University of South Carolina in Charleston.
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www.biotheranostics.com
By Mark W. Linder, PhD

There is a significant level of controversy over the subject of pharmacogenetic testing to guide warfarin therapy. The controversy centers on the questions of efficacy and cost-effectiveness. Unfortunately, neither of these questions has been definitively answered. In the meantime, warfarin continues to be under-utilized in the prevention of stroke and continues to lead the number of medication-associated hospitalizations. Some would argue that until efficacy is demonstrated and cost-effectiveness is established, the use of pharmacogenetic information to manage patients should be discouraged. Others would argue that it is an obligation to disclose known risks to patients and patients have a right to know their individual risks.

It is imperative that the medical community work together for the sake of improving the quality of anticoagulant therapy in a cost-effective manner. At this point, the details of how to tailor therapy based on pharmacogenetic test results have not been fully established, and therefore there is uncertainty and caution with regard to embracing this approach as standard of care. However, there is compelling evidence to support the concept that, by determining patients' genotypes, a tailored approach to managing their warfarin therapy can be achieved to maximize the potential benefits of therapy while minimizing risks.

This brief commentary reviews the pharmacology of warfarin and presents arguments to support the premise that through determining the genotype of patients, sufficient knowledge is gained to support the design of a tailored approach to managing their warfarin therapy with improved safety and efficiency.

**Warfarin Therapy**

Warfarin has been proven effective in managing a variety of thromboembolic risk factors and remains the only orally available anticoagulant. The most common indication for warfarin therapy is to manage the thromboembolic risk associated with atrial fibrillation. Risk of stroke among patients with atrial fibrillation is decreased by as much as 62% when taking warfarin. Although warfarin has proven effective in managing this risk, nearly half of the patients who are eligible for receiving warfarin are not prescribed the medication because of the requirement for ongoing surveillance and physician discomfort with the safety of warfarin. The institution of practice standards and specialized clinics for managing these patients has provided some benefit. However, the fact that warfarin-associated adverse events are among the most common causes of medication-related adverse events is evidence of the need for improvement.

The traditional approach for design of a dosage regimen is to identify a steady-state plasma target concentration and then use pharmacokinetic parameters such as clearance, volume of distribution, and bioavailability to calculate an appropriate dosage rate to achieve that target concentration. The condition of steady-state is the condition when the dosage rate is equal to the rate of elimination over the dosage interval. Under steady-state conditions, the plasma concentration/time profile is consistent day to day for a given dosage and is therefore the time when the dose-response relationship can best be established. A fundamental principle is that the condition of steady-state occurs once continuous dosing has occurred for the period of time equal to seven elimination half-lives of the medication. For medications that have relatively slow plasma clearance and an elimination half-life equal to or longer than the typical dosing interval, a loading dose can be calculated to avoid delay in achieving therapeutic effect, which would result from repeated administration of the maintenance dose. In contrast, this quantitative approach to dosing warfarin has given way to an empirical approach because of the high degree of variability in warfarin clearance and the plasma concentration yielding a therapeutic response.

**Mechanism of Action**

Warfarin is a racemic mixture of R- and S-warfarin enantiomers. Prescription preparations of warfarin consist of equimolar...
concentrations of each R and S enantiomer. Both enantiomers exert their anti-coagulant effect through inhibiting the activity of the vitamin K epoxide reductase complex.\(^6\) The S-warfarin enantiomer is 3 to 5 times more potent an inhibitor of the vitamin K epoxide reductase and is therefore considered the active principle of the racemic medication.\(^6\) The pharmacokinetics of warfarin are predominantly dictated by hepatic metabolism.\(^7\) S-warfarin is metabolized principally by the cytochrome P4502C9 isoenzyme to the inactive metabolites 6-OH and 7-OH-warfarin, which are excreted in the urine.\(^8\) R-warfarin is metabolized by the cytochrome P4501A2 and 3A4 isoenzymes. The elimination half-life of S-warfarin approximates 30 hr in the majority of adults (range: 25 to >60 hr), whereas the average elimination half-life of R-warfarin in adults is on the order of 50 hr. The extended elimination half-life of R-warfarin leads to a plasma concentration ratio of R- to S-warfarin of \(-0.5\)\(^9\) under stable dosing conditions; however, this ratio is highly variable due to inter-subject differences in S-warfarin clearance.\(^10\)

Because of the stereoselective pharmacodynamic potency and the variable clearance of S-warfarin, there is no predictable relationship between total warfarin plasma concentrations and INR. As a result, there has not been a target therapeutic plasma concentration to guide warfarin dosing, even though S-warfarin concentrations most closely reflect the degree of anticoagulation. Until now, the broad range of plasma S-warfarin concentrations observed in stabilized patients has limited the utility of defining a target plasma concentration for purposes of warfarin dosing.

**Individualization of Therapy**

The complexity and difficulties in the current trial and evaluation required to determine the most appropriate warfarin dose for an individual have fueled significant efforts to identify means to improve individualization of warfarin therapy. To this end, inherited diversity in a number of genes linked to the pharmacokinetics and pharmacodynamics of warfarin as well as genes linked more broadly to warfarin's mechanisms of action have been investigated in order to identify quantifiable inherited characteristics that could be leveraged for the purpose of guiding decisions on individualized dosage of warfarin.\(^10,13\) To date, these efforts have led to the identification of several genes for which a statistically significant effect on warfarin dosing can be demonstrated.\(^10,13\)

Recent efforts have identified two genes, cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase complex subunit 1 (VKORC1), which are documented to account for 35–40% of the variability in warfarin dose requirement.\(^10,16,17\) Several alleles of CYP2C9 have been documented; however, only a few alleles are associated with lower maintenance dose requirements. The quantifiable change in warfarin maintenance dose and hepatic clearance has been clearly established for the CYP2C9*2 and CYP2C9*3 alleles in the adult population.\(^10,12,18,20\) Approximately 35–40% of patients treated with warfarin are carriers of at least one of these alleles and thus have a 30–50% reduction in plasma S-warfarin clearance, leading to a two- to three-fold increase in the time to reach steady-state. Determination of the CYP2C9 genotype provides an improved estimate of S-warfarin clearance, which can be applied as a basis for determining dosages and timing the measure of steady-state INR responses. The concentration-dependent pharmacodynamic response to warfarin is mediated through its inhibition of the vitamin K epoxide reductase complex. Vitamin K epoxide reductase complex protein C1 is encoded by the VKORC1 gene.\(^21\)

Several nucleotide sequence polymorphisms giving rise to at least eight haplotypes have been identified for VKORC1.\(^22\) The majority of studies in adults have revealed two single nucleotide polymorphisms in tight linkage disequilibrium (>99%), which demonstrate the highest level of association with warfarin maintenance dose.\(^17,20,22,26\) The 1173A>T polymorphism is silent and therefore is not anticipated to represent a causal change in VKORC1 activity. In contrast, the -1639 G>A nucleotide substitution is located within a cis-transcriptional regulatory domain and is proposed to have a causal effect on warfarin dose requirement secondary to decreased transcriptional expression and protein synthesis.\(^29\) The frequency of the VKORC1-1639A allele is ~0.3 among populations of Northern European descent. As a consequence, the majority of patients treated with warfarin are carriers of this allele.

Recently, our group has demonstrated that the range of effective therapeutic concentrations of S-warfarin observed in the adult population is a composite of three discrete ranges corresponding to the VKORC1-1639G>A nucleotide substitution.\(^17\) Thus, determination of VKORC1 genotype provides an improved estimate of the target S-warfarin plasma concentration, which can be applied in conjunction with the CYP2C9 genotype for determining initial and maintenance dosages. In conjunction with and even prior to determining the causal relationship between genetic variation in each of these genes and variation in warfarin dosage came the general acknowledgment that these genetic variants increase risk of adverse response to warfarin.\(^31,32\)

**The Controversy**

Critics of pharmacogenetics of warfarin argue that this testing has not been demonstrated to be cost-effective. Neither has it been proven to be cost-ineffective. What has been demonstrated beyond a shadow of a doubt are that (1)
warfarin accounts for a majority of medication-related adverse events, (2) under-utilization of warfarin contributes to a higher incidence of stroke, (3) genetic variation in CYP2C9 and VKORC1 increases the frequency of above-range INRs and risk of bleeding, (4) the mechanisms that account for these effects are documented, and (5) testing is available to identify the at-risk portion of the population, which represents the majority of patients. These genetic determinants have significant and quantifiable influences on warfarin dosing and safety and, once determined for a patient, can reveal an estimate of maintenance dose, provide a basis for tailoring a loading dose, identify individuals who will demonstrate a delay in achieving steady-state, and thus provide insight into therapeutic monitoring. Health care professionals trained in clinical pharmacology are equipped to apply this information to the treatment of their patients.

Summary
In conclusion, inherited genetic polymorphism of CYP2C9 and VKORC1 has been clearly demonstrated to increase the risk and complexity of treating patients with the anticoagulant warfarin. The underlying basis for these effects has been linked to decreased metabolic clearance of S-warfarin and a lower therapeutic range. Genotype-associated values for the S-warfarin clearance and target therapeutic ranges have been published. These values can be applied using basic pharmacology to calculate tailored loading and maintenance dosages. The majority of major clinical laboratories are now capable of providing this testing service. The fact that these inherited characteristics increase the risk and complexity of treating patients should be disclosed to all patients prior to initiating therapy.

The physician and patient should weigh these risks and make an appropriate decision for the patient. Physicians and clinical pharmacists should apply fundamental pharmacological practices for developing a tailored therapeutic protocol for that patient’s ability to metabolize and sensitivity to respond to warfarin. Prospective interventional trials should be designed based on the fundamental influence of these genetic determinants on the pharmacology of warfarin and should provide measures of efficacy. In addition, these trials should include tailored loading dosages, INR monitoring protocols, and maintenance dosages. Pharmacoeconomic studies should be designed to provide guidance for cost-effective utilization of these services. In the meantime, the availability of these services should not be withheld or denied to professionals with the desire and expertise to take advantage of this information or to patients who desire to understand their risks.

Dr. Linder is Associate Professor in the Department of Pathology and Laboratory Medicine at the University of Louisville School of Medicine in Louisville, KY. Disclosure: Dr. Linder holds equity interest in and is Senior Vice President of PGx Laboratories, a CLIA-certified laboratory that offers pharmacogenetic testing.

References


Technology in Search of an Application?
By Wayne W. Grody, MD, PhD, and Michael H. Rosove, MD

Personalized medicine is the new buzzword these days, both within and outside the medical profession. But what does it really mean? Isn’t all medicine, with the possible exception of group therapy in psychiatry, personalized? Aren’t physical examinations, histories, laboratory tests, drug prescriptions, blood transfusions, coronary stents, and surgeries conducted on a single person and tailored through the physician’s knowledge and judgment of that one individual? While the available technology has changed, personalized is the way medicine has been practiced since the time of Hippocrates. So what is this sea change that everyone is so excited about?

In truth, what is implied nowadays by personalized medicine is genomic medicine, which really does amount to a sea change; it is more than just a new technology (although it is that, too). Genomic medicine—the examination and potential alteration of a patient’s genome (or that of a tumor or infectious organism within him or her)—is fundamentally different from any previous clinical or laboratory modality. For the first time, it allows detection of disease before there are any signs or symptoms or biochemical perturbations, and selection of therapies based on a genotype rather than on standard physical and laboratory parameters. The latter application is called pharmacogenetics, and, until the long-heralded advent of gene therapy, it represents the major promise (and some would say hype) of personalized medicine.

Pharmacogenetics Applications

The primary application of pharmacogenetics at the time of this writing is in the field of oncology. Certain mutations, amplifications, translocations, transcriptional alterations, and other genetic changes in tumor DNA (or RNA) are associated with response or resistance to chemotherapeutic, monoclonal antibody, or small-molecule targeted antineoplastic drugs. Now beyond its infancy, the approach has demonstrated sufficient utility to have entered mainstream practice. Examples are tests for HER2/neu amplification to determine candidacy for trastuzumab therapy in breast cancer; BCR/ABL gene fusion (and mutations therein) to predict response (or resistance) to imatinib therapy in chronic myelogenous leukemia; k-ras mutations to predict resistance to cetuximab in colon cancer; and so on. Importantly, these molecular targets are all somatic or acquired genetic changes, found only in the malignant cells, and the molecular tests must be performed on a specimen of the tumor.
A second category of pharmacogenetic tests entails the detection of inherited or germline genetic variants whose protein products are involved in drug metabolism or are themselves drug targets. Although this application of pharmacogenetics is relatively little used at present, it could potentially dwarf the previous one, since it potentially covers all classes of diseases and drugs—not just cancers—and some of the genetic variants of concern are very common in the general population. Examples are cytochrome P450 CYP2D6 gene variants involved in the metabolism of certain antidepressants and antipsychotics as well as tamoxifen; variants in UGT1A1 affecting metabolism of irinotecan and steroids; TPMP variants affecting metabolism of thiopurines; CYP2C19 variants affecting metabolism of omeprazole; and many others, including the subject of this pair of articles in Critical Values, variants in the CYP2C9 and VKORC1 genes affecting metabolism of the vitamin K antagonists.

### Warfarin Metabolism

Warfarin, a racemic mixture, is one of the most widely prescribed drugs and has one of the narrowest therapeutic indices. Optimal dosage varies up to 10- to 20-fold among patients; even as little as a 10–15% dosing miscalculation can result in over- or under-anticoagulation, with attendant risks of either bleeding or recurrent thrombosis. Indeed, the number of adverse drug events from warfarin worldwide is among the highest of all drugs. Traditionally, optimal warfarin dosing has been established empirically, by frequent monitoring of functional coagulation parameters in the form of the international normalized ratio (INR) of the prothrombin time. Although this is a well-accepted practice, such a trial-and-error approach is admittedly not ideal, requiring repeated, inconvenient blood testing until the proper maintenance dose is reached. Much of the dose-response variation among patients is due to dietary and environmental factors and/or coexisting hepatic and other diseases; nevertheless, some of the difference is clearly genetic and now testable.

The metabolism of and response to warfarin is complex; many of the key steps have yet to be fully worked out. But variants in two genes have recently come to light as major factors: the vitamin K epoxide reductase gene (VKORC1), which encodes the actual target of warfarin to block or inhibit vitamin K synthesis, and the CYP2C9 gene, which encodes the cytochrome P450 enzyme primarily responsible for metabolism of S-warfarin. Certain nucleotide sequence variants in VKORC1 alter the structure of the reductase gene such that it becomes relatively resistant to inhibition by warfarin and patients carrying these variants would require higher-than-standard dosages, whereas other variants have the opposite effect. Similarly, certain sequence variants in CYP2C9 result in an enzyme with diminished activity so that the half-life of S-warfarin is prolonged, leading to a risk of drug accumulation and over-anticoagulation. These DNA sequence changes are called variants or polymorphisms rather than mutations, because most of them are relatively common in the general population and, to our knowledge, in and of themselves are not associated with any pathology except for variable drug metabolism.

Given the many millions of new warfarin prescriptions every year, there is potentially a huge market for the molecular testing of these variants at the time of drug dispensing, if they are shown to be sufficiently predictive of drug response. Indeed, an FDA panel in 2005 recommended, though has not yet implemented, just such an approach, and in 2007 the agency introduced a label change for warfarin to alert prescribers to the existence of this pharmacogenetic testing (but again, not yet to mandate it). These statements in turn prompted a number of commercial and academic molecular diagnostic laboratories to add this testing to their menus and, in some cases, to market it aggressively. At the same time, molecular reagent and equipment vendors have rushed to develop, and in
some cases attain FDA licensure for, CYP2C9 and VKORC1 genotyping kits and platforms. These platforms utilize a variety of technologies, such as microarray hybridization, multiplex bead array, Invader assay, and DNA sequencing. Whether or not the FDA will eventually issue stronger recommendations, or even requirements, to order testing at the time of dispensing warfarin to a naïve patient will depend on the results of a number of large, controlled-outcome trials currently under way.

Proceed with Caution

In the meantime, we advise caution in the implementation of these tests in routine practice, based on a number of serious concerns about their predictive value. Although the current molecular testing platforms have all been analytically validated and appear to have comparably high reliability and accuracy, results from several prospective clinical trials and meta-analyses suggest that clinical utility and cost-effectiveness remain uncertain.6–9 The existing algorithms for converting CYP2C9/VKORC1 genotype to induction and/or maintenance dosage levels of warfarin are predictive in only one-third to one-half of patients.4 Would any other clinical laboratory test be implemented if it had only 50% positive (or negative) predictive value? Couldn’t the pathologist simply flip a coin for the answer and save on laboratory costs? And aside from the unnecessary expenditure, this testing might not merely be useless, but potentially harmful: What if the algorithm predicts a higher-than-standard dosage for a patient who actually needs a lower dosage because of liver disease or other, often unknown, factors? In contrast, the traditional management approach based on INR monitoring, while not perfect, is more rapid, far less expensive, and more informative for experienced practitioners.

Unfortunately, we think that offering this particular form of personalized medicine is premature and represents a classic example of a case in which a combination of technology, hard-fought-for but incomplete genomic knowledge, and commercial interests have raced ahead of verifiable clinical application. While CYP2C9 and VKORC1 are statistically the strongest determinants that we know of, an expanding number of other gene variants (including γ-glutamylcarboxylase [GGCX], epoxide hydrolase-1 [EPHX1], α1-acid glycoprotein-1 [ORM1], etc.) also affect warfarin response.10 Might some or all of those, in addition to environmental factors, begin to explain or predict behavior in patients whose response is not predicted by CYP2C9/VKORC1 genotyping alone?

We do not for a moment imply that pharmacogenetics in general is to be discounted or rejected. On the contrary, we believe it represents the medicine of the future and is here to stay. But nothing will discredit its perception in the public eye or hinder its development and ultimate acceptance (and reimbursement!) more than the premature offering of only partly fleshed-out molecular genotyping assays that are expensive and not very predictive. While pathologists are all thrilled by the advances in genotyping technology that have brought methodologies formerly restricted to the Human Genome Project into the hands of clinical laboratories, we suggest that it would be prudent to wait until the corresponding genomic knowledge has likewise matured so that more informed decisions can be made about which sequence variants to load onto those fancy DNA analysis instruments.

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References
Molecular testing has been routinely used in clinical microbiology and infectious disease for almost three decades. In the past, a single probe, specific for the intended microorganism, was the diagnostic aim of the test. In present-day medicine with its complicated computer software programs, the molecular world has progressed to the point of sophisticated multiplex testing. This type of testing can include only a few pathogen targets or thousands with the use of microarrays. These multiplex tools allow the detection not only of the common pathogens but also emerging and newly discovered agents of infectious disease. This is especially true for zoonotic infections or those that cross from other species (e.g., severe acute respiratory syndrome [SARS]). In addition, finding co-infections with these new tools will allow therapy to be targeted more appropriately and improve the efficacy of patient care. There may often be a greater morbidity or mortality associated with such co-infections.

Some of the molecular platforms being developed for multiplex testing are real-time polymerase chain reaction (RT-PCR), gene and protein chips (microarrays), flow cytometry, and mass spectrometry. Factors that should be considered in selecting a molecular platform are performance characteristics, instrumentation and reagent cost, throughput, and specimen type.

Acute respiratory disease is the most prevalent disease in the world. Morbidity includes the common cold, influenza, bronchitis, croup, and pneumonia. The disease severity depends upon the patient risk and the type of virus, and there may also be an associated high mortality (e.g., transplant patients). Therefore, early and specific detection is paramount to both prevention and control. Early, specific, and comprehensive detection is part of the rationale for submitting multiplex, RT-PCR tests to the Food and Drug Administration (FDA).

FDA-Cleared Tests

Currently, there are two FDA-cleared test kits for respiratory viruses, and others are in various phases of the FDA clearance submission and review process. The first FDA-cleared RT-PCR assay, ProFlu+™, was developed by Prodesse (Madison, Wisconsin). The ProFlu+™ Assay is a multiplex RT-PCR in vitro diagnostic test for the rapid and qualitative detection of influenza types A and B viruses and respiratory syncytial virus (RSV). An internal control (IC) is included in the reaction mix to control for sample test inhibition. This closed-tube test generates a result from extraction to detection in about 3 hours. Another FDA-cleared test developed by Prodesse is specific for human metapneumovirus and has the advantage of using the same IC, so that a single nucleic acid extraction can be used for detection of all four viruses. A multiplex assay for parainfluenza virus types 1–3 is also in the last stage of clinical trials before submission to the FDA in the spring of 2009.
The other FDA-cleared test for the direct detection of respiratory virus in clinical specimens is the xTAG™ Respiratory Viral Panel (RVP; Luminex, Austin, Texas). The xTAG RVP detects 12 respiratory viruses: influenza type A, influenza A subtype H1, influenza A subtype H3, influenza type B, RSV subtype A, RSV subtype B, parainfluenza type 1, parainfluenza type 2, and parainfluenza type 3, human metapneumovirus, rhinovirus, and adenovirus. This open-tube system can generate a result in approximately 6.5 hours. Luminex technology uses up to 100+ color-coded beads (i.e., microspheres); each bead is coated with a specific reagent. The beads are then detected in a system that uses a combination of flow cytometry, lasers, digital signal processing, and traditional chemistry.
For Research Use Only

Several other multiplex, molecular respiratory tests are in development and at present are labeled For Research Use Only (RUO). Most detect a greater range of respiratory pathogens and offer a more comprehensive all-in-one approach. One such assay is the ResPlex™ II Panel using QIAplex™ and xMAP® technologies on the Qiagen LiquiChip System (Qiagen, Germantown, Maryland). An IC for inhibition and 18 targets can be co-amplified in the same reaction. The respiratory pathogens detected are RSV subtypes A and B, influenza types A and B, parainfluenza types 1–4, human metapneumovirus types A and B, coxsackieviruses/echovirus, rhinovirus, adenoviruses B and E, coronaviruses (NL63, HKU1, 229E, OC43), and bocavirus. Several newly discovered viruses, including human metapneumovirus, coronaviruses NL63 and HKU1, and bocavirus are already in the test menu.

Other companies are also developing tests for respiratory pathogens. EraGen Biosciences (Madison, Wisconsin) offers the MultiCode-PLx Respiratory Virus RUO Panel (RVP). This assay uses RT-PCR and the MultiCode-PLx Technology with Luminex detection and includes a 17-virus panel. Another company, Seegene (Rockville, Maryland), is developing Seeplex®, a respiratory pathogen 18-plex test. The test uses PCR and capillary electrophoresis to detect 13 viruses and 5 bacterial pathogens in a pneumonia panel. Idaho Technology, Inc. (Salt Lake City, Utah) offers an RUO respiratory RT assay capable of multiplex detection of 17 viruses and 4 bacterial pathogens. It has developed a FilmArray system by using a closed system (small pouch) and nested PCR to enhance sensitivity.

Pan-Viral and Pan-Bacterial Systems

Thus far, this discussion has involved the simultaneous detection (multiplex testing) of specific respiratory pathogens, including both bacteria and viruses. The real test for clinical molecular diagnostics is the development of high-performance pan-viral and pan-bacterial systems. These systems are currently in development and have shown great potential in detecting not only the common pathogens but also emerging and newly discovered agents of infectious disease. The Virochip (University of California, San Francisco) is an example of a pan-virus assay that was used for identifying the SARS virus, a newly discovered deadly coronavirus. This system not only achieves results in a short time but also uses a single spot on the chip to perform entire genome sequencing. Another pan-virus microarray, GreenChip, employs the same principle to achieve the same high-throughput sequencing. The final result is arrived at by a combination of complex algorithms and statistics to identify the pathogen.

Improving Patient Care

The ultimate question is, How can these eloquent, complex, and costly systems be used to improve the quality and lower the cost of patient care? The answer lies in the early and specific detection of the pathogen and subsequent cost savings on the part of the patient and health care provider. The recent acquisition (December 2008) of Ibis Biosciences by Abbott Laboratories may offer such a test in the near future. The Ibis technology involves the use of a universal biosensor (Ibis T5000™ Biosensor System). It is currently listed as an RUO, but has the potential of identifying 1,400 potential pathogens in a specimen without culturing or knowledge of the specific pathogen(s). The pathogen can be either bacterial or viral in origin, and bacterial or viral load-type quantitation is also possible. The system consists of a multiple PCR format linked to electrospray ionization time-of-flight mass spectrometry. Time to detection is about 5 hours, and there is the advantage of no additional cost for disposables.

Pathogen detection is only part of the laboratory testing for infection by a microorganism. Determining which antimicrobials to use is the reason culturing is still necessary in many cases. However, genes and mutations that confer antimicrobial resistance are being discovered and incorporated into many molecular tests. The presence of specific virulence factors (i.e., associated genes) is also important in the optimal management of the patient. Staphylococcus aureus (e.g., MecA, PVL, TSST-1), Clostridium difficile (e.g., Tox A and B), and vancomycin-resistant Enterococcus spp. (e.g., Van A) are examples of pathogens for which resistance and virulence gene detection is critical to patient care.

The newer multiplex molecular methods are not intended to replace classic phenotyping methods at present, but are expected to complement them. There are many reasons to use multiplex, molecular testing in the clinical microbiology laboratory: molecular test performance surpasses classical methods; pathogen detection is rapid; and hospital length-of-stay is reduced (i.e., cost savings). These assays have truly revolutionized the type of testing used in the clinical microbiology laboratory and have dramatically improved the quality of patient care.

Eragen Biosciences: www.eragen.com
IBIS Biosciences: www.ibisbiosciences.com
Idaho Technologies: www.idahotech.com
Luminex Molecular Diagnostics Inc.: www.luminexcorp.com
Prodesse: www.prodesse.com/USA/product/usIVD.html
Qiagen: www.qiagen.com
Seegene: www.seegene.com

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Molecular Genetics Testing: The Test Result Is Only One Piece of the Puzzle

By Ira M. Lubin, PhD, FACMG

Mary is a 28-year-old woman pregnant with her first child. She was informed her test for cystic fibrosis was negative and therefore had no risk for having an affected child. Nonetheless, Mary gave birth to a child affected with cystic fibrosis. The test result was correct. How can this happen?

As it turned out, Mary is of Asian ancestry with an uncle affected with cystic fibrosis. The test offered detects selected DNA sequence variations, otherwise known as mutations, within the gene associated with cystic fibrosis. The mutation panel that was used is recommended by the American College of Obstetricians and Gynecologists and the American College of Medical Genetics and has a 48.9% detection rate for Asian Americans.¹ Now, knowing this and also recognizing the presence of a family history, it can be stated there was a significant residual risk for Mary having an undetected mutation. Likely scenarios for how the test result was communicated to Mary include poor or absent information on the test report and/or a failure of understanding or communication on behalf of Mary’s physician. This scenario illustrates that (1) DNA test results must be integrated with other information and (2) both laboratory and clinical professionals must effectively communicate with each other to ensure the test result is understood by the clinician in patient counseling and medical decision making.

Four parameters are necessary for a test to be clinically useful: a test must be analytically and clinically valid, have utility, and be effectively implemented into medical practice. The first three parameters have received the most attention and are typically the criteria evaluated in determining whether a test is to be offered and reimbursed by third-party payers. Limited data are available on how tests are implemented in actual practice and lead to medical and personal decisions in clinical and laboratory settings. In one study, Morgan...
and coworkers' reported that while the majority of obstetrician/gynecologists recognized the value of the guideline for cystic fibrosis, only 22.2% were able to correctly answer a question about residual risk and race/ethnicity, a concept essential for understanding the test and the test result. The importance of this issue has been illustrated in a report from the Secretary's Advisory Committee on Genetics, Health, and Society in which an entire chapter was dedicated to effective communication and clinical decision support. This report cited studies that found that:

- Practitioners are unfamiliar with guidelines about the indications for conducting a genetic test and may order tests inappropriately.
- Practitioners are not adequately prepared to use test information to treat patients appropriately.
- Practice guidelines have been insufficient to communicate and ensure compliance with best practices.
- There is misinterpretation of tests because of confusing, limited, or inaccurate clinical information provided on the test report.

To address these concerns, a collaborative effort among professionals in laboratory and clinical settings across the United States was undertaken to evaluate current practices for DNA-based testing for cystic fibrosis and for reporting molecular genetic test results for certain hereditary conditions. Significant findings were that:

- Approximately 25% of test requisitions received by laboratories were missing information about the patient and/or the family deemed important by laboratories for interpreting the test result.
- Laboratories varied in how they reported residual risk and the uncertainties associated with the interpretation of certain diagnostic test findings.
- Physicians were confused by the wording used in test result reports.
- In clinical settings, tasks related to patient care such as test ordering, reviewing results, and communicating with patients about their test results were sometimes delegated to various staff members, including those lacking formal medical training, such as “secretaries.”

To develop a useful format for effectively reporting test results, three clinician workgroups (pediatric, obstetrics/gynecology, and family practice) were convened, each in a different U.S. city. The most notable outcome of these meetings was consensus among the clinicians that a report should provide the test result and interpretation in a clear, concise, and informative manner, a shortcoming noted with many types of test reports received. Workgroup participants were concerned about reports that inferred a particular interpretation of the test result and buried essential information in a long narrative, which would not be read. This raised the risk for important information being missed.

A proposed solution was to flag those results requiring additional information/knowledge needed to understand their relevance to the patient and indication for testing. For Mary, it would have been important to flag the contribution of ancestry and family history to the interpretation of the test result or otherwise note the implications of this information if it was not provided. Since such information sometimes cannot be provided concisely, the flag can refer the reader to information elsewhere in the report or to an external resource, such as a laboratory Web page or GeneTests (http://www.genetests.org, accessed January 19, 2009).

Clinicians also wanted guidance for next steps in clarifying and/or applying the test result to patient counseling and medical decision making. For Mary, it would have been helpful to suggest what might have been done to refine her risk assessment, such as ascertaining the family mutation contributing to the diagnosis of cystic fibrosis in her uncle, if known.

As a follow-up to these studies, the Centers for Disease Control and Prevention is working with the RAND Corporation to pilot-test the proposed format in a framework for reporting molecular genetic test results that also includes a clinician education component and information resources. It is envisioned that this and related work will provide the basis for enhancing communication among professionals in clinical and laboratory settings and ultimately contribute to effective implementation of molecular genetic tests in practice.

References


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The Centers for Disease Control and Prevention (CDC) will publish “Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions” in the Recommendations and Reports series of the Morbidity and Mortality Weekly Report (MMWR) this spring. This document will report the recommendations of the Clinical Laboratory Improvement Advisory Committee (CLIAC) for good laboratory practices in the areas of molecular genetic testing that have been recognized as needing specific guidance for complying with applicable requirements in the Clinical Laboratory.
Improvement Amendments (CLIA) regulations or as needing quality assurance measures in addition to the general CLIA requirements. The MMWR document is intended to be used by the following laboratories or individuals for improving the quality and utilization of genetic laboratory services:

- Laboratories performing molecular genetic testing for heritable diseases and conditions
- Users of the laboratory services, including (but not limited to) health care professionals, patients, referring or referral laboratories, and payers of laboratory services
- Medical and public health professionals who evaluate laboratory practices and policies.

Since the implementation of the CLIA regulations in 1992, advances in scientific research and technology have led to steady growth in the number of health conditions for which genetic defects or variations can be detected with molecular methods, the number of laboratories performing molecular genetic testing and their test volume, and the spectrum of the molecular testing methods employed in patient testing. Many laboratories performing molecular genetic testing comply with applicable regulatory requirements and adhere to professional practice guidelines. However, issues that have been recognized are related to analytic and clinical validity, proficiency testing, the preanalytic and postanalytic phases of the testing process, and personnel qualifications for certain molecular genetic tests. These issues could affect testing quality and patient testing outcomes and have raised public concerns about the adequacy of regulatory oversight and quality assurance measures for this rapidly expanding area of laboratory testing.

Since 1997, the CDC and the Centers for Medicare & Medicaid Services (CMS) have been working with other federal agencies, professional organizations, standard-setting organizations, CLIAC, and other advisory committees to promote the quality of genetic testing and improve the appropriate use of genetic tests in health care. As part of efforts to enhance the oversight of genetic testing under the CLIA framework, CMS and CDC sought advice from CLIAC to address the quality assurance and quality assessment needs in molecular genetic testing. Considering the complexity of genetic testing overall and the specific quality assurance issues associated with different types of testing, CLIAC first focused on molecular (or nucleic acid-based) testing for heritable disorders or conditions in developing recommendations for good laboratory practices, recognizing that this area presents the greatest immediate need for guidance to promote quality testing. Recommendations for good laboratory practices focusing on other areas of genetic testing, such as biochemical genetic testing, molecular cytogenetic testing, and somatic genetic testing, will be provided in future guidance documents.

The publication in the MMWR Recommendations and Reports series will report the recommendations that CLIAC developed based on professional guidelines, regulatory and voluntary standards, accreditation checklists, international standards and guidelines, and other documents providing general or specific quality standards applicable to molecular genetic testing for heritable diseases or conditions. The recommended good laboratory practices address the total testing process:

- The preanalytic phase (information for users of laboratory services, informed consent, test request, specimen submission and handling, test referral, and preanalytic systems assessment)
- The analytic phase (establishment and verification of performance specifications, quality control procedures, proficiency testing, and alternative performance assessment)
- The postanalytic phase (test report, retention of records and reports, and specimen retention) of molecular genetic testing.

The recommendations also address the laboratory’s responsibilities for authorized persons, confidentiality of patient information and test results, personnel competency, issues to consider before introducing molecular genetic testing or offering new molecular genetic tests, and the potential benefits of the quality management system approach in molecular genetic testing. These CLIAC recommendations are intended to serve as a guide for considering and implementing good laboratory practices to improve the quality and health care outcomes of molecular genetic testing for heritable diseases and conditions, and to enhance the oversight and quality assurance practices for molecular genetic testing under the CLIA regulatory framework.

The MMWR document, once published, will be available on the CDC Web site at www.cdc.gov and the Web site of the CDC Division of Laboratory Systems at wwwn.cdc.gov/dls/default.aspx.

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The findings and conclusions in this article are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.
Developing Characterized Reference Materials for Genetic Testing

By Lisa Kalman, PhD

Reference and quality control (QC) materials are essential for many aspects of genetic testing. These materials, which are tested alongside patient samples, allow laboratories to detect errors due to test system failure or operator error. In addition, reference materials are needed for test development and validation, lot testing of new reagent batches, and proficiency testing/external quality assessment programs.

More than 1,300 genetic tests are currently offered in clinical laboratories; however, for the vast majority of these tests, no publicly available characterized reference or QC materials are available. In the absence of these publicly available materials, laboratories must improvise to obtain these reagents and, in some cases, develop and run assays without adequate controls. Often, DNA derived from leftover patient specimens, which is not easily available or renewable, is used as a reference material. Laboratories also utilize synthetic DNA or DNA isolated from cell lines. All these materials must be validated by the laboratory prior to use as QC or reference materials.

The CDC has been involved since 1995 in efforts to develop appropriate and well-characterized reference materials for use by the genetics community. In 2004, the Genetic Testing Reference Materials Coordination Program (GeT-RM) was established at the CDC in partnership with the genetics community. The goal of this program is to coordinate a self-sustaining community process to improve the availability of characterized genomic DNA materials for QC, proficiency testing, test development/validation, and research. The GeT-RM program also facilitates information exchange between users and providers of reference materials. Although the GeT-RM program is coordinated by the CDC, all the actual work, including decisions about reference material priorities, specimen collection, material development, and characterization occurs through voluntary collaborations with laboratories in the genetics community. Cell lines with confirmed genotypes are considered the preferred type of control for DNA-based genetic testing because they most closely resemble an actual patient specimen. Thus, the GeT-RM program has focused its efforts on this material type.

The GeT-RM program recently characterized more than 90 cell-line-based genomic DNA reference materials for a number of genetic disorders, including fragile X, Gaucher disease, mucolipidosis IV, Neimann-Pick disease, and Tay-Sachs disease, cystic fibrosis, Huntington disease, MTHFR-related homocysteinemia, alpha-1-antitrypsin deficiency, multiple endocrine neoplasia, and BRCA1- and BCRA2-related cancers. Each of these genomic DNA materials was tested in 3–10 clinical genetic laboratories using a variety of genetic assays, including DNA sequence analysis. These materials are publicly available from the Coriell Cell Repositories. The GeT-RM program is currently conducting characterization studies of genomic DNA reference materials for Duchenne muscular dystrophy, as well as a large-scale study of DNA from 107 cell lines to be characterized for a number of polymorphisms in 21 pharmacogenetic loci.

To date, the GeT-RM program has focused its efforts on DNA-based testing for inherited genetic disorders. However, there is a similar lack of reference materials for other areas of genetics, including molecular oncology, molecular infectious disease testing, and biochemical genetic testing. Mechanisms to address reference material needs for these areas are also being considered.

The GeT-RM Web site (www.cdc.gov/dls/genetics/rmmaterials/default.aspx) provides a comprehensive source of molecular genetic reference material information to the genetic testing community. The Web site is grouped into three subject areas: inherited genetic diseases and pharmacogenetics, molecular oncology, and infectious disease. Information about available reference materials, including applicable characterization studies and results, is provided. The Web site also features comprehensive searchable databases of commercially available reference materials for both molecular oncology and infectious disease and general information about reference materials, including pertinent research articles, a list of reference material sources (manufacturers, repositories, and so on), a list of relevant guidance, and oversight Web sites and documents.

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The findings and conclusions in this article are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.
Classification is an important way of describing, defining, and naming diseases that can then be diagnosed, studied, and treated. A classification system should contain diseases that are clearly defined and clinically distinctive, leading to a better understanding of the disease and its biological behavior and prognosis and to a successful means of treatment.

The fourth edition of the *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues* was published in 2008. This classification was the result of an international collaborative project between the Society for Hematopathology and the European Association of Haematopathology. It is a revision and update of the third edition, published in 2001, which was the first true worldwide consensus classification of hematopoietic neoplasms. The current edition is the result of an eight-person steering committee of members of both societies who agreed on a proposed list of diseases. These diseases were categorized further into chapters and subtopics authored by experts from both societies. Input and advice were also sought from clinical hematologists and oncologists to ensure the classification would be clinically useful. More than 130 pathologists and hematologists-oncologists from around the world were involved in writing this new edition.

The principle of the WHO classification system is to build on prior classification systems in an attempt to define diseases that could be recognized by all pathologists and hematopathologists using available techniques and that appeared to be distinct clinical entities. For this undertaking to be initially successful, it was important that proponents of the various hematopoietic classification systems agree to use the new WHO classification. This had been accomplished with the publication of the third edition.

There is no one *gold standard* by which all hematopoietic neoplasms are defined in the WHO classification. Morphology has always been very important, and many diseases have characteristics or diagnostic morphologic features. However, the incorporation of immunophenotypic studies, genetic features, and molecular studies has yielded information that provides and allows a means for a consensus definition, rather than one in which only subjective morphologic criteria are available. Many diseases have a characteristic immunophenotype, while for others the immunophenotype is only part of the diagnosis. Likewise, in some lymphoid and many of the myeloid neoplasms, a specific genetic abnormality is the key defining feature for a diagnosis. The inclusion of immunophenotypic and genetic features has resulted not only in providing a diagnosis but also in identifying antigens or genes that can be targeted for therapy. Examples are rituximab, an anti-CD20 antibody that is being used in the treatment of B-cell neoplasms expressing this antigen, and imatinib, which is being used in the treatment of disorders associated with BCR-ABL fusion gene and other tyrosine kinase gene disorders. Although most of the entities in the WHO classification are considered to be distinct entities, several are not so clearly defined and are listed as provisional entities. There are also borderline categories that do not fit neatly into any one category and that need further study to be placed in an appropriate category in the future.

The WHO classification broadly categorizes the hematopoietic neoplasms into three major divisions based on lineage: the myeloid, lymphoid, and histiocyte/dendritic cell lineages. The major entities in turn are further subdivided...
by precursor neoplasms (acute myeloid leukemia [AML], acute lymphoid leukemia/lymphoblastic lymphoma, acute leukemias of ambiguous lineage and blastic plasmacytoid dendritic cell neoplasms), which are considered separate from the so-called mature neoplasms (myeloproliferative neoplasms, myelodysplastic/myeloproliferative neoplasms, myelodysplastic syndromes, peripheral B-cell and T/NK neoplasms, Hodgkin lymphoma, and histiocytic/dendritic cell neoplasms).

Acute Myeloid Leukemias

The AMLs now take into consideration whether there are recurrent genetic abnormalities, and there are now three leukemias within this category: t(8;21)(q22;q22), inv(16) (p13.1;q22) or t(16;16)(p13.1;q22), and t(15;17)(q22;q12), which are classified as AML without regard to the blast count. It is yet not clear whether all the other cases with the recurrent genetic abnormalities t(9;22)(q21q32), t(6;9)(p23q34), inv(3) (q21q26.2), t(3;3)(q21;q26.2), or t(1;22)(p13;q13) should be categorized as AML when the blast count is <20%.

There is also a subcategory of AML associated with myelodysplasia-related changes and therapy-related myeloid neoplasms. Some of the AMLs with a specific genetic abnormality are associated with a good prognosis and response to therapy, whereas others are associated with a poor prognosis. Cytogenetic analysis is considered a very important component of any leukemic workup and should be obtained in all cases. AMLs with myelodysplastic features are also important to recognize, because these cases generally are associated with a poor prognosis and have a lower rate of achieving complete remission than other AML types. Likewise, the prognosis of therapy-related AMLs or myelodysplastic/myeloproliferative neoplasms is generally poor, although again it is strongly influenced by the associated karyotypic abnormality.

The mature myeloid neoplasms are further stratified according to their biological features, such as myeloproliferative neoplasms with effective hematopoiesis versus myelodysplastic syndromes with ineffective hematopoiesis, which include genetic features. Major revisions in the fourth edition have been incorporated into the classification of the myeloproliferative neoplasms (formerly called diseases). There is the classic BCR-ABL1 fusion abnormality that is diagnostic for chronic myelogenous leukemia (CML). There is now a new term referred to as the BCR-ABL1 negative myeloproliferative disorders, which refers to polycythemia vera, essential thrombocythemia, and progressive myelofibrosis. The diagnostic algorithms for polycythemia vera (PV), essential thrombocythemia (ET), and progressive myelofibrosis (PMF) have substantially changed to include information on the presence of JAK2 and MPL W151L/K tyrosine kinase genes as well as pertinent histologic features of the bone marrow biopsy as diagnostic criteria. Mastocytosis is now included in this category and is associated with another protein tyrosine kinase gene abnormality called KIT D816V.

Cases associated with eosinophilia have also undergone revision. Some cases of what had previously been called chronic eosinophilic leukemia are now categorized in a separate chapter as myeloid or lymphoid neoplasms with eosinophilia and abnormalities associated with the formation of fusion genes encoding an aberrant tyrosine kinase, which includes platelet-derived growth factor receptor alpha (PDGFRα), platelet-derived growth factor receptor beta (PDGFRβ), and fibroblastic growth factor receptor 1 (FGFR1). The importance of recognizing these abnormalities is that the aberrant tyrosine kinase activity may make the disease responsive to tyrosine kinase inhibitors. This has already been realized for myeloproliferative neoplasms with rearrangement of PDGFRα or PDGFRβ, which are responsive to imatinib and other related tyrosine kinase inhibitors.

A number of gene mutations, detected by gene sequencing, allele-specific PCR, and other specialized techniques, have emerged as important diagnostic and prognostic markers in all categories of myeloid neoplasms. Furthermore, the role of gene over- and under-expression as well as loss of heterozygosity and copy number variants detected by microarray analysis are now being recognized as important abnormalities that may well influence diagnostic and prognostic models in the future. Whereas microarray profiling studies are important in the research setting, they have not been fully tested, are expensive, and are not readily available in routine clinical practice at this time.

Lymphoid Neoplasms

The WHO classification contains specific chapters on precursor lymphoid neoplasms, mature B-cell neoplasms, and mature T and NK-cell neoplasms. There are many subentities within each subgroup that are beyond the scope of this article to break down. In addition, there are separate chapters on Hodgkin lymphoma, histiocytic and dendritic neoplasms, and immunodeficiency-associated lymphoproliferative disorders, all of which have been revised with new entities added.

The classification of the numerous lymphoid neoplasms is based on utilization of all available information for defining disease entities. The WHO classification incorporates morphology and immunophenotypic data that are sufficient for the diagnosis of most lymphoid neoplasms. However, no one antigenic marker is specific for any neoplasm, and a combination of morphologic features and a panel of antigenic markers need to be correlated to establish a correct diagnosis. Whereas most B-cell lymphomas have characteristic immunophenotypic profiles that are very helpful in diagnosis, immune profiling is less helpful in the subclassification of T-cell lymphomas. Genetic studies including PCR analysis of IgH and T-cell receptor gene rearrangements and fluorescence-in-situ hybridization (FISH) studies are valuable diagnostic tools for determination of clonality in B- and T-cell neoplasms, which aid in the differential diagnosis of reactive versus neoplastic disorders.
Genetic features are also beginning to have an increasing role in the classification of lymphoid malignancies and of many of the small B-cell lymphomas and leukemias for which recurrent genetic alterations have been identified. However, unlike the myeloid neoplasms, the molecular pathogenesis of most T-cell and NK-cell lymphomas remains unknown. Infectious agents have been shown to contribute to the development of several types of B-cell, T-cell, and NK-cell lymphomas. These are now included as part of the diagnostic criteria for some of these neoplasms. Epstein-Barr virus (EBV) is present in nearly 100% of endemic Burkitt lymphoma cases and is involved in the pathogenesis of many B-cell lymphomas arising in immunosuppressed individuals including post-transplant lymphoproliferative disorders, plasmablastic lymphoma, and EBV+ large B-cell lymphoma of the elderly. Human herpesvirus 8 (HHV-8) is found in primary effusion lymphoma and the lymphoma associated with multicentric Castleman disease. The association between H. pylori and gastric MALT lymphoma is well-known.

The WHO classification has emphasized a multiparameter approach to the classification of lymphomas. This approach has been validated in international studies as being highly reproducible and enhancing the interpretation. The WHO classification also emphasizes the importance of knowledge of the clinical features, both for accurate diagnosis and for the definition of some diseases, and there is a statement that the diagnosis of lymphoid neoplasms needs to include a complete clinical history.

Traditionally, classical Hodgkin lymphomas (CHL) have been considered separately from the non–Hodgkin lymphomas. However, with the recognition that CHL is of B-cell lineage, there are grey zones and the WHO classification now recognizes these grey zones and provides for the recognition of cases that bridge the gap. There are now sections on B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma and B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma.

Significant New Information

The fourth edition of the WHO classification incorporates significant new information that has arisen from both basic science and clinical investigations since the publication of the third edition in 2001. There are new defining criteria for many diseases, and the incorporation of morphology, immunophenotype, and genetic criteria has led to new categories, as discussed. Incorporation of all these diagnostic modalities has led to some interesting findings. For example, small clonal populations of cells have been detected in normal individuals, including small clones of cells with the BCR-ABL 1 translocation (seen in CML), small clones of cells with the BCL2-IgH rearrangement (lymphoma), small clones of cells with the immunophenotype of chronic lymphocytic leukemia, follicular lymphoma, monoclonal B-cell lymphocytosis, and pediatric follicular lymphoma with monoclonal B-cells. It is currently a matter of debate whether these findings indicate early involvement by a neoplasm, a precursor malignant lesion, or simply an inconsequential finding. Further studies will be necessary to resolve these findings and perhaps lead to new algorithms for subsequent diagnosis/classification.

As with any classification system, periodic reviews and updates will be needed to incorporate new information. The Society for Hematopathology and the European Association for Haematopathology have a history of collaboration of more than 10 years. These organizations are committed to updating and revising the classification as needed, and this will undoubtedly occur as additional information from newer technology evolves. New genetic and molecular findings are rapidly being detected and may provide further insight into the etiology and behavior of hematopoietic neoplasms; these most likely will need to be incorporated into future classifications for diagnostic, predictive, and treatment purposes.

Dr. Krause is Professor and Chairman of the Department of Pathology and Laboratory Medicine at Tulane University Medical Center, New Orleans, LA.

References

Robust Job Market for Hematopathology Fellowships

Report of the ASCP Fellow In-Service Hematopathology Job Market Survey

By Thomas J. Bollinger, MD, MPH

The first-ever Fellow In-Service Hematopathology Examination (FISHE) was administered by ASCP in 2008. In keeping with the pathology job market research survey conducted by the ASCP Resident Council, which is administered at the end of the Resident In-Service Examination (RISE), a hematopathology-specific job market survey was administered at the end of the FISHE. The ASCP Resident Council is extremely grateful to all the respondents for taking their time to complete the survey. We also thank Robyn Potts, MD, FASCP, a former council member, for her insight in constructing survey questions.

The job market for graduating hematopathology fellows appears robust. At the time of examination administration, 76 of 103 fellows (74%) intended to apply or had already applied for jobs. Of 65 formal applicants (11 had not yet applied), 62 (95%) had interviewed for jobs and 61 (94%) had received offers. Of graduating fellows not seeking jobs, 25 had applied for or intended to pursue an additional fellowship.

Training

Medical School. Sixty-nine percent of the respondents were U.S. medical graduates; 27% were international medical graduates; 1% were U.S. international medical graduates; and 3% responded “other.”

Residency

Of the 103 individuals surveyed, 84% were from dual anatomic pathology/clinical pathology (AP/CP) programs, while 9% were solely CP and 7% solely AP. Fifty-eight percent were from a university-owned public hospital, 30% from a university-owned private hospital, 4% from a community-based teaching hospital, 3% from a military hospital, and 5% from other institutions.

Fellowship

Of 103 respondents, 24 had completed a fellowship in a different subspecialty. Of those, 13 completed fellowships in surgical pathology or another anatomic pathology subspecialty (54%). Six completed fellowships in molecular pathology. Others completed fellowships in transfusion medicine (3), pediatric pathology (2), and immunohistochemistry (1).

Additional Training Beyond Hematopathology Fellowship

Twenty-five respondents applied for or intended to apply for fellowships instead of seeking jobs. Of 23 fellowship applicants who formally applied, 100% applied for 1–3 fellowships. All received offers. Nineteen (83%) took fellowships and did not seek a job; 2 took fellowships and received no job offers; 1 took a fellowship and declined later job offers; and 1 took a fellowship but later declined to accept a job. Prospective fellows were most interested in surgical pathology and anatomic pathology (including dermatopathology, cytopathology, and gastrointestinal/hepatic pathology), molecular pathology, and subspecialty fellowships. Of fellows applying for additional training, the majority (71%) did so for long-term career interests, and 25% did so because they felt it was necessary to secure employment.

Job Market

Of 76 potential job seekers, 65 formally applied. Thirty-four percent applied for 1–3 jobs; 28% for 4–6 jobs; 20% for 7–10 jobs; and 18% for >10 jobs. Ninety-five percent (62) of those 65 applicants formally interviewed for jobs, with 74% interviewing for 1–3 jobs, 23% for 4–6 jobs, and 3% for 7–10 jobs. Of the 61 who received offers, 46% received 1 offer, 33% received 2 offers, and 21% received 3 or more offers.

Of the 61 job hunters, 87% searched for less than 6 months before finding a job: 18% found a job in less than a month; 36% found a job in 1–3 months; and 33% found a job in 3–6 months. Of the 61 respondents who were offered a job, 24 (39%) were offered positions in their own residency fellowship program, 14 of them declined this position for another offer; 5 accepted and planned on staying at their program; and 5 accepted but continued to look for other offers.

Most new hires took jobs in community practices (44%). Thirty-three percent landed academic clinical practice jobs, and 11%, 7%, and 2% will work in a reference laboratory/corporate setting, academic research, and “other” settings, respectively.

Work will consist of hematopathology, surgical pathology, and other clinical pathology for 33% of new hires. Another 33% will practice hematopathology and surgical pathology only, while 21% and 10% will practice hematopathology only and hematopathology with other clinical pathology, respectively. Three percent responded that their workload will consist of “other” duties.
Compensation

Employment Status. Thirty-nine of 61 new hires (64%) will work in an employee-employer relationship. Twenty-two of 27 new hires (82%) will work in community practices, while the remainder will work as partners or potential practice partners.

Salaries. A question regarding the range of starting salaries (excluding benefits) offered was answered by 60 respondents. Salaries were reported as follows:

<table>
<thead>
<tr>
<th>Salary Range</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;$100,000</td>
<td>2</td>
<td>3%</td>
</tr>
<tr>
<td>$100,000+</td>
<td>16</td>
<td>27%</td>
</tr>
<tr>
<td>$150,000+</td>
<td>24</td>
<td>40%</td>
</tr>
<tr>
<td>$200,000+</td>
<td>12</td>
<td>20%</td>
</tr>
<tr>
<td>&gt;$250,000</td>
<td>6</td>
<td>10%</td>
</tr>
</tbody>
</table>

Bonuses. According to survey results, 90% of employers did not offer signing bonuses, although 56% offered moving bonuses.

Factors in Job Search

Type of Practice. Thirty-seven percent of 76 respondents found that community group practice held the most open hematopathology positions in the market, while 33% thought academic clinical practice offered the most opportunities. Fourteen percent reported that academic research practice positions and 13% thought reference laboratories were most available.

Geographic Region. Of 76 job hunters, 66% restricted their job search to a specific region. The most common reason for their restriction was “lifestyle/family issues” (55%), with area nativity, spouse’s job, and professional contacts in the region mentioned as other reasons. Of applicants who restricted their job searches, most restricted their job search to the Midwest United States (28%). Other regions were as follows: 18% Northeast, 16% Southeast, 14% Southwest, 10% Northwest, 8% “other,” and 6% Canada.

Other Factors. Only 5% of applicants restricted their job search based on visa status. For those seeking a job, multiple job factors rank at varying levels of importance to each applicant. The applicant’s perception of staff and institution at the time of interview was ranked highest in level of importance, with job availability in geographic regions, long-term job security, family factors, and opportunity to practice a subspecialty following. Career advancement opportunities, salary considerations, research opportunities, fiscal pressures (e.g., loan repayments), and teaching opportunities were secondary.

Referrals. When searching for a job, applicants ranked referrals from faculty and word of mouth as most helpful. College of American Pathologists listings were ranked next in importance, followed by random mailings/calls, ASCP Job Finder, and executive recruiters. With regard to using the Internet for job search activities, the vast majority (74%) of respondents indicated that they found most helpful such Web sites as mdconsult.com, careerweb.com, and monster.com.

Dr. Bollinger is in residency training at the Orlando (FL) Regional Medical Center and is currently co-Chair-Elect of the ASCP Resident Council.
Certification
The ASCP Board of Registry (BOR) offers certification as an MP(ASCP) Technologist in Molecular Pathology. The technologist in molecular pathology performs the molecular analysis and diagnosis of acquired, inherited and infectious diseases and is involved in the practice or research of innovative technologies that include histocompatibility, immunogenetics, and the diagnosis, treatment and prognosis of infectious diseases, cancer, and genetic disorders. For more on the certification process, see www.ascp.org/certification.

Education

**Educational Courses**

- **April 2–4:** Update in Pulmonary Pathology: Contemporary Classification and Diagnosis, Santa Fe, NM. Director: Andrew Churg, MD, FASCP
- **April 27–30:** Dermatopathology: Contemporary Diagnostic Criteria and Strategies, Myrtle Beach, SC. Director: Neil Crowson, MD, FRCPC, FASCP
- **May 4–6:** Molecular Surgical Pathology for Practicing Pathologists, Chicago, IL. Director: William K. Funkhouser, MD, PhD, FASCP
- **June 8–10:** Current Issues and Problems in Breast Pathology, Santa Barbara, CA. Director: Fattaneh A. Tavassoli, MD, FASCP
- **July 19–23:** Pathology Update: State-of-the-Art Surgical Pathology with Molecular Diagnostic Applications, Vancouver, BC, Canada. Co-directors: Virginia A. LiVolsi, MD, FASCP, and Jennifer L. Hunt, MD, MEd, FASCP

**Teleconferences**

- **April 2:** Molecular Methods for Rapid Identification of MRSA, Thomas E. Davis, MD
- **May 5:** Molecular Pathology Basics for the Practicing Pathologist, Jennifer L. Hunt, MD, FASCP
- **May 27:** Coding and Reimbursement for Molecular Pathology Assays, Jeffrey A. Kant, MD, PhD
- **June 9:** An Update on the Use of Pap Tests and Human Papillomavirus Testing, Shikha Bose, MD
- **June 12:** Emerging Molecular Diagnostic Tests in Infectious Disease, Matthew J. Bankowski, PhD, D(ABMM), SM(ASCP)

**Weekends of Pathology**

- **February 21:** A Practical Approach to Immunophenotyping and Molecular Genetics for the Diagnosis of Hematologic Neoplasms, Las Vegas, NV, Tsieh Sun, MD, FASCP, and Mary Lowery Nordberg, PhD
- **June 12:** The Use of Immunophenotypic, Molecular Genetics and Cytogenetic Studies in Diagnosis of Lymphoproliferative Disorders, Montreal, QE, Amy Chadburn, MD, FASCP
- **June 14:** Surgical Pathology of Breast Carcinoma: Changing Concepts and Emerging Frontiers, Montreal, QE, Dilip D. Giri, MD, and Syed A. Hoda, MD, FASCP

**Workshops for Laboratory Professionals**

- **April 16:** An Introduction to Molecular Methods and Applications, Chicago, IL, Tina Bocker Edmonston, MD
- **April 27:** Molecular Diagnostics in the Clinical Laboratory, San Francisco, CA, Patrick Cummings, ScD, MS, MT(ASCP), and Kristina Obom, PhD, MPH
- **May 20:** Nucleic Acid Technology—Practical Answers to Real-World Problems, Baltimore, MD, Danny L. Wiedbrauk, PhD

**Resident Review Course**

- **April 16–21:** Chicago, IL. Directors: Michael Laposata, MD, PhD, FASCP, and Carole Vogler, MD, FASCP

Pathologists Note: The Maintenance of Certification (MOC) process adopted by the American Board of Pathology (ABP) encompasses a set of requirements that must be fulfilled every 10 years following certification. As of January 1, 2006, all primary and subspecialty certificates issued by ABP expire on the last date of the 10-year anniversary of their issuance. Specific deadlines must be met at two-year intervals. Total requirements must be fulfilled within 10 years.

Laboratory Professionals Note: Individuals who become ASCP Board of Registry-certified in 2004 and beyond are required to maintain their certification through the ASCP Certification Maintenance Program (CMP) every three years. www.ascp.org/education.asp

Publications

- **Bone Marrow IHC & Molecular Pathology,** by Emina Torlakovic, MD, PhD; Kikkeri Naresh, MBBS, CCP, MD, FRCPath; and Richard D. Brunning, MD, 2009

- **Cytopathology Review Guide,** 3rd edition, by E. Blair Holladay, PhD, SCT(ASCP)®C, 2009


- **Bone Marrow Pathology,** 2nd edition, by Kathryn Foucar, MD, FASCP, 2001

- **Prostate Pathology,** by Peter A. Humphrey, MD, PhD, 2003

Advocacy

ASCP convinced the Florida Board of Clinical Laboratory Personnel in November that it was not necessary for laboratories to use molecular pathology technologists to perform PCR testing for Methicillin-resistant *Staphylococcus aureus* or Group B streptococcus. ASCP argued that the addition of the molecular pathology technologist license was never intended to adversely affect the scope of practice of other laboratory practitioners in such areas as blood banking or microbiology. In fact, the scope of practice for
licensed molecular pathology technologists in Florida was limited to the analysis of human genetic material, and thus should not have hampered testing for MRSA or GBS. In the end, the Board agreed to revise a rule to allow persons licensed by the Board to perform molecular testing in their licensed scope of practice provided they meet existing regulatory requirements on training.

**CLSI Resources**
The Clinical & Laboratory Standards Institute has issued the following new consensus documents on molecular genetic testing:

- **Molecular Methods Searchable CD-Rom**: Includes 16 Molecular Methods searchable standards and guidelines.
- **Verification and Validation of Multiplex Nucleic Acid Assays (MM17-A)**: Guideline provides recommendations for analytic verification and validation of multiplex assays, as well as a review of different types of biologic and synthetic reference materials.
- **Interpretive Criteria for Identification of Bacteria and Fungi by DNA Target Sequencing (MM18-A)**: Sequencing DNA targets of cultured isolates provides a quantitative metric within which to perceive microbial diversity, and can serve as the basis to indentify microorganisms. Intended to catalyze the entry of molecular microbiology into clinical usage by establishing interpretive criteria for microorganism identification.


**ASCP News**

**ASCP Wage and Vacancy Survey Documents Worsening Workforce Shortage**

ASCP’s latest Wage and Vacancy Survey, published in the March 2009 issue of LABMEDICINE, suggests a worsening shortage of laboratory personnel. Nearly one-half of clinical laboratories across the nation report experiencing difficulties hiring personnel. Western states struggle more with recruitment than other regions of the country, as notably fewer laboratories there report success in filling positions within 6 months. Shortages were reported for all laboratory positions surveyed, but vacancy rates for certified medical technologists and histotechnicians were particularly high, at 10.4% and 8.0%, respectively. Increased competition for qualified staff and lower compensation for laboratory work compared with other fields were the predominant reasons cited for the hiring difficulties.

**ASCP Council Nominations**

Do you want to become a leader in ASCP? Do you think that you know what’s best for you and your colleagues? Do you like meeting other individuals in your field? If you answered yes to any of these questions, then submit your nomination to be a member of one of these three ASCP Councils:

- ASCP Council of Laboratory Professionals
- ASCP Fellow Council
- ASCP Resident Council

Nominations are open for the 2009 Councils. For more information and to submit your CV and letter of interest, contact Matt Gibson (matt.gibson@ascp.org) or Betty Sanders (betty.sanders@ascp.org).

**New ASCP Media Spokespersons**

In January ASCP announced its first group of media spokespersons to help raise awareness of pathology and laboratory medicine. The list of spokespersons continues to grow. The following are the latest additions to the spokespersons network:

- **Kathleen Becan-McBride, EdD, MT(ASCP)CM**
  Chair, ASCP Board of Registry (BOR) Board of Governors; Member, ASCP Board of Directors
  Director of Community Outreach & Education, University of Texas Health Science Center, Houston, TX
  Expertise: Phlebotomy/blood collection for patient safety

- **Lucia Berte, MA, MT(ASCP)SBB, DLM**
  ASCP Member; Author, "Quality Qorner" (LABMEDICINE)
  President, Laboratories Made Better! P.C. Broomfield, CO
  Expertise: Laboratory quality management; transfusion medicine
Since 1975, ASCP has celebrated the far-reaching impact of laboratory professionals on our lives. ASCP partners with nine other health care organizations to coordinate National Medical Laboratory Professionals Week: AABB, AACC, American Medical Technologists, American Society for Clinical Laboratory Science, American Society of Cytopathology, Association of Public Health Laboratories, CLMA, College of American Pathologists, and National Society for Histotechnology.

This year, the coalition chose the theme “Laboratory Professionals Get Results” to emphasize the important work of laboratory professionals to deliver accurate and timely test results. Laboratory test results account for about 70% of the patient’s medical record, and nearly 10 billion laboratory tests will be performed in the United States this year alone. Laboratory professionals work diligently to provide the highest quality patient care with the knowledge that there is a face behind every sample and every test result.

Lab Week celebrations offer laboratory professionals an opportunity to celebrate their work with creative and fun parties all week long. Lab Week also is a prime opportunity to raise awareness of the vital role laboratory professionals play in health care. It’s not too late to do your part. Think of simple ways you can extend your celebration of Lab Week beyond the laboratory and into the community. Consider speaking at your child’s school about where you work and what you do. Open your laboratory to the public to conduct a blood screening, and explain to them what you’re doing and why the results you give them are important. Invite physicians and nurses from a department that relies heavily on your work to a lunch-and-learn to discuss what really goes on when they send off for a sample. Take it one step further and invite the news media to your event. Take pictures, take video, join the ASCP Facebook group, and share your experience. And tell us your story, so we can share it with others as well. Send it to labweek@ascp.org.
By Deborah Aschheim

I make installations based on the neurobiology of thought and invisible networks of memory and perception. In the past, I have created nervous systems for buildings, animated by off-the-shelf consumer electronics, and I have built immersive, luminous landscapes of blown-up cellular structures. Recently, I have been investigating memory through a series of experiments that are equal parts science and poetry.

My family has a history of Alzheimer’s disease, which lends an urgent personal dimension to my fascination with memory and forgetting. My grandfather suffered from dementia at the end of his life, but he was an avid photographer and after he died, I inherited his memories on film. My father shot 8 mm movies for the first six years of my life, documenting my own experiences that I can’t remember. In my exhibition “On Memory” (2006–7, Mattress Factory Museum, Pittsburgh, PA), I wove webs of LED-lit nodes around looping video fragment, mapping out the spreading pattern of memory/neural activation that is triggered as I watch these surrogate memories and relocating my private mental world into the public space of the gallery.

Ms. Aschheim received a B.A. in anthropology from Brown University and an M.F.A. from the University of Washington. She has received fellowships from the City of Los Angeles, the Pasadena Arts Commission, the Durfee Foundation, and the New Jersey State Council on the Arts. She has been artist-in-residence at the Memory and Aging Center at UC San Francisco; at Fundacion Valparaiso in Mojácar, Spain; at Headlands in Marin, CA; at Hallwalls in Buffalo, NY; at the Bemis Center in Omaha, NE; and at the Roswell Museum and Art Center, Roswell, NM. This spring, she is Visiting Artist at Roger Williams University in Bristol, RI.

Photo: Owen Smith
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