Published by the North Carolina Institute of Medicine and The Duke Endowment

North Carolina
MEDICAL JOURNAL
a journal of health policy analysis and debate

# Laboratory Medicine and Clinical Pathology: Changing Paradigms of Practice

Also in this Issue:
*Spotlight on the Safety Net*

www.ncmedicaljournal.com
March/April 2007, 68:2

# So Many Reasons to Celebrate!

- Named Charlotte's "Preferred Hospital" for 9 Years by National Research Corporation
- J.D. Power and Associates Distinguished Hospital Program for Excellence in Maternity Services
- HealthGrades—Best Cardiac Care in the Region
- American College of Surgeons Commission on Cancer *Outstanding Achievement Award*
- *CMC Neuroscience and Spine Institute ranked top 10% nationally* by NeuroSource
- First North Carolina Hospital to receive *Chest Pain Center Accreditation*
- Blue Cross and Blue Shield of North Carolina *Cardiac Centers of Excellence*
- Member of the U.R.N. "Neonatal Centers of Excellence" Network
- UnitedHealth Premium *Cardiac Specialty Centers*
- National CareScience Quality *Top Performer for Total Knee and Hip Replacement Surgery*
- CareScience *Most Effective Strategic Approach to Improving Outcomes—Oncology Program*
- Top 40 *Family-Friendly Employers*
- *Most Wired*—recognized by InformationWeek and Hospitals & Health Networks
- Numerous designations for *Excellence in Transplantation*

For a complete list of CMC's awards and designations, please visit our Web site.

Carolinas Medical Center
www.carolinasmedicalcenter.org

# SOMETIMES LESS IS MORE.

**Especially when it comes to surgery. Robotic procedures mean less pain, less scarring, and less recovery time.**

Surgery doesn't always have to mean putting your whole life on hold. With the da Vinci® Surgical System, you should have less pain and fewer side effects following your procedure– which means that you can get home, and back to your family and your life, a whole lot faster.

The da Vinci is an advanced surgical tool that allows our skilled physicians to perform complex, delicate procedures with unmatched precision through very small incisions–a monumental difference from standard open surgeries. Cardiac surgeons at Pitt County Memorial Hospital in Greenville, in conjunction with the Brody School of Medicine at East Carolina University, are leaders in da Vinci surgery, responsible for this country's first robot-assisted mitral valve repair in 2000. Since then, the hospital and university have trained more than 1,000 surgeons from around the globe to use the da Vinci robot. Today, we are expanding our advanced robotics program to include general surgery, gynecology and urology, particularly for prostate cancer.

Surgery is always a major step. But with da Vinci, you could find yourself stepping more quickly back into your own life, and all the things that truly matter.

Is the da Vinci right for you? To learn more about this minimally invasive surgical option, visit www.roboticsurgery.uhseast.com.

PITT COUNTY MEMORIAL HOSPITAL
*University Health Systems of Eastern Carolina*℠

# Publishers of the *North Carolina Medical Journal*

### The North Carolina Institute of Medicine

In 1983 the North Carolina General Assembly chartered the North Carolina Institute of Medicine as an independent, nonprofit organization to serve as a nonpolitical source of analysis and advice on issues of relevance to the health of North Carolina's population. The Institute is a convenor of persons and organizations with health-relevant expertise, a provider of carefully conducted studies of complex and often controversial health and health care issues, and a source of advice regarding available options for problem solution. The principal mode of addressing such issues is through the convening of task forces consisting of some of the state's leading professionals, policy makers, and interest group representatives to undertake detailed analyses of the various dimensions of such issues and to identify a range of possible options for addressing them.

health policy
*North Carolina Institute of Medicine*

### The Duke Endowment

The Duke Endowment, headquartered in Charlotte, NC, is one of the nation's largest private foundations. Established in 1924 by industrialist James B. Duke, its mission is to serve the people of North Carolina and South Carolina by supporting programs of higher education, health care, children's welfare and spiritual life. The Endowment's health care grants provide assistance to not-for-profit hospitals and other related health care organizations in the Carolinas. Major focus areas include improving access to health care for all individuals, improving the quality and safety of the delivery of health care, and expanding preventative and early intervention programs. Since its inception, the Endowment has awarded $2.2 billion to organizations in North Carolina and South Carolina, including more than $750 million in the area of health care.

The Duke Endowment

North Carolina MEDICAL JOURNAL

*Founded by the North Carolina Medical Society in 1849*
*Published by The North Carolina Institute of Medicine and The Duke Endowment*
*(ISSN 0029-2559)*



The North Carolina Medical Journal (ISSN 0029-2559) is published by The North Carolina Institute of Medicine and The Duke Endowment under the direction of its Editorial Board.  Address manuscripts and communications regarding editorial matters, subscription rates, etc., to the Managing Editor at the address below. All advertisements are accepted subject to the approval of the Journal's Editorial Board. The appearance of an advertisement in this publication does not constitute any endorsement of the subject or claims of the advertisement. This publication is listed in *Index Medicus*.

**Managing Editor:** Kristen L. Dubay, MPP, 919/401-6599, ext. 25, kristen_dubay@nciom.org. **Business Manager:** Adrienne R. Parker, 919/401-6599, ext. 28, adrienne_parker@nciom.org. **Graphic Design:** Angie Dickinson, angiedesign@windstream.net. **Printing:** The Ovid Bell Press, Inc., 1201-05 Bluff St., Fulton, MO 65251, 800/835-8919. **Annual subscription (6 issues):** $40 (plus 7% NC tax = $42.80). Institutional subscriptions: $60 (plus tax = $64.20). Single copies: $5.00 (plus tax = $5.35). Periodicals postage paid at Durham NC 27713 and at additional mailing offices. Postmaster: send address changes to The North Carolina Medical Journal, 5501 Fortunes Ridge Drive, Suite E, Durham, NC 27713.

**Co-Sponsors of the Journal are: The Carolinas Center for Medical Excellence, formerly Medical Review of North Carolina / North Carolina Association of Pharmacists / North Carolina Dental Society / North Carolina Health Care Facilities Association / North Carolina Hospital Association North Carolina Medical Society**
Members of these organizations receive the Journal free of charge. Additional major funding support comes from **The Duke Endowment**.

Woodcroft Professional Center • 5501 Fortunes Ridge Drive, Suite E • Durham, NC 27713
phone: 919/401-6599 • fax: 919/401-6899 • e-mail: ncmedj@nciom.org
Internet address: http://www.ncmedicaljournal.com

# How strong is your insurance carrier?

You carry the weight of the world on your shoulders. At Medical Protective, we know just what that's like because more than 70,000 healthcare providers count on us every day. That's why we take such pride in the fact that:

- We are a Berkshire Hathaway company
- We hold an "A++" (Superior) A.M. Best rating and S&P rating of "AAA"
- We have the means and wherewithal to fight

Strength. Defense. Solutions. Since 1899, these are the virtues Medical Protective has stood for. They are what make Medical Protective the nation's premier medical malpractice insurer.

For more information on how Medical Protective can help protect you, call us at 800-4MEDPRO or visit us on the web at www.medpro.com.

MEDICAL PROTECTIVE
Strength. Defense. Solutions. Since 1899.

**Medical Protective is a member of the Berkshire Hathaway group of businesses.**
All insurance products are underwritten by The Medical Protective Company® unless otherwise indicated. The Medical Protective Company® is licensed in all states and the District of Columbia. Product availability varies based upon business and regulatory approval. Medical Protective can offer individual physicians and dentists the right to written consent before settling a claim. Contact Medical Protective and see if you are eligible to receive this important provision at your location. 

North Carolina
MEDICAL JOURNAL
*a journal of health policy analysis and debate*

**March/April 2007, Volume 68, Number 2** **Published by the North Carolina Institute of Medicine and The Duke Endowment**

## SCIENTIFIC ARTICLES



## POLICY FORUM

### *Laboratory Medicine and Clinical Pathology: Changing Paradigms of Practice*

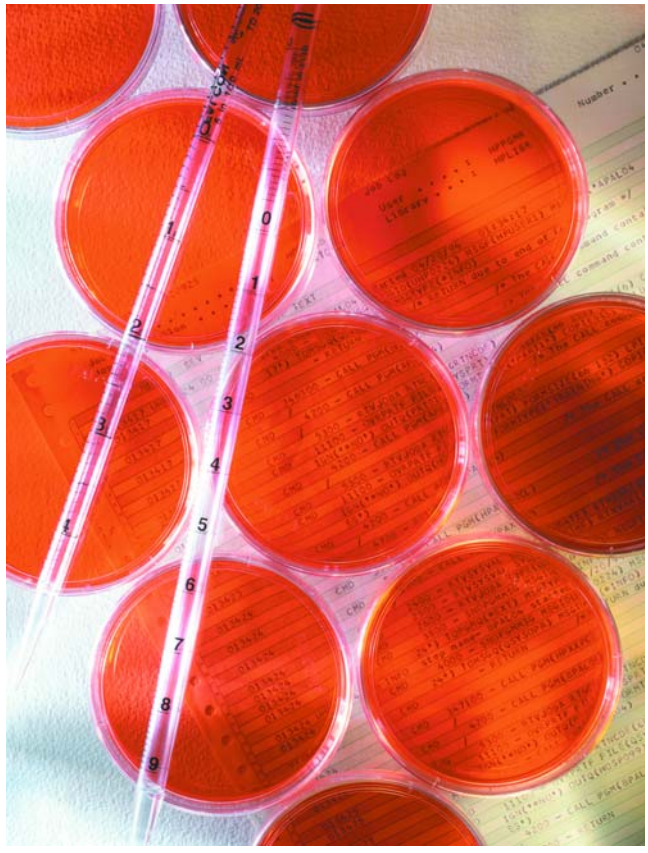


## COMMENTARIES



## DEPARTMENTS





# Tarheel Footprints in Health Care

*Recognizing unusual and often unsung contributions of individual citizens who have made health care for North Carolinians more accessible and of higher quality*

**H. Neil Kirkman, MD**
**Kenan Professor Emeritus of Pediatrics**
**The University of North Carolina at Chapel Hill**

*H. Neil Kirkman, MD*

The Newborn Screening Program of the North Carolina Division of Public Health is considered to be one of the most important public health programs today. The program screens newborns for genetic disorders and provides early diagnosis and timely treatment to those affected. As such, it mitigates the terrible outcomes of undiagnosed and untreated disorders, which may include mental retardation or even death. This screening program has both ethical and financial benefits for the state. Screening and the subsequent treatment of affected newborns is a better use of resources than the long-term care of undiagnosed and untreated children. Moreover, it reduces the emotional burden for families with affected children. Most of the states in the US started to offer this program in the 1960s and North Carolina was no exception. North Carolina started its program in 1965 with screening for a single disorder (phenylketonuria, or PKU) and has, since that time, expanded to screen for more than 30 disorders.

Dr. Kirkman came to North Carolina in 1965, only 6 months before the newborn screening for PKU began. Infants with PKU were initially treated at 2 or 3 university medical centers, but it became apparent that the management for such an uncommon disorder was most economically and effectively done at a single medical center, which became the PKU Center at the University of North Carolina at Chapel Hill (UNC Chapel Hill). Dr. Kirkman served as the Chief of the Division of Genetics and Metabolism at UNC Chapel Hill from 1965 until his retirement in 1991. During his tenure, he cared for nearly all the PKU babies in North Carolina. Along with his medical team, he talked with the parents by telephone the same day he received the word that the baby likely had PKU and made an appointment for the parents to bring the infant to the hospital immediately. He needed to confirm that all the infants who tested positive actually had PKU and that the special PKU diet would not be deadly to the child or be overly restrictive for quality of life reasons. At the hospital, he and his medical team also gave the parents a positive message about early diagnosis of PKU and provided them with an opportunity to ask questions. He continued to care for his PKU patients on a part-time basis even after his retirement. Dr. Kirkman fully retired from seeing patients in 2000. According to Dr. Dianne Frazier, Professor of Pediatrics and a longtime colleague of Dr. Kirkman, "He is loved by all his patients and their families. They still ask about him whenever they come to the clinic."

Dr. Kirkman is not only a clinician but also a laboratorian. He wrote the computer program for confirmatory test for galactosemia, which is still being used in the newborn screening laboratory. After his full retirement in 2000, he made several attempts to develop an automated galatose-1-phosphate uridyl transferase assay, traveling from Chapel Hill to Raleigh. He continues to write and publish scientific papers with his longtime research colleague Dr. Gian Gaetani. His latest project is to write the history of the North Carolina Newborn Screening Program.

Even after his retirement, Dr. Kirkman continues to serve as an active member of the NC Newborn Screening Advisory Committee and campaigns vigorously for the North Carolina Newborn Screening Program. Several years ago, he wrote to the state legislature against privatization when a for-profit commercial company tried to dismantle the state-managed Newborn Screening Program.

His tender care to his patients and his dedication to the North Carolina Newborn Screening Program have won the respect of his patients, their parents, and his colleagues. As Dr. Dianne Frazier summarizes, "He is a scholar and a gentleman, who always went about his work with deep regard for both patients and colleagues."

The Editors of the *NC Medical Journal* are pleased to recognize Dr. H. Neil Kirkman for his lifetime of work dedicated to quality patient care, development of a successful newborn screening program, and contributions to the field of laboratory science and clinical pathology.

## YOU DIDN'T GO THROUGH DECADES OF TRAINING AND 70-HOUR WEEKS TO TRUST YOUR FUTURE TO JUST ANY BANKER.

The SunTrust Medical Specialty Group has nearly two decades of experience addressing the unique and complex financial needs of physicians and their practices. We have the expertise to see you through anything from personal investments[1], to estate planning, to providing credit solutions as your practice grows. After all, you didn't go to medical school to be a banker. At SunTrust, your specialty is our specialty.


Dana Rawls
Client Advisor, Durham/Duke Univ.
SunTrust Investment Services
919-683-6872

Melissa Shoemaker
Client Advisor, Charlotte
SunTrust Investment Services
704-905-5090

Robin Miller
Client Advisor, Winston-Salem
SunTrust Investment Services
336-777-1404


SUNTRUST℠
Seeing beyond money

# Instructions for Authors

Unsolicited manuscripts containing original material are accepted for consideration if neither the article nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the Journal.

All unsolicited manuscripts submitted for peer-review must contain a brief structured abstract including the following (when relevant): Objective; Study Design; Data Source(s)/Study Setting; Data Collection Methods; Intervention; Principal Findings; Limitations; Conclusions; Relevance. Papers submitted without a structured abstract may be considered incomplete and returned to the author.

Submit a cover letter and the article (via e-mail attachment) containing the double-spaced text, preferably in Microsoft Word. The letter should indicate that the article is not under consideration for publication elsewhere and has not previously been published in any form.

For more information visit our web site: http://www.ncmedicaljournal.com/guideline.shtml

North Carolina Medical Journal
5501 Fortunes Ridge Drive, Suite E
Durham, NC 27713
919/401-6599 ext. 25
919/401-6899 fax
ncmedj@nciom.org

North Carolina MEDICAL JOURNAL

# Correlates of Intimate Partner Violence Among Female Patients at a North Carolina Emergency Department

*Melissa Roche, MA; Kathryn E. Moracco, PhD, MPH; Kimberly S. Dixon, MSW; Elizabeth A. Stern, MPH; J. Michael Bowling, PhD*

## Abstract

***Objective:*** *This paper identifies comorbid factors among female emergency department (ED) patients who have experienced intimate partner violence (IPV).*

***Methods:*** *321 adult female patients completed self-administered questionnaires while in an urban North Carolina emergency department. IPV was assessed by questioning whether the patient had ever been afraid of a partner, physically hurt or threatened by a partner, or forced to have sex by a partner.*

***Results:*** *One third of all female patients reported at least one form of IPV in their lifetimes. IPV was associated with a low self-rating of physical and mental health, frequent visits to the ED, and problems with alcohol, drugs, and mental health. In multivariate analysis, only a history of alcohol and mental health problems and a low self-rating of mental health remained significant.*

***Conclusions:*** *The findings illustrate the need for IPV screening protocols that address mental health and substance abuse and also emphasize the importance of screening all women for IPV.*

## Background

It is well established that physical, sexual, and psychological intimate partner violence (IPV) against women is both widespread and a serious threat to women's health. The National Violence Against Women Survey estimates that 25% of women are physically or sexually assaulted by intimate partners in their lifetimes.[1] Physical health consequences of IPV include fatal and nonfatal injuries, trauma-specific and generalized pain, unwanted pregnancies, sexually transmitted infections, and gynecological problems.[2,3,4,5] IPV is also associated with substance abuse and a variety of mental health problems including depression, anxiety, suicide, and post-traumatic stress disorder (PTSD).[6,7,8,9,10] Victimized women view themselves as being less healthy and report lower levels of physical and mental well-being than women who have not been victimized.[1,11,12]

The prevalence of IPV among emergency department (ED) patient populations varies widely depending on the definition of IPV, identification method, sample, and setting. Research indicates that 5% to 19% of all female ED patients have been physically or sexually abused in the previous year and 33% to 54% report a lifetime history of abuse.[13,14,15,16] Moreover, studies suggest that 2% to 7% of *all* female ED patients present with acute trauma due to abuse,[17,18,19] and 30% to 41% of the

* This study was supported by a grant to Dr. Moracco (number R49/CCR322636-01-1) from the National Center for Injury Prevention and Control.

**Melissa Roche, MA**, is a doctoral student in the Department of Health Behavior and Health Education at the University of North Carolina at Chapel Hill.

**Kathryn E. Moracco, PhD, MPH**, is a research scientist at the Pacific Institute for Research and Evaluation, an adjunct assistant professor at the Department of Health Behavior and Health Education and an adjunct associate professor at the Department of Maternal and Child Health at the University of North Carolina at Chapel Hill. She can be reached at moracco@pire.org or 1516 East Franklin Street, Suite 200, Chapel Hill, NC 27514.

**Kimberly S. Dixon, MSW**, is an administrative manager at Duke University.

**Elizabeth A. Stern, MPH**, is the domestic violence program coordinator at the Duke University Health System.

**J. Michael Bowling, PhD**, is a research associate professor at the Department of Health Behavior and Health Education at the University of North Carolina at Chapel Hill.

violence-related injuries to female ED patients are inflicted by intimate partners.[20,21] However, most battered women present in emergency departments with health problems other than injuries.[16,20]

The ED is an optimal setting for identifying and referring victims of IPV because clinicians come into contact with past, current, and future victims daily, yielding multiple opportunities to reduce morbidity and mortality caused by IPV. Accordingly, during the past two decades there has been a call for emergency departments to develop and implement IPV screening protocols for female patients. Since 1992, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has required that accredited emergency departments have IPV policies, procedures, and educational opportunities in place. Despite widespread efforts to train providers and institutionalize IPV protocols, research indicates that IPV screening rates in emergency departments remain low.[22,23] This is in part because health care providers feel they lack effective interventions to respond to the needs of women who disclose violence.[24]

The purpose of this paper is to identify comorbid factors among adult female ED patients who have experienced intimate partner violence. Given the high prevalence of IPV in this population, distinguishing characteristics and conditions that are associated with IPV may enable providers to respond more effectively to these patients by identifying their specific physical and mental health needs.

## Methods

Data for this study come from an evaluation of a hospital-based intervention designed to increase IPV detection and provide appropriate services to IPV survivors in the emergency department of a mid-sized community hospital located in an urban, ethnically diverse county in north central North Carolina. We consecutively approached all female patients age 18 and older who visited the ED to receive care for themselves during randomly selected six-hour shifts within two three-week periods pre and postintervention. Women were excluded from the study if they showed signs of cognitive impairment (including intoxication), were in police custody, did not speak English or Spanish, or were admitted to the hospital.

Participants completed a two-page self-administered questionnaire (available in English and Spanish) that included questions about their demographic characteristics, self-assessed physical and mental health status, history of IPV, and whether they were asked about IPV during their ED visit. Respondents indicated whether they were willing to be called for a 15 to 20 minute phone interview, and if so, they were asked to provide a safe date, time, and number for project staff to call.

In order to protect patients' safety and privacy, participants were offered one of two versions of the questionnaire. Women who were unaccompanied or could complete the form alone received a full version of the questionnaire, which contained questions about adult lifetime IPV experience and IPV screening in the ED. Women who could not complete the form in privacy received an abbreviated version that did not contain questions about IPV. Those women who completed the abbreviated questionnaire and indicated willingness to participate in a phone interview were called and asked the questions about IPV. All participants received $5 in cash for completing the survey.

The Institutional Review Boards of Durham Regional Hospital, Duke University Health System, and the Pacific Institute for Research and Evaluation (PIRE) all reviewed and approved this study.

### *Variable Definitions*

Lifetime experience with IPV was assessed via 3 items on the questionnaire that asked whether the respondent had ever been (1) afraid of a partner, (2) physically hurt or threatened by a partner, and (3) forced to have sex by a partner. For this study, we categorized women as having experienced IPV during their lifetime if they responded "yes" to any of the 3 questions.

Demographic variables included age, race, educational level, and marital status. Health-related variables included single questions about participants' self-assessment of their current physical and mental health ("Compared to women your age, would you say your physical / mental health is: excellent / very good / good / fair / poor?"), disability status ("Do you have a physical disability or health condition that limits your physical functioning?" yes / no), history of problems with mental health ("Have you ever had any mental health problems, like depression, bipolar disorder, or post-traumatic stress disorder?" yes / no), alcohol ("Have you ever had a problem with alcohol?" yes / no), and drugs ("Have you ever had a problem abusing prescription or nonprescription (recreational/illegal) drugs?" yes / no). We also asked participants a number of health care related items, including how many times they had been to the ED in the past 12 months, how most of their medical costs were covered (self pay, Medicare, Medicaid, private insurance, other), the reasons for their current visit (injury, illness, or other), and satisfaction with their current ED visit (very satisfied, somewhat satisfied, somewhat dissatisfied, very dissatisfied).

### *Data Analysis*

We used SPSS version 11.3 (SPSS Inc, Chicago, IL) for all analyses. After examining univariate frequencies, we used Fisher's exact tests for analysis of bivariate associations with whether or not women reported IPV. We then included factors that were significantly associated with experiencing IPV in a logistic regression model and calculated adjusted odds ratios (AOR) and 95% confidence intervals (CI). A p-value of .05 was considered significant for all analyses. We assessed for multi-collinearity among the independent variables in our model and did not find any cause for concern using the criteria of variance inflation factor (VIF) = 2.5.[25]

## Results

A total of 346 female patients completed the survey during a visit to the emergency department, representing 75% of eligible patients. Of those, 321 completed the full form that included questions about their personal experience with IPV and 25

completed the abbreviated form. Of the women who completed the full form, seven failed to provide information about their history of IPV. Of the 25 women who completed the abbreviated form, seven were successfully contacted by telephone and provided information about IPV. In total, 321 women (93%) provided information on their history of IPV and are thus included in the analysis. Of the sample included in this analysis, 124 women were interviewed preintervention and 197 were interviewed postintervention. Given that the intervention was designed to increase identification of IPV among female ED patients and that respondents were, in fact, more likely to have been asked about IPV by ED staff postintervention, there is a possibility that the women surveyed postintervention would be more likely to note a history of IPV on their self-administered survey. However, we found that the pre and postintervention groups did not differ significantly on any of the independent variables nor in their reporting of IPV.

Table 1 describes the characteristics of the study sample. The ages of women ranged from 18 to 74, with a mean age of 37. Two thirds of the patients were African American and more than half (56%) were not married. In addition to the current visit, most (81.2%) of the patients had made at least one other visit to an ED in the previous 12 months, with 63.9% of the sample reporting 2 or more other ED visits in the last year.

One third of women (33.3%) reported that they had experienced some form of IPV in their lifetimes. Table 2 presents the combinations of IPV reported by women who disclosed some form of IPV. As indicated in the table, most types of IPV did not occur in isolation.

Table 3 presents the results of the bivariate analyses of factors associated with reporting IPV. Factors consistently associated with all 3 forms of IPV are describing current mental health as fair or poor, a self-reported history of alcohol problems, a self-reported history of drug problems, and a self-reported history of mental health problems. Factors associated with reporting IPV, but not consistently associated with the individual forms of IPV, are Medicaid status, describing physical health as fair or poor, and two or more visits to the ED in the past year. None of the other factors analyzed were significantly associated with reporting IPV, including whether the woman was at the ED due to an injury or came accompanied by a partner.

We included the variables that were bivariately associated with IPV in a logistic regression analysis, with reporting any IPV as the outcome variable (Table 4). After controlling for age, education, race, and marital status, only a self-described history of mental health problems, history of alcohol problems, and reporting mental health as fair or poor remained significantly associated with experience of IPV. Marital status also independently predicted experience of IPV. Women who were separated or divorced were more than eight times more likely (AOR 8.47; 95% CI: 3.44-20.88) to report a history of IPV compared with single women.

**Table 1.**
**Respondent Characteristics (n=321)**

| | % |
|---|---|
| **RACE** | |
| African American | 66.4 |
| White | 25.5 |
| Latina/Hispanic | 2.8 |
| Native American | 2.5 |
| Other | 2.8 |
| | |
| **AGE GROUPS** | |
| 18 to 24 | 21.9 |
| 25 to 34 | 24.1 |
| 35 to 44 | 26.3 |
| 45 to 54 | 15.9 |
| 55 to 64 | 7.8 |
| 65 and over | 4.1 |
| | |
| **EDUCATION** | |
| Did not complete high school | 23.4 |
| Completed high school | 36.8 |
| Some college | 26.2 |
| Graduated college | 13.7 |
| | |
| **MARITAL STATUS** | |
| Single | 43.9 |
| Married | 29.3 |
| Separated | 9.0 |
| Divorced | 13.4 |
| Widowed | 4.4 |
| | |
| **HOW MEDICAL COSTS ARE PAID** | |
| Self pay | 27.1 |
| Medicare | 8.8 |
| Medicaid | 32.5 |
| Private/group insurance | 27.8 |
| Other | 3.7 |
| | |
| **EXPERIENCED IPV** | **33.3** |
| Hurt or threatened by a partner* | 24.4 |
| Forced to have sex* | 16.3 |
| Afraid of a partner* | 26.5 |
| * IPV categories are not mutually exclusive | |

## Discussion

Our finding that a third of female ED patients have experienced IPV in their lifetimes is consistent with the high prevalence of IPV among female patients found in other ED-based studies.[13,14,15,16] Also consistent with previous research are the findings that most women who have experienced IPV visit the ED for noninjury complaints, and that there are few discernable differences between victims and nonvictims.[13,14,15,16] The differences that remained significant, self-reported histories of alcohol and mental health problems and fair or poor self-assessed

**Table 2.**
**Patterns of IPV Among Respondents Reporting IPV (n=107)**

| Type of IPV | n | % |
|---|---|---|
| Physically hurt or threatened only | 14 | 13.1 |
| Afraid only | 12 | 11.2 |
| Forced sex only | 6 | 5.6 |
| Physically hurt or threatened and afraid | 29 | 27.1 |
| Afraid and forced sex | 11 | 10.3 |
| Physically hurt or threatened and forced sex | 2 | 1.9 |
| All three forms of IPV | 33 | 30.8 |

mental health status, indicate that ED patients who are IPV survivors may have unaddressed mental health and substance abuse needs.

The results of this study indicate that the ED is a good place to identify and assist IPV survivors, and that all women should be screened for IPV, regardless of their presentation. We recognize that there is an ongoing debate over the effectiveness of IPV screening in health care settings, including how to measure the long-term effectiveness of IPV screening.[26,27] While there certainly is an urgent need for rigorous research regarding the effectiveness of screening, universal IPV screening for female ED patients seems warranted given the high prevalence of IPV among female ED patients, support for screening by professional organizations as well as patients,[16,28,29,30] and the lack of evidence that screening is more harmful than not screening.

The fact that IPV survivors were more likely than women who had not experienced IPV to report having ever had alcohol and mental health problems, and that they were more likely to rate their current mental health status as fair or poor, suggests that women who have experienced IPV have potentially unaddressed mental health and substance abuse needs. Previous research has documented the strong association between IPV and mental health problems, particularly depression and post-traumatic stress disorder (PTSD).[6,7,8,9,10] Similarly, alcohol use or abuse has been associated with an increased risk of past or current IPV.[6,10,16,31] The etiology of mental illness and substance abuse among battered women is unclear, as the bulk of previous research cannot establish temporal sequence. Regarding the link between IPV and mental health problems, Frank and Rodowski (1999) note that mental health problems may be more common among female IPV victims "both because mentally ill women are more vulnerable to abuse and because verbal or physical abuse may precipitate or perpetuate psychiatric disorders."[32] Regardless of the exact nature of the relationship, previous research, along with this study's findings, suggest that a high proportion of IPV survivors presenting in the emergency department will have concurrent mental health needs. Referrals to services to address these needs should be part of IPV screening protocols in health care settings.

**Table 3.**
**Bivariate Analyses of Health Status and Emergency Department Visit with Intimate Partner Violence (IPV) Among Adult Female Emergency Department Patients (n=321)**

| | | Any IPV | | Physically hurt or threatened | | Forced to have sex | | Afraid of a partner | |
|---|---|---|---|---|---|---|---|---|---|
| | Total (n=321) | Yes (n=107) | No (n=214) | Yes (n=78) | No (n=242) | Yes (n=52) | No (n=268) | Yes (n=85) | No (n=236) |
| % with medical costs covered by Medicaid | 35.3 | 43.0* | 31.4* | 43.6 | 32.4 | 42.3 | 34.1 | 43.5 | 32.3 |
| % who report physical health as fair or poor | 21.9 | 29.9* | 17.8* | 24.4 | 21.2 | 32.7* | 19.9* | 27.1 | 20.0 |
| % who report mental health as fair or poor | 12.9 | 23.4** | 7.6** | 21.8** | 10.0** | 30.4** | 9.4** | 21.2** | 9.9** |
| % with 2 or more visits to the ED in past year | 63.9 | 71.8* | 60.0* | 72.4** | 61.4** | 80.0** | 60.7** | 72.3 | 60.9 |
| % with history of alcohol problem | 8.4 | 17.8** | 3.7** | 20.5** | 4.5** | 26.9** | 4.9** | 21.2** | 3.8** |
| % with history of drug problem | 4.7 | 11.3** | 1.4** | 13.0** | 2.1** | 17.6** | 2.2** | 13.1** | 1.7** |
| % with history of mental health problem | 30.8 | 55.7** | 18.4** | 61.0** | 21.3** | 59.6** | 25.3** | 53.6** | 22.6** |
| % who came to ED for an injury | 32.4 | 31.8 | 32.7 | 29.5 | 33.1 | 26.9 | 33.2 | 36.5 | 30.9 |
| % who were accompanied by a partner to the ED | 28.1 | 26.2 | 29.1 | 25.6 | 29.0 | 23.1 | 29.2 | 20.0 | 31.1 |

* $P < .05$
** $P < .01$

**Table 4.**
**Logistic Regression Model of Characteristics of Health Status and Emergency Department Visit History that Predict Intimate Partner Violence (IPV) Among Female Patients, Controlling for Age, Education, Race, and Marital Status (n=301)**

| Referent | Adjusted OR | 95% CI |
|---|---|---|
| History of alcohol problem | 4.09 | (1.27, 13.18) |
| History of mental health problem | 2.77 | (1.44, 5.34) |
| Reports mental health as fair or poor | 2.72 | (1.04, 7.16) |
| History of drug problem | 3.94 | (.75, 20.6) |
| Medical costs covered by Medicaid | 1.77 | (.94, 3.34) |
| 2 or more visits to the ED in past year | 1.61 | (.84, 3.06) |
| Reports physical health as fair or poor | 1.35 | (.62, 2.92) |
| Marital status Ref group: Single | | |
| Married | 1.75 | (.79, 3.87) |
| Divorced / separated | 8.47 | (3.44, 20.88) |

C statistic = .788 (95% CI .733 - .843, p < .001)

The results of our study should be viewed within the context of its limitations. First, because the study was conducted in a single urban emergency department, it is not generalizable to all women in the state nor to all female ED patients. The study also only included women who were discharged from the ED. These women may be significantly different from women who were subsequently admitted to the hospital in terms of the severity of their illness or injury. In addition, given that the ED intervention was designed to increase identification of IPV among female ED patients and that respondents were, in fact, more likely to have been asked about IPV by ED staff postintervention, there is a possibility that postintervention respondents would be more likely to note a history of IPV on their self-administered survey. However, we found that the pre and postintervention groups did not differ significantly in the proportions reporting of IPV.

We also asked women about their lifetime experience with IPV without collecting any information about the characteristics (eg, recency, severity, frequency, duration) of those experiences. It is possible that some participants experienced only isolated incidents of IPV in the distant past. However, previous research has demonstrated that IPV has profound and long-lasting effects on women's physical and mental health,[2,3,4] and past victimization is a risk factor for current and future IPV.[33] An additional limitation to the study is potential misclassification bias that could have occurred because respondents provided self assessments for several of the key independent variables, notably their histories of substances abuse and mental health problems. All respondents may not have understood and interpreted these questions in the same way.

Finally, the cross-sectional nature of this research makes it impossible to establish temporality, and the study is subject to both recall and reporting bias.

Despite these limitations, our study provides further evidence that the emergency department is an important setting in which to identify and assist women who have experienced IPV. It also reinforces the need to screen all adult female ED patients regardless of their presenting complaint. Providers should also be cognizant of the potential concurrent mental health needs of women who have experienced or are experiencing IPV and ensure that they are equipped to provide appropriate referrals to mental health providers, substance abuse services, and intimate partner violence agencies. **NCMJ**

*Acknowledgements: The authors are grateful for the cooperation and support of the emergency department staff and patients who participated in this project and for the guidance we received from the Domestic Violence/Sexual Assault Hospital Response Committee.*

## REFERENCES


1 Tjaden P, Thoennes N. Extent, nature, and consequences of intimate partner violence. Publication NCJ 181867. Washington, DC: National Institute of Justice; 2000.

2 Coker AL, Smith PH, Bethea L, King MR, McKeown RE. Physical health consequences of physical and psychological intimate partner violence. *Arch Fam Med*. 2000;9(5):451-457.

3 Campbell J, Jones AS, Dienemann J, et al. Intimate partner violence and physical health consequences. *Arch Intern Med*. 2002;162(10):1157-1163.

4 Campbell JC, Woods AB, Chouaf KL, Parker B. Reproductive health consequences of intimate partner violence. A nursing research review. *Clin Nurs Res*. 2000;9(3):217-237.

5 Campbell JC, Lewandowski LA. Mental and physical health effects of intimate partner violence on women and children. *Psychiatr Clin North Am*. 1997;20(2):353-374.

6 Kilpatrick DG, Acierno R, Resnick HS, Saunders BE, Best CL. A 2-year longitudinal analysis of the relationships between violent assault and substance use in women. *J Consult Clin Psychol*. 1997;65(5):834-847.

7 Jones L, Hughes M, Unterstaller U. Post-traumatic stress disorder (PTSD) in victims of domestic violence: a review of the research. *Trauma, Violence, and Abuse*. 2001;2(2):99-119.

8 Golding J. Intimate Partner Violence as a risk factor for mental disorders: a meta-analysis. *Journal of Family Violence*. 1999;14(2):99-132.

9 Stein MB, Kennedy C. Major depressive and post-traumatic stress disorder comorbidity in female victims of intimate partner violence. *J Affect Disord*. 2001;66(2-3):133-138.

10 Lipsky S, Caetano R, Field CA, Bazargan S. The role of alcohol use and depression in intimate partner violence among Black

and Hispanic patients in an urban emergency department. *Amer J of Drug Alc Abuse*. 2005; 31: 225-242.
11 Kilpatrick DG, Resnick HS, Acierno R. Health impact of interpersonal violence. 3: Implications for clinical practice and public policy. *Behav Med*. 1997;23(2):79-85.
12 Brokaw J, Fullerton-Gleason L, Olson L, Crandall C, McLaughlin S, Sklar D. Health status and intimate partner violence: a cross-sectional study. *Ann Emerg Med*. 2002;39(1):31-8.
13 Dearwater SR, Coben JH, Campbell JC, et al. Prevalence of intimate partner abuse in women treated at community hospital emergency departments. *JAMA*. 1998;280(5):433-438.
14 McCloskey LA, Lichter E, Ganz ML, et al. Intimate partner violence and patient screening across medical specialties. *Acad Emerg Med*. 2005;12(8):712-722.
15 Ernst AA, Weiss SJ, Nick TG, Casalletto J, Garza A. Domestic violence in a university emergency department. *South Med J*. 2000;93(2):176-181.
16 Weinsheimer RL, Schermer CR, Malcoe LH, Balduf LM, Bloomfield LA. Severe Intimate Partner Violence and Alcohol Abuse Among Female Trauma Patients. *Journal of Trauma, Injury, Infection, and Critical Care*. 2005;58(1):22-29.
17 National Center for Injury Prevention and Control. Costs of Intimate Partner Violence Against Women in the United States. Atlanta, GA: Centers for Disease Control and Prevention, 2003. Available at: http://www.cdc.gov/ncipc/pub-res/ipv_cost/index.htm. Accessed March 20, 2007.
18 Coker AL, Derrick C, Lumpkin JL, Aldrich TE, Oldendick R. Help-seeking for intimate partner violence and forced sex in South Carolina. *Am J Prev Med*. 2000;19(4):316-320.
19 McFarlane J, Soeken K, Reel S, Parker B, Silva C. Resource use by abused women following an intervention program: associated severity of abuse and reports of abuse ending. *Public Health Nurs*. 1997;14(4):244-250.
20 Resnick H, Acierno R, Holmes M, Dammeyer M, Kilpatrick D. Emergency evaluation and intervention with female victims of rape and other violence. *J Clin Psychol*. 2000;56(10):1317-1333.
21 McLeer SV, Anwar R. A study of battered women presenting in an emergency department. *Am J Public Health*. 1989;79(1):65-66.
22 Larkin GL, Hyman KB, Mathias SR, D'Amico F, MacLeod BA. Universal screening for intimate partner violence in the emergency department: importance of patient and provider factors. *Ann Emerg Med*. 1999;33(6):669-675.
23 Cohn F, Salmon ME, Stobo JD, eds. Confronting Chronic Neglect: The Education and Training of Health Professionals on Family Violence. Washington, DC: National Academy Press; 2002.
24 Waalen J, Goodwin MM, Spitz AM, Petersen R, Saltzman LE. Screening for intimate partner violence by health care providers. Barriers and interventions. *Am J Prev Med*. 2000;19(4):230-237.
25 Allison PD. Logistic Regression Using the SAS System: Theory and Application. Cary, NC: SAS Institute; 1999.
26 Wathen CN, MacMillan HL. Interventions for violence against women: scientific review. *JAMA*. 2003;289(5):589-600.
27 Ramsay J, Richardson J, Carter YH, Davidson LL, Feder G. Should health professionals screen women for domestic violence? Systematic review. *BMJ*. 2002;325(7359):314.
28 Bacchus L, Mezey G, Bewely S. Women's perceptions and experiences of routine enquiry for domestic violence in a maternity service. *BJOG*. 2002;109(1):9-16.
29 Chang JC, Decker M, Moracco KE, Martin SL, Petersen R, Frasier PY. What happens when health care providers ask about intimate partner violence? A description of consequences from the perspectives of female survivors. *J Am Med Womens Assoc*. 2003;58(2):76-81.
30 Gielen AC, O'Campo PJ, Campbell JC, et al. Women's opinions about domestic violence screening and mandatory reporting. Am *J Prev Med*. 2000;19(4):279-285.
31 Wyshak G, Modest GA. Violence, mental health, and substance abuse in patients who are seen in primary care settings. *Arch Fam Med*. 1996;5(8):441-447.
32 Frank JB, Rodowski MF. Review of psychological issues in victims of domestic violence seen in emergency setting. Emergency Medicine Clinics of North America. 1999;17(3):657-677.
32 Acierno R, Resnick HS, Kilpatrick DG. Health impact of interpersonal violence. 1: Prevalence rates, case identification, and risk factors for sexual assault, physical assault, and domestic violence in men and women. *Behav Med*. 1997;23(2):53-64.

# Call for Papers

John W. Williams, Jr., MD, MHS
Scientific Editor, *North Carolina Medical Journal*

North Carolina is blessed with some of the finest medical research institutions in the world. The work of the medical scientists that labor in our research facilities becomes complete (in many ways) and public when it is published in peer-reviewed journals.

While medical researchers in North Carolina have many journals to which they can submit their manuscripts, we want them to consider keeping their work here at home. To be more specific, we invite the authors of our state to submit their papers to the *North Carolina Medical Journal*.

The Journal seeks papers that convey the results of original research. We are especially interested in publishing research papers that have relevance to the health of the people of our state.

An editor reviews all papers received and those of sufficient quality are peer-reviewed. As with any journal of merit, only papers of high quality will be published. Papers printed in the Journal are indexed in the National Library of Medicine's MEDLINE public database.

We generally accept two types of manuscripts for review: (1) original clinical or health services research contributions and (2) systematic reviews (both regardless of specific topic).

The *North Carolina Medical Journal* is published six times a year. It is distributed free of charge to the members of the North Carolina Medical Society, the North Carolina Hospital Association, the North Carolina College of Internal Medicine, the North Carolina Board of Pharmacy, the North Carolina Association of Pharmacists, the North Carolina Division of Public Health, the North Carolina Dental Society, the North Carolina Health Care Facilities Association, and The Carolinas Center for Medical Excellence. The Journal is available by subscription to others.

For guidance on manuscript preparation, authors should consult the "Author Guidelines," which can be found at www.ncmedicaljournal.com.

# Providing Medical Care in State Psychiatric Hospitals

*Susan Saik, MD; Brian B. Sheitman, MD; Scott Mann, MD; Walter W. Stelle, PhD; James W. Osberg III, PhD*

## Abstract

***Background:*** *Dorothea Dix State Psychiatric Hospital (DDH) was cited by regulatory agencies in 1999-2001 for serious deficiencies in providing medical care to psychiatric patients. This resulted in a change in the discipline responsible for providing medical care. We report here how clinical staff and regulatory agencies evaluated the change. In addition, we sought to determine how medical care is currently provided at other state hospitals across the nation.*

***Methods:*** *A transition occurred whereby the responsibility for medical care (direct care and supervision of physician extenders) was changed from psychiatrists to internists. We surveyed psychiatrists and nurses about their impressions of the change and calculated the number of citations from regulators pre-and post-changeover. In addition, a survey was sent to all 212 state psychiatric hospitals.*

***Results:*** *Response rates were: 100% for DDH psychiatrists, 42% for DDH nurses, and 67% for state hospitals. At DDH, clinicians favorably viewed the changeover with 23 (96%) of the 24 psychiatrists reporting a preference for internists having overall responsibility for medical care. There was also a marked reduction in deficiencies cited by regulatory agencies, with 10 prior to the change and only one after the change. Responses to the State Psychiatric Hospital survey revealed that psychiatrists currently provide or are responsible for at least some portion of the medical care at 69% of all facilities.*

***Limitations:*** *DDH staff evaluated a change from a system that had not been in place for 3 years. Quality of care measures were not available. How these data generalize to other state hospitals is unknown.*

***Conclusions:*** *Having internists responsible for medical care was well received by staff and regulatory agencies. Currently, state psychiatric facilities use different approaches to provide medical care. Further research is needed on how quality of care, and ultimately patient safety, may be impacted by these different service delivery models.*

***Key words:*** *Inpatient psychiatry, state hospitals, medical comorbidity*

## Introduction

Patients with psychiatric and/or substance abuse disorders have an increased prevalence of comorbid medical disorders compared to the general population.[1-4] A recent report on the physical health of the 1500 schizophrenia patients enrolled in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that over 40% had signs and symptoms consistent with the metabolic syndrome.[5] This syndrome is characterized by insulin resistance and associated with an increased risk of diabetes and cardiovascular disease. In addition, among patients hospitalized for either a medical or surgical condition, those patients with schizophrenia, when compared to those without the condition, had significantly more complications, with their average length of stay 10 days longer.[6] The reason for the increased prevalence of medical problems is less clear and likely multifactorial.[7-10] A reduced commitment/ability to maintain overall good health, side effects of prescribed psychotropic medications, an increased neuro-developmental vulnerability, increased use of tobacco products, and some combination of all

**Susan Saik, MD**, is chief of medical services and assistant clinical director at Dorothea Dix State Psychiatric Hospital in Raleigh, NC and clinical associate professor in the Department of Medicine at the University of North Carolina at Chapel Hill. Dr. Saik can be reached at Susan.Saik@ncmail.net or Dorothea Dix Hospital, 820 South Boylan Avenue, Raleigh, NC 27603.

**Brian B. Sheitman, MD**, is chief of adult psychiatry and associate director of clinical research at Dorothea Dix State Psychiatric Hospital and clinical professor in the Department of Psychiatry at the University of North Carolina at Chapel Hill.

**Scott Mann, MD**, is an attending internist at Dorothea Dix State Psychiatric Hospital and clinical assistant professor in the Department of Medicine at the University of North Carolina at Chapel Hill.

**Walter W. Stelle, PhD,** is currently retired and was the prior hospital director at Dorothea Dix State Psychiatric Hospital.

**James W. Osberg III, PhD,** is hospital director at Dorothea Dix State Psychiatric Hospital.

the above have been suggested. Recent recommendations acknowledging the increased medical comorbidity among schizophrenia patients now call for mental health providers to offer physical health monitoring in primary care settings for those patients who do not routinely receive ongoing physical health monitoring.[11]

How to best provide medical care for psychiatric inpatients in state facilities or freestanding psychiatric hospitals (not affiliated with a general medical hospital) has received limited systematic investigation. Given Dorothea Dix Hospital's (DDH) history of regulatory problems directly related to the proper medical care of patients on the psychiatric units, a decision was made in 2001 to change the professional medical discipline responsible for providing and supervising all medical care from psychiatrists to internists. The purpose of this report is to describe the impressions of clinical staff (psychiatrists and nurses) and outside regulatory agencies on how they evaluated the changeover to the current system. In addition, we conducted a survey of all state psychiatric hospitals in the United States, whereby we requested information on which medical disciplines are responsible for providing medical (nonpsychiatric) care to the patients on the psychiatric units.

## Methods

Part I. This study was conducted at DDH in Raleigh, North Carolina. The hospital maintains both Joint Commission on Accreditation of Hospital Organizations (JCAHO) and Centers for Medicare and Medicaid Services (CMS) certification. The hospital is the primary off-site training location for the University of North Carolina at Chapel Hill (UNC-Chapel Hill) Department of Psychiatry. Psychiatric residents and medical students rotate through the adult and adolescent admission wards. In addition, all psychiatric residents spend two months of their medicine rotation on the DDH medical unit. All of the teaching attending physicians have faculty appointments at either the UNC-Chapel Hill Departments of Psychiatry or Medicine.

DDH serves adolescent, adult, and geriatric patients. The hospital also has both a Pre-trial Evaluation Unit and a 90-bed Forensic Treatment Program. There is a separate medical unit that provides a scope of service capable of handling most acute medical problems (ie, with capabilities similar to a general hospital non-Intensive Care Unit bed). There are approximately 4500 admissions per year to the hospital and an average daily census of about 320. The hospital serves both acute patients and those requiring extended stays. The primary diagnoses among the acute admissions patients are substance abuse disorders (60%) and the major mental illnesses (40%), consisting of schizophrenia, schizoaffective disorder, and bipolar disorder. The longer stay patients are primarily diagnosed with a major mental illness.

A transition in the provision of direct medical care began toward the end of 2001. Internists were made responsible for these functions rather than psychiatrists who had previously been providing direct medical care and were also supervising the physician extenders. The change was fully implemented by the end of the year 2002.

Management believed the changeover was remarkably successful and that almost everyone was pleased with the new system. However, data was not systematically collected to verify this opinion. Therefore, in the winter of 2005, a survey was conducted of all psychiatric and nursing staff. The survey was conducted anonymously for nursing staff, but not for the psychiatrists. Conducting the survey anonymously for psychiatrists, as well, was considered but decided against due to the difficulty of achieving true anonymity given the relatively small number of psychiatrists employed (n=24).

The investigators developed the survey and designed it to be brief. The psychiatrist survey consisted of 6 questions, with 5 of the 6 questions requesting a selection of the best response out of 3 or 4 choices (ie, yes, no, not sure). The other question, "What do you like or not like about the way medical care is provided to psychiatric patients at DDH," instructs the psychiatrist to select as many of the listed responses that are applicable. There is also a space left to write in responses. The authors did not formally assess the validity of the instrument before using it. The surveys were sent directly to all psychiatrists, and their supervisor was responsible for following up to see that it was completed. Completed surveys were sent to the clinical director's office. The nursing survey consisted of 3 questions. Similar to the psychiatrists' survey, the nurses' survey included a question asking what they liked or disliked about how medical care is provided at DDH. The nursing surveys were distributed from the director of nursing to nursing supervisors, who then distributed the surveys to the individual nurses. Nursing staff were instructed to send the surveys back to the director of nursing's office. Surveys were sent one time only, though supervisors were asked to remind nurses to respond. No incentives were offered to those who responded. At the time of the survey, there were 24 staff psychiatrists at the hospital, of which 21 were diplomates of the American Board of Psychiatry and Neurology Board (ie, board certified) with the remaining 3 board eligible. Sixteen psychiatrists had worked at either DDH or another state hospital where psychiatrists were directly responsible for providing medical care. There were 155 nurses employed at the time of the survey.

Part II. The Centers for Medicare & Medicaid Services (CMS, formerly known as the Health Care Financing Administration or HCFA) facility and compliance survey records were reviewed for two 3-year periods: 1999-2001 and 2003-2005. All regulator-cited deficiencies specifically related to the medical care of patients for each period were recorded. To be counted as a deficiency, there needed to be a specific reference in the CMS record to care that did not meet either the element, standard, or condition of care as required by CMS. If the same deficiency was cited in more than one place (ie, cited as deficient on multiple elements, standards, or conditions) it was only counted one time.

Part III. Due to the impression of how successful the changeover had been at DDH and to the anecdotal stories of the many different ways medical care was provided in other state hospitals, we sought to systematically collect data on this issue. Therefore, a list of all state psychiatric hospitals (n=212),

including chief executive officers (CEOs) and addresses, was obtained from the National Association of State Hospital Program Directors (NASHPD) website in 2006. A brief survey was developed by the investigators consisting of 5 questions with instructions to choose the best answer from a list provided or to write in a response if the response choices did not fit their institution. The survey was then sent to each hospital's CEO with instructions to please forward the survey to the person at the institution who could best answer questions about which disciplines were providing medical care on the psychiatric units. Questions addressed both normal business hours and off–hours coverage since many institutions use "moonlighting" providers (ie, licensed physicians either within or outside of their specialty who typically work nights or weekends, in addition to their regular jobs, to earn additional compensation). The survey was sent one time only and no incentives were provided.

Given the types of data collected, only descriptive statistics were used for all data analyses.

## Results

*Survey of psychiatrists and nurses at Dorothea Dix Hospital*

### *Psychiatrists*

All 24 psychiatrists responded to the survey. All except one (96%) preferred having internists provide and be responsible for the medical care of patients. One (4%) psychiatrist wasn't sure. The most common reasons sighted for this preference were:

a. Reduces my concern about missing a serious medical problem .....100%
b. Gives me more time to focus on psychiatric issues .....96%
c Reduces my potential medical legal risk .....83%

Psychiatrists described their working relationship with the internists and the physician extenders as follows: excellent 92% (n=22), good 8% (n=2), fair and poor 0%.

### *Nurses*

Of the 155 nurses who were sent surveys, 65 (42%) responded. All except four (94%) stated that they preferred the current approach. Forty-seven nurses had worked at DDH for more than 4 years and had experience with both service delivery systems. The most common reasons sighted for their preference were:

a. I feel more comfortable having a medical provider address medical issues.....88%
b. I prefer to contact the person who will specifically address the problem, rather than often being asked to make more than one call.....71%

### *Deficiencies Cited by CMS*

During the period 1999-2001, there were 10 citations identified by regulators that were directly related to the medical care of patients. Thus, the hospital was found to be out of compliance with the "Conditions of Participation" and needed immediate plans for correction to avoid losing federal funding. During the period 2003-2005, there was one citation related to medical care. This was corrected by the time regulators visited, so there were no requirements for additional follow-up.

### *Survey of State Hospitals*

Responses were received from 145 (67%) of the state hospitals and included the following:

1. Medical (nonpsychiatric) care during business hours was provided as follows:
   Psychiatrists 65/143 (45%), physician extenders 58/143 (41%), physicians other than psychiatrists 137/143 (96%). Note: Many hospitals reported that multiple disciplines provided coverage; therefore, the numerator does not add up to 143.
2. If physician extenders were used, who was responsible for their supervision?
   Physician extenders were used in 70/143 facilities (12 facilities reported using physician extenders as moonlighters). They were supervised by psychiatrists in 35/70 (50%) of facilities and internists in 66/70 (94%) of facilities.
3. Off-hours coverage was provided by moonlighting physicians in 68/143 (48%) of the facilities.
   Psychiatrists provided this coverage in 42/68 (62%) facilities, nonpsychiatric physicians in 52/68 (76%), and physician extenders in 13/68 (19%).
4. Nonpsychiatric physicians solely provided medical care in 44/143 (31%) facilities, while psychiatrists were responsible for medical care by either directly caring for patients during regular business hours, supervising physician extenders, or providing moonlighting coverage in 99/143 (69% ) of the facilities.

## Discussion

These data suggest that the transition from psychiatrists to internists went very well at DDH. Both psychiatrists and nurses overwhelmingly endorsed the current system with most having experience working in the previous model. Psychiatrists unanimously endorsed that the change reduced their concern about missing a serious medical problem. In addition, despite some concerns that there would be an emergence of "turf" battles between psychiatrists and nonpsychiatric physicians, relationships between the two disciplines were described as excellent by 22/24 psychiatrists and good by the other two psychiatrists. Nurses also overwhelmingly reported that they preferred having a medical provider address medical issues and preferred directly contacting the person who would address the problem. Moreover, there was a marked reduction in the number of regulator-cited deficiencies in the medical care provided to patients.

The data received from the survey of all the facilities would suggest that there is currently no consensus on which disciplines should be providing medical care to patients in state facilities. Though psychiatrists do not provide medical care at our facility,

this remains the case at 69% of the facilities. Psychiatrists provide direct medical care during business hours in 45% of hospitals, are responsible for supervision of physician extenders in 50% of facilities that use them, and are responsible for medical care while moonlighting at 62% of hospitals where moonlighting occurs.

We were in favor of the change from psychiatrists to internists because we felt that staying current with the latest psychiatric advances is a full-time job, and it is unrealistic to expect psychiatrists, no matter how competent, to keep up with the internal medicine literature as well. Interestingly, the Psychiatry Board recertification exam contains no questions directly related to internal medicine. Anecdotal accounts suggest that having "split" treatment (ie, mental health care treatment by a psychiatrist and nonmental health care by a nonpsychiatrist) seems to be the way most outpatient psychiatrists operate their practice. Furthermore, the larger issue of how to best provide medical care to a patient hospitalized for a different indication is not only relevant to psychiatric inpatients. A recent publication described a project whereby a hospitalist-orthopedic team worked together in a collaborative model with orthopedic surgery patients, as opposed to the traditional consultant model used in academic medical centers.[12] They reported a reduction in minor postoperative complication rates, with no statistically significant differences in length of stay or cost. Both the nurses and surgeons strongly preferred the comanagement hospitalist model.

This report has its limitations. The survey data are comparing two different time periods and are limited to "satisfaction" with the change, not differences in specific quality of care measures. In addition, psychiatrists were not surveyed anonymously, which could have biased their opinions, and only 42% of the nurses responded. DDH also has a medical unit with a scope of service beyond what some other state hospitals may have, and it also has a strong affiliation with an academic medical center located relatively close to it. Nevertheless, we believe this is a very important topic for the medical field. Currently, state psychiatric facilities use different approaches to provide medical care for patients. These data suggest that further research is needed on how quality of care and, ultimately, patient safety may be impacted by these different service delivery models in order to eventually make best practice recommendations. **NCMJ**

## REFERENCES


1 Koran LM, Sox HC, Marton KI, et al. Medical evaluation of psychiatric patients. I. Results in a state mental health system. *Arch Gen Psychiatry*. 1989;46(8):733-740. [PMID: 2787623]

2 Felker B, Yazel JJ, Short D. Mortality and medical co-morbidity among psychiatric patients: a review. *Psychiatr Serv*. 1996;47:1356-1363. [PMID: 9117475]

3 Dixon L, Postrado L, Delahanty J, Fischer PJ, Lehman A. The association of medical comorbidity in schizophrenia with poor physical and mental health. *J Nerv Ment Dis*. 1999;187:496-502. [PMID: 10463067]

4 Dickey B, Normand SLT, Weiss RD, Drake RE, Azeni H. Medical morbidity, mental illness, and substance use disorders. *Psychiatr Serv*. 2002;53:861-867. [PMID: 12096170]

5 McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res*. 2005;80(1):19-32. [PMID: 16137860]

6 Daumit GL, Pronovost PJ, Anthony CB, et al. Adverse events during medical and surgical hospitalizations for persons with schizophrenia. *Arch Gen Psych*. 2006;63(3):267-272. [PMID: 16520431]

7 Goff DC, Cather C, Evins AF, et al. Medical morbidity and mortality in schizophrenia: guidelines for psychiatrists. *J Clin Psychiatry*. 2005;66(2):183-194. [PMID: 15705003]

8 Nasrallah HA. An overview of common medical comorbidities in patients with schizophrenia. *J Clin Psychiatry*. 2005;66 Suppl 6:3-4. [PMID: 16107177]

9 Koran LM, Sheline Y, Imai K, Kelsey TG, Freedland KE, Mathews J, Moore M. Medical disorders among patients admitted to a public-sector psychiatric inpatient unit. *Psychiatr Serv*. 2002;53:1623-1625. [PMID: 12461226]

10 Fenton WS, Chavez MR. Medication induced weight gain and dyslipidemia in patients with schizophrenia. *Am J Psychiatry*. 2006;163(10):1697-1704. [PMID: 170012676]

11 Marder M, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry*. 2004;161(8):1334-1349. [PMID: 15285957]

12 Huddleston JM, Long KH, Naessens JM, et al. The Hospitalist-Orthopedic Team Trial Investigators. Medical and surgical comanagment after elective hip and knee arthroplasty. *Ann Intern Med*. 2004;141(1):28-38. [PMID: 15238368]

# POLICY FORUM

## *Laboratory Medicine and Clinical Pathology: Changing Paradigms of Practice*



***"The volume and precision of information we can gather has brought us to the threshold of a new paradigm in health care where we are changing from a system in which diagnosis and treatment prevail to one in which prognosis is joined with treatment to anticipate the effects of interventions, even to anticipate the incidence and existence of disease."***

# INTRODUCTION

## Policy Forum:
## *Current Topics in Laboratory Medicine and Clincal Pathology*

Modern day medicine has become a very complex process that depends more and more on specific information about individuals. We are familiar with "tests" that assess the nature and content of our fluids, tissues, and physiological functions and recognize that these tests provide necessary information to ensure the best possible care. What we may not understand is how precise, sensitive, and complex those tests have become and how much the practice of health care has come to depend on these assays and evaluations. In fact, the volume and precision of information we can gather has brought us to the threshold of a new paradigm in health care where we are changing from a system in which diagnosis and treatment prevail to one in which prognosis is joined with treatment to anticipate the effects of interventions, even to anticipate the incidence and existence of disease.

One area of testing that has received perhaps more attention than others is genetic testing for susceptibility to disease. This line of work has evolved such that we are able to assess the overall disease susceptibility of the human genome for groups of people and for individuals in some cases. That work is controversial and raises ethical concerns for the bedside clinician, the laboratorian, and the policy makers who shape payment and information sharing rules. This issue of the *North Carolina Medical Journal* includes discussions of these consequences as well as the promise of the new technologies.

The location of testing has broadened from the hospital, clinic, or laboratory to the home or workplace. Diabetes monitoring and pregnancy testing are the most familiar in-home tests, but there are emerging tests for drug monitoring and other disease self-management. We are seeing intensive testing and screening efforts making use of health fairs, there are a range of tests available in "minute clinics" in pharmacies, health clubs and fitness centers are offering a range of tests, and shopping malls have become the location for testing centers or volunteer efforts that include taking samples. These new opportunities for testing may be seen as a "disruptive technology" that threatens the organization of medical care or as a chance to intervene more effectively in population health.

This issue of the *Journal* ventures into some quite technical areas such as nucleic acid amplification, karytotyping, mass spectromtetry in proteomics, polymerase chain reaction, and flow cytometry. These may seem to be very complex and specialized parts of the world of pathology and laboratory medicine, but they are becoming more and more the workhorse components of day-to-day health care. These techniques and approaches will likely be so ubiquitous that the material covered in this issue of the *Journal* may become part of the standard vocabulary and knowledge base for all caregivers as well as patients in the not-to-distant future

The goal of this issue of the *Journal* is to help the lay person as well as the broadest array of caregivers begin to understand how rapidly this field is developing and how it has the potential to bring even more change to clinical care and prevention of disease as we seek to give people healthier and happier lives.

*Thomas C. Ricketts III, PhD, MPH*
*Editor-in-Chief*

*Kristen L. Dubay, MPP*
*Managing Editor*

# Polishing the Crystal Ball:
## Emerging Trends in Contemporary Clinical Laboratory Medicine

*Dana D. Copeland, MD, PhD*

For clinical laboratory medicine in the 21st century nothing is so important as strong prediction. Strong in the sense of robust and specific detail of the predicted events and strong in the sense of high likelihood of predicted outcomes. For a discipline that has focused primarily on diagnosis for more than a century, this new ascendancy of prognosis in the application of clinical laboratory data represents a paradigm shift. The value of a laboratory test in the modern era is often measured by the utility of the test result in predicting a future clinical event in the patient's course. In some cases the test result will be useful in predicting relevant events that will occur in the next few minutes or hours and, in other cases, events years and even decades in the future.

*"In the new 21st century paradigm, the role of the laboratory will increasingly be one of helping the physician answer the question: What will happen to this patient and will any of several interventions likely change what will happen in a favorable way?"*

The prevailing diagnostic applications of medical laboratory testing in the 20th century are giving way in the 21st century to prognostic implications for risk stratification, prevention, therapeutic design and timing, and ultimately even for disease definition. In the 20th century the laboratory helped the physician answer the question: Is anything wrong with the patient and if so what? This paradigm led to a generalized notion that a laboratory result was either normal or abnormal. In the new 21st century paradigm, the role of the laboratory will increasingly be one of helping the physician answer the question: What will happen to this patient and will any of several interventions likely change what will happen in a favorable way? In the new paradigm, significance for laboratory results will increasingly be measured in incremental impact on likelihood of clinically significant events and methods of prevention or mitigation.

This issue of the *North Carolina Medical Journal* examines some of the factors driving this paradigm shift and the implications of increasing prognostic utility for laboratory testing. We explore some innovations that illustrate the trend and the implications for health care providers and patients alike in commentaries that illustrate emerging technologies, evolving platforms for testing, and new ways of applying the data to shape the interaction of patient and health care provider. For contemporary clinical laboratory medicine, change occurs along 3 principal axes: what we can detect, where the analysis occurs, and how the result is applied in patient management.

What we detect in the modern clinical laboratory changes, as it has for over 150 years, through the power of advances in analytic technology. Today clinical laboratories in most modern hospitals routinely detect analytes down to a level of one part per 10 billion. Not only has the detection level of our assays been improved by several orders of magnitude, but the inventory of analytes with clinical significance has exploded as our more sensitive assays allow researchers to explore in detail the relationships between disease and body chemistry. Dozens of new markers with potential

**Dana D. Copeland, MD, PhD**, is a pathologist in private practice at WakeMed Health and Hospitals. He can be reached at dcopeland@wakemed.org or PO Box 14045, Raleigh, NC 27620-4045.

clinical significance are introduced every year. Advances in proteomics, nucleic acid amplification, and molecular genetic pathology promise to accelerate the introduction of new tests with clinical significance.

Where we test is undergoing a dramatic shift. The first useful clinical laboratory test was the visual, olfactory, and gustatory analysis of urine. Analysis was often performed at the patient's bedside. In the 20th century, the emergence of more sophisticated testing that required either laboratory expertise or expensive equipment led to centralized laboratories in hospitals or at reference sites. Specimens were obtained from the patient and then transported to the testing laboratory, sometimes in the same building and sometimes thousands of miles away. Most testing moved away from the patient and into the remote laboratory. Then with the introduction of semi-quantitative glucose testing with dipsticks in the early 1960s and true quantitative glucose testing with portable glucometers in the 1970s, analytical chemistry testing began to return to the near patient environment. The trend has only accelerated with the introduction over the past two decades of a variety of point-of-care testing devices that put powerful analytic capabilities into the hands of health care professionals at the bedside, require only minimal expertise for operation, and provide real-time data for clinical management and decision making.

In contemporary clinical laboratory medicine, the site of testing is determined in part by the time frame in which prognostic significance applies. If the results of the test predict clinical events or therapeutic impact that will occur within minutes, the testing is likely to occur in a setting near the patient. For tests with prognostic significance in the hour to 24-hour range, a centralized laboratory remains the most likely venue. Intense clinical management of the patient in either the inpatient or ambulatory setting favors rapid turnaround for even routine tests, and economic pressures for efficient and cost-effective care are driving dramatic changes in the centralized hospital laboratory of the early 21st century.

Already for diabetes, and in the near future for other conditions, the ease of operation and reliability of point-of-care devices will facilitate the migration of traditional laboratory testing not only away from the central laboratory but also out of the hands of health professionals and into the hands of patients. Patients so empowered will be able to participate more effectively in the management of their own disease and in triage decisions that determine if and when intervention by medical professionals will be necessary.

A third area of accelerating change, and perhaps the most intriguing, is how the data generated by clinical laboratory medicine is employed in the management of the patient. Modern medicine and the experimental laboratory were born conjoined twins in the 19th century with the discovery of causal agents for disease, especially micro-organisms. A classification of diseases based on etiology and pathogenesis is still used today and continues to evolve in large measure on the basis of discoveries in the experimental laboratory. Once a causal understanding of the disease is established in the experimental laboratory, the clinical laboratory is positioned to test for the presence of etiological agents or their biochemical or immunological footprints. For the 20th century and the latter 19th century, the role of the clinical laboratory was to support or refute a physician's diagnosis.

While advances in the clinical laboratory continue to support this diagnostic paradigm, increasingly the clinical laboratory produces data with direct prognostic implications. Molecular studies can identify patients with genetic risk for the future development of disease; proteomics offers the promise of detecting patients that are evolving toward a disease state long before the disease is clinically manifest; and immunopathological assays may identify which patients among a group with the same type of tumor will do well on one treatment regimen and which will do better on another. Polymerase chain reaction (PCR) detection of microbials offers the promise of detecting and identifying pathogens in real clinical time instead of the days or weeks required by conventional microbiological assays, and identification of human papillomavirus strains in infected patients now rivals and supplements the value of the tried and proven morphologic pap smear in predicting which patients require intervention to prevent progression to cervical cancer.

## Milestones in the History of the Laboratory Medicine

A cursory outline of milestones in the development of clinical laboratory medicine is helpful in understanding the implications of the rapidly evolving discipline. Examination of urine for prognosis was advocated by Hippocrates as early as 400 BC. Kouba et al recently described the 1100 year evolution of the prognostic application of uroscopy to a diagnostic approach advocated by Theophilus.[1] The objective and systematic use of urine examination by Theophilus became a paradigm for the use of an analytic test to establish diagnosis.[1] By 900 AD, guidelines for the use of urine examination as a diagnostic aide were available, and by 1500 AD, color charts for the interpretation of urine in diagnosis were widespread.[2]

The invention of the microscope in the 17th century greatly extended the power of observation as a tool for diagnostic formulation. The microscopic analysis of urine sediment emerged as an important additional quantitative analysis in the latter half of the 18th century with J. W. Tichy's work.[2] The microscopic recognition of the cellular components of blood by Marcello Malpigihi in 1661-1665, and subsequent studies by Antony von Leewenhoek, promoted a second body fluid to importance in laboratory medicine.[3] However, throughout the 17th and 18th century, urine continued to be the sample of choice for medical analysis. The 17th century chemical analysis of blood was significantly advanced by the important work of William Hewson, who first demonstrated the presence of a coagulable substance that could be separated from the cellular component of blood. Hewson's discovery of "coagulable lymph," or fibrinogen, provided the foundation for the laboratory investigation and evaluation of coagulation and disorders of coagulation.[2]

The second century Greek physician Galen is often considered the most influential medical author of all time. Galen taught that illness was a result of imbalance in the 4 fundamental

humors (phlegm, blood, yellow bile, and black bile). This view was unassailed until the mid 18th century when the work of Giovanni Battista Morgagni in the post-mortem laboratory established a systematic correlation between clinical symptoms and anatomical changes in organ structure. Morgagni's seminal work *De Sedibus et Causis Morborum (On the Sites and Causes of Diseases)* became a foundation for the development of the science of pathologic anatomy. Nevertheless, the notion that the anatomical changes were themselves reflective of some imbalance in body humors continued for another hundred years.

The emergence of the germ theory of disease in the late 19th century not only laid to rest the humoral theory of Galen but also forged a relationship between modern medicine and the laboratory that came to dominate western medicine in the 20th century.[5] Physicians and patients had long recognized that outbreaks of epidemic disease implied an element of contagion, but assumed that some ambient and nonliving substance causing an imbalance in humors led to disease. Thus in the great London cholera outbreak of 1854, "miasma," a conjectured, noxious, and airborne substance arising from the decay of organic matter, was proposed by most medical authorities of the time as the cause of the epidemic. Physician John Snow, after a careful study of the patterns of case occurrence, came to the conclusion that the disease was spread by an agent in contaminated water from a particular pump in the city.[6] Snow's work advanced public hygiene and epidemiology and stimulated the search for specific agents for epidemic disease. The work of Snow as well as Semmelweis and Lister, established that at least some diseases were the results of contagious agents and the spread of these agents could be restricted by antiseptic procedures. A search for these contagious agents culminated in the revolutionary laboratory work of Louis Pasteur and Robert Koch that demonstrated the agents to be microbes.[4] The demonstration that living organisms caused disease advanced an approach to classifying disease based on external cause, an approach that persists and dominates our modern view.

A cornerstone in the development of a causal taxonomy of disease was the introduction of Koch's postulates in 1884. The postulates provided criteria for establishing an etiological link between a microbe and a disease. The four postulates in modern form are: (1) the putative causative organism must be found in every patient with the disease, (2) the organism must be isolated from a diseased individual and grown in culture, (3) the organism must produce disease when introduced into a healthy individual (usually an experimental animal), and (4) the organism must be reisolated from the experimentally infected animal.[7] Postulates 3 and 4 fall entirely into the domain of the experimental laboratory. However, the requirements of the first 2 postulates provided great impetus to the emergence of the clinical microbiology laboratory. If Koch's postulates are satisfied and a causal link established between a microbe and a disease, then it should be necessary in a patient with symptoms of that disease to require that the causative agent be recovered from the patient and grown in culture in order to establish a definitive diagnosis. This logic provided a strong tradition for clinical laboratory measures in confirming a medical diagnosis.

By the end of the 19th century, the clinical laboratory provided the culture of microbial pathogens, hemoglobin estimation, counting of red and white blood cells, microscopic identification of some parasites, clotting time in coagulation disorders, examination of sputum in tuberculosis, simple immunological tests such as agglutination tests for typhoid fever, and the demonstration of amino aciduria in liver disease.[2]

The first half of the 20th century saw an explosion of advances in analytical techniques in clinical chemistry, immunology, and blood banking as well as microbiology. With the exception of the important therapeutic applications of blood banking, the emphasis was almost entirely on the application of the methods of the clinical laboratory in diagnosis. The first textbook of laboratory medicine was edited by James C. Todd and published in 1908 as *A Manual of Clinical Diagnosis*. Ninety-eight years and seven editors latter, the 21st edition remains the authoritative reference for clinical pathology under the title, *Henry's Clinical Diagnosis and Management by Laboratory Methods*.[8] The addition of the word management reflects the emerging importance of the laboratory in not only helping make a diagnosis but also in providing data to monitor progression of disease and therapy.

Many diagnostically useful tests in clinical chemistry were developed in the first 50 years of the 20th century: serum phosphorus (1920), serum magnesium (1921), protein electrophoresis (1926), erythrocyte sedimentation rate (1929), alkaline phosphatase (1930), lipase (1932), amylase and acid phosphatase (1938), ammonia (1939), creatinine phosphokinase (1954), lactate dehydrogenase (1955), and alanine aminotransferase (1956).[9] The tests were useful but labor intensive and required manual methods by skilled technologists using sophisticated instrumentation. They were primarily applied in patients only after a physician's thorough evaluation and examination had narrowed the differential diagnosis to a short list of possibilities.

The introduction of the first automated clinical chemistry analyzer by Technicon Corporation in 1959 was a watershed in the application of these clinical analyses.[10] The Technicon Auto-Analyzer and the subsequent development of ever more powerful automated analyzers ushered in an era in which large batteries of laboratory tests could be performed quickly and economically. The ease and economy of performing multiple clinical chemistry tests presented for the first time in laboratory medicine the potential of screening healthy populations with batteries of tests to detect disease early, before pathological damage could occur. In the case of screening neonates for inborn errors of metabolism this strategy has worked exceedingly well. In 2006, the North Carolina Laboratory of Public Health screened 127 175 newborns for 41 genetic disorders. In the well adult population the results have been less satisfactory. For a period of time in the 1970s and 1980s, annual physicals might include batteries of 40 or more laboratory tests; but this approach led to little measurable improvement in outcomes. For most of the analytes in these batteries, there is overlap between values encountered in healthy and diseased populations. The more tests performed, the greater the likelihood that one or

## Prediction and Accuracy

Galen and Gambino and subsequent researchers[a,b] have applied mathematical tools to medical decision making to quantify the justifiable level of confidence a particular test result can offer physicians and patients in predicting the presence or absence of disease. A full understanding of the subject is challenging for many health professionals and formidable for the lay public, however, some generalizations are possible. The overlap in the distribution of values for analytes in diseased and healthy populations means no one test can perfectly discriminate between diseased and healthy individuals.

The *sensitivity* of a test is the probability of getting a positive test result in a diseased patient. The *specificity* of a test is the probability of getting a negative result in a person without the disease. For any given test we can adjust the limit of the reference range to improve sensitivity and capture a greater portion of the diseased population, but in doing so we also increase the number of healthy patients in the test positive group *(false positive)*. If we make an adjustment in the reference limit in the other direction, we can exclude more healthy individuals from the test positive population, but we also exclude some diseased individuals *(false negatives)*. Tests that have both higher sensitivity and specificity for a certain disease are preferred. We can compare tests by plotting the true positive rate against the false positive rate at all cutoff points for reference range. This curve, called the *receiver operating characteristic curve* (ROC curve), provides a measure of the accuracy of the test for that disease. The test with the bend in the curve that is closest to the upper left hand corner of the graph is the more accurate test.[b]

The clinical laboratory strives to develop tests with optimal sensitivity and specificity. Clinician and patients are most interested in the interpretation of a particular test result for a given patient: the *predictive value*. The *positive predictive value* of a test gives the probability of a disease given a positive test result, whereas the *negative predictive value* gives the probability of no disease given a negative test result. A counter-intuitive concept it that the predictive value of a test depends not only on the accuracy of the test, but also on the prevalence of disease in the population tested.[a] Therefore, the same test can have different predictive values when applied to different populations with different prevalence of the same disease.

Consider this example. We have a test that returns a positive result 99% of the time in diseased individuals and only 1% of the time in healthy individuals (false positive rate). We apply the test to a group of 200 000 individuals with a disease prevalence of 50%. The test will return a true positive finding in 99 000 of the 100 000 individuals with disease and a false positive finding in 1000 of the 100 000 individuals without the disease. Accordingly, any one individual with a positive test will have a 99% chance of having the disease.

Now we apply the same test to a population in which the prevalence of the disease is only 0.1%. Only 200 patients out of 200 000 have the disease and 198 (99%) will test positive. Of the 199 800 individuals without disease, 1% or 1998 will test positive. We now have 2196 individuals with a positive test result and only 198 with the disease: a predictive value of 9%. Therefore, in different populations the same test has an entirely different significance for a positive result. This is the reason that some tests may be excellent at confirming a suspicion on the part of the physician that a disease is present, but not very good for screening healthy populations with low disease prevalence. By evaluating relevant medical history, symptoms, and risk factors and then choosing tests for diseases that might fit these findings, the physician effectively creates a test population with a much higher prevalence of disease than the general population. Confirmation by laboratory testing will have much greater positive predictive value in such prescreened populations. It is also the reason that screening healthy individuals with large batteries of laboratory tests in the 1970s and 1980s generated so many false positive results.


a Sox HC. Probability theory in the use of diagnostic tests. An introduction to critical study of the literature. *Ann Intern Med*. 1986;104:60-66.

b Zweig MH, Campbell G. Reciever-operating characteristic (ROC) plots: A fundamental evaluation tool in clinical medicine. *Clin Chem*. 1993; 39:561-577.


more test results will fall outside the reference range, not because the patient has a disease, but simply because of variation in the distribution of values for that analyte in the healthy population. The problem of getting abnormal laboratory results in normal patients led to important advances in the mathematical quantification of predictive value for test results in Galen and Gambino's publication of the landmark 1975 monograph, *Beyond Normality: the Predictive Value and Efficiency of Medical Diagnosis*.[11] Advances in analytical technology have only accelerated at the end of the 20th century with the development of radioimmunoassay (1950), immunoelectrophoresis (1952), high-performance liquid chromatography (1969), enzymatic immunoassay (1972), and the laser cell sorter (1975).[12]

At the start of the modern medical era, Louis Pasteur advocated for the advancement and expansion of the medical laboratory.[13] By the end of the 20th century western medicine was dominated by this diagnostic laboratory paradigm: in the experimental laboratory, understanding the etiology and pathogenesis of the disease and, in the clinical laboratory, identifying the etiologic agent or the footprints of the pathogenic

process to confirm the diagnosis. Then, from the diagnosis, formulate a prognosis and, if necessary, propose a treatment. The dominance of this paradigm was summarized by Andrew Cunningham and Perry Williams in the opening paragraph of their 1992 monograph, *The Laboratory Revolution in Medicine*.

> If you feel unwell and go to see a doctor or are admitted to hospital, the chances are that the physicians will take a sample of your body – generally blood, tissue or urine – and send it away to another place for testing; in such cases the decision as to whether you are ill or not, and if you are, what disease you have, will be primarily taken not by you and not by your doctor but by a laboratory test. If you require treatment, this will probably involve the administration of medicinal substances prepared not by you or your doctor but in a highly specialised factory-like laboratory. If you decide to become a doctor yourself, your formal professional training will begin not with general practice, nor with hospital work, but with study of the medical sciences, in lecture rooms, libraries and laboratories.[5]

Now, at the start of a new century, this diagnostic laboratory paradigm may be undergoing a new revolution.

## The Case of Cardiac Troponin

Cardiovascular disease is the leading cause of death in the United States and has been every year since 1900 except for the pandemic flu year of 1918.[14] More Americans die of cardiovascular disease than of the next 4 leading causes of death combined.[14] Coronary artery disease leading to myocardial ischemia accounts for more than half of deaths due to cardiovascular disease.[14] Despite the importance of this disease, laboratory tests for the diagnosis of myocardial injury due to ischemia lagged the development of tests to detect disease in other organs until the discovery of transaminase elevations following myocardial infarction (MI) in the 1950s.[15] Because glutamate-oxaloacetate transaminase (now aspartate transaminase) and alanine transaminase are also released by damage to other organs such as liver and skeletal muscle, elevations of the transaminases were poor discriminators for injury to cardiac muscle versus other tissue.

A significant advance in the laboratory detection of myocardial injury was the introduction of creatine kinase isoenzyme assay.[16] Creatine kinase (CK) exists in 3 isoforms. One of the isoenzymes, CK-MB, is present in greater concentration in heart muscle than in skeletal muscle. While massive increases of CK can be seen in injury to skeletal muscle, a CK increase with a greater ratio of CK-MB to the other isoforms suggests injury of cardiac muscle. The clinical utility of the assay was initially limited by the need to perform electrophoretic separation of the isoenzymes, so assays could only be performed about once a day. At a time when patients were being admitted to hospitals for several days just to exclude MI, that limitation was acceptable.

With the advent of efficacious therapies for treatment and prevention of MI, the need for rapid laboratory confirmation of MI increased. Direct immunometric assay for CK-MB[17] (CK-MB mass) significantly reduced the time required to perform the test, making stat assays in an hour or less possible. CK-MB mass assay greatly facilitated the laboratory confirmation of a diagnosis of MI. However, since CK-MB is not specific for myocardium, the assay still suffered from low sensitivity for small infarcts and low specificity in the setting of skeletal muscle injury. The initial detection of CK increase in the setting of MI had been possible because of the enzymatic properties of CK.[18] The technology of immunometric assay made possible the detection at low levels of protein markers without enzymatic activity. A search for a protein specific to cardiac muscle culminated in the identification of cardiac troponin subunits I and T (cTnI and cTnT), which are specific to cardiac muscle. Cardiac troponins are released into the circulation following necrosis of myocardial fibers. In the absence of irreversible myocardial damage, the level of cardiac troponin is so low that it is undetectable by most assays. Following myocardial injury, cardiac troponin is released from damaged myocardial fibers and becomes detectable 2 to 4 hours after ischemic onset. Troponin levels rise and peak 24 to 48 hours after the infarct. Elevations of cTnI persist for 5 to 10 days after the infarct.[19]

Because cardiac troponin is only present in heart muscle, its presence in blood is a very sensitive and specific marker for cardiac injury. CK-MB was a significant advance over previous enzyme methods and reached sensitivity levels of 80%. With the most current cTn, assays sensitivity for myocardial injury is 96% to 98%.[19] Because of the greater sensitivity cTn is the preferred marker for detecting and ruling out MI.[19,20,21] The rise in cardiac troponin and CK-MB occurs only 2 to 4 hours after ischemic injury, so samples taken within the first 2 to 3 hours after symptoms may not demonstrate an elevation.[19] Cardiac troponin assay in serial samples taken 1 to 2 hours apart provides the most sensitive means for both detecting and excluding MI. Acute MI can be excluded in those patients with chest pain who, 4 to 6 hours after onset of symptoms, still have nonrising serial cTn levels below the 99% reference cutoff for the assay utilized.[22]

The diagnostic power of current cardiac markers is so strong that in 2000 the American College of Cardiology and the European Society of Cardiology issued a consensus statement redefining MI based on changes in sensitive and specific biomarkers such as cTn and CK-MB. The new clinical definition provides that MI is diagnosed when there is a typical rise and fall of biochemical markers of myocardial necrosis and one of the following: ischemic symptoms, development of pathologic Q waves on the ECG, ECG changes indicative of ischemia (ST segment elevation or depression), or coronary artery intervention (eg, coronary angioplasty).[23] The one finding that has to be present is the temporal change in a sensitive and specific marker for cardiac necrosis such as cTn or CK-MB.

The troponin story to this point is just another illustration of how a clinical laboratory test can be a powerful aid to diagnosis. The prognostic power of cTn emerged when patients with low

or borderline elevations of cTn were studied. The pathologic definition of MI is the irreversible damage of cardiac muscle due to ischemia. While diagnosing and treating MI is important, it's better to prevent it. When cTn assays were first introduced, many physicians complained that the tests were too sensitive because some patients had elevated levels of troponin but did not have clinical evidence of MI. However, when followed, these patients had a much higher incidence of significant cardiac events and sudden death after discharge than did patients with no cTn elevation.[24] Multiple studies have demonstrated that patients with stable or unstable angina or acute coronary syndrome all have significantly worse prognosis if cTn is elevated.[25,26,27] Moreover, the increase in mortality risk in patients with acute coronary syndrome with increased cTn levels is proportional to the increase in cTn.[26] The prognostic significance of small elevations of cTn, less than the cut-off level for diagnosis, has proven to be so prognostically significant that troponin elevation is a key criterion in the risk stratification and clinical management of patients with unstable angina and acute coronary syndrome.[23,28]

Cardiac troponin has proven to be an exquisitely sensitive marker for myocardiac injury arising from any source. Elevations can be seen in cardiotoxicity from drugs, hypothyroidism, sepsis, inflammatory myocarditis, heart failure, and cardiac trauma among others. In these cases the cTn elevation reflects real damage to cardiac fibers. In chronic conditions the cTn tends to be stable and clinical interpretation is necessary to distinguish cTn elevation due to ischemia from elevations due to myocardial injury from other causes. Even in those patients without symptoms or other evidence of cardiac disease, cTn retains prognostic significance. Patients with sepsis, noncardiac patients on critical care units, and emergency department patients without cardiac illness all have increased risk of short-term mortality if cTn is elevated compared to similar patients with normal cTn.[29]

## The Emerging Paradigm

Cardiac troponin is just one of many laboratory assays with strong prognostic significance. Cardiac troponin elevation predicts increased risk for patients with infarction, angina, and acute coronary syndrome, but some patients without elevated cTn still experience significant cardiac events including infarction and sudden cardiac death in the the 60 days following a cTn assay.[19] A search is underway for biomarkers that can predict ischemic events in asymptomatic patients without cTn elevation. No marker with prognostic significance comparable to cTn for this group of patients has yet been identified but several candidates, including C-reactive protein (CRP), sCD40 ligand, matrix metalloproteinases, myeloperoxidase, and ischemia-modified albumin, are being intensely studied.[19] For all of these analytes, prognostic significance is the desired characteristic.

In the case of heart failure, brain-type natriuretic peptide (BNP) is released by myocardium in response to stretch. BNP and its pro peptide NT-proBNP are increased in heart failure and have proved useful in diagnostic triage of patients with dyspnea.[30] High levels of BNP and NT-proBNP indicate poor prognosis in both heart failure patients and patients with acute coronary syndrome.[31,32]

Biomarkers with prognostic significance for disorders other than cardiovascular disease are also proliferating. Molecular genetics already has wide implications in the diagnosis, prognosis, and therapeutic management of neoplasia.[33] There are currently 17 588 disorders, variations, or protein structural alterations demonstrated to have a genetic basis in humans. While the majority of these are rare or cause minor changes of no clinical significance, some have increased risk of subsequent development of disease ranging from amyotrophic lateral sclerosis to hereditary breast cancer.[33] For many common diseases, genetic predisposition may depend on complex interactions of multiple alleles. The possibility of widespread screening using DNA microarray technology for genetic combinations that predispose to disease has attracted wide commentary.[34] Identifying those at increased risk has the potential to benefit the individual by interventions or lifestyle modifications that prevent or delay the onset of the disease. Identifying those at risk also entails significant ethical and social issues and has the potential to stigmatize and harm individuals.

Not everyone who has a demonstrated genetic predisposition for a certain disease will develop the disease. The relative risk factor may vary substantially and most diseases for which a genetic basis has been demonstrated entail complex interactions between several genes and often environmental agents as well. For diabetes mellitus[35] and some other autoimmune diseases[36] there is promise that autoantibodies that appear years before the onset of the symptoms may help predict which patients will go on to develop the disease. In the case of type 1 diabetes, autoantibodies to insulin, glutamic acid decarboxylase, and islet antigen-2 may appear as early as 10 years before onset of the disease. When one antibody is present a person has a 10% chance of developing type 1 diabetes within 5 years. When 2 antibodies are present the risk increases to 50%, and when all 3 antibodies are present the risk exceeds 60%.[35] Similarly in rheumatoid arthritis an autoantibody to citrulline may appear as early as 10 years before onset of the disease and the appearance of the autoantibody increases the risk of onset of rheumatoid arthritis 15 fold.[36] Finally, mathematical techniques will be increasingly used to predict future clinical events based on combinations of biomarkers independent of a patient's specific diagnosis. In a recent report, Gruenewald used recursive partitioning techniques to identify combinations of 13 biomarkers that conveyed higher risk of mortality in a 12-year study of older adults.[37]

In the 21st century, emphasis in clinical laboratory medicine has shifted from diagnosis to prognosis, risk stratification, treatment selection, and monitoring. If the medical paradigm of the 20th century was: first diagnosis then prognosis and treatment; then the paradigm for this century may be: first assess risk, then suggest risk modification or intervention; next monitor for early predictors of progression and, if detected, intervene; if symptoms appear, stratify for selected treatment based on prognostic tests.

## Rocket Science or Stamp Collecting?

This is an exciting time for clinical laboratory medicine. Rapid advances in science and technology are expanding the role and utility of clinical testing in the central laboratory, at the patient bedside, and in patients' homes. New and more sensitive assays provide valuable information for clinical decision making in real time. It's also an intriguing time as research in scientific laboratories identifies a host of markers that provide, for many patients and healthy individuals alike, powerful predictions of clinical events in the near and distant future. These technologies herald a paradigm shift in the relationship between medicine and the clinical laboratory from diagnosis to greater emphasis on prognosis, prevention and management, and from binary decisions about the patient as "diseased or well" to incremental prediction of risk and potential therapeutic benefit.

There is a significant difference in the predictive power of those sciences in which progress in knowledge is manifest by ever more powerful and elegant mathematical formulas and those descriptive sciences in which progress in knowledge is expressed by ever more complex and arcane taxonomies. The distinction was famously articulated by the early 20th century physicist and Nobel prize winner Ernest Rutherford who quipped, "all science is either physics or stamp collecting."[38] Collectors are students and illustrators of the taxonomies created to describe the objects they collect. In the early 20th century when Rutherford made his remark, many sciences including botany, zoology, geology, and medicine were primarily concerned with classification. From Rutherford's perspective, physicists calculated the formulas that orchestrated the universe, whereas other scientists simply classified. The relationship between the laboratory and medicine throughout the 20th century has been based on a taxonomic approach to disease. We have, from Rutherford's perspective, primarily been stamp collectors.

Despite the disdain in Rutherford's remark, we should not underestimate the important advances made through diagnostic taxonomy. Since the mid-19th century a classification of disease has evolved based on scientific understanding of the dysfunctions in anatomy, physiology, and chemistry that cause illness. This understanding is often founded upon, and evolves through, investigations in the experimental laboratory. The critical first step in the approach to an ill patient is to diagnose or classify the patient's disorder. Once the classification or diagnosis is established, the physician can answer the patient's question, "Is something wrong with me, and if so, what will happen to me?" Armed with a diagnosis, the physician can make predictions about the patient's likely clinical course. If the course is unfavorable, intervention can be considered and selected.

Making a diagnosis has prognostic and therapeutic significance because we have studied the natural course and response to therapy of other patients that have been assigned to the same diagnostic category. Of course, we know that the patients assigned to these disease categories are never exactly alike, and natural course and response to therapy will vary among patients with the same diagnosis. So our predictions for outcome, response to therapy, and side effects based upon the classification of the patient's disease are too often couched in terms of probabilities that leave the patient and family confused and dissatisfied. For all the progress scientific medicine and the laboratory have made together, we are humbled when we consider the rocket scientist who, armed with the calculus of physics, can hurl an object into space and predict with stunning accuracy when and where the probe will rendezvous with a speeding comet, millions of miles away and months or even years in the future. Beside the predictive power of scientists who calculate, the prognostic skill of the scientist who classifies seems feeble indeed.

The clinical laboratory has been and will continue to be a powerful source of data for classification and diagnosis. The promise of the clinical laboratory in the 21st century will be to increasingly provide data with which the physician can calculate as well as classify. In some cases the calculation will have clinical significance for the patient well before pathologic changes that permit a diagnosis have occurred. In other cases the data may support calculation of a prognosis that is much more specific than could be rendered on the basis of diagnosis alone. There is much speculation that the future of medicine will entail a highly personalized approach to prevention, treatment, and disease management in each patient. With the help of the clinical laboratory, the physician may well be moving toward a fuller implementation of the dictum "treat the patient and not the disease" and in doing so becoming a little more of a rocket scientist and a little less of a stamp collector. **NCMJ**

### REFERENCES


1 Kouba E, Wallen E, Pruthi R. Uroscopy by Hippocrates and Theophilus. *J Urol*. 2007;177(1):50-52.

2 Berger D. A brief history of medical diagnosis and the birth of the clinical laboratory. Part 1-Ancient times through the 19th century. First published in Medical Laboratory Observer, July, 1999. Medical Laboratory Observer Online. Available at: http://www.mlo-online.com/history/LABHISTORY1.pdf. Accessed April 4, 2007.

3 Ford B. The van Leeuwenhoek Specimens. *Notes Rec R Soc Lond*. 1981;36(1):37-59.

4 Lyons AS, Petrucelli RJ. *Medicine an Illustrated History*. New York, NY: Abrams; 1987.

5 Cunningham A, Williams P. *The Laboratory Revolution in Medicine*. Cambridge: Cambridge Press; 1992.

6 Johnson S. *The Ghost Map*. New York, NY: Riverhead; 2006.

7 Evans AS. Causation and disease: the Henle-Koch postulates revisited. *Yale J Biol Med*. 1976;49:175-195.

8 McPherson RA, Pincus MR. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. Saunders; 2006.

9 Berger D. A brief history of medical diagnosis and the birth of the clinical laboratory. Part 2-Laboratory science and professional certification in the 20th century. First published in Medical Laboratory Observer, August, 1999. Medical Laboratory Observer Online. Available at: http://www.mlo-online.com/history/LABHISTORY2.pdf. Accessed April 4, 2007.

10 Berger D. A brief history of medical diagnosis and the birth of the clinical laboratory. Part 3-Medicare, government regulation and competency certification. First published in Medical Laboratory Observer, October, 1999. Medical Laboratory Observer Online. Available at: http://www.mlo-online.com/history/LABHISTORY3.pdf. Accessed April 4, 2007.
11 Galen RS, Gambino SR. *Beyond Normality: the Predictive Value and Efficiency of Medical Diagnosis*. New York, NY: Wiley and Sons; 1975.
12 Berger D. A brief history of medical diagnosis and the birth of the clinical laboratory. Part 3-Medicare, government regulation and competency certification. First published in Medical Laboratory Observer, October, 1999. Medical Laboratory Observer Online. Available at: http://www.mlo-online.com/history/LABHISTORY3.pdf. Accessed April 4, 2007.
13 Pasteur L. *Le Budget de la Science*. 1868. Quoted by: Vallery-Radot R. *The Life of Pasteur*. Devonshire R, trans. Garden City, NJ: Doubleday; 1937:152.
14 American Heart Association. Heart Disease and Stroke Statistics—2006 Update. Dallas, Texas: American Heart Association; 2006:6-9.
15 LaDue JS, Wróblewski R, Karmen A. Serum glutamic oxaloactic transaminase activity in human acute myocardial infarction. *Ann Intern Med*. 1954;120:497-499.
16 Roe CR. Diagnosis of myocardial infarction by serum isoenzyme analysis. *Ann Clin Lab Sci*. 1977;7:201-209.
17 el Allaf M, Chapelle JP, el Allaf D, et al. Differentiating muscle damage from myocardial injury by means of the serum creatine kinase (CK) isoenzyme MB mass measurement/total CK activity ratio. *Clin Chem*. 1986;32:291-295.
18 Hess JW, MacDonald RP. Serum creatine phophokinase activity. A new diagnostic aid in myocardial and skeletal muscle disease. *Journal of the Michigan State Medical Society*. 1963;62:1095-1099.
19 Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease. *Journal of the American College of Cardiology*. 2006;48(1):1-11
20 Apple FS, Wu AHB. Myocardial infarction redefined: Role of cardiac troponin testing. *Clin Chem*. 2001;47(3):377-379
21 Adams JE, Abendschein DR, Jaffe AS. Biochemical markers of myocardial injury. Is MB cretine kinase the choice for the 1990s? *Circulation*. 1993; 88:750-763.
22 Eggers KM, Oldgren J, Nordenskjold A, Lindahl B. Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial injury. *Am Heart J*. 2004;148:574-581.
23 Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction refined– A consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *JACC*. 2000;35(3): 959-969.
24 deFilippi CR, Tocchi M, Parmar RJ, et al. Prognostic usefulness of marginal troponin T elevation. *Am Journal Cardiol*. 2004;93:274-279.
25 James S, Armstrong P, Califf R, et al. Troponin T levels and risk of 30-day outcomes in patients with the acute coronary syndrome: prospective verification in the GUSTO-IV trial. *Am J Med*. 2003;115:178-184.
26 Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin-I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med*. 1996;335:1342-1349.
27 Tanasijevic MJ, Cannon CP, Antman EM. The role of cardiac Troponin-I (cTnI) in risk stratification of patients with unstable coronary artery disease. *Clin Cardiol*. 1999;22:13-16.
28 Braumwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 Guideline Update for the Management of Patients with unstable angina and non-ST-Segment Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). 2002. Available at: http://www.americanheart.org/downloadable/heart/1022188973899unstable_may8.pdf. Accessed April 5, 2007.
29 Wright RS, Williams BA, Crammer H, et al. Evaluations of cardiac troponin I are associated with increased short-term mortality in noncardiac critically ill emergency department patients. *Am J Cardiol*. 2002;90:634-636.
30 Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriurertic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161-167.
31 Silver MA, Maisel A, Yancy CW, et al. BNP consensus panel 2004: a clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases. *Congest Heart Fail*. 2004;10:1-30.
32 Jernberg T, Lindahl B, Siegbahn, A, et al. N-terminal pro-brain natriuretic peptide in relation to inflammation, myocardial necrosis, and the effects of an invasive strategy in unstable coronary artery disease. *J Am Coll Cardiol*. 2003;42:1909-1916.
33 Nussbaum RL, McInnes RR, Willard HF. *Thompson and Thompson – Genetics in Medicine*. 6th ed. Philadelphia, PA: Saunders; 2004.
34 Bersch, C. A brief history of medical diagnosis and the birth of the clinical laboratory. Part 5a-The foundation of molecular science and genetics. First published in Medical Laboratory Observer, September, 2006. Medical Laboratory Observer Online. Available at:http://www.mlo-online.com/history/LABHISTORY5a.pdf. Accessed April 5, 2007.
35 Notkins, AL. New predictors of disease. *Sci Am*. 2007;296(3):72-79.
36 Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anti-cylic citrullinated protein antibodies in rheumatoid arthritis: A systematic literature review. *Ann Rheum Dis*. 2006;65(7):845-851.
37 Gruenewald TL, Seeman TE, Ryff CD, Karlamangla AS, Singer BH. Combinations of biomarkers predictive of later life mortality. *Proc Nat l Acad Sci U S A*. 2006;103:14158-14163.
38 Birks JB. *Rutherford at Manchester*. London: Heywood; 1962.

# Public Policy Recommendations for Oversight of Molecular Laboratory Tests

*Margaret L. Gulley, MD*

Laboratory tests have long been used to help diagnose and classify disease. Increasingly, these assays are used to predict disease in healthy individuals or to predict outcomes in response to a specific therapy (See Table 1). The subspecialty of molecular genetic pathology (MGP) has recently emerged to promote and recognize physician expertise in DNA- and RNA-based testing. In fact, the University of North Carolina at Chapel Hill has the nation's first accredited MGP fellowship training program to graduate a physician who subsequently became board-certified.

American Pathologists are voluntarily used by many testing laboratories to further check the quality of various DNA- or RNA-based assays. Indeed, laboratorians are widely recognized as leaders among health care practitioners in terms of measuring the quality of our clinical services.

Although demonstration of "clinical utility" for tests is not mandated by law, the vast majority of laboratory tests are known to be clinically useful even if they have not been reviewed by the Food and Drug Administration (FDA). The physician consultant in every testing laboratory has an ethical duty to look out for the best interests of the patients whose samples are being tested, and the laboratory physician assumes the risk of legal action if harm ensues. There are abuses: A recent report from the Government Accountability Office warned that certain genetic tests being marketed directly to the public (via the internet) seem to have no clinical value.[2] These tests may not directly harm the health of a consumer, but they are likely to harm their pocketbook.

**Table 1.**
**Clinical Utility of Molecular Assays**

| Clinical Application | Diagnosis | Screening | Monitoring | Prediction |
|---|---|---|---|---|
| **Heritable trait or disease** | Detect germline mutation causing inherited disease | Determine carrier status | | Predict disease presymptomatically, predict drug toxicity or optimal dose |
| **Oncology** | Help diagnose tumor based on acquired genetic defects | Screen high-risk individuals for cancer | Measure tumor burden, detect early recurrence | Predict drug efficacy, resistance, or toxicity |
| **HLA typing & identity testing** | Help diagnose HLA-linked disease | Match potential organ donors to recipients | Measure engraftment of transplanted hematopoietic stem cells | Predict organ rejection or graft versus host disease |
| **Infectious disease** | Detect pathogen based on unique DNA or RNA sequence | Screen blood donor for transfusable pathogen | Measure viral load during therapy | Predict drug resistance |

The public should be reassured that molecular genetic tests are analytically valid. All clinical laboratories in the United States (with the exception of certain government laboratories) are subject to regulatory oversight by the Centers for Medicare and Medicaid Services (CMS) involving, among other things, demonstration of accuracy and precision, periodic revalidation of assay performance, laboratory inspections, and biennial recertification.[1] Proficiency surveys offered by the College of

**Margaret L. Gulley, MD**, is professor and director of molecular pathology at the Department of Pathology and Laboratory Medicine at the University of North Carolina at Chapel Hill. She can be reached at margaret_gulley@med.unc.edu or 101 Manning Dr, 913 Brinkhous-Bullitt Building, Chapel Hill, NC 27599-7525.

Most people are surprised to learn that many genetic tests are not FDA approved. Achieving FDA approval is costly to those who prepare and submit a completed application (estimated at hundreds of thousands of dollars),[3,4] and that money may be better spent on higher priority efforts such as improving access to health care. Furthermore, the FDA lacks the manpower required to review validation data for all genetic tests. Overcoming this shortage would be burdensome to the FDA and would likely have the unintended consequence of delaying and impeding the availability of testing for patients. Finally, there is no demonstrated evidence that the quality of laboratory testing would substantially improve if FDA clearance were achieved. In this regard, it appears that existing governmental oversight of laboratory testing is adequate.

## The Pathologist as a Resource for Clinicians

It is estimated that at least 60% of medical decision making is based on laboratory test results, implying that the pathologist is among the most important members of the health care team.[5] Clinicians are encouraged to consult pathologist colleagues for advice on which laboratory test(s) to order, optimal specimen collection and handling, interpretation of test results, and implications for patient management. Pathologists, in turn, may formally document each consultation in the patient's medical record (using, for example, procedure codes 80500 or 80502) so that their expert advice and any links to additional resources are recorded in a way that may be accessed immediately by the requesting clinician and later by other members of the health care team.

Clinicians face tough challenges as they are bombarded with massive amounts of medical information, including both patient-specific data and never-ending piles of published literature.[6,7] The amount of medical information is estimated to double every five years, and the pace of progress seems even faster in the realm of molecular pathology where new technologies are now available to inform translational research and clinical practice. These new tools for analyzing DNA or downstream RNA transcripts and proteins encoded by the human genome (or by human pathogen genomes) have resulted in many new opportunities to diagnose and classify disease and to predict outcome in response to various alternative therapies. Every medical journal now seems to deal with novel genotype-phenotype associations or proposed targeted therapy based on analysis of the biochemical pathways that are altered in disease.

*"At least 60% of medical decision making is based on laboratory test results, making the pathologist among the most important members of the health care team."*

Pathologists are well positioned to keep up with the medical literature on the tests that their laboratory offers, as well as guiding use of esoteric tests available from outside laboratories. An increasingly important role is understanding and conveying useful genetic information to clinicians. This consultative role extends to surgical pathologists since molecular assays are increasingly applicable to a wide variety of sample types including formalin-fixed, paraffin-embedded tissues, thus helping to reunite the two major subdisciplines of pathology—anatomic pathology (dealing mainly with biopsy tissues) and clinical pathology (dealing with blood and other body fluids). Furthermore, quantitative DNA amplification assays are being used to monitor disease levels (eg, tumor burden or viral load) so as to inform how a given therapy is working. The exquisite sensitivity of molecular assays can allow us to predict early on (before complete drug resistance develops) that the therapeutic regimen should be altered.[8,9]

## Predicting Drug Efficacy, Optimal Dose, or Toxicity

Pathologists have traditionally been involved in diagnosis of disease, whereas clinicians select therapy. But novel laboratory assays are increasingly informative with regard to optimizing therapy, making it all the more important that each laboratory physician is well versed in validating, interpreting, and assuring quality of test results. An excellent example of the drive for quality improvement is a recent guideline jointly issued by the American Society of Clinical Oncology and College of American Pathologists on the performance of ERRB1 (Her2) assays for predicting trastuzumab (Herceptin) efficacy in breast cancer patients.[10] Some of the early work developing molecular assays for Her2 was done at the University of North Carolina at Chapel Hill.[11] Another pharmacogenetic test with local ties targets the VKORC1 gene and predicts (at least in part) optimal dose and toxicity of warfarin (eg, Coumadin) therapy. The VKORC1 gene was first characterized in 2004 at the University of North Carolina in Chapel Hill by Darryl Stafford and colleagues.[12] The clinical importance of this discovery was quickly recognized so that, within two years, molecular tests for alterations in VKORC1 were being correlated with clinical outcome in response to warfarin therapy.[13]

## Progress through Clinical Research

New molecular tests further expand our ability to predict as well as detect disease. This creates new challenges for policy

makers who will be asked to support the costs of these tests as well as fund the new knowledge necessary to optimally apply them. More backing for translational research is needed to support clinical trials that will ultimately define algorithms for managing patients based on molecular test results. The utility of our powerful new molecular tools is only just beginning to be understood, but already their promise is quite evident. **NCMJ**

*Acknowledgements: The author thanks Charles Jennette, MD, Joe Grisham, MD, and James D. Folds, PhD for support and encouragement to develop molecular pathology services. In the spirit of full disclosure, the author acknowledges advice given to several nonprofit and governmental groups as well as service on the Advisory Board of Roche Diagnostics Corporation; however, the author alone determined the content and the decision to submit this manuscript for publication.*

## REFERENCES

1 Department of Health and Human Services, Centers for Medicare and Medicaid Services. Clinical Laboratory Improvement Amendments of 1988; Final Rule. *Fed Register [42CFR493.1256(D)(3)(II)]*. 2003;(Jan 24):7166.
2 Kutz G. Nutrigenetic testing: Tests purchased from four web sites mislead. *United States Government Accountability Office Report #GAO-06-977T*. Available at: http://www.gao.gov. Accessed April 9, 2007.
3 Anonymous. Medical Device User Fee and Modernization Act (MDUFMA) of 2002. *Food and Drug Administration, United States Government Department of Health and Human Services*. Available at: http://www.fda.gov/cdrh/mdufma/. Accessed April 9, 2007.
4 Lundblad RL, Wagner PM. Ruminations on the issue of assay validation for biopharmaceuticals. *Preclinica*. 2004;2:243-245.
5 Regan M, Forsman R. The impact of the laboratory on disease management. *Dis Manag*. 2006;9:122-130.
6 Jerome RN, Giuse NB, Gish KW, Sathe NA, Dietrich MS. Information needs of clinical teams: analysis of questions received by the Clinical Informatics Consult Service. *Bull Med Libr Assoc*. 2001;89:177-184.
7 Giuse NB, Koonce TY, Jerome RN, Cahall M, Sathe NA, Williams A. Evolution of a mature clinical informationist model. *J Am Med Inform Assoc*. 2005;12:249-255.
8 Hughes T, Branford S. Molecular monitoring of BCR-ABL as a guide to clinical management in chronic myeloid leukaemia. *Blood Rev*. 2006;20:29-41.
9 Carter TA, Wodicka LM, Shah NP, et al. Inhibition of drug-resistant mutants of ABL, KIT, and EGF receptor kinases. *Proc Natl Acad Sci U S A*. 2005;102:11011-11016.
10 Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. *Arch Pathol Lab Med*. 2007;131:18.
11 Dressler LG, Thor AD. HER2 testing: laboratory, technical and clinical considerations. *Breast Dis*. 2000;11:77-87.
12 Li T, Chang CY, Jin DY, Lin PJ, Khvorova A, Stafford DW. Identification of the gene for vitamin K epoxide reductase. *Nature*. 2004;427:541-544.
13 Li T, Lange LA, Li X, et al. Polymorphisms in the VKORC1 gene are strongly associated with warfarin dosage requirements in patients receiving anticoagulation. *J Med Genet*. 2006;43:740-744.

# The Ethics of Genetic Testing:
## Is More Always Better?

*Nancy M. P. King, JD*

The recent explosion of interest in prognostic genetic testing raises a host of ethical issues for patients, research subjects, physicians, investigators, policymakers, and the public. None of these issues is really new, but all of them have gained new significance as the science of gene finding accelerates and new genetic tests become more widely available.

Public expectations are high regarding the potential value of genetic information. This confidence extends to the information obtained from new genetic tests, especially those identifying genes associated with common complex disorders. After all, nearly everyone knows someone with diabetes, heart disease, depression, asthma, attention deficit hyperactivity disorder, osteoarthritis, cancer, or any of the other common multifactorial disorders that mark the human condition, and the promise of the Human Genome Project[a] has always been both to explain the human condition and to ameliorate it.

*"Is it meaningful to base clinical recommendations, health behavior change, or public policy on predictive genetic testing?"*

Today, science is increasingly able to assign precise percentages to at least some of the genetic contribution to an individual's chance of developing a common complex condition. This quantification of risk is a seductive enterprise. Simply knowing that many people develop emphysema later in life does not seem to mean as much as knowing that individuals with a particular genetic test result are a specified percentage more likely to develop emphysema than those whose test is negative. But are we right to think this? Does more precision mean more accuracy, or more truth? Is it meaningful to base clinical recommendations, health behavior change, or public policy on predictive genetic testing?

Ethical questions arise in the process of research, development, and marketing of predictive genetic tests; in their use and interpretation by physicians and patients; and in the utilization of predictive genetic test results in public health and other policy contexts. The issues to consider include understanding probabilistic and uncertain information, informed decision making, the medicalization of nondisease states, stigmatization of individuals and groups, genetic essentialism and fatalism, and the potential for genetic discrimination.

Logically, first among issues are those surrounding gene finding. To identify genetic associations of interest requires large-sample gene discovery research and biospecimen collection, "biobanking," and specimen sharing. Long-standing questions exist about the scope of consent to biospecimen research and sharing, how biobanks should be established and overseen, and how research results should be reported and interpreted.[1,2] It is far from clear, for example, that everyone who provides a biospecimen for genetic research into one disorder (eg, Tourette syndrome) would agree to share that specimen with investigators seeking genes associated with a different disorder (eg, colon cancer or

a The US Human Genome Project was begun in 1990 by the US Department of Energy and the National Institutes of Health to identify all the genes in human DNA, determine the sequences of the base pairs that make up human DNA, store this information in databases, improve tools for data analysis, transfer related technologies to the private sector, and address the ethical, legal, and social issues that may arise from the project. (US Department of Energy Office of Science. Human Genome Project Information. Available at: http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml. Accessed March 21, 2007.)

**Nancy M. P. King, JD**, is a professor in the Department of Social Sciences and Health Policy and director of the Program in Bioethics, Health, and Society at Wake Forest University School of Medicine. She can be reached at nmpking@wfubmc.edu or Medical Center Boulevard, Winston-Salem, NC 27157.

cystic acne). Should they be asked? Or should consent forms simply inform specimen providers that their DNA could be shared and studied for any scientific purpose? And is such a broad consent really consent at all?

Once research is underway, questions arise about its results. There is considerable uncertainty about the significance of genetic associations in common complex disorders and gene-environment interactions. Even though knowledge is expanding rapidly in genetics, it is simply not yet known how the interplay of multiple genetic and environmental factors affects the likelihood of developing a disorder or its probable severity.[3] Thus, associating a gene with a disorder is only a small piece of a rather large puzzle. How, then, should researchers and clinicians describe that single piece? Moreover, as is already well recognized, population-based research results are difficult to translate into individual application. Although the espoused goal of genetic research is "personalized medicine" (ie, prediction at the individual level), at present, genetic associations are usually reported in broad general categories of questionable meaning. Most notably, genetic research results are grouped by race and ethnicity (eg, "X gene, associated with Y disease, is three times as common in African-Americans as in whites."). Although genetic research has definitively shown that racial categories have no biological meaning, such racialized characterizations remain all too common.[4,5] Ironically, these categories help to wrongly reify race as genetically significant. Not incidentally, reporting about research in this way is often highly stigmatizing to members of the racial and ethnic groups thus identified (eg, "Another 'Jewish gene' has been identified by researchers.").[6]

The process of translating such imperfect data into a genetic test used predictively in individuals is similarly fraught with ethical challenges. Standards for the development and marketing of genetic tests are at present nearly nonexistent. Whether and how to regulate these tests is the subject of major policy debate.[7,8] What counts as a valid and reliable test? How are commercial genetic tests advertised to practitioners and consumers? Even when these questions have been answered satisfactorily, others loom regarding the best uses of such tests. Should children be tested for genetic predispositions to adult-onset disorders?[9,10] Does it matter whether the test results are used to monitor the child's health, to initiate a prophylactic regimen, or to help the child's parents make decisions about future reproduction?

How should doctors decide whether to base recommendations to their patients on genetic test results? It has long been known that health care providers may themselves have difficulty understanding and explaining probabilities to patients. Making use of probabilistic information in the context of risk reduction, which is how predictive genetic test results will be used, is even more complex than applying probabilities to treatment choices. This difficulty is compounded in genetic testing by the temptation to view genes as deterministic and, thus, to overestimate their importance—especially in common complex disorders.[11] Since the beginning of the Human Genome Project, much attention has been given to providing genetic education to primary care providers and the general public. However, the available information changes so quickly that it's necessary to run very fast to keep up—and it's all too easy to fall behind. As a result, much decision making about genetic testing is likely to be based on poor information and poor understanding. Not surprisingly, poor information and poor understanding make for imperfect decisions about whether to test, how to interpret the results, and what to do with them.

What should be done with the information that predictive genetic testing provides? It is essential to acknowledge that even with perfect information, there is a substantial gap between gene identification and effective prophylaxis (let alone treatment).[12] Just consider the decision making challenges faced by women who learn they have a breast cancer (BRCA) gene: intensive monitoring? prophylactic drug regimens? radical surgery? or only standard exams and mammography, since having a BRCA gene is far from a guarantee of developing breast or ovarian cancer?[13] Now multiply that range of options by every new genetic association identified by prognostic testing, such as other cancers, type II diabetes, cardiac disease, obesity, psychiatric and behavioral disorders, asthma and allergies, and lots more we probably haven't even thought of as disorders—yet.[14]

One issue of principal concern has not materialized as a significant reality, but profoundly affects public perceptions about genetic testing information. The risk of genetic discrimination can deter testing, even when test results are well characterized and prophylaxis can make a difference. There is little evidence to date of discrimination in the cost or availability of health insurance, or in employment, on the basis of genetic predisposition information, although discrimination on the basis of existing disease is common, and troubling.[15,16] However, many states—North Carolina included[17]—have legislation in place prohibiting genetic discrimination, and federal legislation (the Genetic Information Nondiscrimination Act, "GINA"[18]) stands an increasingly good chance in Congress.

Another kind of discrimination by health insurers, in the name of health promotion, is actually somewhat more likely. Many health insurers are beginning to offer incentives to their insured members to change their behavior in an effort to reduce health care costs. Could an insurer require members to undergo predictive genetic testing and use the results to adjust premium rates? Could an insurer base those adjustments not solely on the test results, but on whether members with certain test results make use of certain preventive or health maintenance services (eg, stop smoking, successfully lower cholesterol or blood pressure levels, or maintain a certain weight) because their genetic profiles make them more likely to develop associated disorders? This may make good fiscal sense, or even good public health sense, but it can be quite intrusive on personal privacy. In most cases it makes little sense to distinguish between those with and without incriminating genetic profiles for disorders that are common in the general population.

Will the future bring us to more precise information and the truly personalized genome? Perhaps, in awhile; but what we do until we get there matters a great deal. If we can encourage both health care providers and patients to learn more about the meaning of genetic information, ask lots of questions about genetic information, and examine each use of genetic information

carefully and comprehensively, then it may be possible to make both scientific and moral progress.[19]

There are, unfortunately, no easy answers. The best way to address these ethical issues is the hard way: taking great care in how we think about, talk about, understand, and use genetic information. We are not just our genes. For every genetic test that informs us of a susceptibility to a common complex disorder, there are many ways to alter the environmental influences that we know are also implicated, both at the individual level and as matters of public health and social policy. We already have ample reason to change habits of diet and exercise, improve the availability of healthy food choices in shops and schools, reduce environmental pollutants and hazards in the workplace, and make safe physical activity possible in all communities. The discovery of genetic associations adds scant momentum, if any, to these efforts and could be detrimental if poorly understood.[20]

More information isn't always better; only good information is better. It may be time to say no to the genetic testing explosion —at least until we know what is hype and what is not. **NCMJ**

## REFERENCES


1 Rothstein M. Expanding the ethical analysis of biobanks. *J Law Med Ethics*. 2004;33:89-101.
2 National Institutes of Health. First generation guidelines for NCI-supported biorepositories. Federal Register. 71:25184-25203 (April 28, 2006).
3 Welch HG, Burke W. Uncertainties in genetic testing for chronic disease. *JAMA*. 1998;280:1525-1527.
4 Wolf S, ed. Symposium. The responsible use of racial and ethnic categories in biomedical research: Where do we go from here? *J Law Med Ethics*. 2006;34:483-558.
5 Collins FS. What we do and don't know about 'race', 'ethnicity', genetics and health at the dawn of the genome era. *Nature Genetics*. 2004;36:S13-16.
6 Weiss R. Discovery of 'Jewish' cancer gene raises fears of more than disease. Washington Post. September 3, 1997:A03.
7 Pollack A. The wide, wild world of genetic testing. New York Times. Available at: http://www.nytimes.com. September 12, 2006.
8 Caruso D. Genetic tests offer promise, but raise questions, too. New York Times. Available at: http://www.nytimes.com. February 18, 2007.
9 American Academy of Pediatrics Committee on Bioethics. Position statement: Ethical issues with genetic testing in pediatrics. *Pediatrics*. 2001;107:1451-1455.
10 Rhodes R. Why test children for adult-onset genetic diseases? *Mt Sinai J Med*. 2006;73:609-616.
11 Giardiello FM, Brensinger JD, Petersen GM, et al. The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. *NEJM*. 1997;336:823-827.
12 Geller G, Botkin JR, Green MJ, et al. Genetic testing for susceptibility to adult-onset cancer: the process and content of informed consent. *JAMA*. 1997;277:1467-1474.
13 Klitzman R. Genetic testing creates new versions of ancient dilemmas. New York Times. Available at: http://www.nytimes.com. January 17, 2006.
14 National Office of Public Health Genomics. Obesity and genetics: What we know, what we don't know, and what it means. June 2006. Available at: http://www.cdc.gov/genomics/training/perspectives/files/obeseknow.htm. Accessed March 12, 2007.
15 Hall MA. Genetic Discrimination. Paper commissioned by the North Carolina Genomics and Bioinformatics Consortium, LLC. Nov. 2001. Available online at: http://www.ncbiotech.org/services_and_programs/genomics_consortium/consortium_projects_and_events/geneticdiscrimination.pdf. Accessed March 12, 2007.
16 Greely HT. Banning genetic discrimination. *NEJM*. 2005;353:865-867.
17 General Assembly of North Carolina, 1997 Session, SL 1997-350, SB 254. An act to prohibit discrimination in health insurance and employment based on genetic information.
18 H.R.493, 110th Congress 1st session.
19 North Carolina Task Force on Genomics and Public Health, North Carolina Public Health Genomics Plan (2004). Available online at: http://statgen.ncsu.edu/ggibson/nc_gph/nc_public_health.html. Accessed March 12, 2007.
20 Grady D. Genetic test for diabetes may gauge risk, but is the risk worth knowing? New York Times. Available at: http://www.nytimes.com. August 8, 2006.

# Molecular Diagnosis of Infectious Diseases

*Melissa B. Miller, PhD*

During the past 10 to 15 years, we have seen expansive growth of the use of molecular technology in the clinical laboratory for diagnosing infectious diseases. As a result, many laboratories are able to offer more sensitive testing, faster turnaround times, and ultimately improved patient care. The gold standard in bacteriology largely remains culture, primarily due to cost accounting and the potential complex nature of associated infections (ie, urine, wound, and respiratory cultures). However, in circumstances in which there may be minute quantities of a specific pathogen present, the patient may have received antibiotics prior to specimen collection, or the etiologic agent may require unusual culture conditions, molecular detection offers a great advantage to culture techniques. In many virology laboratories, molecular detection has supplanted cell culture techniques for the identification of several viral pathogens and in many cases has become the new gold standard. Though molecular techniques can offer an abundance of added benefits when used to augment current gold standards such as culture and/or serology, the optimal use of molecular methodologies in microbiology resides with specimens in which a limited number of pathogenic organisms are sought and in cases where the enhanced sensitivity and faster turnaround time of molecular methods far outweighs the increased cost.

*"The optimal use of molecular methodologies in microbiology resides with specimens in which a limited number of pathogenic organisms are sought and in cases where the enhanced sensitivity and faster turnaround time of molecular methods far outweighs the increased cost."*

## Applications in Bacteriology

A classic example of successful nucleic acid amplification (NAA) testing in microbiology is the detection of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) from vaginal, cervical, urethral, and first-void urine specimens. Sexually transmitted infections such as those caused by CT and NG can be rapidly and accurately identified using NAA, thus improving treatment and transmission prevention. Implementation of routine screening for CT has lowered the prevalence rates of CT and associated pelvic inflammatory disease.[1] The increased sensitivity offered by NAA detection of CT and NG is important not only for the diagnosis of symptomatic patients, but also for the asymptomatic individuals that account for more than 70% of positive cases. Until implementation of NAA testing for CT and NG, culture was the gold standard, although it has subsequently been shown to have only 60% to 75% sensitivity compared to NAA.[2] A further disadvantage of culture is that organism viability must be preserved during transport. The implementation of routine confirmatory testing should be considered when using NAA for a low prevalence population that results in a positive predictive value below 90%.[2]

Another prime example of NAA results positively impacting patient care is the laboratory diagnosis of tuberculosis. Using

**Melissa B. Miller, PhD**, is an assistant professor of pathology & laboratory medicine, director of the molecular microbiology laboratory, and associate director of the microbiology-immunology laboratory at the School of Medicine at the University of North Carolina at Chapel Hill. She can be reached at MBMiller@unch.unc.edu or Campus Box 7525, Chapel Hill, NC 27599.

direct detection of *Mycobacterium tuberculosis* (MTB) from respiratory samples, tuberculosis can be confirmed in less than 24 hours as opposed to 6 to 8 weeks. The sensitivity of NAA detection of MTB in smear-positive respiratory specimens is 96.9%, and the specificity is 100%, whereas the sensitivity and specificity in smear-negative specimens is 72.0% and 99.3%, respectively.[3] It should be noted that NAA of MTB does not replace the need for routine mycobacterial culture and susceptibility testing. In addition to the direct detection of MTB, techniques such as probe-based technology and sequence analysis can be applied to cultured isolates to decrease the time to identification over routine biochemical analysis. Rapid identification of MTB impacts not only patient care, but also infection control. Due to the increasing frequency of isolation of mycobacterial species associated with immunocompromised hosts and the increased incidence of multi-drug resistant MTB, it has become imperative to offer accurate yet rapid diagnostic tools for the detection and identification of mycobacteria.

A debate exists regarding the gold standard for the laboratory diagnosis of *Bordetella pertussis*. Historically, culture plates collected at the patient's bedside (ie, cough plates) have been considered the reference method. Although culture is very specific, its sensitivity suffers partially due to the organism's fastidious nature, but primarily because the highest sensitivity for culture occurs before patients are symptomatic. NAA remains positive for longer after therapy than culture, and NAA is also positive for a longer period after onset of symptoms.[4] Therefore, NAA is useful for patients presenting later in their illness. NAA testing allows for same-day results and since erythromycin-resistant *B. pertussis* is still rare, a cultured isolate is rarely needed for antimicrobial susceptibility testing. Multiple studies have demonstrated significant increased detection of *B. pertussis* when comparing NAA to culture: reported PCR-positive, culture-negative samples range from 13% to 88%.[5] However, due to potential false positive and false negative results with *B. pertussis* NAA procedures, it is strongly recommended that results be considered in the context of patient clinical presentation, and clinically inconsistent results should be confirmed by a second method.

NAA is also being used in bacteriology to detect antimicrobial resistance. Since antimicrobial resistance can be multi-factorial, this practice is limited to organisms in which the results can be interpreted with confidence in regard to the genotypic relationship to clinical treatment and/or infection control precautions. Such examples are direct detection of vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) from rectal and nares surveillance cultures, respectively. Screening patients for VRE and MRSA carriage is a key strategy for preventing the spread of these organisms in health care settings. NAA technology reportedly increases VRE detection by up to 120%.[6] In addition, enterococci that confer low-level intrinsic resistance, and thus not considered "true" VRE, are accurately ruled out preventing unnecessary contact precautions and contributing to hospital savings.[6] NAA detection of MRSA has been shown to be equal in sensitivity to culture-based methods, but has the advantage of offering a faster turnaround time, thus impacting hospital cost savings.[6] However, it should be noted that direct specimen testing for MRSA comes with limitations, often including a lower positive predictive value than conventional methods.[7,8] More recently, new strains of MRSA have appeared that are associated with skin and soft tissue infections in outpatients and are called community-associated MRSA (CA-MRSA).[9] The increasing incidence of CA-MRSA is causing overall rates of MRSA to rise. Therefore, it has become even more important to quickly and accurately identify resistant isolates.

## Applications in Virology

Monitoring the viral load (quantified determinations of virus using NAA) in patients infected with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) is useful for tracking therapeutic response to antivirals and potential antiviral resistance. In addition, viral load monitoring for cytomegalovirus (CMV) in transplant recipients has allowed clinicians the benefits of identifying patients most at risk for developing clinical CMV disease, monitoring antiviral therapy response, and optimizing pre-emptive treatment.[10] Analogously, Epstein-Barr virus (EBV) viral loads can be monitored in the posttransplant setting to identify patients at risk for developing posttransplant lymphoproliferative disorder.

Molecular detection of viruses has extended beyond the standard therapeutic monitoring of viral loads in specific patient populations. For example, NAA testing for the laboratory diagnosis of herpes simplex virus (HSV) encephalitis and enterovirus (EV) meningitis has become the standard of care. Cell culture techniques are insensitive due to the low viral burden typically found associated with encephalitis and perhaps also the presence of host neutralizing antibodies.

HSV is the most common cause of nonepidemic encephalitis in the US, accounting for up to 20% of cases. CSF culture for HSV detects less than 2% of clinically determined adult HSV encephalitis cases and 40% of neonatal central nervous system (CNS) disease.[11] In contrast, HSV NAA is positive in most adult cases resulting in sensitivity and specificity > 95%[11] and is 75% sensitive and 100% specific for neonatal meningitis.[12] The rapid diagnosis of HSV encephalitis can prevent a brain biopsy and rapidly determine the need for acyclovir therapy.

Enterovirus is the most common cause of aseptic meningitis in the summer and fall months in temperate climates and accounts for 10% to 20% of encephalitis cases. A wide array of cell lines must be utilized to recover the majority of EV types by culture, and culture sensitivity still remains approximately 70%.[13] The sensitivity and specificity of CSF NAA for EV are estimated to both be > 95%.[12]

Nucleic acid amplification has also been successfully applied to other etiologies of viral CNS disease, such as CMV and varicella-zoster virus (VZV), but these assays have not been implemented as broadly as those for HSV and EV, so are still transitioning to becoming the method of choice. It should be noted that not all encephalitis viruses are readily detected by NAA. For example, due to the short period of viremia in many

arboviral infections (ie, West Nile Virus), CSF NAA has low sensitivity, and the gold standard remains serology.[14] CSF NAA false negative results can occur due to collection of CSF very early or very late in illness, rapid viral clearance in immunocompetent hosts, and NAA inhibitors.[12] False positive CSF NAA results also occur primarily due to lack of data to suggest the detection of certain viral nucleic acids correlates with clinical CNS disease, but can also be caused by the presence of peripheral blood in the CSF.[12] While CSF NAA is considered by many the diagnostic standard of care as discussed above, the lack of standardized FDA-approved assays has made implementation of CSF NAA difficult in nonacademic settings. While most laboratories offering CSF NAA use qualitative methods, data indicate a role for quantitative CSF NAA in differentiating nonspecific presence of virus and virus-associated disease, to aid in prognosis for improved patient management, and in monitoring antiviral therapy.[14]

*"With the use of molecular technology to detect potential etiologic agents of disease, we need to remember Koch's postulates."*

## Challenges and Opportunities

The field of molecular infectious disease testing has grown so rapidly that the diagnostic industry has not kept up. To fill this void, independent investigators have turned to the development of user-defined, or "homebrew," molecular detection methods in the clinical laboratory. The implementation of user-defined NAA testing has revolutionized clinical molecular infectious disease testing. In addition, commercially-available non-FDA-approved NAA assays are increasingly becoming available as analyte specific reagents (ASRs). Though all reagents necessary for the amplification reaction can be purchased commercially, assay development and verification studies must be performed by individual laboratories. In many cases, there are no comparative studies between user-defined NAA procedures, including ASRs, limiting the comparative value of assays between institutions (particularly in viral load monitoring) and restricting the application of such procedures to more experienced laboratories.

It is not without considerable cost that a molecular infectious disease diagnostic lab is developed. It represents an institutional commitment because the costs may only be offset when analysis of hospital-wide cost savings is employed (ie, shorter hospital stays, decreased use of unncecessary antibiotics). The costs incurred not only stem from instrumentation purchases, but also from the dedicated, expert staff required for such testing. Since many academic medical centers have resorted to implementing user-defined assays, verification and validation studies are substantial and require extensive resources, including time, staff, and expertise. These studies are crucial to defining the performance of the assay and determining appropriate clinical utilization. Most laboratory directors view the implementation of user-defined assays and ASRs as a temporary fix until FDA-approved assays are available. However, many diagnostic companies are opting not to seek FDA-clearance to replace current ASRs or "research use only" tests. The FDA, diagnostic companies, and major molecular infectious disease laboratories need to work together to resolve the poor standardization that exists between laboratories using user-defined assays or ASRs. Further, in the absence of FDA-approved tests, many nonacademic medical centers will not have the opportunity to enter the field of molecular infectious disease diagnostics.

## Conclusion

The applications of molecular technology in clinical microbiology are endless, but challenges also abound. We are still learning what many NAA results mean in terms of infectious etiology. With the use of molecular technology to detect potential etiologic agents of disease, we need to remember Koch's postulates.[15] Is the mere presence of an organism's nucleic acid convincing evidence of disease causation? Undoubtedly, additional clinical scientific evidence is needed to make such a claim, and such evidence or lack thereof should be considered when interpreting molecular infectious disease results. Though there is still much to be learned regarding the appropriate application and interpretation of molecular infectious disease testing, there are numerous exciting opportunities on the horizon. User-defined assays and ASRs have allowed experienced laboratories to offer critical diagnostic services that have yet to become available with FDA clearance. As investigators refine molecular applications for infectious disease testing, diagnostic companies market such applications, quality control and government organizations standardize results, and as costs associated with implementation decrease and reimbursement increases, molecular infectious disease testing will not only be available in academic medical centers and reference laboratories, but will also transition to community hospitals, thus more globally impacting patient care. **NCMJ**

## REFERENCES


1 Centers for Disease Control and Prevention. Screening tests to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections. *MMWR*. 2002;51(No. RR-15):1-38.
2 Chapin KC. Molecular tests for detection of the sexually-transmitted pathogens *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. *Med Health R I*. 2006;89(6):202-204.
3 Amplified *Mycobacterium tuberculosis* Direct Test, Gen-Probe Inc., San Diego, CA.
4 Murdoch DR. Molecular genetic methods in the diagnosis of lower respiratory tract infections. *APMIS*. 2004;112 (11-12):713-727.
5 Ieven M, Goossens H. Relevance of nucleic acid amplification techniques for diagnosis of respiratory tract infections in the clinical laboratory. *Clin Microbiol Rev*. 1997;10(2):242-256.
6 Espy MJ, Uhl JR, Sloan LM, et al. Real-time PCR in clinical microbiology: applications for routine laboratory testing. *Clin Microbiol Rev*. 2006;19(1):165-256.
7 Becker K, Pagnier I, Schuhen B, et al. Does nasal cocolonization by methicillin-resistant coagulase-negative staphylococci and methicillin-susceptible *Staphylococcus aureus* strains occur frequently enough to represent a risk of false-positive methicillin-resistant *S. aureus* determinations by molecular methods? *J Clin Microbiol*. 2006;44(1):229-231.
8 Desjardins M, Guibord C, Lalonde B, Toye B, Ramotar K. Evaluation of the IDI-MRSA assay for detection of methicillin-resistant *Staphylococcus aureus* from nasal and rectal specimens pooled in a selective broth. *J Clin Microbiol*. 2006;44(4):1219-1223.
9 Naimi TS, LeDell KH, Como-Sabetti K, et al. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA*. 2003;290(22):2976-2984.
10 Razonable RR, Emery VC. Management of CMV infection and disease in transplant patients. 27-29 February 2004. *Herpes*. 2004;11(3):77-86.
11 Romero JR, Kimberlin DW. Molecular diagnosis of viral infections of the central nervous system. *Clin Lab Med*. 2003;23(4):843-865.
12 Debiasi RL, Tyler KL. Molecular methods for diagnosis of viral encephalitis. *Clin Microbiol Rev*. 2004;17(4):903-925.
13 Romero JR. Diagnosis and management of enteroviral infections of the central nervous system. *Curr Infect Dis Rep*. 2002;4(4):309-316.
14 Cinque P, Bossolasco S, Lundkvist A. Molecular analysis of cerebrospinal fluid in viral diseases of the central nervous system. *J Clin Virol*. 2003;26(1):1-28.
15 Fredericks DN, Relman DA. Sequence-based identification of microbial pathogens: a reconsideration of Koch's postulates. *Clin Microbiol Rev*. 1996;9(1):18-33.

# New Developments in Proteomics

*Mark W. Massing MD, PhD; Judyta Misiurek; Srinivas R. Chadaram, PhD; Christine E. Marx, MD, MA; Roger Madison, PhD*

Genes are relatively static instruction sets for protein manufacturing processes in the cell. Fundamental genetic components (encoding regions) are linked, modified, and combined to create a wide variety of unique protein products. The total number of human protein-encoding genes has been estimated by the Human Genome Sequencing Consortium to be 20 000 to 25 000 genes.[1] The size of the proteome, the complete set of proteins expressed from the genome, is far larger and may exceed 100 000 proteins in humans.[2] Proteomics, the study of the proteome, is the next great challenge in biology and medicine and may rival genomics in complexity, costs, and benefits.

Legacy protein chemistry techniques such as chromatography, electrophoresis, and affinity columns have been used for decades and are an effective means to identify and characterize individual proteins. Proteomics is distinguished from protein chemistry in that proteomics tends to focus on patterns and systems of protein expression rather than on single components.[3] Proteomic techniques are capable of simultaneously examining the expression of thousands of proteins to identify unique patterns associated with phenotypes, tissues, disease states, and responses to environmental or therapeutic exposures.[4] Clinical proteomics encompasses an understanding of protein systems in pathologic processes leading to new diagnostic and prognostic tests, the discovery of protein targets for new pharmacologic therapies, and the identification of patients most likely to benefit from these therapies.[5]

*"New and emerging technologies in the application of mass spectrometry to the field of proteomics offer clinicians a means to rapidly identify markers of disease leading to new diagnostic tests and treatments."*

The central problem in clinical proteomics is to distinguish and identify multiple proteins related to a disease or condition, even when these proteins are initially unknown. The underlying assumption is that a given disease or condition is manifested by a pattern of protein expression that is unique and identifiable. Proteomic methods compare protein expression in patients with and without a given condition to identify unique patterns or profiles of protein expression related specifically to that condition. Once a condition-specific protein expression pattern is discovered, its constituent proteins are identified

**Mark W. Massing, MD, PhD**, is a senior REAP fellow at the Research Service of the Veteran Affairs Medical Center in Durham, North Carolina. He can be reached at madis001@mc.duke.edu or 508 Fulton Street, Durham, NC 27705.

**Judyta Misiurek** is a senior research technician at the Research Service of the Veterans Affairs Medical Center in Durham, North Carolina, and attends the University of Miami Miller School of Medicine.

**Srinivas R. Chadaram, PhD**, is a research fellow at the Research Service of the Veterans Affairs Medical Center in Durham, North Carolina, and the Department of Surgery at Duke University Medical Center.

**Christine E. Marx, MD, MA**, is an assistant professor at the Research Service of the Veterans Affairs Medical Center in Durham, North Carolina and the Mid-Atlantic Mental Illness Research, Education, and Clinical Center and the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center

**Roger Madison, PhD**, is a career research scientist at the Research Service of the Veterans Affairs Medical Center in Durham, North Carolina, and associate professor in the Departments of Surgery and Neurobiology at Duke University Medical Center.

as potential biomakers for diagnosis and prognosis and as targets for treatment.

Mass spectrometry (MS) has become a promising technique in proteomics following advances supporting the processing of large molecules.[4] Mass spectrometry enables the separation and characterization of proteins in a complex tissue sample based on their different physical and chemical properties. The 2002 Nobel Prize in chemistry was awarded to John Fenn and Koichi Tanaka for their pioneering work in this area. Tanaka's approach utilized laser induced protein ionization and led to the development of matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) in the 1980s and to surface-enhanced laser desorption/ionization mass spectrometry (SELDI-MS) during the 1990s.[6-8]

In practice, these MS techniques are carried out in a series of steps. First, proteins are extracted from tissues by disruption of cellular structures and removal of nonprotein components. Next, protein solutions are cocrystallized with a matrix substance on specially developed chemically inert (in the case of MALDI-MS) or chemically active (in the case of SELDI-MS) surfaces. The matrix facilitates ionization of proteins when excited by laser energy.

Mass spectrometry devices identify patterns of protein expression by measuring the abundance of proteins at different molecular weights with a technique known as time-of-flight (TOF) detection. Figure 1 illustrates the basic concept of TOF detection. Proteins are ionized when struck by laser light and "fly" (ie, leave the surface). Ionized proteins are then captured by a high voltage electrical field and are accelerated in a vacuum chamber. During this acceleration period, or "flight," proteins become separated based on their charge and mass, arriving at a detector at different times. The more massive the protein, the less it is accelerated and the later it arrives at the detector.

Proteins striking a detector after TOF separation create a signal with an intensity related to the number of molecules arriving at the detector. The greater the abundance of molecules, the greater is the amplitude of the signal. Proteins with similar masses and charges arrive at the detector at approximately the same time creating a high amplitude spectral "peak" (Figure 1). The pattern of peaks in a complex sample creates a spectrum—a unique fingerprint characterizing protein expression in a given tissue (Figure 2).

The MS spectrum graphically relates a protein's mass and charge (X-axis) to its abundance as measured by its signal intensity (Y-axis). Spectra from different tissue samples can be compared and common patterns of expression identified. Expression pattern differences can be mapped and analyzed. Peaks at similar mass-to-charge ratios (clusters) are identified across spectra (Figure 2) and relative signal amplitude differences are compared using sophisticated pattern recognition software to identify expression patterns that uniquely characterize specific diseases or conditions.

Recent developments in MS proteomics incorporate the use of chemically active surfaces on commercially available arrays known as protein chips.[9,10] Chemically active surfaces allow for on-chip selective extraction of proteins based on chemical properties to simplify processing of complex clinical samples.

Despite the promise of this new technology, a number of

**Figure 1.**
**Basic Components of a Laser Desorption-ionization Mass Spectrometry System Used in Clinical Proteomics.**

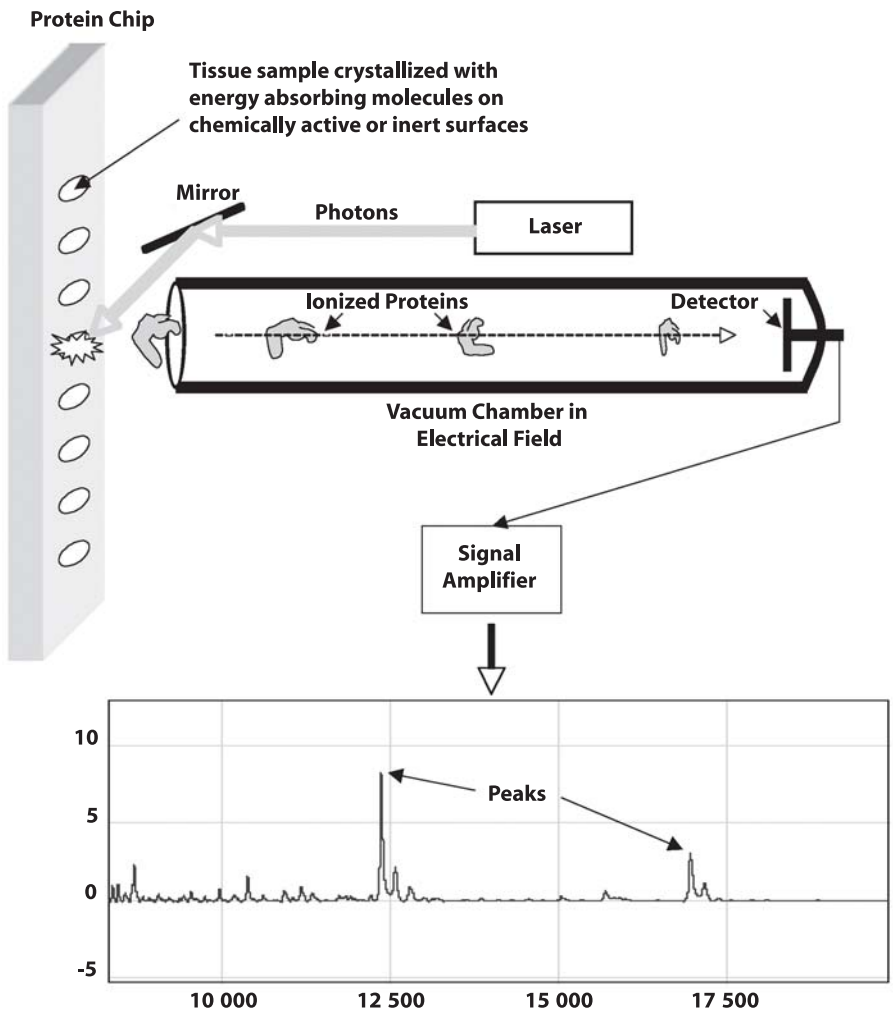
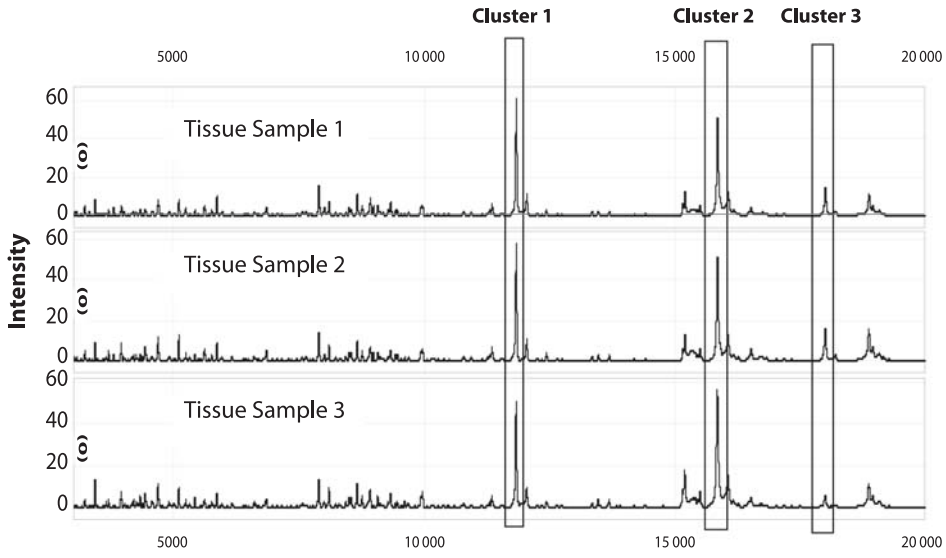


**Figure 2.**
**Spectra from Three Samples of Rat Quadriceps Muscle Showing Three Signal Peaks Sharing Mass-to-Charge Ratio Values (Clusters).**




technical obstacles impede its rapid adoption. Often the most difficult issue is defining and obtaining clinical samples suitable for proteomic analyses. Variations in patients, sample handling, and collection protocols constitute substantial challenges. The first step in any proteomics experiment is to obtain and prepare the tissue sample for processing. Tissue preparation is frequently the most resource intensive activity.

Investigators are currently developing and refining SELDI-MS protocols to process a variety of tissue types including serum/plasma, brain, cerebrospinal fluid, urine, tears, saliva, cells from washes and biopsies, and muscle. The earliest efforts at biomarker discovery with SELDI-MS focused on markers associated with various cancers, especially those remaining asymptomatic until late stages such as ovarian[11] and pancreatic[12] cancers. Diagnostic and prognostic tests for these diseases were desirable and tissue preparation protocols for blood were developed early and have been refined considerably over the years.[13]

An issue of critical importance for proteomics analysis of complex biological and clinical samples for discovery of biomarkers is the need for reduction of tissue sample complexity prior to MS analysis. Most tissue samples contain far too many proteins to be evaluated on a single protein chip. These complex samples are broken down into a series of less complex fractions based on the chemical properties of constituent proteins. Conventional methods such as fractionation of complex clinical samples by ionic exchange chromatography and new methods such as enriching low abundant proteins by affinity capture with a combinatorial library of ligands[14] provide much needed tools for processing complex biological and clinical samples for proteomics research.

Another major concern is ensuring that tissue preparation and subsequent processing is standardized and does not vary between samples within experiments. Tissue samples from different individuals are never uniform. Even if gross tissue mass is identical, differences in connective tissue, vascularization, and fat content may result in differences in tissue protein expression patterns.

In examining the entire proteome, it is frequently the case that multiple protein expression differences are found when comparing tissues from different sources or time frames. A challenging problem in proteomics is the identification of patterns of expression associated with a given condition of interest using voluminous experimental data.[15] Mass spectrometry analysis of the proteome can generate an intimidating amount of data. A single clinical tissue sample could generate many thousands of data points describing protein expression patterns. Even small experiments generate too much data to be processed manually. A variety of different approaches, frequently borrowed from genomics, have been used including decision tree analyses, genetic algorithms, and neural networks.[16-18] Development of standardized and universally accepted approaches to analyze protein expression patterns is a goal that has yet to be realized.

It is hard to overstate the potential clinical relevance of the application of MS to the field of proteomics. New and emerging technologies offer clinicians a means to rapidly identify markers of disease leading to new diagnostic tests and treatments. Objective screening tests for conditions such as psychiatric illness based on proteomic techniques could revolutionize the care of patients and lead to better treatments. However, it is important to temper our enthusiasm with an understanding of the challenges that await us as nascent proteomics technologies mature. Sound experimental protocols and analytic methods must keep pace with the rapid development of proteomics tools and hardware. A rush to process experiments without considering common standards and potential pitfalls could generate misleading results and wasted effort. With this caveat in mind, the upcoming era of proteomics should complement genomics and provide a direct clinical relevance not possible by genomics alone. **NCMJ**

*Acknowledgement: This work was made possible by a Research Enhancement Award Program (REAP) to the Veterans Affairs Medical Center in Durham, NC from the Biological Laboratory and Research Service of the Office of Research and Development of the Department of Veterans Affairs (RM principal investigator).*

## REFERENCES


1 Finishing the euchromatic sequence of the human genome. *Nature*. 2004;431:931-945.
2 Harrison PM, Kumar A, Lang N, Snyder M, Gerstein M. A question of size: the eukaryotic proteome and the problems in defining it. *Nucleic Acids Res*. 2002;30:1083-1090.
3 Liebler DC. *Introduction to Proteomics: Tools for the New Biology*. Totowa, New Jersey: Humana Press, Inc.; 2002:1-24.
4 Walker SJ, Xu A. Biomarker discovery using molecular profiling approaches. *Int Rev Neurobiol*. 2004;61:1-30.
5 Petricoin E, Wulfkuhle J, Espina V, Liotta LA. Clinical proteomics: revolutionizing disease detection and patient tailoring therapy. *J Proteome Res*. 2004;3:209-217.
6 Issaq HJ, Veenstra TD, Conrads TP, Felschow D. The SELDI-TOF MS approach to proteomics: protein profiling and biomarker identification. *Biochem Biophys Res Commun*. 2002;292:587-592.
7 Karas M, Hillenkamp F. Laser desorption ionization of proteins with molecular masses exceeding 10,000 daltons. *Anal Chem*. 1988;60:2299-2301.
8 Hutchens TW, Yip TT. New desorption strategies for the mass spectrometric analysis of macromolecules. *Rapid Commun Mass Spectrom*. 1993;7:576-580.
9 Tang N, Tornatore P, Weinberger SR. Current developments in SELDI affinity technology. *Mass Spectrom Rev*. 2004;23:34-44.
10 Reddy G, Dalmasso EA. SELDI ProteinChip(R) Array technology: Protein-based predictive medicine and drug discovery applications. *J Biomed Biotechnol*. 2003;4:237-241.
11 Zhang Z, Bast RC, Yu Y, et al. Three biomarkers identified from serum proteomic analysis for the detection of early stage ovarian cancer. *Cancer Res*. 2004;64:5882-5890.
12 Koopmann J, Zhang Z, White N, et al. Serum diagnosis of pancreatic adenocarcinoma using surface-enhanced laser desorption and ionization mass spectrometry. *Clin Cancer Res*. 2004;10:860-868.
13 Petricoin EF, Liotta LA. SELDI-TOF-based serum proteomic pattern diagnostics for early detection of cancer. *Curr Opin Biotechnol*. 2004;15:24-30.
14 Huang HL, Stasyk T, Morandell S, et al. Enrichment of low-abundant serum proteins by albumin/immunoglobulin G immunoaffinity depletion under partly denaturing conditions. *Electrophoresis*. 2005;26:2843-2849.
15 White CN, Chan DW, Zhang Z. Bioinformatics strategies for proteomic profiling. *Clin Biochem*. 2004;37:636-641.
16 Li L, Umbach DM, Terry P, Taylor JA. Application of the GA/KNN method to SELDI proteomics data. *Bioinformatics*. 2004;20:1638-1640.
17 Qu Y, Adam BL, Yasui Y, et al. Boosted decision tree analysis of surface-enhanced laser desorption/ionization mass spectral serum profiles discriminates prostate cancer from noncancer patients. *Clin Chem*. 2002;48:1835-1843.
18 Ball G, Mian S, Holding F, et al. An integrated approach utilizing artificial neural networks and SELDI mass spectrometry for the classification of human tumours and rapid identification of potential biomarkers. *Bioinformatics*. 2002;18:395-404.

# Specialized Testing in Hematopoietic Disorders Aids Diagnosis and Prognosis

*Matthew J. Snyder, MD*

## Introduction

The classification of hematopoietic, or bone marrow and lymph node, disorders (eg, leukemia, lymphoma, myelodysplastic syndrome, myeloproliferative syndrome) has changed significantly over the last 10 to 15 years. Historically, leukemias and lymphomas had been categorized largely by morphology (microscopic appearance). The resulting broad categories gave some prognostic and therapeutic guidance, but the heterogeneous nature of disease entities within each group limited the accuracy of the information.

The tide started turning in the early 1970s with the discovery of the so-called Philadelphia chromosome in patients with chronic myelogenous leukemia,[1] a blood disorder in which the bone marrow typically produces too many white blood cells, which have impaired function. The Philadelphia chromosome is a result of a chromosomal translocation that juxtaposes the gene *ABL* on chromosome 9 to the gene *BCR* on chromosome 22. This results in the production of an abnormal protein that causes the unregulated growth of bone marrow cells. This monumental discovery added focus to the genetic basis of many disorders, especially hematopoietic ones.

There are many methods in the clinical pathology laboratory to examine chromosomes and their respective genes. Karyotyping involves microscopic examination of the chromosome structure itself. It offers an overview of all the chromosomes and can detect some abnormalities. This method remains very useful, despite being time-consuming and requiring cells to divide in culture, a potential technical challenge. If a known, specific genetic abnormality is being sought, fluorescence *in-situ* hybridization (FISH) can be used to detect translocations, gene deletions, monosomies (loss of an entire chromosome), trisomies (gain of an entire chromosome), and other abnormalities. The most sensitive method for detecting targeted chromosomal abnormalities is the polymerase chain reaction (PCR). However, this is used on a somewhat more limited basis due to the technically demanding nature of the test and the general requirement of an unfixed specimen in some circumstances, although recent advances in PCR automation are making its use more widespread.

While the science of cytogenetics has been evolving, another technology called flow cytometry has found a vital niche in the categorization of leukemias and lymphomas. The power of this technology lies in its ability to help classify these disorders based on the pattern of expression of certain cell surface molecules and to detect a very tiny population of abnormal cells among predominantly normal ones.

*"Karyotype, FISH, PCR, and flow cytometry are being used currently in everyday practice to aid diagnosis and prognostication of hematopoietic disorders and to guide therapy. While each test can add an important level of understanding to a patient's disease, none of them should be used in isolation or without regard to other clinical information."*

**Matthew J. Snyder, MD**, is medical director of anatomic pathology at WakeMed Health & Hospitals. He can be reached at matsnyder@wakemed.org or 3000 New Bern Ave, Raleigh, NC 27610.

All of these technological advances are used in the clinical pathology laboratory, and data from these tests, in conjunction with morphologic features, form the foundation of the most recent classification scheme for disorders of the hematopoietic system from the World Health Organization (WHO).[2] This scheme is widely accepted by health care professionals around the world because it is based largely on genetic characteristics that have direct impact on treatment and prognosis. Elucidation of mechanisms by which these genetic abnormalities produce disease has led to the discovery of targeted therapies with dramatic clinical success. One example is imatinib mesylate (Gleevec® from Novartis Pharmaceuticals), which has proved a great therapeutic success for patients with chronic myelogenous leukemia.

Although targeted therapies are not available for many hematopoietic disorders, the genetic and flow cytometric characteristics of a hematopoietic disease can play an enormous role in evaluating an individual's prognosis and choosing the most appropriate therapy. These methodologies will be explained in greater detail as they relate to the new classification scheme of hematopoietic disorders, and examples of how the technologies are used for diagnostic, therapeutic, and prognostic purposes will be given.

## Karyotype

Karyotyping, the standardized arrangement and morphologic analysis of cell chromosomes, has long been used to diagnose congenital genetic abnormalities, and its significance in evaluating hematopoietic diseases is now well entrenched. Since karyotyping requires cells to divide, this technique is useful in the evaluation of primary bone marrow diseases such as myelodysplastic syndrome, myeloproliferative disease, and acute leukemia. Diseases producing more mature cells, such as many types of lymphoma, are difficult to study using this method because they do not divide readily in culture. Multiple, well-documented cytogenetic abnormalities have been described in patients with myelodysplastic syndrome (MDS). These include abnormalities involving chromosomes 5 and 7 and trisomy 8.[2] In conjunction with morphology, detection of these abnormalities is used to help make the diagnosis of MDS and to track the progression of disease. For example, as some patients with MDS progress toward acute leukemia, additional cytogenetic abnormalities are acquired and serial karyotype analyses can detect this evolution. These changes help predict which patients will persist with a relatively indolent disease versus those who are at a greater risk of developing acute leukemia. Also, there is a particular type of MDS, known has 5q minus syndrome, in which a unique set of clinical and morphologic findings exist. The loss of the genetic material on the long arm of chromosome 5 confers a good prognosis with a very low risk of progression to acute leukemia.[3]

There are several acute leukemias that are now classified primarily based on cytogenetic findings that directly affect treatment and prognosis (Table 1). One example is acute promyelocytic leukemia (APML), which is characterized typically by a translocation of the *PML* gene on chromosome 15 next to the *RAR*α gene on chromosome 17. The translocation results in the overproduction of the retinoic acid receptor, making retinoic acid an essential component of the therapy by inducing maturation of the abnormal promyelocytes.[4] The cytogenetic

**Table 1.**
**Examples of Genetic Findings Used for Prognosis**

| Disease based on WHO classification | Prognosis | Characteristic flow cytometric or morphologic findings |
|---|---|---|
| Myelodysplastic syndrome | | |
| Multiple chromosomal abnormalities or complex karyotypes | Poor | |
| 5q minus | Good | X |
| Acute myeloid leukemia | | |
| Translocation (8;21) | Good | X |
| Inversion 16 | Good | X |
| Translocation (15;17) | Good | X |
| Abnormalities of 11q23 | Intermediate | |
| Acute lymphoid leukemia | | |
| Hyperdiploid (>50 chromosomes) | Good | |
| Translocation (12;21) | Good | X |
| Translocation (9;22) | Poor | |
| Abnormalities of 11q23 | Poor | X |
| Translocation (1;19) | Poor | |
| Hypodiploid | Poor | |
| Chronic lymphocytic leukemia/Small lymphocytic lymphoma | | |
| Trisomy 12 | Poor | |
| Deletion 13q14 | Good | |
| Deletion 17p13 | Poor | |
| Deletion 11q22-23 | Poor | |
| Multiple myeloma | | |
| Deletion 13q14 | Poor | |
| Translocation (11;14) | Good | |
| Deletion 17p13 | Poor | |

finding is important to recognize due to this unique therapy. It also predicts a good prognosis, and bone marrow transplantation is often not considered as a treatment option. This is in contradistinction to many other types of acute leukemia for which it occasionally offers the only chance for extended remission.

## Fluorescence *In-situ* Hybridization (FISH)

This technology offers similar information to a karyotype but generally detects abnormalities on a much more targeted part of the genome. However, FISH has the advantage of not requiring dividing cells and, hence, can be performed much more quickly and on a wider variety of specimens than a karyotype. Cells are incubated with fluorescently-labeled primers (manufactured segments of DNA) that bind, or hybridize, to a specific DNA sequence within the cell. The cells are then viewed under fluorescent microscopy and the fluorescent signals analyzed. The relatively rapid turnaround time is important in certain situations, such as in APML. If certain features present in an acute leukemia raise the suspicion of APML, FISH for the translocation can confirm the diagnosis and appropriate therapy can begin promptly. This is vital in this setting because conventional chemotherapy can actually be harmful for patients with APML. Another instance where FISH plays a role in rapid confirmation of a diagnosis is Burkitt lymphoma. This lymphoma grows very rapidly due to overreplication of the *c-MYC* gene on chromosome 8 that causes the cells to remain in a near constant state of division. The confirmation of Burkitt lymphoma is important because treatment typically begins very soon after diagnosis, and it is treated more aggressively than other types of lymphoma.[5]

FISH plays a crucial role in prognostication of diseases that have historically been difficult to characterize by karyotype because they do not divide readily in culture. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and multiple myeloma are two notable examples. (See Table 1.) A panel of FISH studies is typically performed on these to arrive at a genetic profile of an individual's disease. This information is then integrated with clinical parameters to arrive at an overall prognosis that guides treatment options. Consequently, some patients are treated with a "watch and wait" approach because of a very low risk of significant progression, whereas others are treated very aggressively at initial diagnosis because of a significant risk of rapid progression. Prior to these genetic advances, the outcome of patients with CLL/SLL and multiple myeloma was quite variable, and there were only limited ways to predict how an individual's disease would behave.

## Polymerase Chain Reaction (PCR)

Polymerase chain reaction is an exquisitely sensitive method of genetic investigation and has many applications. Relevant to this discussion, PCR is used to detect genetic abnormalities and, in some instances, to measure the quantity of the abnormality. Although advances in automation are currently available, PCR remains time consuming and requires relatively high technical expertise due to the sensitivity of the method to contamination. The test can use an unfixed sample or, for some PCR primers, a fixed sample. A series of tightly controlled steps amplify, by making many copies, and then detect a genetic target. A practical application of PCR in evaluating lymphomas is the detection of clonality in B and T cell lymphomas. Detecting monoclonality can confirm malignancy, but it is generally not used as the sole determining factor. Furthermore, the PCR characteristics of an individual's lymphoma are often unique and can be used to determine if a subsequent tumor is a recurrence of the former lymphoma or a new primary. This distinction is often of prognostic and therapeutic importance.

Quantitative analysis precisely measures the amount of PCR product, and this can be of value in some settings. Quantitation of the gene fusion product resulting from translocation between chromosomes 9 and 22 that characterizes chronic myelogenous leukemia (CML) can be followed over time to assess the response to imatinib mesylate, the targeted therapy for CML. A negative or decreasing quantitative PCR test is reassurance that the current treatment regimen is controlling the disease, whereas an increasing amount of PCR product could trigger an increase in the dose of imatinib mesylate or consideration of other treatment, such as bone marrow transplant.

## Flow Cytometry

Flow cytometry is a technology that detects the presence and quantity of certain molecules that exist on cell surfaces or in the cytoplasm. By examining the pattern of expression (presence) of these molecules, cells from peripheral blood, bone marrow, or a lymph node are grouped into populations of similar cells. Flow cytometry is used primarily as a diagnostic aide in the classification of lymphoma and leukemia, and, as mentioned, the diagnostic categories in the WHO classification[2] carry therapeutic and prognostic significance. One practical application of flow cytometry allows classification of acute leukemia into two major categories, myeloid and lymphoid. Lymphoid tumors can be further subcategorized into B and T lymphoblastic types. These categories of acute leukemias are treated differently and carry different prognoses, especially when correlated with genetic findings. (See Table 1.) Some acute leukemias express molecules that are not characteristic of a particular cell line, known as aberrant expression. These aberrant markers can be unique to an individual's disease and offer a useful way to detect minimal residual disease by easily separating the abnormal cell population from primarily normal cells.

The molecules that are detected by flow cytometry can serve as a surrogate marker for some of the genetic findings described earlier. (See Table 1.) For example, APML has a distinctive profile by flow cytometry in that it lacks expression of HLA-DR and CD34, two molecules that are very frequently present on other types of acute leukemia.[6] Along with morphology, these findings prompt the pathologist to investigate for the characteristic translocation.

## The Future

The methods of molecular and genetic evaluation discussed so far originated as research tools, and their utility in the clinical pathology laboratory has evolved quickly. Another type of test that might make this transition is gene microarray technology, sometimes called "gene chip." The results of this test, on a research basis, have been shown to be a very powerful tool to further evaluate how hematopoietic diseases relate to each other and, in some instances, offer an even clearer understanding of the mechanism of disease, prognosis, and optimal therapy.[7] Researchers hope that the identification of specific gene expression in these diseases will lead to effective gene-targeted therapies. This assay entails extracting DNA from tissue and simultaneously analyzing for the overexpression or underexpression of thousands of genes to create a gene expression profile. At present, the gene microarray chips are generally too expensive for routine clinical testing, and the amount of data generated can take many hours to analyze using today's fastest computers. Moreover, storage of these massive amounts of data presents another challenge. Great advances in automation of this test have been made recently, and the cost has also decreased substantially in just a few years. As all of these technological and economic aspects improve, this test will very likely play some role in the evaluation of hematopoietic disorders and may subsequently alter the classification of these diseases.

**Table 2.**
**Examples of Genetic Findings Used for Diagnosis**

| Genetic Abnormality | WHO Classification Diagnosis |
|---|---|
| Translocation involving 8q24 | Burkitt lymphoma |
| Translocation (14;18) | Follicular lymphoma |
| Translocation (11;14)* | Mantle cell lymphoma |
| Translocation (11;18) | Extranodal marginal zone lymphoma |
| Translocation (2;5) | Anaplastic large cell lymphoma |

* This translocation defines mantle cell lymphoma but has also been reported in some cases of multiple myeloma.[2] These diseases can be differentiated by morphology and flow cytometry.

## Conclusion

Karyotype, FISH, PCR, and flow cytometry are being used currently in everyday practice to aid diagnosis (Table 2) and prognostication of hematopoietic disorders and to guide therapy. While each test can add an important level of understanding to a patient's disease, none of them should be used in isolation or without regard to other clinical information. The pathologist plays a critical role in this process by correlating the microscopic morphology with these data from specialized tests and making an overall assessment. Pathologists oversee the performance of these tests, interpret the results in light of the clinical context, and communicate this information to oncologists, radiation oncologists, surgeons, and other treating physicians. This invaluable information about an individual patient's disease has a direct, and often dramatic, impact on the type and duration of therapy and offers an indication of the individual patient's prognosis. **NCMJ**

### REFERENCES


1 Rowley, JD. A new consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine fluorescence and Giemsa staining. *Nature*. 1973;243:290-293.

2 Jaffe ES, Harris NL, Stein H, Vardimann JW, eds. World Health Organization Classification of Tumours. *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2001.

3 Boultwood J, Lewis S, Wainscoat JS. The 5q- syndrome. *Blood*. 1994;84:3253-3260.

4 de The H, Chomienne C, Lanotte M, Degos L, Dejean A. The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. *Nature*. 1990;347:558-561.

5 Weitzmann DJ, Greenberg ML, Thorner P. Treatment of non-Hodgkin's lymphoma in childhood. In: Wiernik PH, Canellos GP, Kyle RA, CA Schiffer. *Neoplastic Diseases of Blood*. 1 vol. 2nd ed. New York, NY: Churchill Livingstone; 1991:753-768.

6 Orfao A, Chillon MC, Bortoluci AM, et al. The flow cytometric pattern of CD34, CD15, and CD13 expression in acute myeloblastic leukemia is highly characteristic of the presence of PML-RARalpha gene rearrangements. *Haematologica*. 1999;84:405-412.

7 Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B cell lymphoma identified by gene expression profiling. *Nature*. 2000;403:503-511.

# Human Papillomavirus Testing for Precancerous Lesions of the Cervix

*Fidel A. Valea, MD*

## Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted viral infection. An estimated 20 million Americans are currently infected with HPV and approximately 6 million new cases develop each year with the majority occurring in the adolescent age group.[1] The annual burden of cervical HPV-related diseases in the United States is estimated to cost between $2.25 billion and $4.6 billion, and the annual burden of cervical cancer is approximately $181.5 million to $393 million.[2] Persistent HPV infection is the most important risk factor for the development of cervical cancer and constitutes the basis for screening. The incidence of cervical cancer has decreased in every country that instituted mass screening for the disease.

Until recently, screening for cervical cancer was predominantly cytology based, relying on the detection of dysplasia, or cellular abnormalities, which are a precursor to cervical cancer. Screening with conventional smears has a sensitivity ranging from 50% to 60%. Despite this poor sensitivity, it was responsible for a 75% reduction in the incidence of cervical cancer in the United States since its introduction as a screening test in 1949.[3] With the advent of liquid-based cytology, where the sample is suspended in a fixative solution instead of smeared on a slide, cytologic screening is not only more sensitive, but also more versatile. Liquid-based cytology enables cytotechnologists to perform further tests on the specimen in solution, such as HPV DNA testing, which cannot be performed on the slide. Recent well-controlled clinical trials with verification of positive and some negative results have found sensitivities of 70% to 80% for conventional cervical cytology and 85% to 95% for liquid-based cytology.[4,5] Despite this, even the liquid-based methods can miss between 15% and 35% of high-grade dysplasia or cancer.[6] Unfortunately, given the current health care dollars spent on HPV infections, even small imperfections in the screening process can have significant financial implications.

*"The annual burden of cervical HPV-related diseases in the United States is estimated to cost between $2.25 billion and $4.6 billion."*

## Computer-Assisted Screening Technology

Liquid-based screening was first introduced over a decade ago. It is now the preferred method of screening, and its versatility has paved the way for other advancements in cervical cancer screening. The specimen in suspension can be filtered and sprayed evenly on a slide, allowing for less artifact and a more consistent specimen to evaluate, which results in fewer false negatives. The uniformity and clarity also enable the use of computer-assisted screening using an automated microscope to further decrease false negative results and increase the ability to identify the truly abnormal Pap test. There are currently 2 Food and Drug Administration (FDA) approved automated systems: the Focal PointTM Slide Profiler (FPSP) and the ThinPrep® Imaging System (TPIS).[7,8] They both use the principle of morphometry, the appearance and size of the cells, and both use slides created with the liquid-based technology. However, the FPSP is also approved for screening conventional Pap test slides.

The FPSP system is only approved for screening specimens from a defined low-risk population of patients. The slides are evaluated using FPSP image analysis software and assigned to

**Fidel A. Valea, MD**, is an associate professor of gynecologic oncology at Duke University Medical Center. He can be reached at valea001@mc.duke.edu or Box 3079 DUMC, Durham, NC 27710.

one of following groups: (1) *negative for intraepithelial lesion or malignancy*, needing no further review; (2) *review*, requiring manual review by a cytotechnologist; (3) *quality control*, requiring manual review of slides with the highest probability of having an abnormality; and (4) *process review*, requiring manual review of slides that cannot be successfully processed by the FPSP system. This system limits the amount of manual review by a cytotechnologist and focuses him/her on the slides of concern. It can use any of the currently available liquid-based systems.

The TPIS system can only evaluate slides that use the liquid-based thin layer technology, but it can be used in both low- and defined high-risk patient populations. It scans every slide and identifies cells of interest and the 22 fields that contain them. The cytotechnologist reviews these fields using an automated microscope and assigns them as no intraepithelial lesions if all fields are judged to be normal or, if any cell is suspicious, the entire slide is reviewed and abnormal cells are evaluated by a pathologist. With this technology, all slides are reviewed, but the computer directs the cytotechnologist to the areas of concern.

## HPV Testing

The ability to detect HPV DNA in the liquid-based Pap vial has led to a paradigm shift in cervical cancer screening. Instead of just looking for cellular abnormalities, the current technology allows for the assessment of the causative agent, HPV. However, there are over 100 different types of HPV and each has a different oncogenic risk. For clinical simplicity, they are usually stratified into two groups: low and high risk for the development of cervical cancer. In 2001, the results of the landmark *Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS)* were published.[6] They compared three different methods of triaging patients with equivocal Pap testing results, atypical cells of uncertain significance (ASCUS). The results indicated that women with an ASCUS Pap test can undergo high-risk HPV DNA testing from the same liquid-based Pap test vial to evaluate for the presence of high-risk DNA. If high-risk DNA is present they should undergo further diagnostic evaluation. But, if a woman was high-risk HPV DNA negative, she had less than a 1% chance of developing a high-grade lesion within the year and could undergo routine screening the following year. The reported sensitivity of this combination of tests was 96%. As a result, fewer women were referred for costly diagnostic tests and reflex high-risk HPV DNA testing became the recommended management for women with ASCUS Pap test results.

As a result of numerous studies confirming the low prevalence of HPV in women over the age of 30, high-risk HPV DNA testing can be offered to women in addition to the liquid-based Pap test.[9] This is different than reflex testing because it is done in conjunction with, rather than as a result of, the liquid-based Pap test. If both Pap test and HPV test are negative, the woman can be rescreened in three years because she is at very low risk of developing a high-grade lesion during this time. Unfortunately, this is only cost effective in the 30 and older age group because the prevalence of HPV in the younger age group is so high.

## HPV Vaccine

In June of 2006, the FDA approved the first HPV vaccine, Gardasil®, a quadrivalent vaccine against HPV 6 and 11, the low-risk types associated with 90% of anogentital warts and low-grade lesions, as well as HPV 16 and 18, the high-risk types responsible for 70% of high-grade lesions and cervical cancer.[3] Cervarix®, a vaccine against HPV 16 and 18, was also developed, but is not yet approved by the FDA. Both vaccines approach 100% efficacy in the prevention of HPV 16 and 18 associated high-grade lesions in the patients that received vaccination before contact with either virus. Gardasil® is also effective at preventing the low-grade lesions and anogentital warts associated with HPV types 6 and 11.[10] Based on available data, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices suggested routine vaccination for girls as young as 9 years of age.[11] Several other groups such as the American College of Obstetricians and Gynecologists have also supported these recommendations.[12] Patients that are HPV naïve (ie, women who have never been exposed to the virus) will be best served by this vaccine because they have the most to gain. Although its utility in males is still not proven, if efficacy is shown, vaccination for males may be recommended as well. The true impact of the HPV won't be realized for several years, but its impact on the low-grade lesions may be apparent sooner.

## Summary

As new technologies are introduced that increase the sensitivity of detecting patients at risk and the incidence of cervical cancer continues to decrease in the US, annual screening for this disease may actually be overscreening. It has been shown that the screening interval can safely be increased to every 2 years if liquid-based testing is performed with reflex HPV testing in patients under 30 and can be increased to every three years in patients over the age of 30 if they are done together and both are negative.[13,14] As we move into the age of risk stratification as a screening tool with HPV testing and liquid-based screening, it is imperative that the aforementioned recommendations are followed in order to keep the costs of screening at a minimum. Unfortunately, despite data confirming its safety and efficacy, many patients are unconvinced.[15] The overwhelming respondents in one series would still seek to obtain annual screening. In order to complete the paradigm shift in the screening for cervical cancer using the current technologies, more education will be required of the public and health care community to understand and accept the differences, most notably the increased screening interval. The true effects of the HPV vaccine will not be known for some time. Therefore, appropriate screening is still imperative even for those vaccinated because it does not offer complete protection from other strains of the HPV virus. **NCMJ**

## REFERENCES


1 Weinstock H, Berman S, Cates W Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. *Perspect Sex Reprod Health*. 2004;36:6-10.

2 Fleurence RL, Dixon JM, Milanova TF, Beusterien KM. Review of the economic and quality-of-life burden of cervical human papillomavirus disease. *Am J Obstet Gynecol*. 2007;196:206-212.

3 Saslow D, Castle PE, Cox JT, et al. American Cancer Society guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin*. 2007;57:7-28.

4 Clavel C, Masure M, Bory JP, et al. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. *Br J Cancer*. 2001;84:1616–1623.

5 Hutchinson ML, Zahniser DJ, Sherman ME, et al. Utility of liquid-based cytology for cervical carcinoma screening: results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma. *Cancer*. 1999;87:48–55.

6 Solomon D, Schiffman M, Tarone B. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. ASCUS-LSIL Triage Study (ALTS) Group. *J Natl Cancer Inst*. 2001;93:293–299.

7 Focal PointTM Slide Profiler. Available at: http://www.tripathimaging.com/nonus_products/nonus_fp.html. Accessed March 23, 2007.

8 ThinPrep® Imaging System. Available at: http://www.thinprep.com/pap-test/thinprep-imaging.html. Accessed March 23, 2007.

9 Wright TC, Schiffman M, Solomon D, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. *Obstet Gynecol*. 2004;103:304-309.

10 Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomized double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol*. 2005;6:271-278.

11 Centers for Disease Control and Prevention. HPV vaccine [human papillomavirus (HPV) and the HPV vaccine]. Atlanta, GA: Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/nip/vaccine/hpv/. Accessed March 25, 2007.

12 Human papillomavirus vaccination. ACOG Committee Opinion No. 344. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2006;108:699–705.

13 Goldie SJ, Kim JJ, Wright TC. Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more. *Obstet Gynecol*. 2004;103:619-631.

14 Bidus MA, Maxwell GL, Kulasingam S, et al. Cost-effectiveness analysis of liquid-based cytology and human papillomavirus testing in cervical cancer screening. *Obstet Gnecol*. 2006;107:997-1005.

15 Sirovich BE, Woloshin S, Schwartz LM. Screening for cervical cancer: Will women accept less? *Ann J Med*. 2005;118:151-158.

# Automation in the Clinical Pathology Laboratory

*Michael Weinstein, MD, PhD; Grover Smith, PhD*

A large proportion of hospital pathology laboratories in the US were built or renovated in the 1960s or 1970s, and prevailing medical practice and the medical economics of the time led to common design themes. The forces felt by laboratory directors and managers today are considerably different from those that shaped the labs of the earlier era. A widening gap between what is desired from many laboratories and what they are physically capable of delivering is becoming increasingly apparent. The requirement for timely, accurate, well-communicated laboratory results is crucial. Approximately 70% to 80% of major clinical decisions are based, at least in part, upon information coming from the pathology laboratory.[1,2] Thus, the impact of a successful laboratory on the efficiency and quality of care is far-reaching. Current pressures for design and process change include cost, turnaround time, the tightening technologist market, and reduction in clerical and preanalytical errors.

### Cost

The advent of diagnosis-related group-based reimbursement for inpatients shifted hospital laboratories from revenue generators to cost centers. Since then, the requirement to reduce the cost of testing has been relentless.

### Turnaround Time

The desire to reduce turnaround times stems from both the impact of rapid delivery of data-based therapy on outcomes in some circumstances (eg, chest pain and stroke protocols) and the drive to reduce hospital lengths of stay.

### Tightening Technologist Labor Market

The average age of medical technologists is continuing to increase and, in some markets, as many as 84% of laboratories report that finding and hiring medical technologists is either difficult or extremely difficult.[3]

### Reduction in Clerical and Preanalytical Errors

Recent years have seen increasing national awareness that a significant number of poor outcomes for hospitalized patients are avoidable. Clerical and identification errors are responsible for a large fraction of such outcomes, and as many as 40% of errors occur during the preanalytical phase of testing. Reduction of human involvement in this process can result in improved patient safety, with fewer errors due to sample misidentification. Automation can also reduce sample processing time.

While our primary intention is to discuss automation in the clinical pathology laboratory, it must be emphasized that, ideally, implementation of automation should be coupled with process review. Automation often allows optimization of processes in ways that are not possible in a manual laboratory, and implementation of automation without thorough assessment of current laboratory processes is likely to result in missed

*"Thus, the impact of a successful laboratory on the efficiency and quality of care is far-reaching. Current pressures for design and process change include cost, turnaround time, the tightening technologist market, and clerical and preanalytical errors."*

**Michael H. Weinstein, MD, PhD**, is director of pathology laboratories at WakeMed Health and Hospitals.

**Grover Smith, PhD**, is deputy director of pathology laboratories at WakeMed Health and Hospitals. He can be reached at gsmith@wakemed.org or PO Box 14045, Raleigh, NC 27620-4045.

opportunities. The flow of specimens and information and the activities of laboratory personnel should be examined with fresh eyes. Although this reevaluation may be difficult, it represents a crucial responsibility of the laboratory leadership, and everything should be put on the table. In particular, all preanalytical processing steps should be optimized to gain the full benefit afforded by automation. Container selection, specimen collection, specimen labeling, identification, receiving, and accessioning, and, ultimately, specimen tracking through the laboratory should be reevaluated. Autoverification of results, reporting methods, specimen retrieval for add-on testing, and ease of result interpretation are also vital considerations as processes are examined. Merely recapitulating the manual laboratory with machinery is not likely to reap the greatest possible benefits in efficiency and service improvement from the expenditure of resources.

Laboratory automation reduces the number of steps in testing requiring human intervention. When suitably implemented, automation reduces turnaround times for many tests. Automated systems do not reduce turnaround times by virtue of an ability to perform any individual step faster than a skilled technician does. Instead, these systems operate at or near maximum throughput up to capacity and do not suffer from potential lapses of attention. They allow a smaller number of skilled medical technologists to operate the instruments in a large laboratory. A specific example is the automated location and retrieval of specimens stored in a refrigerated stockyard for add-on testing. This does not require any human intervention, saves time, and avoids human error. With automation, the technologists expend a greater fraction of their time and energy on judgment tasks, making assessments and decisions that require their training and intelligence. Thus, the affect of the tightening labor market can be blunted.

The combination of automation and computerized interfaces has the potential to reduce the risk of clerical and identification errors. Primary sources of such errors are the preanalytical phase, the postanalytical phase, and, less commonly, any point in the analytical phase in which there is a hand-off from one person to another. Positive patient identification entails unique bar coding of the patient armband. Corresponding unique bar codes are printed at the bedside on specimen labels, which allow each specimen to be tracked during its travel through the automated system. Results are unerringly associated with the proper patient. In combination with a robust laboratory information system, this has the potential to drastically reduce errors, especially in the preanalytical phase of testing.

It is not clear a priori that the capital expenditure required to purchase the equipment to automate any individual laboratory will eventuate in an overall cost reduction. Moreover, the physical layout of some laboratories may not be amenable to large-scale automation. Thus, careful financial analysis must take into account current and projected specimen volumes, personnel costs based upon efficient management of laboratory staff, and the cost of the automation equipment and any required renovations of the laboratory space. Another factor that should be considered is that consistently short turnaround times may obviate a clinically relevant need for some types of point-of-care testing, which is usually manifoldly more expensive than testing within the laboratory.

In summary, the circumstances in which pathology laboratories now find themselves are very different from those that drove the design of a great fraction of laboratories decades ago. Laboratory automation can be a powerful tool to help many laboratories meet the challenges of the current environment and pressures. **NCMJ**

## REFERENCES


1 Becich, MJ. Information management: Moving from test results to clinical information. *Clin Leadersh Manag Rev*. 2000;14:296-300.
2 Boone, DJ: Quality in laboratory medicine. *Accred Qual Assur*. 2005;10:76-77.
3 G-2 Survey shows high marks for lab automation. *Diagnostic Testing and Technology Report*. 2005;6(2):5-10.

# Point-of-Care Testing:
## Guidelines and Challenges

*Robert L. Sautter, PhD, HCLD (ABB), Edward H. Lipford, MD*

Laboratory diagnostics play an important role in managing patients. With the pressures to reduce hospital length of stay and with newer therapy options, the laboratory has been asked to decrease the turnaround time from sample to result. Therefore, point-of-care testing (POCT), testing near the patient or bedside, was developed to generate quicker results. The goal of POCT is to provide the clinician with rapid results, which can improve patient outcomes and quickly supply therapeutic interventions as compared to those results obtained from the core laboratory.[1] Laboratory point-of-care testing is not new; however, it experienced a veritable explosion in manufacturing, clinical oversight, and regulations following the "waived provision" of the Clinical Laboratory Improvement Amendments (CLIA) of 1988.[1,2,3] The number of laboratories holding a Certificate of Waiver increased from 67 294 in 1993 to 105 138 in 2004.[3] In addition, the number of Medicare Part B waived tests performed increased from 14 million to over 23 million between the years 2000 and 2004.[3] (See Table 1.) Inherent with POCT growth come challenges in performing high quality accurate testing. Decreasing laboratory errors and improving patient safety must also be considered as POCT increases.

The Centers for Medicare and Medicaid Services (CMS) regulates laboratory testing on humans through CLIA to ensure quality testing. CLIA classifies tests as "waived complexity," "moderate complexity,"[a] and "high complexity" based upon criteria developed by the federal Department of Health and Human Services. Waived complexity tests are simple laboratory examinations that are approved for home use and which employ methodologies that are simple and accurate. They render the likelihood of erroneous results negligible or pose no risk of harm to the patient if the test is performed incorrectly. Quality standards for moderately and highly complex tests are designated for proficiency testing, patient test management, quality control, personnel qualifications, quality assurance, and quality control.[2] The more complex the test, the more stringent the testing requirements. A complete listing of the tests by classification can be found on the website of the Center for Devices and Radiological Health of the US Food and Drug Administration.[4]

*"When considering that millions of laboratory tests are performed at the point-of-care each year, it is imperative that we, as health care providers, do everything we can to dispense quality laboratory care for all patients."*

a An additional subcategory classification under moderate complexity is "provider-performed microscopy." It was developed as a special consideration to allow laboratories that are otherwise classified as "waived" to perform moderately complex tests utilizing microscopic analysis.[3]

**Robert L. Sautter, PhD, HCLD (ABB)**, is director of microbiology and point-of-care with Carolinas Laboratory Network at Carolinas Healthcare System and a member of Carolinas Pathology Group, PA. He can be reached at Robert.Sautter@carolinashealthcare.org or PO Box 34455, Charlotte, NC 28234-4455.

**Edward H. Lipford, MD**, is medical director of Carolinas Laboratory Network at Carolinas Healthcare System and a member of Carolinas Pathology Group, PA.

**Table 1.**
**Increases in Waived Analytes and Test Systems, Certificate of Waiver Laboratories, and Medicare Part B Reimbursed Waived Testing, 1993–2004**

| Waived testing measurement parameter | 1993 | 1998 | 2000 | 2003 | 2004 |
|---|---|---|---|---|---|
| No. of analytes for which waived test systems are available | 9 | 40 | 53 | 74 | 76 |
| No. of waived test systems* | 203 | 608 | 832 | 1495 | 1638 |
| No. of laboratories with a Certificate of Waiver | 67 294 | 78 825 | 85 944 | 102 123 | 105 138 |
| Percentage of laboratories with a Certificate of Waiver† | 44% | 50% | 52% | 57% | 58% |
| No. of Medicare Part B reimbursed waived tests | § | § | 14 663 751 | 20 781 297 | 23 041 693 |
| Percentage of Medicare Part B reimbursed laboratory testing that is waived | § | § | 6.5% | 7.8% | 8.1% |
| Medicare Part B payment amount for waived tests | § | § | $69,765,453 | $112,247,706 | $128,169,398 |

* Numbers reflect multiple names under which individual tests are marketed and might include waived tests no longer sold.

† Does not include Clinical Laboratory Improvement Amendments (CLIA) exempt laboratories in New York and Washington

§ Not available

Source: Centers for Disease Control and Prevention. Good laboratory practices for waived testing sites, survey findings from testing sites holding a certificate of waiver under the clinical laboratory improvement amendments of 1988 and recommendations for promoting quality testing. Recommendations and reports. *MMWR*. 2005;54(RR-13):1-23.

Several regulatory bodies are primarily involved in inspections for the POCT laboratory. Point-of-care testing occurs on floors of hospitals, nursing homes, clinics, physician offices, radiology suites, and any other location where testing is classified as a regulated laboratory test. Laboratories may apply for a Certificate of Waiver, Certificate of Compliance, or a Certificate of Accreditation.[b,3] Those that are accredited are usually accredited by private peer organizations such as the College of American Pathologists (CAP) and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). These two organizations have been inspecting hospital laboratories inside health systems for quite some time. Recently, both the CAP and JCAHO have been granted "deemed status" to inspect laboratories for CMS.[5] Laboratories are inspected in regard to directorship, quality assurance, quality control, testing personnel (training and competency), reporting, and verification of testing procedures. Accredited laboratories are inspected on a two-year cycle. All inspections are now performed on an unannounced basis. However, those laboratories that obtained a certificate of compliance or certificate of waiver have not been inspected on a regular basis in the past due to a lack of resources available to inspect the thousands of laboratories doing this testing.

Two state pilot inspection programs of physician office laboratories (POL) with certificates of waiver showed that a significant number of laboratories had serious deficiencies with regard to their compliance with regulations.[3] Testing without employee training, failure to document procedures, or failure to follow manufacturer's packaged instructions were among the most concerning deficiencies identified. Subsequent inspections of more than 1000 laboratories confirmed these problems nationwide. CMS plans to inspect only 2% of the waived laboratories yearly. Inspection results in several states have shown improvement; however, without oversight overall improvement may be difficult to achieve. The executive summary of the waived laboratory project from CMS included this review of compliance with manufacturer's instructions for performance of tests:

> *Expanded pilot studies by the Centers for Medicare and Medicaid Services (CMS), formerly the Health Care Financing Administration (HCFA), of laboratories issued a certificate of waiver (COW) and provider performed microscopy procedures (PPMP) laboratories demonstrate that 50% of laboratories performing waived tests do not follow the manufacturer's instructions or do not have manufacturer's instructions. The only CLIA requirement for COW laboratories is to follow the manufacturer's test instructions. These findings mirror those of previous pilots conducted by Colorado, Ohio, New York and most recently, the Office of the Inspector General (OIG). If these percentages are nationally representative, as many as 60,000 laboratories may not be following manufacturer's instructions and may be performing tests incorrectly to potentially harm patients.*[6]

b A Certificate of Waiver is issued to a laboratory that only performs waived tests. A Certificate of Compliance is issued to a laboratory following inspection by the state department of health that determines the laboratory is compliant with CLIA requirements. A Certificate of Accreditation is issued to a laboratory based on accreditation.

Tests designed to be performed in the point-of-care setting are manufactured to be relatively fast and easy to operate. The results should be made available while the patient is present or so that the provider can respond to him during the visit. Many point-of-care tests offer these advantages and ideally result in better outcomes for the patient.[7] Pressures to see more patients in the office or to free space in an emergency department have stimulated a real need for faster results. However, faster is not always better if the result's timeliness has little or no impact on the outcome of care.[8] Unfortunately, there are few studies available showing that patient outcomes improve with tests performed at point-of-care location over those performed in the clinical laboratory. Therefore, more research is needed in this area.[7]

When considering that millions of laboratory tests are performed at the point of care each year, it is imperative that we, as health care providers, do everything we can to dispense quality laboratory care for all patients. Some problems in achieving this goal include the lack of adequate accessibility of laboratory data by those in charge of oversight, poor training and low competency of testing personnel, and lack of evidence-based studies linked to patient outcomes.

Evidence-based guidelines for point-of-care testing have been developed by the National Academy of Clinical Biochemistry (NACB) in cooperation with the College of American Pathologists and the American Society for Microbiology.[8] The guidelines cover subjects in POCT ranging from management to technical areas such as critical care, coagulation, cardiac markers for diagnosing acute coronary syndromes, infectious diseases, and renal function tests.[9] The monograph answers critical clinical and managerial questions using literature searches and grading outcome-generated studies into various categories of recommendations based upon the available literature. A key component in performing POCT at any site is managing the program. The monograph divides the management of POCT into quality control, technical oversight, data management, training and education of operators, and continuous quality improvement with quality indicators.[10]

Multidisciplinary approaches to POCT are necessary to implement a successful program.[10] Administration can supply the appropriate resources to achieve this goal along with technical expertise from physicians, nursing, and the laboratory. Each health care professional must realize his/her responsibility to achieve this goal. Decisions made by the group need to be based upon factual data or observations. These data must include a balance between sensitivity, specificity, positive and negative predictive values of the tests evaluated, and the clinical need for the results. Cost for disseminating the results is also an important consideration.

Handling laboratory data electronically clearly offers an advantage over manual systems in tracking quality care issues, following patient test results, and assuring compliance with regulations.[10,11] Remote monitoring allows technically skilled individuals to monitor performance and evaluate problems with instrumentation and suggest corrective action. A universal connectivity information system is imperative to be able to manage the many manufacturer options in POCT. Until recently, manufacturers were reluctant to connect test systems from companies not in business relationships with each other. There are now systems that allow such a connectivity to be instituted for a fee.[10,11,12] The performance of quality assurance and quality control is an expensive and time-consuming portion of laboratory medicine. In order to improve the quality of POCT, the NACB recommends developing a formal process of risk management and reducing medical errors by using an interdisciplinary committee to manage POCT, instituting POCT training programs, implementing data management systems, and instituting continuous quality improvement with quality indicators.[9]

It has been shown that 25% to 40% of laboratory tests are unnecessary.[13] Furthermore, there is potential for over utilization of point-of-care testing and the potential to do harm with results.[9,13] This makes it extremely important to make sure that all laboratory testing is warranted and that the results affect the outcome of patient management. In the critical care arena, few well-controlled outcome studies have been performed to show the benefit for POCT.[14] One positive study in sepsis patients demonstrated a decrease in mortality from 47% to 31% when early directed therapy to point-of-care arterial blood gases (including direct response to pH, oxygen saturation, and lactate) was instituted rapidly. Therefore, the Laboratory Medicine Practice Guidelines (LMPG) state there is fair evidence that arterial blood gases in the point of care should be performed for intensive care unit patients.[14] The evidence for other POCT is absent or less convincing.

For example, the detection of *Trichomonas vaginalis* in the physician office laboratory is usually made by performing microscopic examination of a wet preparation (WP). Unfortunately, the sensitivity of this testing is between 49% and 89%.[15] Although the use of POCT is recommended by the LMPG, outcomes based upon a wet mount for *T. vaginalis* do not link this agent with premature rupture of membranes.[15] The lack of sensitivity of WP necessitates a need for more sensitive tests. When tests with increased sensitivity are used in the point-of-care or core laboratory, *T. vaginalis* may in fact be associated with premature rupture of membranes.[15]

Point-of-care testing has the ability to improve outcomes and result in decreased mortality when performed correctly and following laboratory guidelines.[1,14] Using good laboratory practices, POCT will be beneficial at any patient site.[3] Some example benefits of POCT include faster decision making for cardiac patients, quicker optimization of treatment for anticoagulation, and increased patient satisfaction. Point-of-care testing will only increase in numbers and diversity of methods in coming years. The advent of complete electronic medical records including home health testing with regional databases will undoubtedly make more data available to the clinician. **NCMJ**

## REFERENCES


1 Price CP. Regular review: Point of care testing. *BMJ*. 2001;322:1285-1288.

2 Centers for Medicare & Medicaid Services, US Department of Health and Human Services. Title 42—Public Health, Chapter IV, Part 493—Laboratory Requirements, Subpart A—General Provisions. Available at: http://a257.g.akamaitech.net/7/257/2422/05dec20031700/edocket.access.gpo.gov/cfr_2003/octqtr/42cfr493.17.htm. Accessed March 16, 2007.

3 Centers for Disease Control and Prevention. Good laboratory practices for waived testing sites, survey findings from testing sites holding a certificate of waiver under the clinical laboratory improvement amendments of 1988 and recommendations for promoting quality testing. Recommendations and reports. *MMWR*. 2005;54(RR-13):1-23.

4 US Food and Drug Administration, Center for Devices and Radiological Health. Search CLIA Database. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm. Accessed March 16, 2007.

5 Centers for Medicare & Medicaid Services. Clinical Laboratory Improvement Amendment (CLIA). Accreditation Organizations/Exempt States. Available at: http://www.cms.hhs.gov/CLIA/13_Accreditation_Organizations_Exempt_States.asp#TopOfPage. Accessed March 16, 2007.

6 Centers for Medicare & Medicaid Services. Certificate of Waiver Laboratory Project. Available at: http://www.cms.hhs.gov/CLIA/08_Certificate_of_%20Waiver_Laboratory_Project.asp#TopOfPage. Accessed March 16, 2007.

7 Nichols JH, ed. NACB: Point of Care Testing. The National Academy of Clinical Biochemistry laboratory medicine practice guidelines: Evidence-based practice for point-of-care testing. American Association for Clinical Chemistry. Available at: http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/poct/. Accessed March 16, 2007.

8 Scott MG. Faster is better—it's rarely that simple. *Clin Chem*. 2000;46:441-442.

9 Nichols JH, Christenson RH, Clarke W, e al. Executive summary. The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guideline: Evidence-based practice for point-of-care testing. *Clin Chim Acta*. 2007;379(1-2):14-28. Epub 2007 Jan 12.

10 Jacobs E, Goldsmith B, Larrson L, Richarson H, St. Louis P. Management. Chapter 1. In: Nichols JH, ed. *Evidence Based Practice for Point-of-Care Testing: A National Academy of Clinical Biochemistry Laboratory Medicine Practice Guideline*. Washington, DC: AACC Press; 2006:1-4.

11 Dyer K, Nichols JH, Taylor M, Miller R, Saltz J. Development of a universal connectivity and data management system. *Crit Care Nurs Q*. 2001;24:25–38.

12 Clinical and Laboratory Standards Institute. Point-of-care connectivity; Approved standard. Document POCT1-A2. Wayne, PA: CLSI; 2006:306.

13 Gopal Rao G, Crook M, Tillyer ML. Pathology tests: Is the time for demand management ripe at last? *J Clin Pathol*. 2003;56:243-248.

14 D'Orazio P, Fogh-Andersen N, Okorodudu A, Shipp G, Shirley T, Toffaletti J. Critical Care Chapter 5. In: Nichols JH, ed. *Evidence Based Practice for Point-of-Care Testing: A National Academy of Clinical Biochemistry Laboratory Medicine Practice Guideline*. Washington DC: AACC Press; 2006:30-43.

15 Campbell S, Campos J, Hall GS, et al. Infectious Disease. Chapter 8. In: Nichols JH, ed. *Evidence Based Practice for Point-of-Care Testing: A National Academy of Clinical Biochemistry Laboratory Medicine Practice Guideline*. Washington DC: AACC Press; 2006:76-87.

# The Feasibility of Home or Patient Self-Testing

*Thomas E. Wall, MBA*

In contemporary society, the most prevalent and the most demanding forms of illness are chronic diseases. These can involve daily regimens of care and self-management, usually for a lifetime, and often require significant modifications in the lifestyles and activity patterns of those affected. Recent year estimates suggest that as much as 75% of total health care costs can be attributed to the treatment of persons with chronic illnesses and their associated comorbidities and acute care episodes.[1] In decades past, the predominant concerns of health and medical care were largely related to the burden of illness associated with communicable and infectious diseases. However, today, our focus has shifted to the prevention and long-term management of chronic diseases.

Over many years, the emphasis in chronic illness care has been on the protocols for disease management and attempts to increase patient adherence to specific regimens of care. Health care technology applications have sought better methods for the detection and monitoring of disease indicators and the collection and analysis of trends in these indicators as part of overall strategies for patient care management. Despite the efforts of many, there continue to be widespread feelings of frustration and disappointment in the health care professions over the inability to achieve high levels of control of hypertension, diabetes, asthma, and other chronic conditions where patterns of personal health-related decisions and behaviors can affect these critical indicators of chronic disease self-management.

If satisfactorily controlling these vital health indicators among chronic disease patients were easy, it would not have required the efforts of so many over such a long period of time, with so few examples of successful and sustained outcomes. The good news is that there are now promising new forms of computer-assisted technology that offer the possibility of bringing the best knowledge in fields like health behavior and health education, clinical medicine, and information technology together to achieve a much more effective interventional mode of long-term management of chronic diseases. Effective disease management care can significantly improve quality of life for those with these diseases, lead to a more effective outcome of medical therapies, and decrease overall costs of care.

## New Technologies Available for Chronic Disease Self-Management

There are a number of exciting and promising developments in the field of chronic disease self-management that take advantage of existing technologies and integrate them in new ways to achieve greater efficiency and more effective self-management. For a number of years physicians and other health care professionals have used telephones to give patients the opportunity to dial in to report or upload recent readings of key clinical indicators and to contact them for reinforcement of medical advice and counseling. To date, many of these telehealth solutions have been tethered to the patient's home telephone line. They provided solutions for the critically ill, but were not ideal for the large population living a mobile lifestyle while trying to manage a chronic disease. The emergence of the cellular phone and its

*"The emergence of technology for data signal transmission to and from cellular telephones has opened up an entirely new dimension of communicating basic clinical information to and from a central site."*

**Thomas E. Wall, MBA**, is vice president of Confidant International LLC. He can be reached at thomas.wall@confidantinc.com or 2530 Meridian Parkway, Suite 300, Durham, NC 27713.

growing ubiquity and enhanced capabilities have provided a mobile platform to support chronic disease management in this on-the-go community.

The emergence of technology for data signal transmission to and from cellular telephones has opened up an entirely new dimension of communicating basic clinical information to and from a central site. Now it is possible, with the development of home medical devices recording biomedical indicators, to digitally transmit this information using Bluetooth® communications protocol to a cellular telephone and then to a file server. The file server can then interpret this information, comparing it to other measures taken over time, and send encouraging or instructional messages back to the patient to motivate positive health actions related to the chronic health condition. Simultaneously, a summary of this same information can be sent to the physician or other health care professional involved in the care of the patient. All of the data are accessible through a secure internet portal to the health care professional and the patient. These measurements can be taken, transmitted, interpreted, and commented upon within a few seconds, thus making it possible for both patient and health care provider to communicate about the ongoing management of one's chronic condition in near real-time.

Figure 1 depicts the way in which this new communication linkage can work with a telehealth software application installed on an off-the-shelf cell phone. Recent feasibility (acceptance) trials for Type 1 and 2 diabetes and congestive heart failure have shown that patients and their health care providers find this system an easily usable tool.

## What are the Implications of These Technologies for Chronic Disease Care?

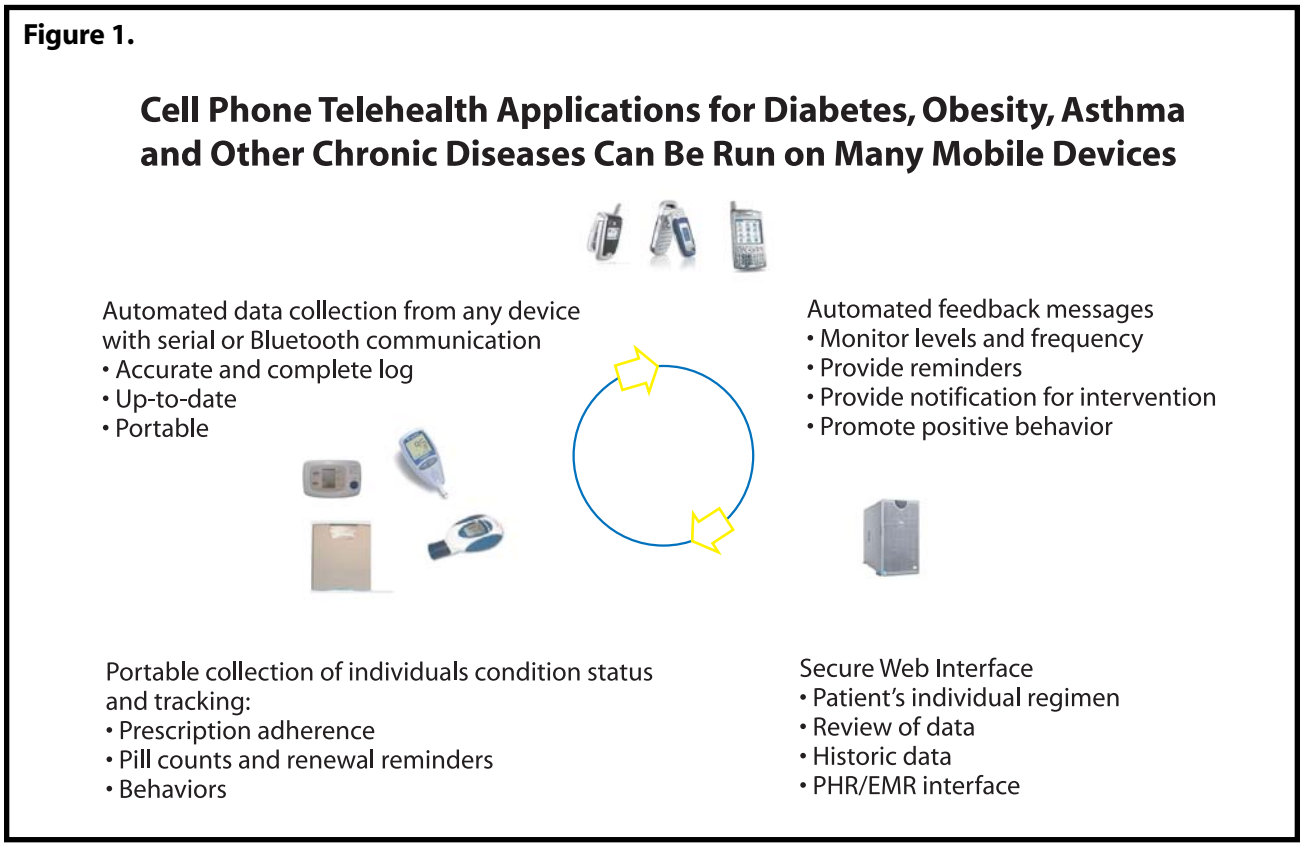
To be successful in managing chronic diseases the individual must take ownership of his/her disease. By using new mobile technology to provide a link to the doctor and to reinforce positive behaviors, the individual becomes empowered. The linkage enhances the physician-patient relationship and, through automatic notifications, keeps patients and providers updated on key aspects of the patient's treatment plan.

From a payer's perspective, good chronic disease management is good business. This new mobile telehealth tool has proven effective in early product trials with diabetes patients. It produced improved outcomes including more frequent testing, better glucose control, and lower HbA1cs. In addition to better short-term outcomes that translate to fewer emergency room visits, improving self-management and education is proven to reduce long-term complications and costs of care.

Other chronic diseases that require home medical device testing bear many of the same self-management issues and can benefit from this technology tool. For instance, by using an electronic weight scale, a cell phone-based weight management application can be used to promote positive behaviors in the individual's home. A protocol of self-reported symptoms and peak flow/spirometer readings can support improved asthma management. Patient reporting of prescription adherence, coupled with reminders and real-time biometric data, can be valuable to the patient as well as the provider.

In order for this or any tool to be successful in improving

**Figure 1.**



chronic disease self-management, it must be easy to use, nonintrusive, and be perceived to add value to the user. Using the cell phone, which is becoming an integral part of daily life, greatly reduces the complexity barrier and allows for the strengthened connection to the provider to become part of the user's daily routine. **NCMJ**

## REFERENCES


1 Centers for Disease Control and Prevention. Chronic Disease Overview. Available at: http://www.cdc.gov/nccdphp/overview.htm#2. Accessed March 23, 2007.

# How to Reach Us

### LETTERS TO THE EDITOR

- Our e-mail address is NCMedJ@nciom.org
- Our fax number is 919-401-6899
- Or you can send your letter to: *North Carolina Medical Journal*, Letters, 5501 Fortunes Ridge Drive, Suite E, Durham, NC 27713
- Please include the writer's full name, address, and daytime phone number. Letters may be edited for clarity or space.

### SUBSCRIPTIONS AND GIFTS

- Customer services for subscriptions or gifts can be accessed via e-mail NCMedJ@nciom.org or by calling the North Carolina Medical Journal's business and advertising manager, Adrienne R. Parker, at 919-401-6599 ext. 28.

### SUBMITTING PEER-REVIEWED ARTICLES

- For instructions on how to submit an article to the *North Carolina Medical Journal*, please visit http://www.ncmedicaljournal.com/guideline.shtml.
- Please send your articles via e-mail NCMedJ@nciom.org or mail to: *North Carolina Medical Journal,* Submissions, 5501 Fortunes Ridge Drive, Suite E, Durham, NC 27713.

### CHANGE OF ADDRESS

- Please send your change of address via e-mail NCMedJ@nciom.org or by calling the North Carolina Medical Journal's business and advertising manager, Adrienne R. Parker, at 919-401-6599 ext. 28.

### REPRINTS AND PERMISSIONS

- Information is available at the website www.ncmedicaljournal.com/reprints.
- To request photocopy permission or content licensing, e-mail NCMedJ@nciom.org.

### ADVERTISING

- For advertising information visit www.ncmedicaljournal.com/media.htm or contact the North Carolina Medical Journal's business and advertising manager, Adrienne R. Parker, at 919-401-6599 ext. 28; adrienne_parker@nciom.org.

North Carolina MEDICAL JOURNAL

When the day comes and you are accused of malpractice,

choose defense attorneys who have the experience you deserve.

After all, it's only your reputation.

WALKER ALLEN
TRIAL ATTORNEYS

Walker, Allen, Grice, Ammons & Foy, L.L.P.
1407 West Grantham Street / Post Office Box 2047
Goldsboro, North Carolina 27533-2047
Telephone: 919.734.6565 / Facsimile: 919.734.6720
www.nctrialattorneys.com

# Readers' Forum

***To the Editor:***


The November/December 2006 issue of The *North Carolina Medical Journal* offered a comprehensive discussion on the issue of worksite wellness and health promotion, providing both the most current research and field-based insights into what can work and how to implement those successful components. Employers have been faced with increasing employee health care costs for several years and many have considered worksite wellness as an option to address cost containment. At issue has been the true definition and scope of successful worksite wellness.

At Blue Cross Blue Shield of North Carolina we have been developing our employee health promotion program over the past several years. Among others, we sought the insight of several of the contributors to the recent issue. In part, as a result of that consultation and subsequent implementation of several initiatives, we have realized a significant increase in the proportion of members participating actively in our health and wellness programs.

In addition, we recently held our annual Health Care Symposium, which was attended by approximately 150 human resources and benefits managers from our business customers. This year's program focused on the topic of worksite and employee wellness. As a takeaway from the conference, we presented each attendee with a copy of your November/December issue as a resource to them as they further develop their own worksite wellness solutions.

Our ultimate goal is not only to successfully offer the type of worksite wellness programming highlighted in the last issue but also to continue to demonstrate objective improvements in employee health, productivity, and retention. As we accumulate more experience and develop or revise programs, we will share our experiences and success with our partnering employer groups and interested audiences across the state and nation.

Thank you for defining the issues, presenting achievable strategies, and setting the bar for the direction of worksite wellness in North Carolina.

*Sincerely,*
*Don Bradley, MD*
*Chief Medical Officer*
*Blue Cross and Blue Shield of North Carolina*

---

***To the Editor:***

*Primum non nocere*, first do no harm. While many consider this maxim dated and irrelevant in our techno modern world of medicine, no concept applies better in the debate of physician participation in capital punishment. The American Medical Association and North Carolina Medical Society have firmly stated that even physician presence at an execution is unethical and unacceptable. While the North Carolina Medical Board has officially stated that physician presence will not be sanctioned (in deference to North Carolina state law that requires physician presence), active participation is strictly forbidden, which includes monitoring of vital signs, levels of consciousness, etc.

*Primum non nocere.* As physicians, our duty is to always advocate for our patients. To always acts in their best interests. To eschew all other interests but those that best serve our patients. So how is it that a physician is brought into the realm of a state-sponsored execution to ensure proper sedation and level of consciousness so that a lethal combination of drugs will lead to an individual's demise? This was the requirement that was imposed upon the state to allow executions to continue, so that the United States constitutional requirement that prohibits cruel and unusual punishment is satisfied. But that policy conflicts with our basic tenants and ethics. How can we sedate and anesthetize, only to allow lethal drugs to be administered?

*Primum non nocere.* State sponsorship, state sanctioning, legislative approval, popular vote do nothing to remove physicians from their sacred duty to always act in the best interests of their patients. And our patients are anyone who we touch, treat, review, or opine. To act otherwise undermines our profession and our raison d'etre (ie, reason for existence).

*Primum non nocere.* We physicians must resist any action, by anybody, for any reason, that attempts to move us to violate our ethics, our tenants, and our sacred profession.

*Primum non nocere.*
*Douglas K. Holmes, MD*

# Spotlight on the Safety Net

*A Community Collaboration*
*Kimberly M. Alexander-Bratcher, MPH*

## Community Health Network of Henderson County

In the southwestern corner of North Carolina, local health and social service providers have joined into the Community Health Network of Henderson County (CHN). Community Health Network is a network of providers who access a shared client information system (Case Management Information System – CMIS). That system was adapted by Partnership for Health, Inc (PFH), 5 Rivers Systems, the NC Foundation for Advanced Health Programs, and the Office of Rural Health and Community Care to meet the network's needs. The CMIS electronically links health care providers and human services agencies in a 3-county area in western North Carolina to share client protected information to better serve clients, reduce duplication of efforts and services among various social service agencies and health care providers, and decrease gaps in access to services for low-income people in the Hendersonville-Brevard-Saluda area. The CMIS shared electronic database provides access to resource information used to quickly assist low-income people in finding health care, medications, and other basic human needs.

The collaboration began in 1997 when a post graduate resident physician in the Mountain Area Health Education Center (MAHEC)-sponsored Hendersonville Family Medicine Residency Program started a free clinic for homeless clients at the Henderson Rescue Mission. In 1998, MAHEC provided a licensed physician as the medical director for the Henderson County Health Department. This forged a unique relationship between the two organizations. As they encountered difficulties with mental health reform and expanded coordination with a local community health center, more stakeholders began working collaboratively. A Healthy Communities Access Program (HCAP) grant from the Health Resources and Service Administration (HRSA) was applied for and received to fund the CHN program under the umbrella of Partnership for Health (PFH), a Healthy Carolinians Partnership.

From its simple beginnings, CHN now includes more than thirty partners and is a model of community collaboration. Of 2157 applicants to the network program, 1929 have been enrolled in the network at the 15 enrollment sites. Although CHN does not provide direct services, the member organizations offer a variety of services in 9 primary care sites and 5 integrated behavioral health care sites. More that 4000 prescriptions valued at $400,741 have been filled for 742 patients. The target conditions of the program are diabetes, depression, and asthma, and more than 40% of the over 1900 CHN enrollees are affected by one of the 3 conditions. The full list of CHN members are listed in the table to the right.

When asked to describe the Community Health Network of Henderson County, medical advisor Steve Crane, MD, shared these thoughts, "Over the years there has been an extraordinary degree and breadth of cooperation between agencies and individuals in our community who care about access and quality of our health system. Each success has fostered a new project or collaboration resulting in today's multi-faceted approach. I trace the kernel of these efforts back to Jim Bernstein, who encouraged and mentored many of us to move in this direction."

**Primary Care**
- Blue Ridge Community Health Services, Inc.
- Foothills Medical Associates
- The Free Clinics of Henderson County
- Henderson County Department of Public Health
- Hendersonville Family Health Center
- Hendersonville Family Health Center—Etowah Clinic
- Hendersonville Rescue Mission
- Saluda Medical Center
- Springs Health Care Center
- Valley Family Health

**Mental Health Care**
- Appalachian Counseling
- Families Together, Inc.
- Family Preservation Services
- Parkway Behavioral Health

**Emergency & Inpatient Care**
- Margaret R. Pardee Memorial Hospital
- Park Ridge Hospital
- St. Luke's Hospital
- Transylvania Community Hospital

**Other Support**
- Access II Care of Western North Carolina
- Community Care of North Carolina
- El Centro Comunitario
- Henderson County Government
- Henderson County Department of Social Services
- Interfaith Assistance Ministry
- Land of Waterfalls Partnership for Health
- North Carolina Foundation for Advanced Health Programs, Inc.
- Partnership for Health
- Polk County Dept of Public Health
- Thermal Belt Outreach Ministry
- Transylvania County Health Department

# Classified Ads

**PHYSICIAN WANTED for part-time hours** at the following locations: Hickory, Gastonia, Charlotte, Monroe; working with patients seeking recovery from addictions doing histories and physicals, minor medical issues including treatment of mood disorders. Background in primary care preferred; experience in addiction medicine a plus. To apply, please visit www.mcleodcenter.com or send resume to McLeod Center, Attn: Dept WG, 145 Remount Rd, Charlotte, NC 28203. EOE.

**Urgent Care/Occupational Health Practice Opportunity:** Well established Urgent Care/Occupational Health Centers in Charlotte, NC. Physician owned and operated clinics offering competitive compensation for the right individual. Send Fax C.V. to 704 521-5092 or e-mail to althea@pro-med.org Attention: Althea Callaway.

**MEDICAL/DENTAL SPACE FOR LEASE.** Hwy 401 & State Road 1010 between Garner and Fuquay-Varina. Available late 2007. Rosamund Property 919-357-9238.

**MOVE TO THE BEACH: BOARD CERTIFIED PHYSICIANS** needed for Family Medicine/Urgent Care/Occupational Medicine offices in Jacksonville and Wilmington, NC. Contact: Bob Kastner, MD, FAAFP, FACEP 910-392-7806. Fax: 910-392-2428. kastnerr@bellsouth.net, www.medcareofnorthcarolina.com.

**PHYSICIANS**. Seeking full-time and part-time physicians to perform Independent Medical Evaluations in our offices in Asheville (4-5 days per month), Ahoskie (1-2 days per month), Greenville (1-2 days per month), and Franklin (1-2 days per month). Prefer training in **Internal Medicine, Family Practice, IM/Peds or Emergency Medicine.** Will provide referrals, scheduling, billing, transcription, office assistant, logistical support, and training. No call. No emergencies. No managed care. No weekends or holidays. Call Susan Gladys, Operations Manager, 1-866-929-8766 or fax CV to: 304-525-4231. Tri-State Occupational Medicine. www.tsom.com.



**North Carolina—Charlotte Area.** Progressive Urgent Care Centers seeking physicians for shift work to include evenings and weekends. Outpatient only. No call. Flexible schedule. Competitive salary and benefits. Fax CV toTammy at Piedmont HealthCare: 704-873-4511 or call 704-873-4277 ext. 202. No J-1 waiver.

## POSITION ANNOUNCEMENT

**Department of Family Medicine Behavioral Medicine**
**Brody School of Medicine at East Carolina University**
**Greenville, NC 27834**

**Vacancy Number:**
**Working Title: Head, Behavioral Medicine**

The Department of Family Medicine announces an opening for Head of Behavioral Medicine. This position is responsible for the administration and coordination of the behavioral medicine curriculum for residents; teaching of residents and medical students; and collaborative clinical and educational work with graduate students in Psychology and Marriage and Family Therapy; provision of clinical services including individual, couple and family therapy; collaboration with other medical providers; and supervision of other behavioral clinicians. Scholarly and other creative activity expected. Innovation and leadership are encouraged.

**Minimum requirements:**

1. Ph.D./Psy.D. in Psychology, Marital and Family Therapy or related field.
2. Two years post-doctoral clinical training or experience in ambulatory medical setting.
3. Licensed in North Carolina or immediately license eligible.
4. Experience in teaching behavioral medicine in a family medicine residency program or other medical setting strongly preferred.

The Brody School of Medicine is known nationally for its commitment to family medicine. ECU with approximately 22,000 students is the third largest university in the 16-member UNC system. Greenville, NC home of ECU, has consistently won awards for its quality of living.

To apply, send a letter of interest, a current CV, and names with addresses of three references to Valerie Gilchrist, MD, Chair, Department of Family Medicine, Brody School of Medicine, East Carolina University, 600 Moye Boulevard, Brody 4N-84, Greenville, NC 27834.

East Carolina University is an EEO/AA employer, which accommodates individuals with disabilities. All applicants must comply with the immigration Reform and Control Act.

# Index of Advertisers

# State-of-the-Art Technology with a Hometown Touch.

At Southeastern Regional, you'll find some of today's most modern advancements in medicine, such as state-of-the-art CT and MRI scanners that precisely and safely guide neurosurgery in the brain and spine by feeding information directly to computers in the operating room.

From new noninvasive surgery techniques to our recently opened Heart Center, you might be surprised that a medical center in southeastern North Carolina would offer the same services and expertise usually found only in larger regions. But having these new technologies here in Lumberton bring patients the best in care without their having to drive hours from home. And that, we believe, is one of the most important parts of the healing process—being close to home, with the support of family and friends.

**64-Slice CT Scanner**
**Acid Reflux Surgery**
**Oxinium Knee Replacement**
**Minimally Invasive Surgeries**
**Balloon Sinuplasty**
**AdminRx**
**GreenLight® Laser**
**PillCam ESO®**
**Stealth Technology**
**Novasure®**
**Computed Radiography**
**Phaco Emulsification**
**Diagnostic and Interventional Cardiology**
**Open-Heart Surgery**
**Endovascular Surgery**

SOUTHEASTERN REGIONAL MEDICAL CENTER

www.srmc.org | 910-671-5000 | Lumberton, NC

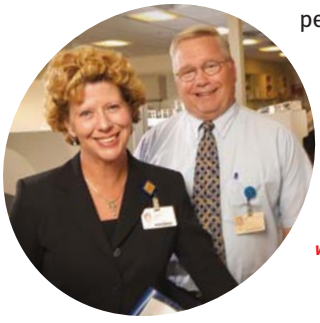

# Move your lab into the fast lane.

## How PinnacleHealth Built An Automation Superhighway.

The four hospital campuses of PinnacleHealth in Harrisburg, Pennsylvania were billing 2.4 million tests per year. They knew their efficiency and consistency could be improved, so they approached Beckman Coulter for an automation solution.

PinnacleHealth selected from dozens of scalable, open platforms and configurations and engineered a perfect fit. In one centralized facility, PinnacleHealth installed a Power Processor sample-processing system, two SYNCHRON LX®20 clinical systems and the DL2000 data management system. The results are breakthrough. Test volume has increased 11 percent without adding staff. Turnaround time is 28 percent faster. And employee morale is higher than ever.

From automating a single process to delivering full-scale automation, Beckman Coulter can increase your lab's efficiency and reliability and decrease overall costs. So contact your Beckman Coulter representative or visit www.beckmancoulter.com/automation. And put your lab on the road to advanced automation.



*"I was always interested in automation, but never thought it would work for our lab."*
**Doug Schreffler, MT, AMT, PinnacleHealth Laboratory Operation Manager**

*"Our new laboratory automation system has met or exceeded all of PinnacleHealth's standards of success. And most importantly, we now have the capacity to double our workload without increasing our staff. We're very happy and pleased."*
**Judy Darr, MS, MT (ASCP) DLM, PinnacleHealth Laboratory Administrative Director**

BECKMAN COULTER®

General Chemistry · Immunodiagnostics · Centrifugation · Molecular Diagnostics · Hematology
Disease Management · Hemostasis · Information Systems · Lab Automation · Flow Cytometry · Primary Care

**Simplify · Automate · Innovate**