

# Perspectives

Diagnostic Solutions for Improving Patient Care

SIEMENS

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## Your Perspective

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Regional hospital improves performance and revenue with integrated analytics





**Donal Quinn**  
Chief Executive Officer  
Siemens Healthcare Diagnostics

## Dear Valued Customer,

There is a new approach to patient care that is transforming healthcare delivery. Physicians are leveraging advanced technology and informatics to deliver better, more personalized medicine, and brick and mortar walls between hospital departments and health systems are no longer barriers to the fluid exchange of patient data. The clinical laboratory plays an important role in this future-oriented, integrated approach to patient care, and we are excited to work alongside the pioneers who are taking diagnostics to a new level.

This issue of *Perspectives* features the unique voice of a laboratory professional dedicated to the evolution of healthcare. Dr. Aurea Mira, Manager of Biomedical Diagnostics at the Hospital Clínic de Barcelona in Spain, is the first to author the magazine's new guest column, "Your Perspective." She is a leader in the groundbreaking approach to integrated healthcare under way at Hospital Clínic de Barcelona. Her sharp insight into process design is invaluable for anyone pursuing an integrated model for their institution.

Whether your interests include new diagnostic frontiers or advanced technologies for infectious disease testing, molecular diagnostics, and core laboratory disciplines, *Perspectives* delivers information that will help position your laboratory for success.

It is clear that clinical laboratories make valuable contributions to the development of advanced healthcare models. As a leader in healthcare innovation for more than 130 years, Siemens can help you diagnose, treat, and prevent disease in ways never before possible. We can build the next generation of healthcare, together.

Warm regards,

A handwritten signature in black ink that reads "Donal Quinn". The signature is written in a cursive, slightly slanted style.

**Donal Quinn**



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## A Customer's Point of View



Aurea Mira, PhD  
Manager of the Diagnostic  
Biomedical Center  
Hospital Clínic de Barcelona  
Barcelona, Spain

“The partnership between Siemens and Hospital Clínic de Barcelona is based on a shared vision of the evolution of healthcare delivery. Together, we will find innovative pathways for improving patient care.

The Hospital Clínic’s organizational model, which is focused on the patient, our knowledge of clinical problems, and our experience in translational research, in conjunction with Siemens technological development and integrated diagnostic vision, drives us to seek and find innovative pathways for improving patient care.”

# International Reference Center to Research Integrated Diagnostics

By Aurea Mira, PhD

This year, Hospital Clínic de Barcelona began what promises to be a groundbreaking initiative to functionally integrate our laboratory diagnostics (in vitro), medical imaging (in vivo), and healthcare information technology. Our goal in bringing the disciplines together is to give our clinicians access to the most comprehensive patient information possible, and allow for quicker and safer decision making in all stages of the healthcare continuum.

Since Hospital Clínic de Barcelona is one of the first hospitals in the world to initiate clinical research programs on integrated diagnostics, we've become an international reference center, enhancing our ability to truly improve the standards of care at our institution.

Many aspects of this initiative break new ground for us. One of the most exciting is the cross-functional clinical and management team we have assembled within the hospital, another step ahead in our organizational model focused on the patient and translational research. Some of these disciplines have not collaborated before in research and process improvement. Now, we're fully aligned as a team, ready to embark on rigorously designed research protocols – pioneers in a collaboration that has the potential to transform the way our patients are treated.

Our research team, together with Siemens experts, is working to develop specific diagnostic practices, starting in three principal areas: hepatology, gastroenterology, and fetal medicine. As an example, in liver fibrosis, we will study how to reduce or replace the number of biopsies by a comprehensive integrated diagnostic practice that can be used in the pre-symptomatic stages of disease.

With this new research project, the goal is to find a new noninvasive approach for the precise assessment of liver cirrhosis. This could be developed by combining biochemical markers with diagnostic imaging analysis. The current method for determination of the level of liver fibrosis is to undergo a liver biopsy, which is uncomfortable and can be unsafe for the patient.

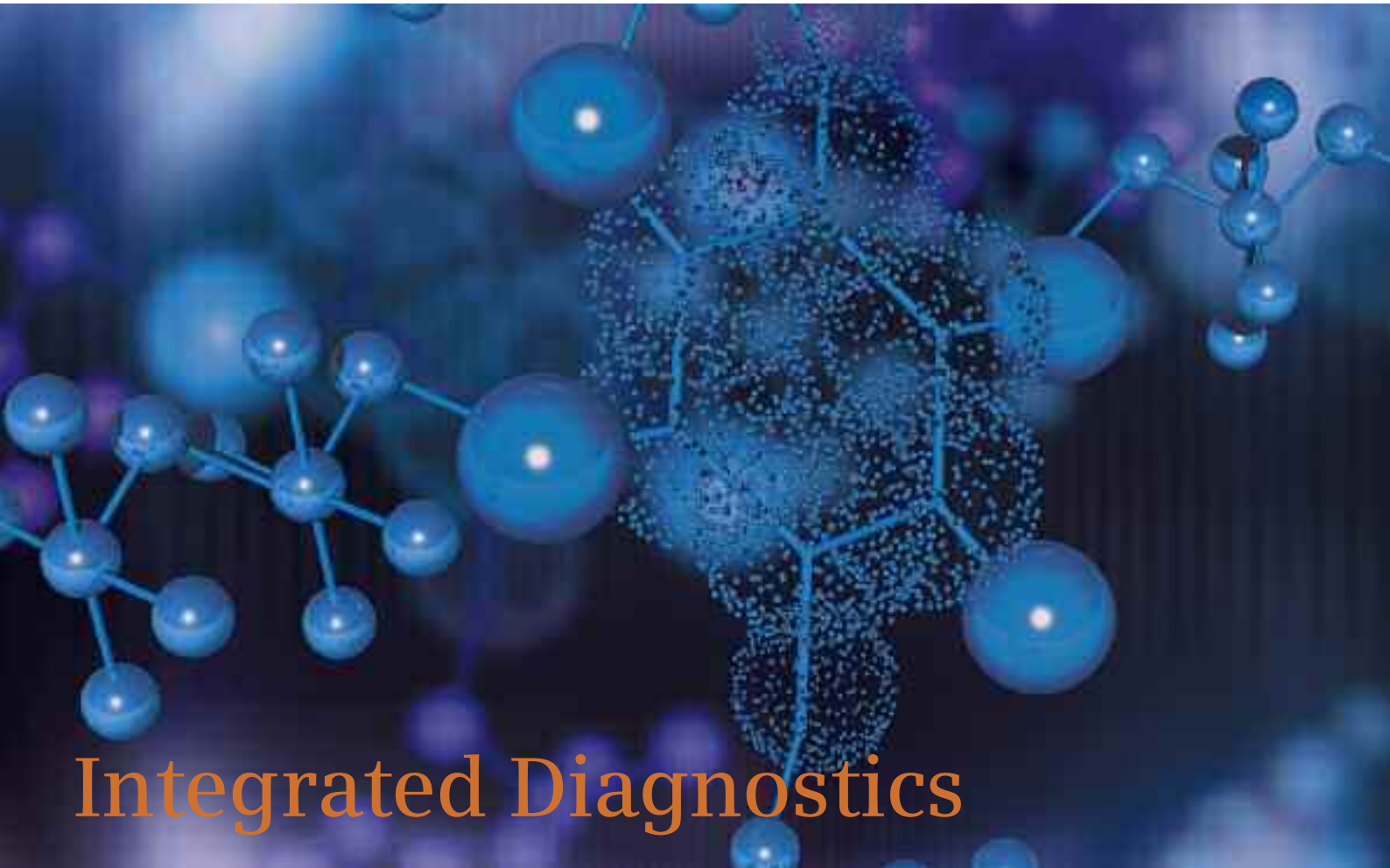
In the area of fetal medicine, Hospital Clínic de Barcelona hopes to combine its knowledge of diagnostic methods with the technological skills of Siemens to improve quality of life for the mother and the fetus. Biomarkers, new IT algorithms, and the development of new imaging methods for analyzing the fetal brain and heart are the areas of greatest joint development potential.

In many fields, not just healthcare, complex challenges demand an interdisciplinary solution. When multiple disciplines can be leveraged simultaneously with the adequate technology, the possibilities for real breakthroughs multiply. This is the case with integrated diagnostics: the convergence of imaging technology and in vitro diagnostics – enabled by advanced healthcare information technology.

This will not only mean earlier and presumably better diagnoses and outcomes, it will also move the patient through the healthcare system with increasing efficiency, and help to reduce costs. Three disciplines, working as one, could radically change diagnosis and treatment for many chronic diseases. At Hospital Clínic de Barcelona, this is our vision for the future of diagnostics.

## For more information

[www.siemens.com/  
integrated-diagnostics](http://www.siemens.com/integrated-diagnostics)



# Integrated Diagnostics

## Advancing Personalized Medicine

The spotlight was on personalized medicine as radiologists, laboratorians, pathologists, IT experts, and healthcare executives came together at the second annual Molecular Summit. Through robust discussion and lively debate, they exchanged ideas about one of the industry's hottest trends – the integration of molecular imaging, molecular diagnostics, and healthcare informatics.

By Amy K. Erickson

The healthcare innovators participating in the 2009 Molecular Summit in Philadelphia, Pennsylvania, USA, in February had something especially exciting to talk about: The integration of diagnostics and imaging information, combined with a healthcare information technology (IT) platform, can dramatically improve the way patients are treated.

With the computerization of in vivo and in vitro diagnostics, stunning new medical insights and data are emerging.

According to Jared Schwartz, MD, PhD, Pathology and Lab Medicine at Presbyterian Healthcare in Charlotte, North Carolina, USA, molecular diagnostics integrated with therapeutics represents a major new

opportunity in the era of personalized medicine. "To leverage this opportunity," he says, "the information from pathology and radiology sources needs to be combined into a single, comprehensible, understandable, and actionable report." "It is my belief that the integration of technology will be the factor that transforms healthcare," says Don Rucker, MD,

Chief Medical Officer of Siemens Healthcare in the USA. "This conference is about everyone learning best practices on how to combine the information from pathology and radiology. It's very new, very fluid, and because it's so fluid, it's extraordinarily exciting." Rucker notes that as these fields converge, they have the power to provide more accurate diagnoses and personalized patient care.

### A New Kind of Workflow

Overcoming the challenges of integration was a topic of much discussion at the Summit. "The practice of medicine is holistic," says Ossama W. Tawfik, MD, PhD, Director of Anatomic and Surgical Pathology and Vice Chairman of the Department of Pathology and Lab Medicine at the University of Kansas Medical Center in Kansas City, Kansas, USA. "It's not just pathology, and it's not just radiology. There will be integration, and that could include a new kind of workflow." According to Mark L. Redick, MD, Assistant Professor of Radiology at the University of Kansas, a major challenge to integration is poor communication between siloed healthcare services. "Today, the clinical demands are so high that it inhibits us from being able to get out of our treatment suites or reading rooms," he explains, noting that other factors to consider are cost and quality implications.

### A Pathology-Radiology Case Study

One forward-looking physician leader who attended the Summit is advancing the notion of integration from concept to practical implementation. Jonathan Braun, MD, PhD, Chair of the Department of Pathology and Laboratory Medicine at the David Geffen School of Medicine at UCLA, University of California, Los Angeles, California, USA, is developing a unique cancer center that brings together the university's radiology and pathology departments. The UCLA Radiology Pathology Center is designed to use radiology (computed tomography, magnetic resonance imaging, and ultrasound) to isolate and sample suspicious lesions, and pathology to process and diagnose the specimens. The pathology information will be combined with the radiology information

in an estimated 48- to 72-hour turnaround time to create a comprehensive single report for physicians. The report will be accessible online for viewing by the entire healthcare team. Braun and his group launched the project about 18 months ago. "We are currently in the process of finalizing financials and funding transfers, completing the validation of integrated IT reporting mechanisms, and working on facility upgrades," says Braun.

According to the Summit's keynote speaker, George Poste, DVM, PhD, Chief Scientist, Complex Adaptive Systems Initiative, and Director of The Biodesign Institute of Arizona State University in Tempe, Arizona, USA, multimodality diagnostics will play an essential role in how healthcare evolves toward a

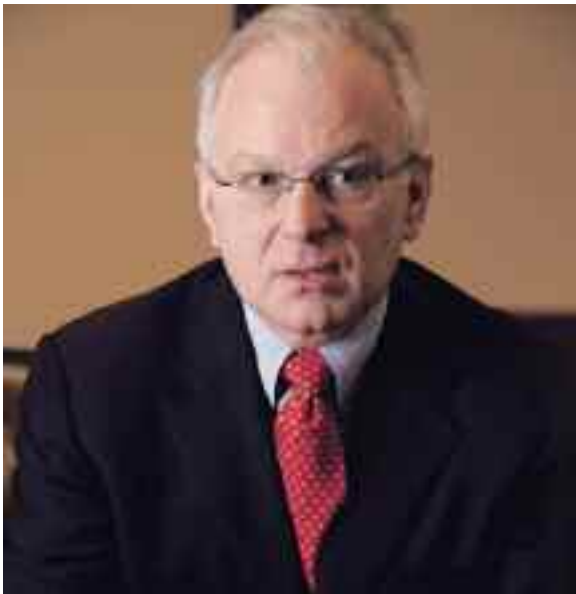
proactive healthcare system organized to serve the needs of personalized medicine – and it will require the optimum use of costly resources. "This is a field in chaos to some extent," says Poste. "Only when we can think beyond the siloed structure can we integrate across the entire spectrum of healthcare."

Poste believes that there are three forces shaping the evolution of healthcare – molecular medicine and personalized medicine; access, cost, and quality of care; and the proficient use of information. "We live in an exciting time, where there is a dramatic acceleration of science and medicine," says Poste. "We are entering an era of targeted care using new molecular diagnostics to expand individualized medicine."



**"It is my belief that the integration of technology will be the factor that transforms healthcare."**

Don Rucker, MD, Chief Medical Officer  
Siemens Healthcare USA



“Molecular diagnostics integrated with therapeutics represents a major new opportunity in the era of personalized medicine.”

Jared Schwartz, MD, PhD  
Pathology and Lab Medicine  
Presbyterian Healthcare  
Charlotte, North Carolina, USA

### Digitizing Anatomical Pathology

The digitization of information is essential to synchronizing pathology and radiology workflows and furthering an integrated model of care. A panel discussion at the Summit explored the healthcare industry's progress toward digital images and digital pathology systems.

Bruce A. Friedman, MD, Professor Emeritus of Pathology at the University of Michigan Medical Center in Ann Arbor, Michigan, USA, served as the panel's moderator.

“In the radiology world, adoption of digital images is near 100 percent,” explains Friedman. “However, in the pathology world, the percentage is much lower.”

With that idea as a starting point, the other panelists weighed in on the progress toward digital pathology systems.

Dirk Soenksen, Chief Executive Officer of Aperio Technologies, Inc., in Vista, California, USA, has observed the adoption of digital technology in pathology

routinely in Sweden, Japan, and other countries, but says there are many regulatory hurdles in the United States that still need to be overcome. Michael R. Descour, PhD, Chairman of DMetrix, Inc., in Tucson, Arizona, USA, believes that in addition to regulatory issues, cost is also an obstacle that is impeding the widespread adoption of digital slides in pathology. According to Descour, there needs to be a certain level of cost savings in terms of dollars per slide in order for it to make sense financially.

## Wired for Success

Susquehanna Health, located in north central Pennsylvania, has an ambitious mission to create the healthiest region in the United States. It was named one of the nation's Most Wired Hospitals by *Hospital & Health Networks* magazine for eight consecutive years and partners with Siemens to help deliver high-quality care to its community.

Susquehanna Health is a three-hospital health system comprising Divine Providence Hospital, Muncy Valley Hospital, and the Williamsport Hospital & Medical Center. Serving patients in an 11-county region, Susquehanna Health offers a broad array of services, including

cardiovascular care and cancer treatment. From prevention and early detection to diagnosis, therapy, and follow-up care, Siemens technology is integrated throughout Susquehanna Health to offer patients a full spectrum of personalized care.

Susquehanna Health uses a strong healthcare information technology (IT) platform to facilitate the integration of medical imaging with laboratory diagnostics throughout the facility. “Susquehanna has been a Siemens customer for over 30 years. We feel

Public necessity could become a main driver in advancing digital technology. Mohan Uttarwar, Cofounder and Chief Strategy Officer of Biomagene in Cupertino, California, USA, is convinced that it is not a question of whether digital pathology will happen, but when. He believes that once the adoption of digital slides becomes mainstream, all pathologists will jump on the bandwagon. Descour agrees. "The faster we can bridge the gap between glass and digital slides, the faster we can facilitate acceptance," he says.

Even though the challenges are there, Friedman and his fellow panelists concluded that there is a very strong desire to pursue the goal of close collaboration between pathologists and radiologists in a digital environment. "The momentum is strong right now, and we have to find a way to lead the pack," states Tawfik. "The breakthroughs in technology have the potential to bring the two practices together."

**The Take-Home Message**

When the Summit came to a close after two days of spirited discussion, intelligent debate, and the sharing of ideas among thought leaders and experts in the fields of radiology and pathology, it was clear that the



participants had reached a conclusion: The integration of technology is critical to advancing personalized medicine.

As the independent disciplines of laboratory diagnostics and medical imaging are bridged through IT solutions and collaborative efforts, healthcare is moving into a new era of streamlined workflows, improved clinical outcomes, and more affordable care. Vital information from multiple sources and multiple

modalities will reside in one electronic patient report accessible by all physicians along the care continuum. The result will be earlier, quicker diagnoses and improved quality of life for patients.

**For more information**  
[www.siemens.com/integrated-diagnostics](http://www.siemens.com/integrated-diagnostics)

very strongly that Susquehanna should have one common platform for our IT, and Siemens was the vendor of choice for that whole endeavor," says Karen M. Armstrong, Senior Vice President and Chief Information Officer (CIO). "As the practice of medicine evolves and becomes more complex, the need for a well-executed technology strategy is without question."

**The Power of Interoperability**

As the first facility in the world to go live with both Soarian® Clinicals and Financials, Susquehanna Health realizes the power of interoperability to deliver advanced healthcare.

According to George Manchester, MD, Executive Vice President and Chief Medical Officer (CMO) of Susquehanna Health, one of the primary benefits of a hospital-wide integration of systems is the free flow of data and information between the different systems and components. "There are so many different data sources that you're looking at, and Siemens gives us the ability to access many different kinds of data and pull from many sources in an easily accessible manner," explains Manchester.



(continued on page ten)



Because Susquehanna Health houses a Siemens IT platform as well as Siemens imaging and lab technologies, having the Soarian workflow engine that can speak to all three of those applications really makes a huge difference, says Armstrong: "The workflows can help us with notifications to both physicians and nurses. It can create a lot of efficiencies and notifications throughout the entire system."

This integrated healthcare model allows physicians at Susquehanna Health to keep the patient at the center of care. "Healthcare is sometimes like a puzzle," says Manchester. "The IT infrastructure provided by Siemens allows us to put all the pieces on the table at one time and it gives us the best chance of coming up with the right picture."

### Measurable Results

Susquehanna Health was named one of the Best Places to Work in Pennsylvania for 2008. "We believe this honor is due in part to the implementation of Siemens technologies and we have the metrics to prove it," explains Armstrong. "We conduct regular physician surveys that show that with the implementation of technology applications, physicians' satisfaction with the hospital also increases."

During the last three years, overall physician satisfaction with technology went from the 86th percentile to the 96th percentile, which directly corresponds to the installation of Siemens systems. Clinician access to lab/radiology information increased to 83 percent, compared to the industry average of 74 percent.

According to Donald Leathers, MD, Medical Director of Laboratory Services and President of the Medical Staff at Susquehanna Health, "I know that the implementation and integration of these technologies has increased my ability to practice pathology efficiently and accurately, because it's easier to make accurate diagnoses when you have all the information you need." Additionally, notes Armstrong, after the picture archiving and communication system (PACS) implementation, radiologist productivity increased by nearly 40 percent.

An additional link between technology integration and better patient care is the fact that Susquehanna Health carries the Gold Seal of Approval from the Joint Commission for Primary Stroke Centers. "We received this award largely because Soarian and the SOMATOM Definition™ CT [computed tomography] system allows our physicians to treat stroke patients very quickly and efficiently, and time is a crucial element when it comes to diagnosing and treating stroke patients," says Armstrong.

"I think one of the trends in healthcare right now is to do more with less and do it at a higher quality," says Leathers. "Our relationship with Siemens has made us much more efficient, while at the same time maintaining or exceeding the quality that we had before." Susquehanna Health is currently conducting a study to evaluate the impact of IT implementation in the emergency department. Hospital administrators are looking for additional opportunities to expedite diagnosis,

particularly in heart attack and stroke patients, where quick decisions are critical to care. The impact of IT implementation on patient satisfaction and patient outcomes will also be studied.

### On the Horizon

Although this community hospital system is already well positioned to provide patients with superior care, Susquehanna Health, supported by Siemens, continues its goal of fully integrated healthcare. The hospital system is in the process of completely upgrading and automating its laboratory operations. There are also plans to completely renovate, modernize and expand capacity for Susquehanna's cath labs, including the addition of electrophysiology services. Additionally, Susquehanna and Siemens are collaborating on the construction of a new hospital tower. Dubbed Project 2012, the new facility will include Siemens imaging equipment, healthcare IT, automation technologies, energy efficiency equipment, and more.

"Susquehanna and Siemens share a common goal of delivering the best possible care," says Armstrong. "An integrated system gives our healthcare team the information they need, when they need it, allowing our patients to be treated with the highest quality at every point along the care continuum."



“As the practice of medicine evolves and becomes more complex, the need for a well-executed technology strategy is without question.”

Karen M. Armstrong, FACHE  
Senior Vice President and CIO  
Susquehanna Health System  
Williamsport, Pennsylvania, USA

## A Holistic Approach to Integrated Healthcare

Siemens is the primary provider for IT, medical imaging, and laboratory diagnostic solutions for Susquehanna Health. These solutions include:

### Healthcare IT

Soarian® Clinicals, Soarian® Financials, Clinical Access, Common Clinicals, Clinical Team, Med Administration Check™ (MAK), Soarian Revenue Cycle, Patient Access, Soarian Scheduling, Computerized Physician Order Entry (CPOE), Soarian Cardiology, Soarian Critical Care, Soarian HIM, Data Warehouse, Soarian Portal, NextGen® EMR, SIGNATURE Practice Management System, Remote Access, Siemens OPENLink™ Integration Engine, Biometric Identification and Sign-on, Document Imaging, HDX®, Groupware

### Radiology

syngo® Suite, syngo® Dynamics (Cardiology), AXIOM Multix, MAGNETOM Espree™, MAMMOMAT® Novation<sup>DR</sup>, SOMATOM Definition™, SOMATOM Emotion®, UROSKOP® Access

### Laboratory Diagnostics

NOVIUS® Lab, RAPIDPoint® 405 Automated Blood Gas Analyzers, RAPIDComm® Data Management Solution, ADVIA® 1200 and 1800, ADVIA Centaur® CP and XP Immunoassay Systems, ADVIA® LabCell® Automation Solution, ADVIA Centralink® Data Management Solution

# Living with Metastatic Breast Cancer



One simple, routine, minimally invasive blood test: For women with HER-2/neu positive metastatic breast cancer, a particularly aggressive cancer, this test could be the key that helps determine their fate. Siemens innovative Serum HER-2/neu test is the only Serum HER-2/neu test available for sale in the U.S. that can indicate whether metastatic breast cancer is progressing or responding to treatment.

By Diana Smith

HER-2 positive breast cancer is a virulent cancer identified every year in 25 percent of the nearly 1.3 million women diagnosed with breast cancer worldwide annually. HER-2/neu positive patients are often given devastating prognoses – shorter survival rates and higher recurrence. That's why identifying changes in health are critical.

For women with HER-2/neu positive metastatic breast cancer, the Serum HER-2/neu test from Siemens Healthcare Diagnostics provides accurate information which helps determine whether the disease is advancing, so that patients and clinicians can face the disease head-on.

### One Woman's Story

As a career health educator, New Jersey-native Christine Druther, MSPH (Master of Science in Public Health), practiced what she preached – following a healthy lifestyle, eating right, and performing regular breast self-exams. In 1990, she found a small lump in her left breast. "It was hard, like a marble, and I definitely knew something was wrong," she says.

At age 41, Druther was married with two small daughters, ages six and four. Only ten months earlier, she had watched her mother battle and die from breast cancer. Now, she was facing her own struggle with the same disease. Druther had a lumpectomy and underwent a grueling regimen of chemotherapy and radiation. For the next nine years, she was cancer-free and thought she had beaten the disease. But in 1999, the cancer came back. This time, the diagnosis was dire: Stage IV breast cancer, which had spread to her brain. And the cancer was HER-2/neu positive.

### What Is HER-2/neu Cancer?

"HER-2 positive breast cancer is a breast cancer that tests positive for a protein called Human Epidermal growth factor Receptor 2 [HER-2]," explains Walter P. Carney, PhD, inventor and developer of the Siemens Serum HER-2/neu test. "A normal breast cell has two copies of the HER-2/neu gene, which makes proteins that help control how the body's cells grow."

In HER-2 positive breast cancer, the cancer cells make an excess of HER-2. When there are too many copies of the HER-2/neu gene or too many of its proteins in a tumor, a particularly aggressive cancer can result. These cancers are less responsive to hormone therapy, but new treatments that specifically target the HER-2 protein, such as the drugs Herceptin® and Tykerb®, have proven to be effective in blocking tumor cell growth.

“I trust my life to the Serum HER-2/neu test. Women with metastatic breast cancer who are not getting this test are being underserved.”

Christine Druther, MSPH  
Breast Cancer Survivor, Founder of HER2 Support Group  
Carlsbad, California, USA



Patients with a positive HER-2 tissue test qualify for targeted HER-2/neu therapy. Carney adds, “It is very important to determine HER-2/neu status because that information is needed to guide therapy in these patients. The HER-2/neu blood test shows how well women are responding to targeted therapy.”

### Winning the War in the Laboratory

“Life has changed a lot,” says Carney. “It used to be that if a woman was diagnosed with metastatic breast cancer, it was pretty much a death sentence. Now it is still serious, but there are many more therapies available so that people can live longer – and not only live longer, but with a better quality of life.” That is the primary reason why he developed the Serum HER-2/neu test. A cancer researcher for two decades, Carney theorized that materials lurking in the blood might play a key role in cancer diagnosis. “Scientists had this concept for a long time that things on the outer surface of cells probably break off and get into the blood,” he says.

The serum test monitors HER-2/neu, an oncoprotein found elevated in the blood of some breast cancer patients. Generally, a normal Serum HER-2/neu level is below 15 nanograms per milliliter (ng/mL), while an elevated level is 15 ng/mL or greater. Increasing levels reflect cancer progression. Falling levels signify treatment response or stable disease. Studies have shown that up to 90 percent of metastatic breast cancer patients can have an elevated Serum HER-2/neu level.

Serum HER-2/neu positive metastatic breast cancer patients whose primary tissue HER-2/neu was negative may benefit from additional testing of tissue from the primary site or sites of metastasis to determine if their HER-2/neu status has changed. “For patients with HER-2/neu positive cancer, changes in Serum HER-2/neu levels can help tell if treatment is effective or not,” says Carney. “It’s really an example of how therapies can be personalized.”

### Striking a Balance Between Science and Hope

“Even with more advanced stages, like Stage IV metastatic breast cancer, there are reasons to be very hopeful and optimistic because we have new therapies available,” says Daniel Vicario, MD, Druther’s oncologist and a partner at the San Diego Cancer Center in Encinitas, California, USA. “And we see, every day, women with metastatic breast cancer who live beyond limits, live beyond all of the statistics, even beyond what we could have imagined 15 years ago.”

The Siemens HER-2/neu test gives the physician one more tool to use while monitoring women diagnosed with metastatic breast cancer. “The Siemens Serum HER-2/neu test can help identify that cancer may be progressing before its progress is identified by imaging,” says Vicario. Periodic HER-2/neu blood tests help doctors monitor the response to current therapies and plan new ones. By combining advanced drug therapies with diagnostics, doctors have been able to fight metastatic cancers. With the

unique Serum HER-2/neu test plus an advanced array of sophisticated diagnostic tools, including mammography, magnetic resonance imaging, breast ultrasound, and positron emission tomography-computed tomography solutions, Siemens is leading the way and providing maximum information to physicians and patients to monitor and manage metastatic breast cancer. The result? Doctors can monitor and treat their patients with more targeted, more effective therapies.

### No Time to Waste

Druther’s cancer was particularly aggressive and spread to her brain and chest. Yet, she says, “I took matters into my own hands. I knew education was my best tool for survival.” Already a career health educator, she became a specialist in the complex world of HER-2/neu positive breast cancer. Druther was well-versed about chemotherapy drugs and the side effects of each, as well as clinical trials and new research. She could decode medical jargon and peppered her visits to the oncologist with questions about the latest treatments and most effective protocols.

“It is bad news to be diagnosed with HER-2/neu positive cancer, but the good news is that there are targeted drugs that can work for this kind of cancer,” says Druther. “Because of my research, I knew I wanted Herceptin.” Druther’s cancer responded well to the Herceptin, and she also underwent gamma ray radiation for the cancer in her brain.



“Even with more advanced stages, like Stage IV metastatic breast cancer, there are reasons to be very hopeful and optimistic, because we have new therapies available.”

Daniel Vicario, MD  
San Diego Cancer Center  
Encinitas, California, USA

### Future Applications

The Serum HER-2 test offers a two-pronged benefit for both physicians and patients. Medically, the test helps physicians optimize treatment for HER-2/neu positive breast cancer patients. On an emotional level, it can help keep patients informed about their health status.

“My position is that anyone who gets diagnosed with metastatic breast cancer should have a baseline Serum HER-2 level and, if it is elevated, be monitored for life, especially if they are HER-2/neu positive by tissue tests,” says Carney.

Additionally, the test is showing promise for use in other cancer diagnoses. “The Serum HER-2/neu test was first used as a breast cancer marker for HER-2 positive breast cancer,” says Carney. “But as it turns out, there are HER-2 positive gastric cancers and HER-2 positive lung cancers, so now we’re seeing it used in studies for these cancers as well.” He continues, “We’ve focused efforts over the years on breast cancer, but what is really clear is that this can go beyond breast cancer, and it already has. The Serum HER-2 test may cross over a number of cancers and may cross over a variety of therapies. In a way, we’ve only scratched the surface of the value of this test. I see HER-2 as a model for how we should be building biomarkers for the future.”

### A New Role

Today, Christine Druther has been in remission for nine years from HER-2/neu positive metastatic breast cancer.

“I am happy to say I survived it, and I have a great quality of life,” she says. “I wish that for everyone.”

Druther and her husband, Joe, have started a comprehensive website, [www.her2support.org](http://www.her2support.org), to provide help and valuable information to HER-2/neu positive patients. The website was launched on December 24, 2001.

“I had this vision that we had to create a website to inspire women to take control of their health,” she says.

“The best patient is the one who is best informed about her own disease.” In addition, every month, Druther gets the Siemens Serum HER-2/neu blood test to monitor her condition. “I trust my life to this test,” she says. “Women who are not getting the Serum HER-2/neu test are being underserved.”

### For more information

[www.siemens.com/herstory](http://www.siemens.com/herstory)  
[www.usa.siemens.com/herstory](http://www.usa.siemens.com/herstory)



# The Changing Face of Healthcare–Associated Infections and MRSA

Healthcare-associated infections have moved from hospitals, medical centers, and long-term care facilities into the community. Can screening programs assist in the control of these infections?

By J. Michael Janda, PhD



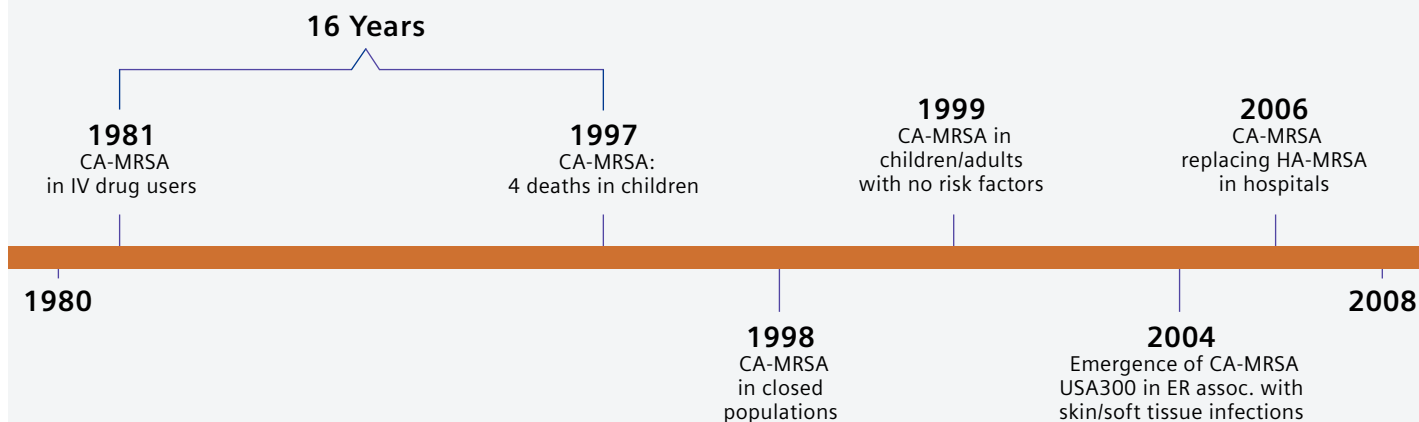
Healthcare-associated infections (HAIs) or the older term “nosocomial infections” have been a major concern of hospitals, medical centers, and long-term care facilities for decades. The importance of HAIs has long been recognized in that the Centers for Disease Control and Prevention (CDC) has monitored HAIs through the National Nosocomial Infections Surveillance System (NNIS)

for years.<sup>1</sup> While NNIS was initially established with 62 hospitals in 1970, by year 2000 the number of participating centers had ballooned to more than 225. Through NNIS, recommendations on performance improvement and infection control strategies were developed for such HAIs as surgical site (SSI) and bloodstream infections (BSI). In 2005, this long-standing infrastructure was

replaced by the National Healthcare Safety Network, which not only includes NNIS but also the Dialysis Surveillance Network (DSN) and the National Surveillance of Healthcare Workers (NaSH). Their first report of data collected during calendar year 2006 was released in 2007.<sup>2</sup>

1

## CA-MRSA Timeline



**1** By 2004, CA-MRSA was a major cause of skin and soft tissue infections in the community in persons with no known risk factors and was no longer confined to hospital settings.

Currently, between 5 and 10 percent of patients admitted to modern hospitals in developed countries acquire one or more infections; 15 to 40 percent of those admitted to critical care are affected. The risk is 2 to 20 times higher in developing than in developed countries. The burden of disease outside hospitals is practically unknown due to the absence of surveillance (World Health Organization). In the United States, the CDC estimates that over 1.7 million HAIs occur annually with approximately 99,000 associated deaths (<http://www.cdc.gov/incidod/dhqp/hai.html>). Of all HAIs, approximately one-third involved the urinary tract, slightly over one-fifth are associated with surgical site infection (SSI) and another 30 percent are almost equally divided between bloodstream infection (BSI) and pneumonia. Each HAI has dramatic ramifications for both patients and healthcare practitioners alike, resulting in extended hospitalizations and monitoring, possible additional medical testing, and required intervention in the form of antimicrobial chemotherapy. These additional economic consequences do not even take into account such things as loss of productivity in person-years, possible increasing drug resistance in HAIs, and subsequent litigation. HAIs are simply "Pandora's Box" in its most frightening form.

### The Changing "Face" of HAIs: CA-MRSA

As far back as the 1980s and even into the early 1990s, HAIs were considered to be an institutional problem restricted to hospital environments and certain subsets of patients with serious underlying disease, lengthy hospitalizations, or those undergoing medical procedures such as surgery and catheterization. While HAI outbreaks did occur sometimes over protracted periods of time in some centers, these typically involved limited numbers of persons and did not affect the community at large. The public health sector, per se, did not view this as a serious threat outside of those environs.

This philosophy radically changed with the onset of community-associated MRSA (CA-MRSA) in the general population in the early 1980s. Although MRSA had emerged as an important healthcare-

associated pathogen in the 1960s<sup>3</sup> it was only in the early 1980s that it made its first appearance as a community-associated pathogen with a reported outbreak of disease in intravenous drug abusers in Detroit.<sup>4</sup> Subsequent to that report, CA-MRSA seemed to remain dormant more or less for approximately 16 years until the late 1990s when several outbreaks of CA-MRSA erupted in clustered groups, including Indian reservations, prisons, the military, the homeless, and daycare centers (Figure 1). Once CA-MRSA emerged in these closed populations it began to spread like wildfire into other groups, including persons participating in contact sports, and most recently, in men who have sex with men. By 2002–2004, CA-MRSA was a major cause of skin and soft tissue infections in the community in persons with no known risk factors and was no longer confined to hospital settings. An even more alarming trend

CA-MRSA is now established in open communities and it will take years, if not decades, to significantly reduce or eradicate this pathogen in established reservoirs.

Step	Process	Year
1	MRSA in hospitals	1960s
2	Introduction of HA-MRSA into community	Late 1970s
3	Development of CA-MRSA strains	1982
4	Emergence and clonal spread of subtypes	1997
5	Rapid emergence	2000
6	Endemicity and epidemics	2003
7	Re-introduction into hospitals	2006
8	Altered virulence, new subtypes	?

**2 Potential steps in the evolution and spread of CA-MRSA**

has been the spread and expansion of a predominant unique clone with a designated pulsed field gel electrophoresis (PFGE) pattern (USA300) as the major cause of CA-MRSA in the United States.<sup>5</sup> This rapid expansion seems to parallel a similar phenomenon that occurred in the 1950s when penicillin-resistant *S. aureus* pandemics appeared and were predominantly caused by phage-type 80/81.<sup>6</sup>

In the recent past, CA-MRSA infections were distinct from hospital-acquired MRSA (HA-MRSA) in regards to patient populations, disease settings, and phenotypes and genotypes of infecting strains. CA-MRSA strains in the past were predominantly found in the community in individuals with skin and soft-tissue infections but no underlying illness.

Isolates contained the subtype IV staphylococcal chromosome cassette (SCC) *mec* genes and often additionally harbored the Panton-Valentine toxin. CA-MRSA strains were typically more susceptible to a number of antimicrobial agents than HA-MRSA, including clindamycin, fluoroquinolones, gentamicin, and trimethoprim-sulfamethoxazole. In contrast, HA-MRSA strains were in healthcare settings in seriously ill persons with life-threatening infections. HA-MRSA isolates, in contrast to CA-MRSA strains, belonged to different SCC *mec* subtypes, lacked the Panton-Valentine toxin, and were much more resistant to the antibiotics described above.

This clearly demarcated line between CA-MRSA and HA-MRSA infections is rapidly changing during recent years. A national prevalence study of MRSA in

inpatients at over 1,200 healthcare facilities conducted in 2006 found that 30 percent of strains analyzed had a phenotype that was more consistent with CA-MRSA.<sup>7</sup> Seybold, et al. has also recently reported that the CA-MRSA USA300 genotype caused 34 percent of BSI in a major public hospital in Atlanta, Georgia, USA in 2004.<sup>8</sup> This latter study has been followed by a report from an inner city hospital in Chicago, Illinois, USA of BSI between 2000 and 2006. Although the total hospital-onset MRSA BSI rate remained relatively stable over the six-year period, the percentage of CA-MRSA causing BSI rose from 24 percent to 49 percent.<sup>9</sup> These results suggest that strains are co-mingling, if not replacing HA-MRSA, in many if not most major medical centers today.

## Issues and Concerns

Figure 2 lists a number of the steps MRSA isolates have undergone in morphing from a hospital to also a community-associated pathogen with enhanced virulence characteristics. Of critical importance in this process are steps 3 to 5 where MRSA developed into a more versatile microbe able to colonize, persist, and multiply in the community. Complete genome sequencing of one USA300 strain suggests that endemic CA-MRSA may have possibly arisen by horizontal gene exchange with *S. epidermidis* receiving essential genetic elements for survival at low pH on human skin and within phagocytic cells.<sup>10</sup> This event coupled with its sudden rapid clonal expansion and emergence has led to its increasing incidence in community-associated infections that we now face.<sup>6</sup>

Emergence of CA-MRSA has enormous ramifications for both healthy persons and those hospitalized. CA-MRSA is now established in open communities and it will take years, if not decades, to significantly reduce or eradicate this pathogen in established reservoirs.<sup>11</sup> Published studies already cited suggest that this genotype is now being introduced into tertiary care facilities and public hospitals with the possibility it may also spread to smaller local community medical centers.<sup>7,8,9</sup> CA-MRSA strains in these settings with enhanced virulence capabilities may also acquire increasing resistance to drugs that have been effective in the past, increasing both morbidity and mortality in these backgrounds. A frightening addendum to this assumption is the recent spread of methicillin-susceptible *S. aureus* (MSSA) USA300 strains in the community and its linkage to higher frequencies of invasive infections in children.<sup>12</sup> Finally, there are at present very few antimicrobial agents useful in treating invasive MRSA infections (vancomycin, trimethoprim-sulfamethoxazole, linezolid) and it is unclear whether or not the pharmaceutical industry will be able to develop new drugs to add to this limited arsenal, although several investigational drugs such as ceftobiprole and ceftaroline seem to hold some promise. If increased frequency of resistance to front-line therapies such as vancomycin emerges, serious HA-MRSA or CA-MRSA infections could become untreatable.

## The Clinical and Public Health Challenge

One of the formidable challenges we all face is to develop a systematic effort to identify, control, and prevent HA-MRSA and CA-MRSA. This challenge has several major obstacles. A 2007 study of over 1,200 healthcare facilities in the United States found that only 29 percent of surveyed hospitals performed active surveillance for MRSA.<sup>7</sup> Of those sites, over half performed routine cultures only, clearly not the most sensitive nor rapid method to detect MRSA. Other studies suggest that few coordinated efforts have been made to reduce the transmission and number of MRSA HAIs and control the spread of multi-resistant strains in the hospital environment.<sup>13</sup> The best available evidence we currently have is

that the scope and magnitude of the MRSA problem is underreported and underappreciated and that current efforts fall increasingly short in dealing with this immense issue.

A number of steps need to be taken to begin to curb the prevalence and incidence of MRSA infections on a worldwide basis. To understand the scope and magnitude of MRSA infections, one potential public health approach to this important issue would be to develop a surveillance model for collecting and collating data regarding *S. aureus* and MRSA infections.<sup>14</sup> Collected annual data would then be disseminated to medical facilities through periodic surveillance reports.

Globally, the World Health Organization is implementing three major strategies:

- Campaigning to build global awareness of the importance of HAI and to help catalyze leadership, commitment and action
- Country pledges to ensure political commitment and leadership at the highest level
- Testing implementation strategies worldwide

It is very clear that past practices will be insufficient in addressing the expanding MRSA problem.



Some of the challenges at the country level are to catalyze and sustain strong and visible leadership and stewardship by the government, health authorities and professions; invest in the development of monitoring tools; and support the establishment of independent systems to track progress and impact. To accomplish such an aggressive approach requires legislative action at the state and/or country level.

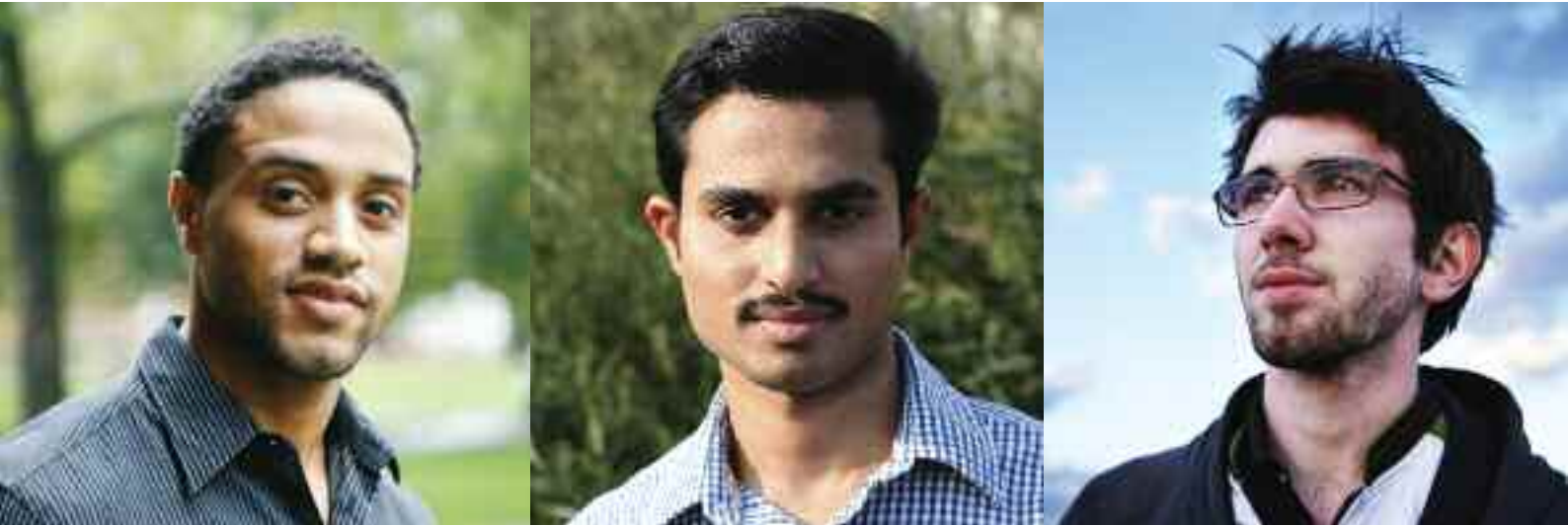
### Final Thoughts

It is very clear that past practices will be insufficient in addressing the expanding MRSA problem. The changing face of how HAIs impact us is not only represented by MRSA but other agents such as *Clostridium difficile* associated diarrhea (CDAD) where hypervirulent clones are emerging that are less responsive to treatment and are causing more cases of community-associated disease.<sup>15</sup> Methods must be improved to detect, treat, and report MRSA and other important HAIs.

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# The Case for Increased Chlamydia and Gonorrhea Screening of the At-Risk Male Population Worldwide

It is of concern to see recent dramatic increases in preventable, communicable, sexually transmitted infections (STIs) worldwide. Two STIs, chlamydia and gonorrhea, which are increasing at an alarming rate, have been somewhat forgotten and given poor resource allocation worldwide.

By Professor Dennis V. Ferrero

While chlamydia and gonorrhea may have attracted less attention and, indeed, resources in recent years, their insidious health effects, coupled with the negative social and economic impact, need to be recognized. The good news is that thanks to both research and industry, we have the tools to mitigate the effects of these diseases. Sensitive tests are permitting early detection and allowing us to reach and treat the at-risk male population.

The medical and social burden of sexually transmitted *Chlamydia trachomatis* (Ct) and *Neisseria gonorrhoeae* (Ng)

infections is well known.<sup>1</sup> While much literature regarding Ct disease in women has led to increased attention to the negative health outcomes of genital tract infection in women, and the usefulness of subsequent screening programs, less information is available regarding the effects of the Ct disease in men. Recently, Cunningham and Beagley suggested that up to 39.5 percent of prostatitis cases may be due to Ct.<sup>2</sup> The authors note there is compelling evidence of an association between Ct infection and the development of prostatitis and other less-known genital tract diseases in men.

The authors go on to discuss further considerations for the role of Ct infection and infertility.

## The Value of Screening Programs

Because both Ct and Ng can cause asymptomatic infections, it is important to realize that screening programs have been shown to be the most effective means to control asymptomatic disease.<sup>3,4</sup> Utilizing noninvasive specimens such as first-catch urine (FCU) has advantages, and the use of this specimen type is well documented.<sup>5,6</sup>



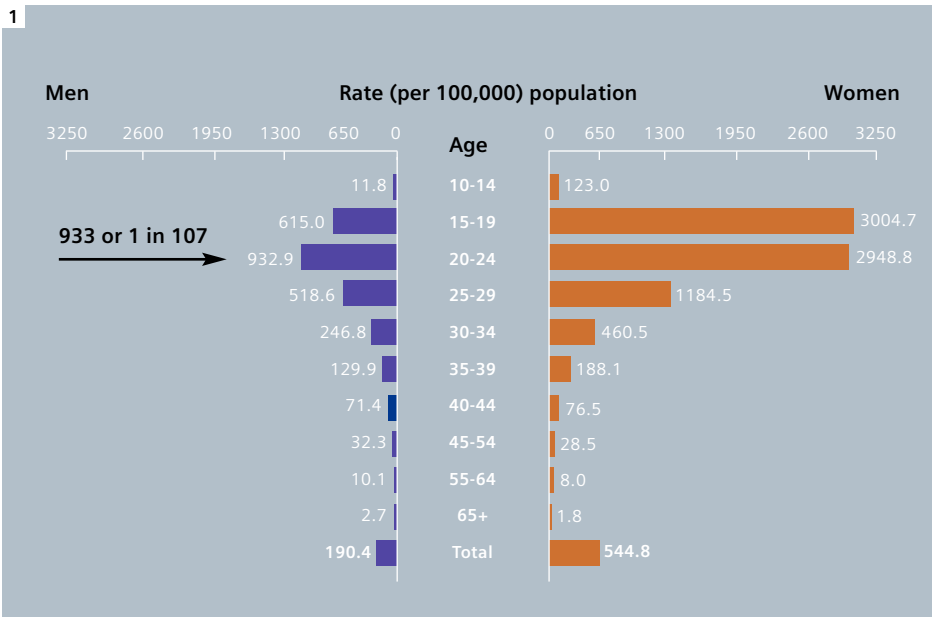
Urine screening has broadened STI-testing capabilities from the traditional public health STI clinic to innovative venues, such as juvenile detention centers, dance clubs, mobile clinics, and other venues frequented by adolescents, to reach the main reservoir of infection. Coupled with nucleic acid amplification tests (NAATs), urine-based screening provides superior assay performance,

which is also well documented.<sup>7,8</sup> This is particularly important for screening programs where asymptomatic patients are most vulnerable to silent infection; advancing to more serious disease. Individuals with asymptomatic infection continue to serve as a reservoir of infection, and the argument can be made that asymptomatic patients are those most important to identify in

## Molecular Diagnosis Using NAAT Testing

In vitro diagnostic tests are necessary to specifically identify patients infected with Ct/Ng. Nucleic acid amplification tests (NAAT) are not only more sensitive than other methods, but also effective for screening non-invasive clinical samples such as first-catch urine.<sup>5,7,10</sup> NAAT assays, designed to operate on high-throughput platforms, are sensitive for screening programs to identify infected individuals.

The VERSANT® CT/GC DNA 1.0 Assay (kPCR) used with the VERSANT® kPCR Molecular System, is a kinetic polymerase chain reaction (kPCR) assay for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in both symptomatic and asymptomatic individuals. The assay is being developed to work with a proprietary sample collection device in order to provide greater sample stability and primary tube handling, coupled with state-of-the-art nucleic acid extraction from clinical samples.



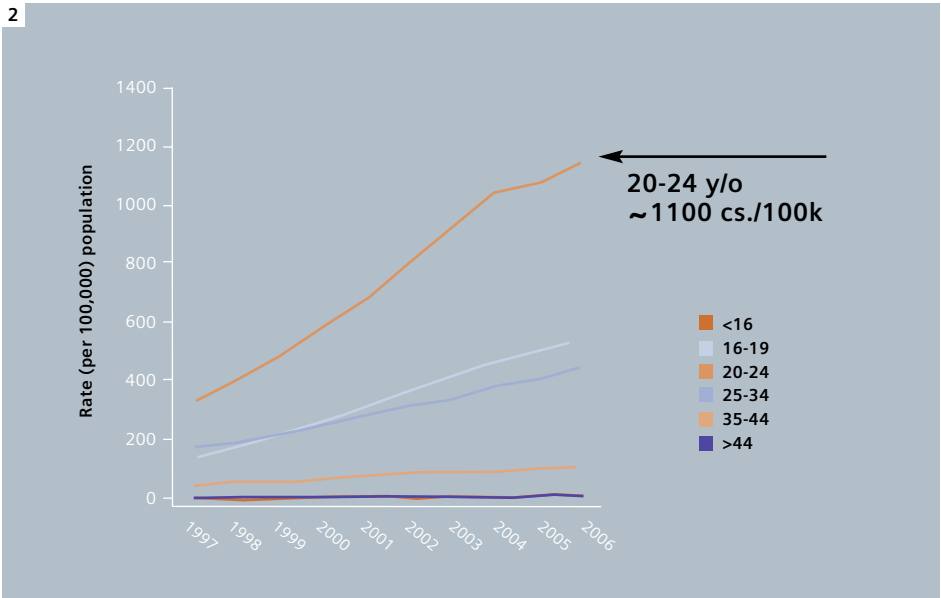
**1** Chlamydia: age- and sex-specific rates in the USA, 2007 (Centers for Disease Control, USA)

order to decrease the overall prevalence of disease. Because current efforts have not adequately controlled these diseases, public health officials must consider additional means.

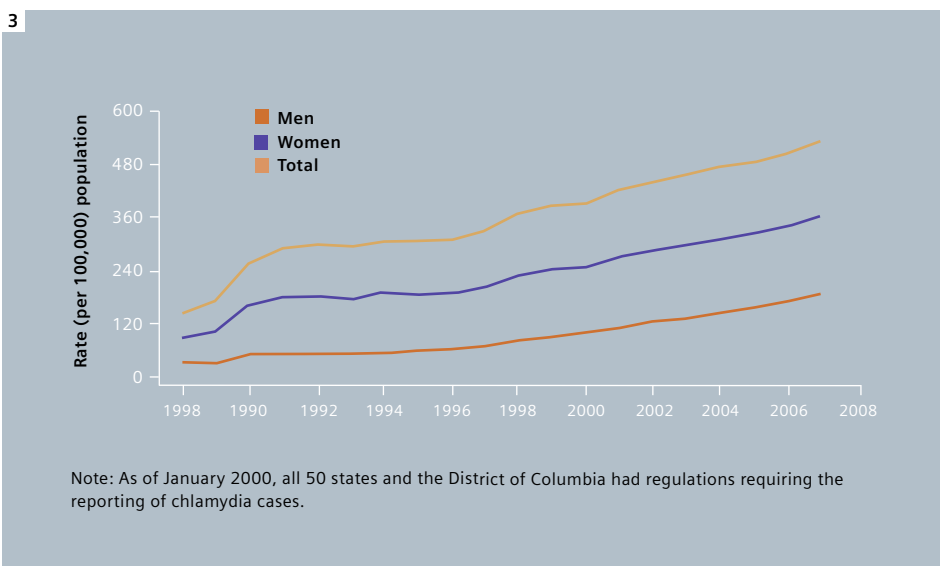
The latest national data with respect to the most affected groups in the USA mirrors the pattern we have seen for some time now (Figure 1). Women and men in the 15 to 24 year old age group are those

most affected according to the most recent data available from the Centers for Disease Control (CDC). The UK has also collected STI rate data that give us some insight into disease trends outside of the USA. In fact, when we drill down to specific age groupings and rates, we see similar patterns of Ct disease within the UK as in the USA regarding Ct increases in men (Figure 2).

Increasing Ct rates in both women and men, and ever-present Ng infections in women, have given rise to consideration of a targeted national male screening program in order to address the silent male reservoir. Given the continued increases in disease burden, one could wonder if the emphasis on screening, identifying, treating women, and not aggressively attacking the male reservoir, has been the best public policy.



**2** Rates of diagnosis of uncomplicated genital chlamydial infection in males according to age group in the UK, 1997–2006 (Genitourinary Clinics, Health Protection Agency, UK)



Note: As of January 2000, all 50 states and the District of Columbia had regulations requiring the reporting of chlamydia cases.

**3** Chlamydia rates: total and by sex in the US, 1988–2007 (Centers for Disease Control, USA)

Unfortunately, even with significant infusion of public funds, Ct disease rates continue to rise for both women and men in the USA (Figure 3). Initially, public health officials and researchers considered the rise in rates to have been due to the introduction of significantly more sensitive NAAT assays. However, this theory has given way to the realization that the significant and sustained increase, especially of Ct disease rates, is due to a combination of social and economic factors, as well as questions concerning the biology of the organism and the disease it causes. In turn, this has led to questions as to the best approach for national screening programs.

### Expert Consultation

To that end, and to their credit, the CDC held an Expert Consultation in 2007 that brought together opinion leaders from state and local public health organizations and key members of the research field. The aim was to review the literature, share experiences, and develop consensus information to guide US policy regarding Ct screening in men. The first documents from the Consultation were made available and distributed by the CDC in May of 2007 and are available on the CDC's website.<sup>9</sup> A summary of the Consultation findings is found in Figure 4.

One outcome of the CDC Expert Consultation process included a recent publication by Consultation attendees Gaydos, Ferrero, and Papp regarding a review of Ct laboratory aspects. In the paper, key recommendations for advancing male Ct screening in the USA were made.<sup>10</sup> The review supports the notion that NAATs are the test of choice for Ct screening of males and that the use of non-invasive FCU specimens best advances the potential for increased screening of males. The review concludes

that increasing the number of at-risk males screened may provide potential reduction in overall disease burden in both men and women.

### Screening the Male Population

Just as health maintenance organizations, (HMOs), family planning organizations, the military, and numerous professional organizations came to realize that screening for certain STIs was in their

acquired sequelae and infertility, and all the while, advancing the mission to protect women.

Public health cannot do this alone and in a vacuum. While the case can be made that a high percentage of positive test findings do come from the public sector, the numbers of tests rendered to many of the at-risk populations come from the military, HMOs, family planning, and

populations outside of the public sector. Robust data collection and analysis is needed coupled with an economic incentive for the military, HMO, family planning, and other non- and for-profit sectors who will be important in providing this access.

Normally, it would be unacceptable to have preventable disease rates that increase by over 50 percent during a five-year time frame in any developed country, but somehow, we have managed to do just that in male Ct rates during the most recent five-year period for which we have current data (Figure 5).

### Reducing Transmission

Several articles published in late 2008 following the CDC's Expert Consultation on male screening have led the way to a better understanding of where we need to consider enhanced screening activities. Clearly, we cannot veer from any policy aimed at reducing morbidity in women; however, enhanced screening of selected male populations can only enhance efforts toward women.

In an article published in 2008, Dunne, et al. noted that male infection can result in transmission to female partners and suggested that screening men should be considered as a means of reducing transmission risk to female partners. They further suggested that rescreening men found to be infected could impact Ct morbidity in males, as is currently recommended for women.<sup>11</sup> Dunne, et al. also posed the question in a recent editorial: "Key activities that lead to significant reductions in morbidity are needed, and enhancing activities to identify and treat men with Ct infection might be a step to reducing Ct morbidity."<sup>12</sup> Others have pointed out that Ct infections in men serve as a reservoir for transmission to females.<sup>13,14</sup>

Economic considerations, as well as moral obligations, led to more robust screening activities directed toward women some 12 years ago. This was accompanied by a significant infusion of federal dollars. Similar discussions have occurred regarding the need to increase attention toward men.

4

Recommendation	Strength
Urine specimen using NAATs are preferred	Strongly Recommend
Males attending STI clinics	Strongly Recommend
Males attending National Job Training Program	Strongly Recommend
Males in military	Strongly Recommend
Males entering juvenile facilities	Recommend
Communities with high Ct prevalence should consider screening men	Recommend

4 Compilation of the Centers for Disease Control 2007 Expert Panel's Recommendations regarding male screening

Ct: *Chlamydia trachomatis*; NAATs: nucleic acid amplification test; STI: sexually transmitted infection

5

Age	Sex	2002	2007	% Increase
15-19 years	Female	2619.1	3004.7	14.7%
	Male	408.4	615.0	50.6%
20-24 years	Male	691.5	932.9	35.0%
Total	Female	456.5	544.8	19.3%
Total	Male	130.4	190.4	46.0%

5 Increase in *Chlamydia trachomatis* rates in selected age groups and total by sex in the USA, 2002–2007

best economic interest and was the proper health policy for women; it will come to pass that many of the same cost-effective policy measures will be put in place for men. Finding ways to have men avail themselves of simple relatively inexpensive, accurate, easy-to-do NAAT screening tests will lead to increased cost-savings versus treating male-

other non- and for-profit sectors via military, hospital, and independent clinical laboratories. Without all provider sectors engaged, the necessary screening of both women and men in sufficient numbers to affect disease trends will never be realized. We must foster a partnership combining public health sector expertise with access to special

Regarding Ng infection in males, simply, we have more work to do here as well, lest we think the battle against genital tract infections due to Ng has been won. In the USA, while significant strides were made from the late 1970s to now, it is predicted that the USA will not meet the overall total rate for the 2010 Healthy People goal for Ng disease. As a matter of fact, for men, we are very far from the goal of 19 cases per 100,000 with 113.7 cases per 100,000 recorded in 2007. Furthermore, when one delves into the data available, we find regional outbreaks occurring,<sup>15</sup> sustained Ng activity in certain sectors, and case rates for some age groups increasing. For the two-year period of 2005 to 2007, we saw case rates increase by 9.5 percent for males aged 15 to 19; from 261.2 per 100,000 to 286 per 100,000.

## Dual Screening

It is important to realize that many women and men (up to 50 percent of those infected) are dually infected with both Ct and Ng. One significant armament we have in the arsenal for battle is the fact that all major NAAT assays have the capability to test both Ct and Ng from the same FCU specimen at the same time.

To summarize, much of the evidence today points to the realization that we need to find innovative ways to reach the at-risk male population to identify and treat significant disease potential in the male population and at the same time better protect the female population worldwide. Fortunately, with state-of-the-art NAAT assays, we have the ability to provide the most sensitive means to detect Ct and Ng disease using easy-to-obtain noninvasive specimens.



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## Confronting the AIDS Epidemic: New Guidelines and Programs Offer Hope for Reduction of the Global HIV Burden

Recent data suggests increased HIV transmission in many countries, including regions in both Europe and the USA.<sup>1,2</sup> This article discusses the importance of early identification of infected individuals to both reduce new transmission and promote earlier intervention with antiretroviral therapies. Revised guidelines from both the USA and European Union may dramatically increase screening for HIV infection. Sensitive testing technologies are central to this move toward more widespread screening, providing tools for early detection that support both optimal patient management and infection control.

By Katherine Soreng, PhD

Infection with the Human Immunodeficiency Virus (HIV) leads to significant damage to the immune system and the clinical development of the Acquired Immune Deficiency Syndrome (AIDS). Without treatment, infection with opportunistic disease is almost certain. Common opportunistic diseases are listed in Figure 1. Death can occur from opportunistic infection or from co-infection, such as with hepatitis C. Although many factors can influence disease progression following HIV infection, the average new infection requires approximately 10 years to progress to the disease state clinically defined as AIDS. A diagnosis of AIDS indicates that substantial damage to the adaptive immune system has occurred, and the patient is at extreme risk for infection with opportunistic disease. Figure 2 lists the current clinical definitions of AIDS.

The stunning success of antiretrovirals and improved education on HIV risk factors has led many to believe that HIV infection could be on the wane. The recent downward adjustment by the World Health Organization (WHO) of global estimates of HIV prevalence may have served to reinforce this perception.

That optimistic picture was shaken with the release of data in October 2008 by the Centers for Disease Control and Prevention (CDC) showing that in the USA, the annual rate of new HIV infections was much higher than previously estimated.<sup>2</sup> The back calculation suggested a current annual infection rate of about 56,000 per year versus the previous estimate of 40,000 new HIV infections per year. However, study investigators suggested that the number of new infections likely represented the improved detection of early infection vs. a significant increase in overall rate. Men who have sex with men and black individuals remain disproportionately at risk in the USA. In the WHO European Region, the annual rate of HIV infection has almost doubled between 2000 and 2007, rising from 39 to 75 per million population.<sup>1</sup> IV drug abuse, heterosexual sex, and male-to-male sex all significantly contribute to the transmission of new infection.

These numbers emphasize the importance of identifying HIV-infected individuals and the need to develop effective prevention programs. While male-to-male sex remains a leading risk factor for HIV infection in men in the USA, heterosexual

sex is a common route of transmission for women. In many countries with high prevalence of HIV, such as those in sub-Saharan Africa, heterosexual transmission is the most common route for both men and women.

In recent years, data has clearly demonstrated that many new HIV infections in the USA were transmitted by sexual partners unaware of their infection status.<sup>3</sup> In addition, a troubling number of patients were being identified as HIV-positive within just one year of developing AIDS, often eliminating an important therapeutic window. Early knowledge of HIV infection allows initiation of highly-active antiretroviral therapy (HAART) that can dramatically improve life expectancy, particularly if begun prior to the onset of severe immunosuppression.<sup>4,5</sup> Recognizing this, in 2006, the CDC revised the previous recommendations for HIV screening to move from screening only those considered "at risk" (such as males who have sex with males, IV drug abusers, and individuals who received blood or blood-derived products before the implementation of blood donation screening) to a general screening of anyone between the ages of 13 and 64 presenting in a healthcare setting.<sup>6</sup> The need for comprehensive screening of all expectant mothers was also emphasized in the revised guidelines, underlining the fact that intervention can substantially reduce transmission from mother to child if the woman's infection status is known. The previous CDC guidance requiring written (opt-in) permission for an HIV test was altered to a verbal opt-out approach. In addition, the prior requirement for patient counseling for all confirmed positive results was removed. While many states in the USA are still operating under the previous guidelines, some have already updated their recommendations to reflect the new CDC guidelines. In 2009, the American College of Physicians (ACP) released similar screening guidelines, emphasizing general HIV screening for anyone 13 years and older as well as all pregnant women.

The 2008 European Guidelines on HIV suggest offering HIV testing to individuals aged 16 years and older presenting to a clinic for sexually transmitted infection regardless of signs, symptoms, or risk.

<b>1</b>	<b>Candidiasis (Thrush)</b> is a fungal infection of the mouth, throat, or vagina.
	<b>Cytomegalovirus (CMV)</b> is a viral infection that causes eye disease that can lead to blindness.
	<b>Herpes simplex viruses</b> can cause oral herpes (cold sores) or genital herpes.
	<b>Mycobacterium avium complex (MAC or MAI)</b> is a bacterial infection that can cause recurring fevers, general sick feelings, problems with digestion, and serious weight loss.
	<b>Pneumocystis pneumonia (PCP)</b> is a fungal infection that can cause a fatal pneumonia.
	<b>Toxoplasmosis (Toxo)</b> is a protozoal infection of the brain.
	<b>Tuberculosis (TB)</b> is a bacterial infection that attacks the lungs, and can cause meningitis.

**1 Common opportunistic infections seen with AIDS**

<b>2</b>	<b>Infected with HIV and:</b> A CD4+ T-cell count below 200 cells/μl (or a CD4+ T-cell percentage of total lymphocytes of less than 14%)
	Or
	<b>Infected with HIV and:</b> Presenting with an AIDS-defining illness (see reference for full list of AIDS-defining disease)

**2 Centers for Disease Control, USA, definition of AIDS**

# The REACH Program

## Resources Embracing Africa with Care and Hope



## Siemens – Reaching Those Who Need It Most

Africa contains some of the countries most burdened with high endemic rates of HIV. An estimated 22.5 million people in Africa are HIV-positive and 2 million new infections occur yearly. Programs are becoming available to help some of the hardest-hit countries both reduce transmission and improve management of HIV-infected individuals. One example is the REACH Program, where Siemens works with local partners to make critical molecular testing available to HIV-positive individuals living in areas with limited access to modern healthcare. Improved serology-based HIV screening and availability of molecular testing, particularly in remote areas endemic for HIV, are offering hope for increased prevention and better clinical outcomes in HIV-infected individuals.

For more information on the REACH Program please visit [www.siemens.com/reach](http://www.siemens.com/reach)

Screening recommendations in other countries vary. In 2007, the WHO published "Practical Guidelines for Intensifying HIV Prevention" that included a risk reduction strategy and assessment of prevalence and risk by country in the adoption of HIV prevention measures (including testing). Globally, HIV testing and treatment access are often a barrier to both HIV screening and optimal clinical intervention in many resource-limited countries.

New and more sensitive testing technologies are becoming available that allow earlier detection of HIV infection. Assays capable of recognizing IgM as well as IgG antibody to HIV can allow detection in as little as three weeks (based on seroconversion panels). Use of a combination test that picks up the HIV p24 antigen (p24 is a protein that composes the HIV nucleocapsid) as well as antibody to HIV (an HIV Combo test) may provide a slight improvement in earlier detection when compared to existing, sensitive antibody-only immunoassays. It is important to remember that commercial immunoassays often contain design differences and can vary in sensitivity and specificity. Labs should be aware of both the strengths and limitations of the assay they are using. While the HIV Combo is becoming the standard screening technique recommended by the European Union, the USA currently has only FDA-approved HIV antibody screening assays. However, advances in the design characteristics of antibody screening technology,

such as detection of both IgM and IgG and "two-pass" assays that improve sensitivity, are providing an increasingly robust and sensitive method for early detection of HIV antibody.

Point-of-care (POC) manual HIV tests can provide a rapid result compared with some bead or automated HIV immunoassays and have become widely available. POC testing is beneficial in some settings where an immediate result is desired (such as some STI clinics or field-based testing). For general HIV screening, both cost and time generally favor a move to automated immunoassays for the detection of HIV infection. Commercially accessible, fully-automated HIV assays are available with high sensitivity and specificity. In addition, some assays offer the designed detection of HIV-1 Group M (and subtypes), HIV-1 Group O, and HIV-2 antibodies, providing an extraordinarily broad spectrum of detection to HIV infection. Not all assays offer designed detection of HIV-1 Group O, so labs should be aware as to whether their testing method relies on cross-reactivity or is constructed to specifically include detection of HIV-1 Group O virus as well as detection of Group M subtypes and HIV-2.

While only time will tell how many countries will ultimately move to either general screening for HIV or enhanced targeting of at-risk individuals, it is clear that early detection will support both optimal patient management and infection control. Most encouraging is

the increasing availability of both serology testing and molecular testing in areas that previously had little access to these important testing modalities. Automated testing is a trend for many infectious disease states that includes not only HIV, but testing for other common infectious organisms, such as viral hepatitis, syphilis, and EBV. As labs move to face the increasing demand for ID testing, as well as deal with staffing challenges, automation and consolidation are likely to be key players.

**Sources**

Figure 1: <http://www.aids.org/factSheets/500-Opportunistic-Infections.html#anchor51213>.  
 Figure 2: <http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm>.

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While only time will tell how many countries will ultimately move to either general screening for HIV or enhanced targeting of at-risk individuals, it is clear that early detection will support both optimal patient management and infection control.





## Myeloperoxidase in Evaluation of Cardiac Patients

A key question facing clinicians is evaluating which of their patients experiencing chest pain are at risk for major adverse cardiac events, including myocardial infarction, the need for revascularization, and even death. Myeloperoxidase (MPO) is a tool that can aid clinicians in the prediction of a patient's future risk and may be used in conjunction with clinical history, ECG, and cardiac biomarkers.

By Tricia A. Bal, MD

## Introduction

Evidence suggests that myeloperoxidase (MPO) is involved in processes such as endothelial dysfunction, inflammation, and the formation of vulnerable atherosclerotic plaques that underlie cardiovascular disease.<sup>1-3</sup> MPO is secreted by leukocytes and is a potent antimicrobial enzyme that plays an important role in host defense through the formation of free radicals and diffusible oxidants. MPO and its oxidized products have been found in low-density lipoprotein (LDL) cholesterol and atherosclerotic lesions.<sup>1-4</sup> MPO also consumes endothelial-derived nitric oxide, which has roles in both vasodilation and suppressing inflammation. Moreover, through its consumption of nitric oxide, MPO may contribute to plaque instability.<sup>5</sup> Consistent with this evidence, MPO has been shown to be a marker of adverse cardiac events.<sup>1-3</sup>

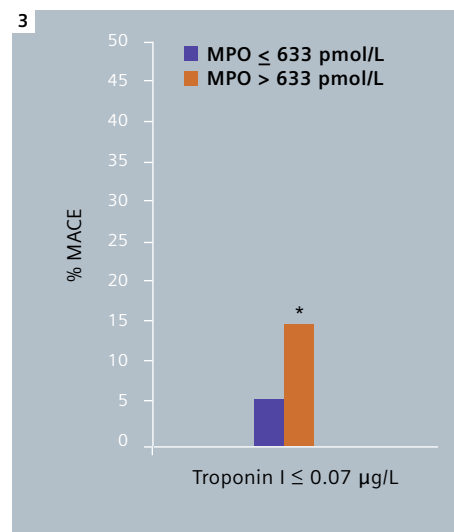
Siemens Healthcare Diagnostics is committed to providing a comprehensive menu of biomarkers that help manage patients throughout the continuum of care. MPO is an additional tool that can aid clinicians in the care of their patients with cardiac disease. This paper will address the clinical utility of MPO in selected patient populations.

## Clinical Utility of Myeloperoxidase

MPO's role in cardiovascular disease has been explored in several studies. It has been shown to be a prognostic marker of major adverse cardiac events (MACE) across the spectrum of cardiovascular disease: in patients with symptoms suggestive of acute coronary syndromes (ACS), in patients with non-ST elevation acute coronary syndrome (NSTEMI), in patients with heart failure, and in patients after myocardial infarction.<sup>1-3,5-8</sup> Studies have demonstrated varied clinical applications for MPO using different assays. Currently, there is no universally accepted cutoff value for MPO assays and, consequently, each assay has its own recommended cutoff.

### Symptoms Suggestive of ACS and Elevated Troponin

MPO has value for the prediction of future cardiac events in patients with symptoms suggestive of ACS and elevated troponin. A study of 457 patients presenting with symptoms suggestive of ACS on admission were evaluated using several biomarkers, including troponin and MPO, to examine whether abnormal levels of these markers were associated with adverse outcomes. The study showed that patients with increased levels of both MPO (greater than 896.8 pmol/L) and troponin



**3** MPO provides improved risk stratification for major adverse cardiac events (MACE) when added to troponin.<sup>9</sup> Data shown represent incidence of MACE at 30 days; incidence of MACE at 180 days was similar.

\* p = 0.008 MPO > 633 pmol/L vs MPO ≤ 633 pmol/L. One-sided p values were calculated using Fisher's Exact test.

(≥0.1 µg/L) had a significantly higher cardiac event rate of 43 percent (almost threefold) compared with an event rate of 15 percent for those with normal levels of MPO and elevated levels of troponin (Figure 1).<sup>6</sup>

In another study, MPO levels were measured in 400 patients who presented to the emergency department or acutely to outpatient facilities with symptoms suggestive of ACS. Patients were assessed for MACE, defined as myocardial infarction, revascularization (defined as coronary artery bypass graft, percutaneous coronary intervention, or placement of a cardiac stent), or death. The incidence of MACE was assessed at 30 days and 6 months; MACE rates increased with increasing quartiles of MPO (Figure 2).<sup>9</sup> Among patients with troponin I values ≤0.07 µg/mL, those with MPO levels above a cutoff of 633 pmol/L had almost threefold higher (p=0.008) adverse event rates compared with those below the cutoff at 30 days (Figure 3). Rates at 6 months (180 days) were also similar.<sup>9</sup> In this study, adding N-terminal pro-brain natriuretic peptide (NT-proBNP) measurements did not provide any additional information regarding the likelihood of MACE.

MPO relative to cutoff	cTnI relative to cutoff	Cumulative event rate (%)	p value
Lower or equal	Lower	5.8	0.96
Higher	Lower	5.0	
Lower or equal	Higher or equal	14.6	0.05
Higher	Higher or equal	42.6	

**1** MPO and cardiac troponin I levels (cTnI) by cardiac event rate. Patients with both increased MPO (cutoff 896.8 pmol/L) and cTnI (cutoff 0.1 µg/L) had a significantly higher event rate.<sup>6</sup>

Quartile	MPO (pmol/L)	Odds ratio	95% confidence interval
Q1	94–581	1.00	Reference values
Q2	582–894	1.41	0.51–3.89
Q3	895–1657	3.03	1.19–7.76
Q4	1658–5000	4.31	1.62–11.5

**2** Increasing quartile levels of MPO are associated with increasing risk of major adverse cardiac events at 30 days after adjustment for race, gender, hyperlipidemia, and C-reactive protein.<sup>9</sup>

**Non-ST Elevation Acute Coronary Syndrome**

MPO levels have also been shown to be associated with higher levels of adverse cardiac events in patients with NSTEMACS. MPO was measured in 1,524 NSTEMACS patients who survived to 180 days as part of the TACTICS-TIMI 18 (Treat angina with aggrastat and determine cost of therapy with invasive or conservative strategy – thrombolysis in myocardial infarction 18) trial.<sup>10</sup> In this trial, patients were treated with tirofiban and randomized to early invasive versus conservative management. Plasma was collected from patients within 24 hours of presenting with NSTEMACS. An elevated baseline MPO was associated with a nearly twofold higher risk (adjusted odds ratio 2.1, 95 percent confidence interval [CI] 1.36–3.23) of a non-fatal myocardial infarction or recurrent ACS at 30 days, adjusted for ST-deviation, diabetes mellitus, history of coronary artery disease, baseline troponin I, high-sensitivity C-reactive protein (CRP), and soluble CD40 ligand.<sup>10</sup>



4

Patient values relative to median values		
MPO	NT-proBNP	Adverse event rate (%)
Lower	Lower	5
Higher	Lower	10
Lower	Higher	16
Higher	Higher	29

**4** MPO provides additional prognostic information regarding the occurrence of adverse cardiovascular events in patients after myocardial infarction. MPO median value 392.7 pmol/L, NT-proBNP median value 110 pmol/L.

5

Patient values relative to median values		
MPO	LVEF	Adverse event rate (%)
Lower	Higher	6
Higher	Higher	11
Lower	Lower	15
Higher	Lower	29

**5** MPO provides additional prognostic information regarding the occurrence of adverse cardiovascular events in patients after myocardial infarction. MPO median value 392.7 pmol/L, LVEF median value 49 percent.<sup>2</sup>

**Post-Myocardial Infarction Mortality**

In addition to its value in predicting risk of adverse cardiac events in patients with symptoms suggestive of ACS and elevated troponin, ACS and in patients with NSTEMACS, MPO levels after myocardial infarction are predictive of mortality. MPO was evaluated in patients with acute myocardial infarction (n=512) on hospital admission to determine the relationship between MPO levels and clinical outcomes after myocardial infarction. Compared with heart healthy controls (n=156), MPO concentrations were higher in the acute myocardial infarction cohort. MPO levels above the median concentration (392.7 pmol/L) were independently and significantly predictive of mortality with an odds ratio of 1.8 (95 percent CI 1.0–3.0, p=0.034).<sup>2</sup> Patients with above median levels of MPO had a twofold higher mortality rate (21 percent) than patients with below median levels (10 percent). MPO levels provided additional prognostic information when combined with NT-proBNP or with left ventricular ejection fraction (LVEF). Patients with



levels of MPO and NT-proBNP above the median values had approximately sixfold greater event rates (29 versus 5 percent) compared with patients with below median levels of both markers (Figure 4). Patients with above median levels of MPO and below median LVEF had approximately fivefold higher event rates, 29 versus 6 percent, than those with below median levels of MPO and above median LVEF (Figure 5).<sup>2</sup>

### Chronic Heart Failure

Chronic heart failure is a disease that is associated with high morbidity and mortality, and is a significant burden on healthcare systems globally. MPO evaluation has also been shown to add value in predicting adverse events in patients with chronic heart failure. One hundred and forty ambulatory

patients with stable, chronic systolic heart failure (LVEF <35 percent, New York Heart Association functional classes II to IV) underwent echocardiographic evaluation of systolic and diastolic performance as well as plasma sample collection for MPO measurements. MPO levels were compared with echocardiography results and adverse clinical outcomes that included death, cardiac transplantation, or hospitalization. Increasing MPO levels were associated with an increasing likelihood of advanced heart failure and were predictive of adverse clinical outcomes. This study found that adding MPO to BNP for prediction of adverse events increased diagnostic accuracy as reflected in ROC (receiver operating characteristics) analysis by an increase in the AUC (area under the curve) value from 0.66 to 0.70.<sup>3</sup>

## Conclusion

As the studies presented demonstrate, MPO has utility among patients with various manifestations of cardiac disease. Incorporating MPO evaluation into the care of cardiac patients provides clinicians with insight into a patient's risk for future adverse events. Various clinical studies have shown that MPO levels in cardiac patients are useful for prediction of the risk for adverse cardiac events, such as the need for revascularization, myocardial infarction, or death among patients with chest pain, heart failure, ACS, and post-myocardial infarction.

The MPO assay provides clinicians with an additional tool to use in the management of cardiovascular patients across the spectrum of this disease.

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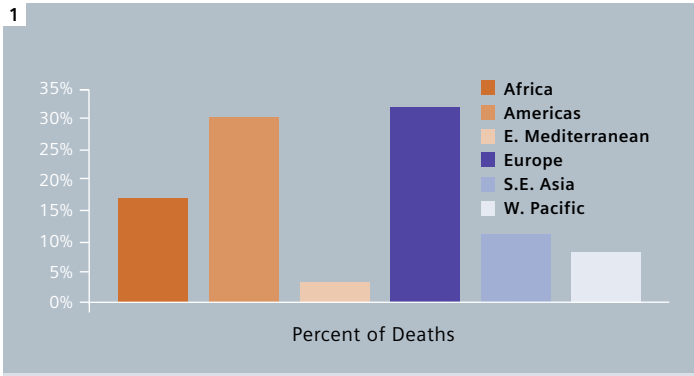
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## Complexed PSA: A First-Line Aid in Prostate Cancer Detection and Management

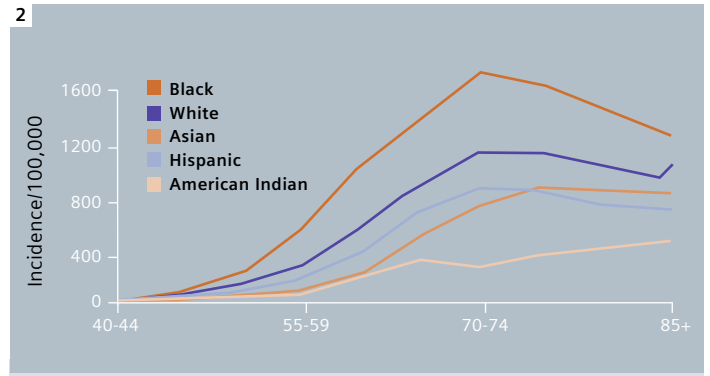
Prostate cancer is one of the leading types of cancer in men, and complexed PSA has been shown to be valuable as a first-line test, aiding in its early detection.

By Tricia A. Bal, MD





**1** World Health Organization estimated percentage of prostate cancer deaths by region for 2008<sup>14</sup>



**2** Prostate cancer incidence varies with age and ethnicity (USA data).<sup>15</sup>

### Introduction

Complexed prostate specific antigen (cPSA) is a first-line test used in the detection of prostate cancer and has been endorsed in the National Comprehensive Cancer Network (NCCN) guidelines.<sup>1</sup> cPSA is a single test that offers the advantage of higher specificity than total PSA for the detection of prostate cancer.<sup>2,10</sup> Use of cPSA, instead of total PSA, has been shown to reduce the number of unnecessary biopsies.<sup>3, 6, 11, 12</sup> cPSA is also a valuable aid in prostate cancer management.<sup>1</sup>

### Epidemiology of Prostate Cancer

Prostate cancer is one of the leading types of cancer in men. About 680,000 men are diagnosed yearly worldwide.<sup>13</sup> The World Health Organization (WHO) projected that in 2008 prostate cancer would have accounted for 0.6 percent of deaths (347,000) worldwide. Over 60 percent of these deaths were projected to occur in the Americas and Europe (Figure 1).<sup>14</sup> Prostate cancer incidence has been shown to vary with ethnicity and age, with certain ethnic groups having a much higher incidence of disease at every age (Figure 2).<sup>15</sup>

### Prostate Cancer Detection and Management

While the diagnosis of prostate cancer can only be made definitively by biopsy, PSA tests are used by clinicians in conjunction with digital rectal examinations (DRE) as aids in prostate cancer detection.<sup>1</sup> Tumor grade (a measure of tumor aggressiveness) is quantitated by Gleason scores, which evaluate the microscopic pattern of cancer cells.

The Gleason system assigns a grade from 1 (least aggressive) to 5 (most aggressive) based on the amount of architectural differentiation of the tumor. The Gleason score is obtained by adding the most predominant grade (the grade that occurs most often in the biopsy) to the highest grade for a total score between 2 and 10. Aggressive tumors include those with Gleason scores of 7 to 10, and the most aggressive tumors have scores of 8 to 10.<sup>16</sup> cPSA and total PSA assays play crucial roles in prostate cancer management. An increase in cPSA or total PSA levels during treatment indicates disease progression; increasing PSA values in a patient who is being managed by active surveillance may trigger the initiation of therapy.<sup>1</sup>

### Types of PSA

PSA (human kallikrein 3) is primarily produced by prostatic epithelium and is thus a prostate-specific marker.<sup>17, 18</sup> PSA is a product of the human glandular kallikrein gene locus on chromosome 19 and is one of the dominating prostate-derived proteins found in seminal fluid. The mature form of PSA, a single chain glycoprotein of 237 amino acids, is a serine protease with restricted chymotrypsin-like activity. PSA is mainly responsible for gel dissolution in freshly ejaculated semen by proteolysis of the major gel-forming proteins, semenogelin I and II, and fibronectin. In semen, approximately two-thirds of PSA is enzymatically active. The remaining 30 to 40 percent is inactive due to internal cleavage(s).<sup>18</sup>



3

System	Assay	Analytical Sensitivity (ng/mL)	Upper Limit (ng/mL)
ADVIA Centaur CP®/ADVIA Centaur XP®	PSA	0.01	100
	Complexed PSA	0.03	100
	Free PSA	In development	In development
IMMULITE® 1000/2000/2500	PSA	0.04	150
	Free PSA	0.02	25
	Third-Generation PSA	0.005	20
Dimension® Vista <sup>a</sup>	PSA	0.010 <sup>b</sup>	100
	Free PSA	0.015 <sup>b</sup>	20
Dimension EXL™	PSA	In development	In development
	Free PSA	In development	In development
Dimension® RxL Max/Dimension® Xpand Plus	PSA	0.05	100
	Free PSA	0.05	45

<sup>a</sup> Not currently FDA approved; <sup>b</sup> Limit of detection

**3 Siemens Healthcare Diagnostics PSA menu**

PSA elevations are associated with cancer, but are also associated with noncancerous conditions such as prostatitis (infection or inflammation of the prostate), trauma, or benign prostatic hyperplasia (a non-cancerous enlargement of the prostate due to tissue hyperplasia that can lead to obstruction of urine flow).<sup>1</sup> PSA exists bound to protease inhibitors, primarily alpha-1-antichymotrypsin (ACT) (up to 95 percent of PSA) or in a free, unbound form in serum.<sup>19</sup> PSA complexed to ACT constitutes the predominant molecular form of serum PSA. PSA also forms stable complexes with alpha-2-macroglobulin *in vitro*, but since PSA epitopes are completely masked in these complexes, specific immunodetection would be quite difficult.<sup>18</sup> PSA also forms complexes with alpha-1-antitrypsin.<sup>20</sup> Free PSA constitutes a minor fraction of the serum PSA but the major fraction of intracellular PSA. PSA in semen is also bound to protein C inhibitor.<sup>18, 21</sup>

**Siemens PSA Testing Portfolio**

The Siemens portfolio consists of total PSA assays (including the Third-Generation PSA assay) that detect both free and bound PSA, free PSA assays that detect only free PSA, and a cPSA assay that detects PSA bound to ACT (Figures 3 and 4). While free PSA must be used in conjunction with a total PSA assay, cPSA and total PSA assays are first-line assays used for aiding prostate cancer detection.

**The Value of cPSA**

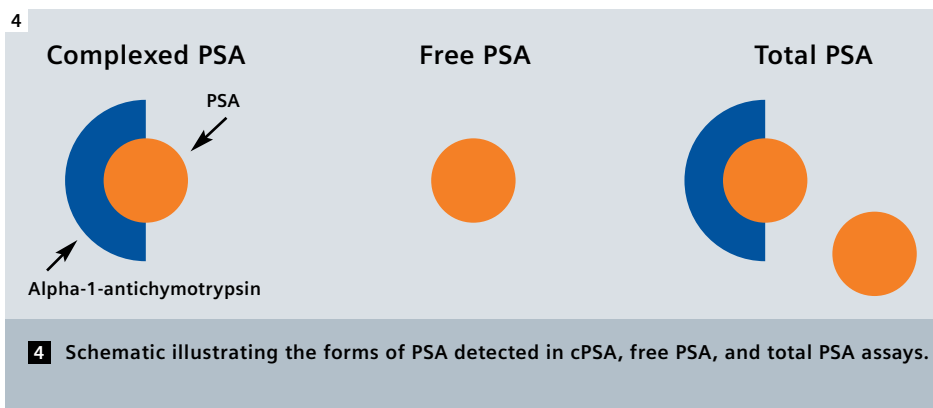
cPSA is included in NCCN guidelines for use as an aid in the detection of prostate cancer in conjunction with DRE. cPSA is also used to monitor/manage prostate cancer. cPSA testing offers certain advantages when compared to total PSA testing.<sup>1, 9</sup> Interestingly, cPSA values have been shown to be lower than comparable total PSA values (Figure 5).<sup>10</sup>

**cPSA Is a First-Line Aid in Detection**

Several studies have demonstrated the utility of cPSA as an aid in the detection of prostate cancer and have shown that cPSA performs as well as or better than total PSA (evaluated by receiver operating characteristics [ROC] analysis) (Figure 6).<sup>2, 5, 22, 23</sup>

In a study of apparently healthy males, most cPSA values were below 3.5 ng/mL (Figure 7). Similar to total PSA, cPSA values tend to increase with age.<sup>24</sup> As cPSA levels increase, the probability of a positive biopsy result increases (Figures 8 and 9). If the patient has a suspicious DRE, the probability of a positive biopsy result is higher than the probability of a positive biopsy result in a patient with a negative DRE (Figures 8 and 9).<sup>24</sup>

4



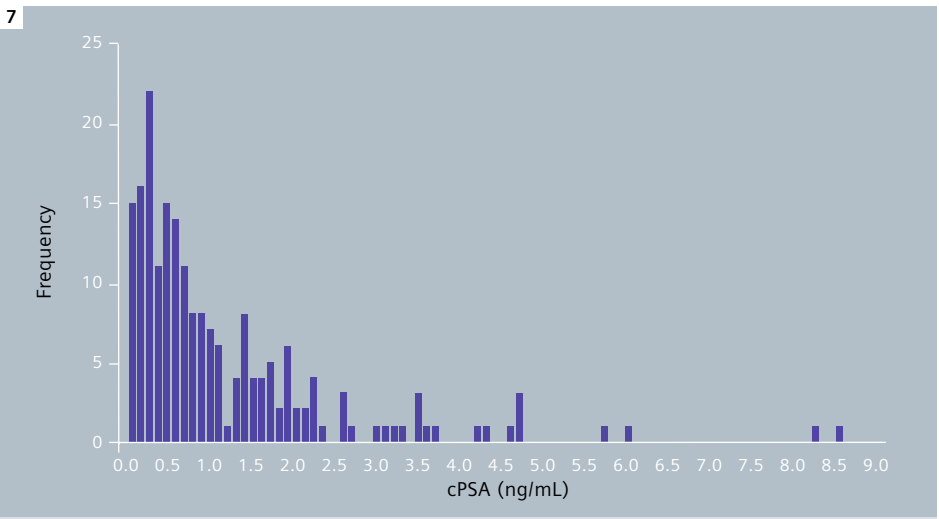
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tPSA (ng/mL)	cPSA (ng/mL)
0–2.0	0–1.5
2.0–4.0	1.5–3.2
4.0–6.0	3.2–5.1
6.0–8.0	5.1–6.3
8.0–10.0	6.8–8.3
>10.0	>8.3

**5 cPSA and total PSA (tPSA) comparable levels<sup>10</sup>**

Study	Total PSA Range (ng/mL)	ROC Analysis (AUC)	
		Complexed PSA	Total PSA
Parsons 2004	2–4	0.63	0.56
Babaian 2006	2.5–6	0.689	0.632
Bratslavsky 2008	2–10	0.52	0.53
Fillella 2004	0.18–55	0.672	0.633
Okihara 2006	1–100	0.741	0.721

**6** ROC analysis showing the diagnostic performance of complexed PSA compared with total PSA over a wide range of total PSA values.<sup>2, 3, 8, 22, 23</sup>



**7** The distribution of cPSA in 199 apparently healthy males with ages ranging from 42 to 92 years.<sup>24</sup>

cPSA (ng/mL)	N	Cancers (N)	Risk (%)	95% Confidence Interval
< 3.6	147	40	27.2	20.8–35.1
3.6 to 5.0	89	35	39.3	30.2–50.2
> 5.0	119	61	51.3	42.7–60.5

Probability of positive biopsy results for DRE alone negative is 38.3% (136/355; 95% CI 33.5% – 43.6%).

**8** cPSA levels and probability of a positive biopsy result with a normal DRE.<sup>24</sup>

cPSA (ng/mL)	N	Cancers (N)	Risk (%)	95% Confidence Interval
< 3.6	70	37	52.9	41.9–64.9
3.6 to 5.0	29	17	58.6	42.3–76.5
> 5.0	50	39	78.0	66.3–88.5

Probability of positive biopsy results for DRE alone positive is 62.4% (93/149; 95% CI 54.8% – 70.2%).

**9** cPSA levels and probability of a positive biopsy result with a DRE suspicious for cancer.<sup>24</sup>

## PSA Assays – At-a-Glance

### Total PSA

- First-line test
- Aid in the detection of prostate cancer in conjunction with DRE in men aged 50 years or older
- Management (monitoring) of prostate cancer

### Free PSA

- Used in conjunction with total PSA
- Aid in distinguishing prostate cancer from benign prostate conditions in men aged 50 years or older with total PSA of 4-10 ng/mL and DRE not suspicious for cancer

### Complexed PSA

- First-line test
- Aid in the detection of prostate cancer in conjunction with DRE in men aged 50 years or older
- Management (monitoring) of prostate cancer



### cPSA Has Higher Specificity

cPSA, in addition to performing as well as or better than total PSA for detection of prostate cancer by ROC analysis, has also been shown to be more specific than total PSA for detection of prostate cancer (Figure 10).<sup>8, 11, 23</sup> This higher specificity has resulted in fewer false positives (positive by PSA test but negative by biopsy).

The increased specificity of cPSA compared with total PSA is consistent across a range of sensitivities (Figure 11) and across a range of total PSA values including the gray zone (4–10 ng/mL range) where total PSA is less effective at discriminating between prostate cancer and benign prostatic hyperplasia.<sup>25</sup>

### cPSA Means Fewer Tests, Fewer Biopsies

Percent-free PSA was developed to address the low specificity of total PSA particularly in the 4–10-ng/mL range. cPSA is a single test that offers the advantage of higher specificity than total PSA. Because cPSA is a single first-line test, it may offer the lab certain operational efficiencies over running both a total PSA and a free PSA test.<sup>1</sup>

Consistent with its higher specificity, cPSA was shown in one study to reduce the number of unnecessary biopsies by 11 percent in the total PSA range of 2–6 ng/mL, and by 20 percent in the total PSA range of 2–4 ng/mL compared with total PSA (Figure 12).<sup>2</sup> Other studies have also shown that compared with total PSA, cPSA reduced the number of unnecessary biopsies by 10–20 percent.<sup>6, 12</sup>

### cPSA and Prostate Cancer Management

There are several management options for prostate cancer. Options for local disease include watchful waiting (monitoring without the intent to actively treat), active surveillance (monitoring with the intent to treat if needed), surgery, and radiation (external beam and brachytherapy). Management options for metastatic disease include hormonal (androgen deprivation therapy) and chemotherapy.<sup>1</sup>

Because prostate cancer is a slowly-growing cancer, early detection and treatment of local disease has a high success rate.<sup>26, 27</sup> Metastatic disease, however, is much harder to treat, especially if it is hormone insensitive.

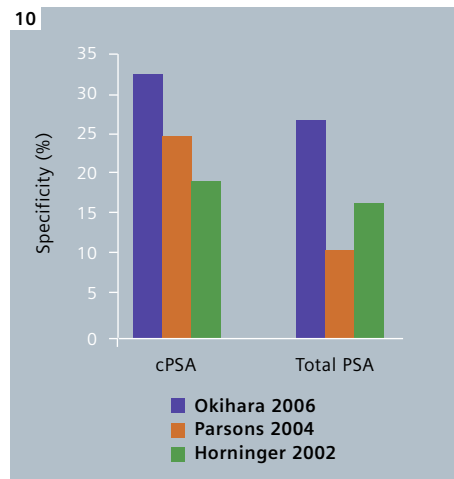
cPSA, like total PSA, is an integral aid for managing/monitoring prostate cancer. Trends in cPSA levels provide information regarding disease status and response to therapy. Increasing levels are associated with residual disease, poor response to therapy, progressive disease, and recurrent disease, while persistently elevated levels after therapy are associated with residual disease. In contrast, decreasing levels after therapy are associated with response to therapy.<sup>1, 15, 16, 28, 29</sup>

### cPSA Is More Stable Than Total PSA and Free PSA

In terms of analyte stability, cPSA is more stable than both total PSA and free PSA in serum (Figure 13).<sup>30</sup> This is important for samples that are stored for extended periods prior to measurement. Serum samples should be stored at 4°C when the analysis will be performed within 8 hours of sample collection. Samples should be stored at -80°C if analysis will occur after 8 hours.<sup>30</sup>

### Conclusion

The cPSA test offers the advantage of higher specificity for the detection of prostate cancer than total PSA,<sup>8, 11, 23, 25</sup> making cPSA a preferred first-line test. It has also been shown to perform as well as or better than total PSA as an aid in prostate cancer detection.<sup>2, 3, 8, 22, 23</sup> Using cPSA instead of total PSA has resulted in a reduction in the number of unnecessary biopsies by as much as 20 percent.<sup>2, 6</sup> cPSA is also an important tool in prostate cancer management.<sup>9</sup> Overall cPSA is a valuable test that can assist clinicians and patients through the prostate cancer care continuum, from early detection to disease management.

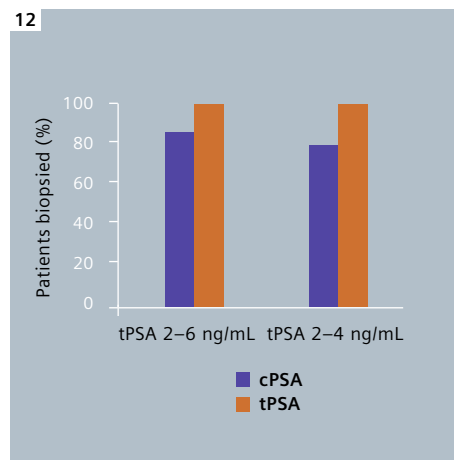


**10** cPSA has a higher specificity than total PSA for the detection of prostate cancer (specificity at 90% sensitivity).<sup>8, 11, 23</sup>

**11**

Total PSA between 4.0–10.0 ng/mL		
Sensitivity (%)	Total PSA	cPSA
80	30	37
85	21	31
90	21	25
95	7	18

**11** Comparison of cPSA specificity and total PSA specificity over a range of sensitivities among patients with total PSA values between 4–10 ng/mL. cPSA showed higher specificity over a range of sensitivities.<sup>25</sup>



**12** cPSA has been shown to reduce the number of unnecessary biopsies by 11 percent (total PSA 2–6 ng/mL) and by 20 percent (total PSA 2–4 ng/mL).<sup>2</sup>



**13** Complexed PSA is more stable than total PSA and free PSA at 4°C.

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## Comparison of Whole Blood Total Bilirubin Determination in Neonates

Managing the care of newborn patients requires integration of multidisciplinary professionals, skills, and processes. Patients' needs fluctuate constantly, and the necessity for accurate and fast results is urgent. Real-time dissemination of information allows clinicians to make critical clinical decisions in a timely manner. In this article, we look at a new alternative for monitoring bilirubin in newborns.

By Dennis Dietzen, PhD, and Tim Wilhite

## Background

About 60 percent of newborn babies display mild jaundice (yellowing of the skin) within the first two days after birth due to shortened lifespan of red blood cells coupled with slow maturation of liver glucuronyl transferase activity. Mild jaundice is usually not detrimental. However, some newborns develop severe jaundice from high levels of unconjugated bilirubin circulating in the blood. If left untreated, unconjugated bilirubin may deposit in the basal ganglia and brainstem, causing irreversible neurologic damage, a condition known as kernicterus. Kernicterus can cause cerebral palsy; problems with hearing, vision and teeth; and mental retardation. Some newborns have a higher risk of developing elevated bilirubin concentrations than others. Risk factors include prematurity, family history, bruising at birth, jaundice in the first 24 hours of life, unrecognized maternal-fetal Rh incompatibility and other causes of severe hemolysis (e.g., glucose-6-phosphate dehydrogenase deficiency).

Simple and non-invasive phototherapy is the first approach to reduce high levels of neonatal bilirubin. However, if phototherapy does not lower the baby's bilirubin blood levels, an exchange transfusion may be required. As untreated hyperbilirubinemia may cause severe permanent health problems, all newborns should be checked for jaundice. The practice guidelines of the American Academy of Pediatrics include provisions for measurement of total bilirubin to evaluate the degree of jaundice and the necessity for intervention.

Because of the complication of collection, limited blood volume and higher hematocrit, testing neonatal blood can be challenging. Large reagent-based chemistry analyzers require the separation of plasma from the red blood cells prior to analysis. Blood gas analyzers offer an alternate method for assessing the risk of kernicterus using direct multiwavelength spectrophotometry on small volumes of whole blood. Additionally, blood gases, pH, electrolytes, metabolites, total hemoglobin and CO-oximetry can be measured simultaneously on the same whole blood specimen.

We present a neonatal whole blood total bilirubin performance evaluation of two blood gas systems: the RAPIDLab® 1245 from Siemens Healthcare Diagnostics compared to the RADIOMETER ABL 735, a member of the RADIOMETER ABL 700/800 family of systems. The ABL 735 uses an on-board sonicator to hemolyze the red blood cells for CO-oximetry and optical bilirubin analysis. The RAPIDLab 1245 performs the optical measurements directly on unhemolyzed whole blood.

## Materials and Methods

Whole blood samples were collected from babies less than 100 days of age in the neonatal and pediatric intensive care units of St. Louis Children's Hospital, St. Louis, Missouri, USA. The protocol was approved by the Human Subjects Committee of Washington University, St. Louis, Missouri, USA. Whole blood, originally drawn from these patients via heparinized arterial lines, was measured first on the ABL 735 (Radiometer, Copenhagen, DE) and results reported.

Remaining whole blood volume from the same draw was then analyzed on the RAPIDLab 1245 system within 10 minutes of the ABL 735 analysis. The same two blood gas analyzers were used throughout the nine-week study. Paired bilirubin values from the two analyzers were compared on all neonatal samples that were greater than the analyte detection limit (2.0 mg/dL) of the RAPIDLab. Any samples exhibiting preanalytical error were removed from the analysis.

Imprecision was evaluated using aqueous quality control (QC) material measured in duplicate daily. Manual QC was run according to manufacturers' directions with one QC sample tested per vial using the respective manufacturer-recommended adapters. Radiometer QUALICHECK™ was used on the ABL 735, and Siemens RapidQC™ Complete was used on the RAPIDLab 1245 system. The optional automatic quality control material (AQC) available on the RAPIDLab 1245 was also tested for imprecision.



## Results

### Imprecision

A minimum of 50 manual aqueous QC samples per level were measured on each blood gas analyzer throughout the study. Two levels (representing low and high bilirubin ranges) were run on the ABL 735, and three levels (low, mid, and high) were analyzed on the RAPIDLab 1245. Mean bilirubin concentration (in mg/dL), total standard deviation (Total SD), and coefficient of variation [%CV = 100 x (Total SD/Mean Concentration)] were calculated. The Total SD and %CV incorporate within-run and day-to-day imprecision. Based on the data in Table 1, the imprecision of the manual quality control material for the two platforms was similar and ranged from 2.2% to 7.0% CV. In addition, the performance of the control materials on the RAPIDLab 1245 was comparable across the two different types of quality control application (manual versus automatic quality control).

### Accuracy

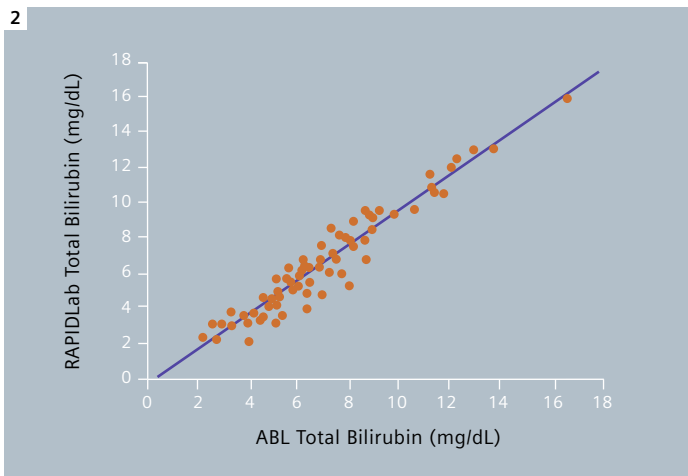
A total of 77 paired clinical neonatal whole blood specimens were evaluated. Age of the patients ranged from birth to 100 days old. Total bilirubin levels ranged from 2.2 to 16.7 mg/dL, per the ABL 735. Four samples were excluded (1 rejected due to the >10 minute elapsed time criteria and 3 rejected due to ABL 735 sampling errors). The total bilirubin values of the 77 pairs were graphically compared. The ABL 735 total bilirubin results represent the x-axis and the RAPIDLab 1245 total bilirubin values represent the y-axis in Figure 2.

Linear regression analysis of the neonatal total bilirubin data was performed to provide estimates of proportional (slope) and constant (intercept, in mg/dL) bias, along with estimates of relative error (standard error of the estimate, referred to as root mean square error or Syx) and agreement (correlation coefficient, r<sup>2</sup>) between the two instrument models. Regression analysis yielded the following relationship:

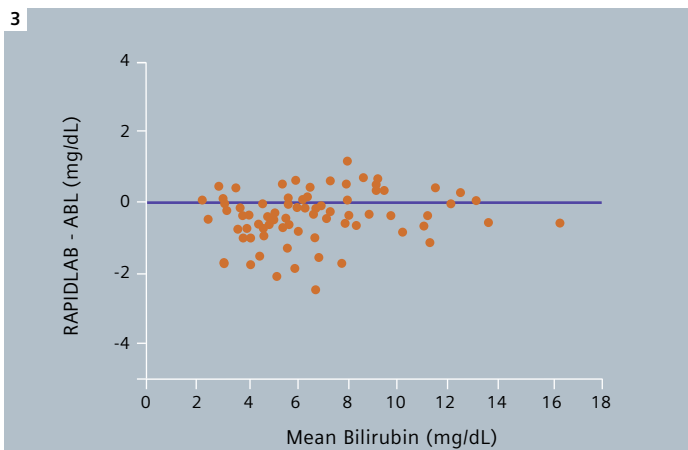
$$\text{RAPIDLab} = (1.01 \times \text{ABL}) - 0.48$$

Device	Material	Mean Conc. (mg/dL)	N	Total SD	CV (%)
ABL	Qualicheck	4.2	140	0.29	7.0
ABL	Qualicheck	22.3	140	0.49	2.2
RAPIDLab	Complete	5.1	53	0.19	3.7
RAPIDLab	Complete	12.4	50	0.39	3.1
RAPIDLab	Complete	19.8	51	0.94	4.7
RAPIDLab	AQC	5.0	32	0.21	4.2
RAPIDLab	AQC	11.9	33	0.32	2.7
RAPIDLab	AQC	20.0	12	1.03	5.2

**1** Quality control precision statistics



**2** Neonatal total bilirubin concentration using the RAPIDLab 1245 vs. the ABL 735



**3** Bland-Altman plot of neonatal whole blood total bilirubin (bias vs. mean)



The Syx was 0.79 and  $r^2$  was 0.93. The results indicate good total bilirubin correlation between the two blood gas instrument platforms.

Total bilirubin bias was determined (RAPIDLab 1245 – ABL 735). Average bias was  $-0.4$  mg/dL and ranged from  $-2.7$  to  $1.3$  mg/dL. A Bland-Altman plot (Figure 3) displaying bias against mean [(RAPIDLab bilirubin + ABL bilirubin)/2] indicates a consistent pattern across the entire range.

## Conclusion

As demonstrated in the hospital setting using diverse clinical specimens from neonates, whole blood total bilirubin analysis on the Siemens RAPIDLab 1245 blood gas analyzer is accurate and precise when compared to the Radiometer ABL 735. Analysis of unhemolyzed whole blood using the RAPIDLab 1245 or RAPIDLab 1265 is a clinically acceptable method for monitoring the development of pathologic concentrations of bilirubin in neonates.

## Results and Conclusions

Imprecision of controls on the RAPIDLab was 3.7%, 3.1%, and 4.7% (CV) at 5.1, 12.4, and 19.8 mg/dL ( $n=50$ ), respectively. Similarly, imprecision of the ABL was 7.0% and 2.2% (CV) at 4.2 and 22.3 mg/dL ( $n=140$ ), respectively. Whole blood bilirubin values ranged from 2.2 to 16.7 mg/dL. Linear regression of the RAPIDLab vs. the ABL (see Figure 2) yielded the following statistics: slope, 1.01; intercept,  $-0.48$ ;  $r$ , 0.964; Syx, 0.79. Absolute bias between the RAPIDLab and the ABL averaged 0.4 mg/dL (range:  $-2.7$  to  $1.3$  mg/dL). Whole blood bilirubin analysis on the RAPIDLab 1245 and RAPIDLab1265 is substantially equivalent to that on the ABL 700/800 system family and provides a new alternative for monitoring bilirubin in newborns.

Presented at the Annual Meeting of the American Association for Clinical Chemistry (AACC); Washington, DC, July 27 –31, 2008.

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# Assuring Control Quality for Quality Controls

## Creating Smart Protocols – and Putting Them to the Test.

by Renee DiIulio

In October 2008, Quest Diagnostics Inc. initiated a recall/retesting program for what will likely amount to thousands of patients. The problems began in 2007, when the national laboratory changed its testing method for 25-hydroxy vitamin D or vitamin 25(OH) D testing. The switch to liquid chromatography tandem mass spectrometry (also referred to as LC/MS/MS) resulted in testing errors that went unnoticed by Quest into 2008.

Part of the problem, as revealed to the *New York Times* by Wael A. Salameh, MD, medical director for endocrinology at the Quest Nichols Institute in San Juan Capistrano, California, USA, was that “some materials used to calibrate test results had been faulty.”<sup>1</sup> In addition, as reported by the *NYT*, four of Quest’s seven national testing laboratories did not always follow proper procedures, Salameh said.<sup>1</sup>

The consequence has been thousands of potentially erroneous results—a laboratorian’s worst possible nightmare and one that laboratory processes are often created to avoid. A quality control program is one of those processes and is designed to make sure all of the other elements are working. But what if its own elements are faulty?



“The whole purpose of quality control is to give you confidence in the quality of the results that you are reporting,” says Marcia Zucker, PhD, director of clinical support for Response Biomedical Corporation, Vancouver, BC, Canada. The process is often a balancing act. Laboratories want to perform enough testing to ensure quality care at the same time they want to avoid wasting resources on excessive and unnecessary testing.

“Laboratories have to find a way to do what is necessary—not more and not less. But then they have to actually demonstrate that this is the case. It’s a very big challenge to figure out the appropriate metrics to apply in order to develop a robust system,” says Zucker.

Those metrics should include measurements to determine if control materials are actually in control. Regulations often set the minimum requirements, but laboratories are charged with developing quality control procedures that maximize the performance of their specific testing menus and instrumentation. Key elements to a successful program include laboratorian education, appropriate technology and materials, and careful use of checks.

### Need to Know It All

Knowledge provides the basis for creating smart testing protocols and is necessary for anyone performing a test and/or running controls, whether it be a laboratorian, nurse, or other clinician. As the laboratorian employee crunch becomes more severe, there is greater reliance on generalists and clinicians, who may not be as familiar with laboratory processes, including quality control, to perform tests. Indeed, even laboratorians may not know as much as they should.

“Many clients have said they don’t know what they are supposed to be doing according to CLIA guidelines,” says John Innocenti, president of Audit MicroControls, Inc in Las Vegas, Nevada, USA. Although medical technology curriculums touch on quality control, advancing technology and changing regulations can outdate knowledge quickly. Sue Read, manager of QC strategy for Siemens Healthcare Diagnostics, notes one of the challenges frequently cited during focus groups is investing the time and money to train

more technicians on laboratory quality control. Budget and personnel resources tend to be scarce everywhere.

Educational opportunities are not, however. Instruction can range from classes and seminars to simply reading the directions enclosed with the controls. “We get a lot of customers who request new copies of the instructions when they run into problems,” says Innocenti, who suggests those missing copies are often in the trash.

The instructions are important to review because they cover not only proper use but also proper storage. “For example, if a control needs to be stored frozen, the lab really needs to avoid storage in a frost-free freezer because it goes through many defrost cycles, and the control will thaw and freeze over and over again.

This can degrade a control,” says Paul Hardy, business unit marketing manager at Bio-Rad Laboratories Quality Systems Division in Irvine, California, USA.

In addition to providing specific product information, many manufacturers will also organize or sponsor broader educational opportunities. Associations, such as the American Society for Clinical Pathologists and the American Association for Clinical Chemistry, also produce seminars and conference programs addressing quality control.

These opportunities supplement the knowledge acquired through on-the-job training. But it’s a lot to absorb. According to Greg Cooper, CLS, MHA, manager of clinical standards and practices with Bio-Rad Laboratories, “Labs really need to understand the capability of the testing that occurs in the lab. They need to understand how robust the instrument they are using is. They should be able to characterize how that instrument works in their own unique laboratory environment and with their own staff. Labs also need to understand the capabilities of process control, which can be theoretical and difficult to understand.”

### Supplementing Staff with Technology

Technology can help—it can’t replace the laboratorian or a proper quality control program—but it can reduce error, provide guidance, standardize processes, and expand data collection and analysis. Technology can even help with theory.

Theoretical decision making can be programmed into software and can tell a laboratorian what to do. “For instance, software has been used for many years to calculate certain statistical parameters from quality control data, such as bias, imprecision, and total error for a test. With recent innovations, software can now use these statistical parameters to recommend which quality control rules

“Laboratories have a responsibility to track their daily performance with a control and not just read a value off the package insert and say, ‘As long as we get within 20 percent of this number, we’re good.’”

Kevin Jones  
Vice President of Sales and Marketing  
Aalto Scientific Ltd.  
Carlsbad, California, USA

should be applied. So [laboratorians] don't have to worry about theoretical understanding or which rules to use," Cooper says. This is a boon to labs that have a shortage of certified laboratory specialists and rely in part on generalists.

"We've seen some really remarkable technological advances in informatics that allow real-time data processing, sharing of information, and proactive monitoring of instruments, ensuring patient results," Read says.

Those advances have impacted laboratory information systems (which help to standardize processes within a laboratory), middleware, and peer group analysis programs (which help to standardize outside the lab). "I think that if the technologies continue to incorporate more control processes into a test methodology, that will help laboratories to find that happy medium in their quality control program," Zucker says. Comparison with peers is key to that effort. Programs such as these are designed to be invaluable troubleshooting tools. "Users compare the results they are

getting to peer groups using the same instrument and controls to analyze for the same analyte," says Andrew Schaeffer, an R&D scientist with Quantimetrix Corp. in Redondo Beach, California, USA. With Internet convenience, this can be done as frequently as every day.

When an individual institution's results stray from the pack, it can raise a red flag. That red flag could be associated with a flaw in the instrument, the controls, or the process. Laboratorians are responsible for assuring the quality of all of these elements.

### Controlling Quality

In general, reputable vendors produce reputable products, including controls. Naturally, compatibility between the instrument and the controls helps, but complete reliance on manufacturer-matched controls is not recommended. Experts suggest laboratories still make proper use of third-party controls.

"Laboratories have a responsibility to track their daily performance with a control and not just read a value off the package insert and say, 'As long as we get within 20 percent of this number, we're good,'" says Kevin Jones, vice president of sales and marketing for Aalto Scientific Ltd, located in Carlsbad, California, USA.

"If we look at how controls have evolved, we can see that the control products produced today—speaking generically—are far superior to the control products offered 20 years ago," says Quantimetrix's Schaeffer. Schaeffer cites characteristics that include improved stability and easier use (if the storage and usage directions are followed). "Typically, most controls have ranges assigned by the manufacturer, and the laboratories don't have to assign their own if they don't choose to," Schaeffer says. This can save a laboratory's resources, an issue that is of major concern for many. "Fifteen, 20 years ago, cost was maybe the third or fourth issue when a laboratory looked at controls. Money was important but was not one of the top three priorities.



Now, it's at top of mind," Innocenti says. Although controls are not the largest line items in a laboratory's budget, these expenses must still maximize workflow efficiency and drive cost-effectiveness.

Others believe liquid controls offer advantages related to savings in laboratorian time and a reduction in the risk of human error introduced by manual mixing.

“Laboratories want to perform enough testing to ensure quality care at the same time they want to avoid wasting resources on excessive and unnecessary testing.”

There are a number of ways laboratories can increase the value of their control purchases while reducing cost:

- One is to use a multi-constituent control, one control material that can run many assays. Rather than buy four, five, or six controls, a laboratory can buy one, more useful, control. According to Innocenti, this can save up to \$1,000.
- The industry has trended to human-based controls, which tend to behave more similarly to patient samples, although there are some animal serum-based controls still on the market.
- A control should have a very long shelf life and open-vial stability, which reduce waste and the frequency of crossover studies.
- Controls should also be purchased in lots that minimize the need for crossover studies while maximizing shelf life.

The debate surrounding lyophilized versus liquid controls continues. Some argue that lyophilized products offer greater value through longer shelf lives, greater stability, and multi-analyte use.

Laboratories have also looked to equivalent quality control (EQC) to help reduce expense by reducing the frequency of testing quality control materials. However, some experts caution the cost may not be worth it. “EQC basically allows a laboratory to reduce the frequency of quality control based on certain conditions or circumstances occurring as defined in the interpretive guidelines for CLIA,” Bio-Rad Laboratories’ Cooper summarizes.

But, Cooper continues, this may not be enough. Laboratories shouldn't just rely on meeting the minimum requirements. Rather, they should continually evaluate their quality control programs for areas of improvement. “If they really investigate device performance and laboratory conditions that might contribute to risk, I think they will find they need to run quality control a bit more frequently for some tests than what may be allowed or required by regulation,” Cooper says.

## Control in the Future

Currently, the Clinical and Laboratory Standards Institute (CLSI) has two subcommittees working on documents regarding quality control. CLSI EP22 *Presentation of Manufacturer Risk Mitigation Information for Users of In Vitro Diagnostic Devices* focuses on the information that a manufacturer should provide to users about device risk mitigation features. The purpose is to help laboratories make appropriate and effective decisions about the quality control testing that is needed.

CLSI EP23 *Laboratory Quality Control Plan Based on Risk Management* is intended to guide laboratories in the development of a quality plan. It suggests that alternative control processes should take shape around the relevant risk factors—including those defined in the manufacturer's device information and those present in the laboratory's unique environment—which could contribute to reporting test results that, if acted upon, could result in harm to the patient.

These documents will help standardize processes across laboratories, leading to greater consistency in results across institutions and, ideally, disciplines. As new tests are developed, new controls and processes will be developed as well. Some of the more promising opportunities lie in the fields of molecular diagnostics, nanotechnology, and personalized medicine (e.g., drug monitoring).

Where gaps exist, laboratories fill in—even new tests require controls to ensure quality results and avoid negative consequences in patient care. The goal is to keep the process as simple, error-proof, and inexpensive as possible while ensuring success—and avoiding having to retest thousands of patients.

### Reference

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## Case Study: White Plains Hospital Center

While research is increasingly showing the benefits of automating laboratory processes as labs continue to face rising demand for their services, experts agree the human touch is still essential. An automated integrated system helps the clinical laboratory of White Plains Hospital achieve performance, business, and patient safety objectives.\*

Annual billings soared 554 percent after White Plains Hospital Center implemented the ADVIA WorkCell system.



Less cost, increased productivity. Less error, more speed. Less hands-on drudgery, more time for complex tasks. Research is showing that automating laboratory processes can help labs meet the overwhelming demand to do more with less.

Analytics were the first area to become predominantly automated, but robotics and digital processes have extended into the pre- and post-analytical stages, where their impact has been marked. In a study, Sarkozi, et al. found that the introduction of a robotics system for peri-analytical automation in one laboratory brought a large improvement in productivity as well as a decrease in operational cost.<sup>1</sup>

In the study, the number of reported test results per employee per year within that laboratory increased from 10,600 to 104,558, while the cost per test decreased from \$0.79 to \$0.15.<sup>1</sup> "It enabled us to significantly increase our workload together with a reduction of personnel. In addition, stats are handled easily and there are benefits such as safer working conditions

and improved sample identification, which are difficult to quantify at this stage."<sup>1</sup>

In other recent research, study author Da Rin wrote that, "It has been estimated that more than 2,000 clinical laboratories worldwide use total or subtotal automation supporting pre-analytic activities, with a high rate of increase compared to 2007"<sup>2</sup>. The clinical laboratory of White Plains Hospital Center, a not-for-profit healthcare organization serving Westchester County, New York, USA, is one of those laboratories. The facility has installed automated chemistry and immunoassay systems and added an automated workstation that integrates clinical chemistry, immunoassay, specimen processing management, centrifugation, and decapping. The main motivation for the acquisition was patient safety, but the benefits have impacted all aspects of the laboratory's operation, from a 94 percent reduction in aliquoting to a 554 percent increase in annual billings.

## Wanting It All

The decision to add or upgrade automation in the laboratory is often based upon a risk-benefit analysis that takes into account current and future needs and objectives. Considerations include the laboratory's patient population and testing menu, volume, space, staffing, business goals, and budget.

Some labs may just wish to automate their processes, allowing a little room for growth but primarily improving the quality of their service. Other labs may want to automate to increase their capacities and permit an increase in revenues through outreach. White Plains wanted to do it all. The primary objective in its acquisition of the ADVIA WorkCell® CDX automation solution by Siemens Healthcare Diagnostics was to reduce patient errors, largely through the elimination of aliquoting. In 2003, the hospital had issued a proclamation to meet The Joint Commission's standards for performance improvement and error reduction declared the previous year. Reducing the manual handling of tubes and specimens in the laboratory would minimize the opportunities for error.

"We instituted a 'We will not aliquot' objective," says Marilyn Leonard, the laboratory's chemistry supervisor.

Aliquots were not the only targeted objective, however. The laboratory also wanted the new instrument to help grow volume capacity, speed turnaround time, increase revenues, reduce blood draws, maximize space, and integrate with existing systems.

Although it seems a tall order, many laboratories have a similar laundry list of needs. The best way to maximize their investment and subsequent performance is, therefore, to approach automation with their specific list in mind and a method to measure success.

## Choosing Wisely

Included on that list should be the infrastructure requirements, both physical and digital. Every laboratory has a unique framework that may include an LIS, middleware, existing automated systems, space limitations, and staffing requirements.



For instance, White Plains had a weight-bearing wall in the laboratory that constrained the available space. "We looked at systems that were monstrous and way too long to fit into our space," says Leonard. The instrument they selected occupies 320 square feet, a good fit for the lab.

The solution would also fit in with the existing instrumentation (which includes other Siemens systems), information systems (also Siemens), and consumables (which included multiple tube sizes). "Some vendors said we'd have to draw two tubes or we could only use one tube size," says Leonard.

The selected instrument provides not only for multiple tube sizes, but it also supports primary tube sampling: a single primary tube is intelligently routed to all required instruments, reducing aliquots. The efficiency permits a reduction in tube size and draw volume, an objective included on White Plains' list.

## Having It All

Aliquots were a major focus for the laboratory because technologists aliquoted two-thirds of tubes at least once, and in many instances, up to seven times. Each time the technologist handles a tube presents an opportunity to introduce error. Hence the patient safety measure to eliminate aliquots.

The "no aliquot" policy has not yet been completely achieved, but the number of aliquots has been reduced by more than 94 percent. Technologists process approximately 800 fewer aliquot tubes a day and aliquot only samples that need to be frozen, about 50 PTH and IgE samples daily. The laboratory has switched to 7.5 mL tubes, down from 10 mL.

The associated decrease in consumption of tubes and labels has saved the facility money, and the reduction in manual handling has saved the technologists time. "We use the strength of our techs for validating test results, not delivering specimens," says Leonard.

Productivity is, therefore, up. Before installing the integrated system, the laboratory processed 400 chemistry samples a day. Post-installation, that number rose to 1,200. And the capacity has not yet been maximized; the system can handle 400 tubes an hour. "This has allowed us to shift from batch testing to routine testing 24/7," says Leonard.

Tests brought in-house:

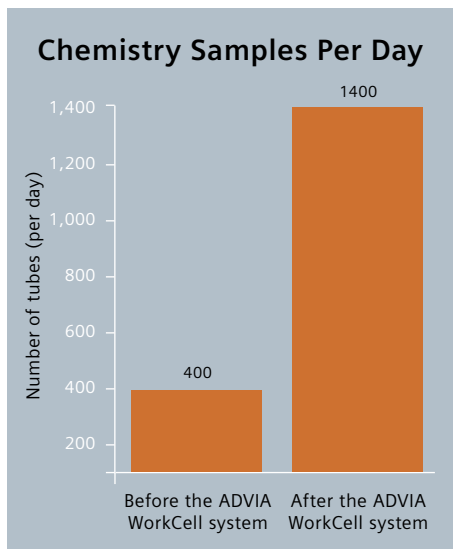
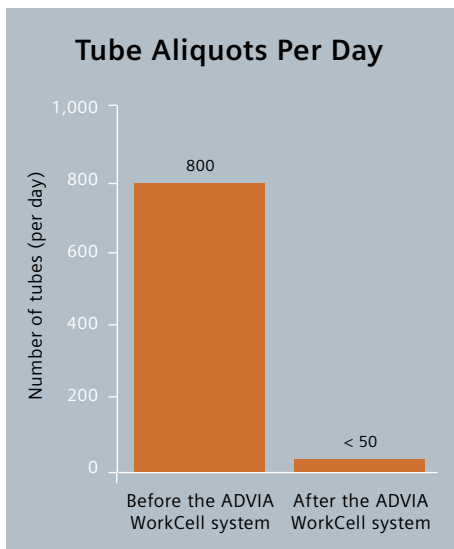
BNP, Caffeine, CA19-9,  
Hgb A1C, Intact PTH,  
Urine electrophoresis

2003

Gross billings: \$6.8M

“We use the strength of our techs for validating test results, not delivering specimens.”

Marilyn Leonard  
Chemistry Supervisor  
White Plains Hospital Center  
White Plains, New York, USA



Routine results are now typically available within one hour, half the time taken previously; stats are delivered in slightly less time. “A methadone clinic sends us 300 samples at once, and each one has five screens. It used to take up to 17 hours to process these, whereas we can do them in an hour with the new

system,” says Matt Palazola, MS, administrative director of clinical diagnostic services at White Plains.

The laboratory has also been able to expand its testing menu and outreach, bringing nearly two dozen tests in-house and allowing test volume to increase by

350 percent over the past six years. Profitability has improved as well.

Outreach now comprises 30 percent to 45 percent of White Plains’ testing volume and generates more than \$500,000 per month in revenue. Overall gross billings have increased 554 percent since 2006; the laboratory bills roughly \$4.6 million a month.

Naturally, management is happy with these results, as are the technologists, who feel neither overworked nor bored.

“I can promise the techs that they will not be doing the same thing every day,” says Leonard.

The system has improved recruiting and retention efforts. Leonard notes that the prestige drew seven new hires and has contributed to a low turnover. “The system helps us retain staff because it provides technicians with a good quality of life,” says Palazola.

2004	2005	2006	2007	2008
Intraoperative PTH	CA27.29, Prealbumin, Fetal fibronectin	Molecular testing, HIV and HCV viral loads	PLAC, EBV-3 test panel, Free kappa and lambda light chains, Parvo Virus-2 test panel	25OH Vitamin D, HSV-3 test panel, all thyroid and hepatitis testing, including HIV moved to the automated system, allowing 24/7 testing
\$7.7M	\$7.8M	\$7.4M	\$25.1M	\$44.5M

The phone is not constantly ringing (physician calls have been halved), the system and optional decapper have reduced the risk of repetitive strain injuries (such as carpal tunnel syndrome), and job security has not changed. One full-time employee was lost to attrition and another redeployed to handle a newly adopted molecular assay, but there have been no reductions in force as a result of automating the laboratory.

The cost for these improvements has been minimal, comparatively, having risen 17 percent, a figure well below the increases in volume and revenue, both of which continue to rise. Minimal downtime has helped to maximize the investment. The system has gone down only once—during a blackout. Use of the associated networking solution ensures the system continues to function even if the LIS is down.

“When our hospital information system is down, other departments wonder how they’re going to manage. When it comes to chemistry, we just print and fax the results, which really makes life easy,” says Leonard.

Reliability is a benefit that helps to ensure the laboratory continues to deliver results that are timely, clinically relevant, and profitable. “We could have never managed the growth in testing volume without automation,” says Leonard. With the right automation, White Plains chemistry laboratory has increased its turnaround, revenue, and patient safety while decreasing sample sizes, manual labor, and, ultimately, cost.

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- \* Individual results may vary
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“The ADVIA WorkCell system has always been more than a tool to handle our current volume of testing. It’s enabled us to achieve the volume we hoped we could reach.”

Matt Palazola, MS  
Administrative Director  
Clinical Diagnostic Services  
White Plains Hospital Center  
White Plains, New York, USA

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# Perspectives

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1717 Deerfield Road  
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USA

### Editor

Lauran Hoders

### Project Managers

Dyann Bartus Calder  
Christine Larriva

### Editorial Team

Gary Allen  
Lauren Foohey  
Marie Hebron  
Marianne Hurewitz  
Luis LaSalvia  
Jean Metzgar  
Alessandro Ortisi  
Sue Read  
Carola Wagner

### Contact

Letters and e-mails are welcome and should be addressed to:  
Christine Larriva  
Siemens Healthcare Diagnostics  
500 GBC Drive  
Newark, Delaware 19702, USA  
Tel. +1 302 631 0440  
Fax +1 302 631 8511  
christine.v.larriva@siemens.com

### Layout and Editorial Services

Creative Services  
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### Authors of this issue

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Associate Professor of Pediatrics  
Washington University School of Medicine  
Director, Core Laboratory  
St. Louis Children's Hospital  
St. Louis, Missouri, USA

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Technical Specialist, Core Laboratory  
St. Louis Children's Hospital  
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Siemens AG  
Wittelsbacherplatz 2  
80333 Muenchen  
Germany

#### **Global Siemens Healthcare Headquarters**

Siemens AG  
Healthcare Sector  
Henkestrasse 127  
91052 Erlangen  
Germany  
Telephone: +49 9131 84 - 0  
[www.siemens.com/healthcare](http://www.siemens.com/healthcare)

#### **Global Division**

Siemens Healthcare Diagnostics Inc.  
1717 Deerfield Road  
Deerfield, IL 60015-0778  
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