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- Advanced Microbial Identification with MALDI Mass Spectrometry for Streamlined Therapeutic Treatment

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Advanced Microbial Identification with MALDI Mass Spectrometry for Streamlined Therapeutic Treatment

The Microbiology Laboratory at the New Hanover Regional Medical Center, North Carolina, has transformed its microbial identification capabilities with MALDI mass spectrometry, in an automated workflow.

Working with Bruker

Dr. Kevin McNabb, Director of Microbiology, Immunology and Molecular Testing at the New Hanover Regional Medical Center has introduced Bruker's MALDI Biotyper® CA System (MBT) to the Microbiology Laboratory, revolutionizing the Center's capacity for microbial identification and antimicrobial susceptibility testing (AST).

"We can now identify organisms that we couldn't in the past, at a much faster rate, so clinicians can deliver the most suitable therapies to patients sooner."

New Hanover Regional Medical Center, North Carolina

New Hanover Regional Medical Center (NHRMC) is a county-owned, non-profit teaching hospital, regional referral center, Level II trauma center, and University of North Carolina (UNC) School of Medicine branch campus based in Wilmington, NC. For 50 years, NHRMC has been leading the community to outstanding health by providing specialty medical and surgical care through an 800-bed system that includes women's and children's, orthopedic, rehabilitation, and psychiatric hospitals. Services include 24-hour care at three emergency departments under NHRMC's license (and an additional emergency department under Pender Memorial Hospital license), adult intensive care, neonatal and pediatric intensive care, neurosurgery, pediatric surgery, inpatient and outpatient heart care, vascular surgery and oncology.

New Hanover Regional Medical Center (NHRMC) in Wilmington, North Carolina, US

The Bruker MALDI Biotyper® CA System is FDA cleared with a library covering 425 bacteria and yeast.
Other applications including molds and mycobacteria are for research-use-only that would require self-validation by the user for clinical application.

Recently, Forbes listed New Hanover Regional Medical Center among its annual list of America's Best Large Employers, the only North Carolina healthcare system to make the list. Dr. Kevin McNabb, Ph.D., MBA, MT (ASCP), Director of Microbiology, Immunology and Molecular Testing in the Department of Pathology

and Laboratory Services, joined Wilmington Pathology Associates in 2012 and began work at NHRMC at the same time. His prior experience as a Colonel in the U.S. Army Medical Service Corps for 28 years has paved the way for him to lead the Microbiology Laboratory at NHRMC. His areas of expertise are in immunology, allergy testing, autoimmune diseases, initiation of immune response, vaccine development, molecular diagnostic testing, antimicrobial therapy and susceptibility testing.

Since joining Wilmington Pathology Associates and NHRMC, he has played a crucial role in developing the Microbiology Laboratory into the third fully automated microbiology laboratory in the country, and the first in North Carolina as of 2016. Dr. McNabb is also the Technical Director for the laboratory, and is responsible for helping select instrumentation. In his current role, Dr. McNabb works with all clinical staff at the hospital, where he provides guidance on appropriate therapies and testing for different infectious diseases.

There are approximately 200 staff in the Pathology and Laboratory Services Department, and approximately one quarter of the workload for the department falls under microbiology and immunology, where there are 25 staff who run a 24/7 service.

Identifying microbes in the clinical setting

There is a wide variety of pathogenic microorganisms that cause disease in humans. Different microbial strains cause different levels of disease, from a common cold to potentially life-threatening infections such as Tuberculosis (TB). Similarly, different strains sit at various points along the antimicrobial susceptibility scale, with some strains being entirely resistant to a multitude of drugs. Antimicrobial resistance is a serious threat to global health, and is placing a huge burden on healthcare systems worldwide. For example, multidrug-resistant (MDR)-TB remains a public health crisis and a health security threat, particularly in countries such as India, Indonesia and China. The World Health Organization (WHO) estimates that in 2017, there were 558,000 new cases with resistance to rifampicin – the most effective first-line drug – of which 457,560 had MDR-TB [1]. Microbial species regularly evolve into new strains, so the race is on to discover and develop novel therapeutics to combat them, as well as innovative technologies to detect these microbes in patient samples.

The Microbiology Laboratory at the NHRMC is one group that is leading the way in efforts to reduce the turn-around-time (TAT) and increase accuracy of microbial identification (ID), which in turn enables earlier assessment and diagnosis of potentially resistant strains. Dr. McNabb comments:

> "The MBT system offers increased speed, accuracy and confidence in ID, allowing clinicians to deliver the most suitable treatment to patients in the shortest time frame possible, which leads to improved morbidity and mortality rates."

The move to mass spectrometry

When Dr. McNabb first joined NHRMC in 2012, the Microbiology Laboratory was reliant upon traditional biochemical and culture techniques for microbial ID. With the conventional methods, ID can take two to three days and antimicrobial susceptibility testing (AST) can take up to five days. Fastidious, slow growing, non-viable or non-cultivable organisms were difficult to identify and most of these had to be shipped out to a reference laboratory for further work.

About a year after starting his position at NHRMC, Dr. McNabb discussed introducing mass spectrometry (MS) testing into the microbiology laboratory with the medical director, in hopes of reducing TAT for microbial ID. Having already successfully implemented molecular testing into the lab to reduce patient sample turn-around-times and the subsequent improvement in patient

outcomes, Dr. McNabb believed moving to mass spectrometry for microbial identification would have a similar impact. Dr. McNabb explains the process of introducing MS to the laboratory:

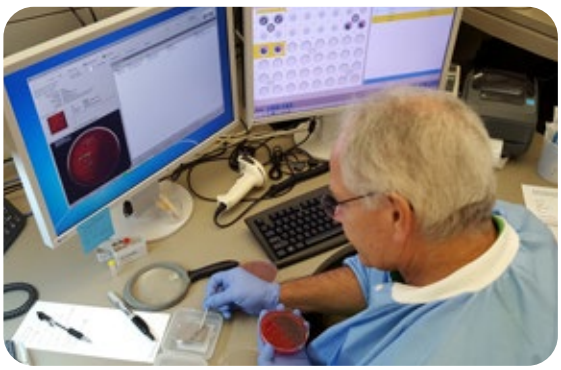
"The percentage of identifications on MS was much better than with traditional biochemical methods, which only identified 82% of samples. With MS, we get a definitive ID around 95-96% of the time.

In addition, biochemical methods take a lot longer and often require re-testing, so in the interim clinicians place patients on broad-spectrum antibiotics as a precaution. However, without an official ID, this might not be the most appropriate therapeutic treatment, is costly, and has implications for the spread of antimicrobial resistance."

Another argument for bringing in MS was the potential for cost savings. Approximately 15% of isolates were outsourced per year, and implementing MS technology would enable the NHRMC to keep a large proportion in-house due to the extensive and expanding reference library and ability to provide highly accurate ID over 95% of the time. In 2014, the medical director approved the decision and, in 2016, the first MS system, the Bruker (Matrix-Assisted Laser Desorption/Ionization) MALDI Biotyper CA System (MBT) was installed. The laboratory now uses this FDA cleared MS microbial identification platform for identification of bacteria and yeast, and applies molecular testing for virus and Mycobacteria (TB) ID. The classification and identification of microorganisms with the MBT is based on proteomic fingerprinting using high-throughput MALDI time-of-flight (TOF) MS technology.

A changing laboratory workflow

The installation of the MS system allows patients to be diagnosed and treated faster. Once the decision had been made to move to MS, Dr. McNabb consulted with experts in the field, spoke to existing users of the various systems available, and visited the American Society for Microbiology (ASM) conference to evaluate what was available on the market before deciding on what he believed to be the most appropriate system for his laboratory. There were various factors that contributed to the decision to acquire the Bruker MBT: the associated cost savings of the lower power requirements of the MBT compared to other systems, its smaller footprint, and Bruker's expertise in MS.



Easy sample preparation for analysis on the MALDI Biotyper®

Dr. McNabb describes how he integrated the Bruker MBT system into his laboratory workflow:

"We decided we wanted to automate with the Beckton Dickinson (BD) Phoenix system, which is used in conjunction with the MBT, as Bruker and BD have partnered together and interfaced the MBT with the Epicenter software. The time to definitive ID initially reduced from 3-5 days to 1-2 days before the laboratory even became fully automated.

After automation, the MBT could provide next day turn-around on ID testing, speeding up the time to correct diagnosis and enabling clinicians to narrow therapies for patients much earlier in the process. Clinicians really noticed a difference."

The Microbiology Laboratory processes between 400-700 specimens per day, with approximately 40% of the laboratory's workload coming from inside the hospital and the remainder coming from external practices in the surrounding Wilmington area. Between 2012 and 2015, the laboratory was completing an average of approximately 65,000 ID's per year (not including re-tests) over all sections of the Microbiology Laboratory. Over an 18-month period in 2016-2017, after the installation of the MBT, this rose to 100,000 IDs on average per year (including re-tests). Dr. McNabb comments on the impact of introducing the MBT to the laboratory:

"During the first three to four months of the instrument's installation, the challenge was to get the microbiologists to work in a way that was producing accurate and fast identifications.

Our microbiologists weren't used to this kind of technology, having used biochemical assays and cultures until now, but within just 12 weeks of having the systems installed the laboratory was achieving a 93% first time identification rate.

The workflow for obtaining the ID was also simplified, as the sample now goes directly from the culture plate to the MBT system, helping to reduce the amount of time to identification. With MBT and Phoenix, the laboratory is now able to achieve a positive identification rate of 97% the first time with the updated reference library and an AST within the next 15 hours on the Phoenix system."

Cost savings

One of the key drivers behind the move to MS and automation was the potential to save money on ID and AST. There have been some significant results here for the NHRMC laboratory. With the incorporation of the Bruker MBT, the laboratory can provide a definitive ID quicker which results in the de-escalation of antibiotic therapy faster. Achieving fast identification has allowed antibiotic therapy to be de-escalated in 60% of patients, which has resulted in an estimated $200,000 cost saving per year.

"The other impact that Bruker made was in the overall costs of conducting biochemical testing" explains Dr. McNabb, adding:

"In the first year of using the MBT, we reduced the cost of ancillary testing by around $100,000. We also minimized administrative work for technical staff, by around 70% or more.

We think this year we are going to reduce another $30,000-40,000 in ancillary cost of reagents in the laboratory."

Dr. McNabb also calculated the cost savings per definitive identification with the MBT. ID with the MBT costs approximately $1, and AST with Phoenix costs an average of $2, so the total per patient is around $3. The old system of ID (biochemical testing) cost $7-8, so the hospital is saving $4-5 per patient for ID and AST (Table 1). Dr. McNabb has calculated that the return on investment time for the purchase of the MALDI system is a maximum of three years and four months, but could be as fast as two years and six months, depending on the volume of testing. These return on investment costs do not include savings made on antibiotics, reduced labor expenses and other indirect savings.

Clinical impact of MS

Cost savings are only part of the measures that the hospital has in place to recognize the effectiveness of the new MBT system. The laboratory itself has noticed reduced labor expenses as the microbiologists are working up fewer samples than they would using biochemical testing. Physicians have seen a noticeable improvement in TAT for ID and infectious disease staff noticed faster consults (Table 2).

Dr. McNabb comments on the feedback he has received from hospital staff:

"We started our transition to the MALDI Biotyper CA System in 2015 into 2016, and it took about six months to go 'fully MBT'. So many physicians have approached me since, telling me there is a night and day difference between the information they used to get three years ago and the information they get now."

Table 1: Comparison between previous cost of biochemical methods used at New Hanover Regional Medical Center in the Bacteriology Section in 2015 for identification (ID), and the costs associated with the change to Matrix-Assisted Laser Desorption/Ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker MALDI Biotyper CA System) in 2017.

Laboratory cost savings per reportable ID using Bruker MALDI	Cost per ID	Laboratory cost savings using MALDI ID
Biochemical ID (2015)	$8.57	**$6.67**
Bruker MALDI ID (2017)	$1.90	

Table 2: Turn-around times (TAT) of five organism identifications (IDs) with biochemical analysis and MALDI-TOF ID (MALDI Biotyper CA System, Bruker Daltonics) at the New Hanover Regional Medical Center. * Molds and mycobacteria were identified using the non-FDA cleared software and reference library (for research use only) included with the Bruker MALDI Biotyper CA System.

Turn-around time (TAT) (averages)	Biochemical analysis	MALDI-TOF ID	Estimated TAT reduction
Bacterial ID	48 - 96 hours	24 - 48 hours	**24 - 48 hours**
Anaerobic ID	48 - 96 hours	24 - 48 hours	**24 - 48 hours**
Yeast ID	24 - 48 hours	24 hours	**24 hours**
***Mold ID**	2 - 3 weeks	10 days	**4 - 11 days**
***Mycobacterial ID**	2 - 6 weeks	1 - 3 weeks	**1 - 3 weeks**

As well as confidence in ID and faster TAT, the MBT has enabled the laboratory to identify organisms that they previously could not, due to poor growth or slow metabolism. For example, there have been cases of patients receiving dental surgery and developing an oral infection. Microorganisms responsible for oral infections are difficult to ID since many oral bacteria are not on traditional biochemical panels. The laboratory can now identify sepsis contracted through oral infection, whereas in the past these would have been sent to the reference laboratory, without a guarantee of ID. Almost all of these cases were resolved within a few days once the organism was identified.

For infection control, the introduction of the MBT has led to the more active promotion of antibiotic stewardship to reduce MDR organisms, because of the near real-time ID of some organisms. The service is also able to more rapidly initiate the correct infection control measures due to the faster ID.

A case example

One example of a case where the MBT has directly impacted the clinical outcome of a patient at the NHRMC is with a 21-year-old male, who presented to the emergency department with a fever and a headache. The patient had Graves disease – an autoimmune disorder affecting the thyroid – and a history of hypertension, with no other outstanding health issues.

Benefits of using the Bruker MALDI Biotyper® (MBT) for microbial identification and susceptibility testing:

- Reduced costs of reagents
- Reduced labor expense
- Faster TAT for ID of most bacteria, fungi and yeast
- Decreased time to effective treatment of patient
- Decreased length of stay, cost and readmission
- Reduction in broad spectrum antibiotic usage
- Additional analyses direct from fluids such as urine and positive blood culture

The Bruker MALDI Biotyper CA System is FDA cleared with a library covering 425 bacteria and yeast. Other applications including molds and mycobacteria are for research-use-only that would require self-validation by the user for clinical application.

The patient was admitted and the laboratory collected blood cultures, urinalysis, chemistry and hematology profiles. The meningitis panel and other laboratory tests all returned negative, however

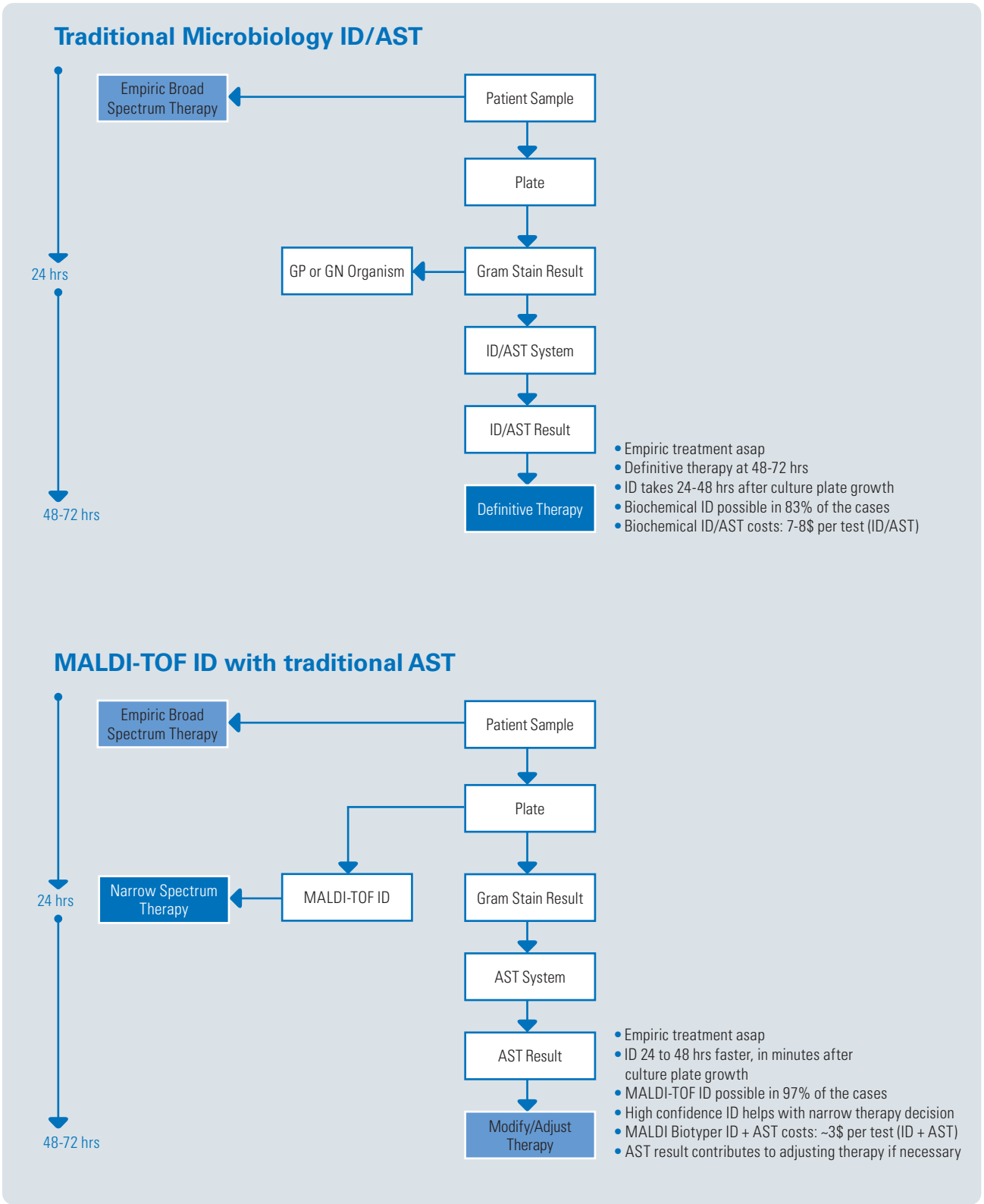
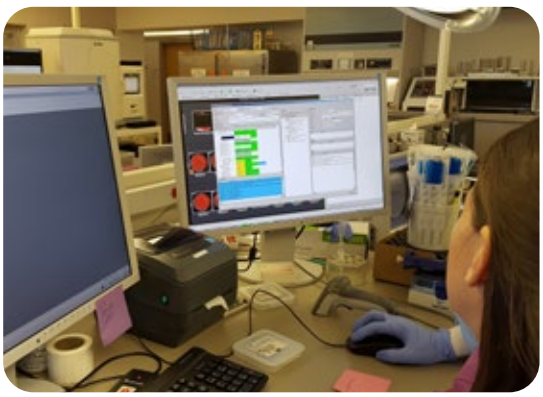


Figure 1: Comparison of the traditional identification (ID)/antimicrobial susceptibility testing (AST) workflow, using biochemical ID methods, to the newly established ID/AST workflow using the MALDI Biotyper for microorganism ID.



both the anaerobic blood culture bottles turned positive at 20 hours after admission. A Gram stain was performed and showed Gram negative, long thin rods. The physician called the next day and requested to look at the culture, which was growing anaerobically at 18 hours (38 hours from admission).

MALDI-TOF MS identification with the MBT found the organism to be *Fusobacterium necrophorum* – the causative bacterial species of Lemierre's syndrome, which can lead to serious complications such as sepsis. The physician was immediately notified and the patient was changed to ceftriaxone and metronidazole, at a higher than standard dosing. The patient had already been on ceftriaxone since admission, but at a much lower dose. Within 6 hours of the change in therapy, the patient was responding and was moved from the intensive care unit (ICU) to a regular hospital bed, 44 hours from admission. Without this faster identification, the change in therapy would likely have been much slower which would likely result in a much longer admission and/or a poor clinical outcome.

Working with Bruker in the future

Dr. McNabb's laboratory primarily conducts yeast and bacteria IDs on the MBT, and recently piloted a three-month study to evaluate the use of the MBT for identification of molds and acid-fast bacilli (AFB) using the non-FDA cleared software and reference library (for research use only) included with the Bruker MALDI Biotyper CA System.

This is an area which Dr. McNabb wishes to focus on in the near future, but has not been pursued yet so as not to disrupt the successful bacterial and yeast ID workflows.

Dr. McNabb comments on the quality of service after the installation of the MBT:

"The Bruker team, including maintenance and training, has been really great. They trained our staff well before we went live, and when some technicians weren't confident, they came back in and re-trained and offered one-on-one sessions. That was really valuable."

The introduction of MS to the NHRMC has been so successful among the entire hospital, the Microbiology Laboratory is now considering an upgraded MBT model. Dr. McNabb elaborates:

"It is really gratifying to talk to the clinicians and hear how happy they are. My team used to spend hours every day answering calls from physicians asking where their IDs were – we could certainly never go back! We are already talking about upgrading our system to the next model and we've only had it for two years."

Research staff using the MALDI Biotyper®

The next model would have a higher capacity, with the ability to process 96 patient IDs in less than 15 minutes, in comparison to the current system which can accommodate 48 samples in 16 minutes. This would have a huge impact on the laboratory's productivity, particularly where repeat identifications are needed.

"MALDI-TOF MS for microbial identification is one of the most important advances in microbiology testing in decades" comments Dr. McNabb.

For more information on New Hanover Regional Medical Center, please visit https://www.nhrmc.org/

For more information on Bruker's MALDI Biotyper, please visit https://www.bruker.com/products/mass-spectrometry-and-separations/maldi-biotyper-systems.html

References:

[1] World Health Organization (WHO) Tuberculosis Key Facts (updated February 2018) https://www.who.int/tb/publications/factsheet_global.pdf?ua=1

NHRMC Betty H. Cameron Women's & Children's Hospital in Wilmington, North Carolina, US

New Hanover Regional Medical Center (NHRMC) in Wilmington, North Carolina, US

Expert Insights

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About New Hanover Regional Medical Center

New Hanover Regional Medical Center is a quality driven network of hospitals, outpatient centers, emergency services and physicians. The Laboratory Services Department provides anatomical pathology and clinical laboratory medicine services to NHRMC, NHRMC Orthopedic Hospital and the surrounding community. The department enables healthcare professionals to accurately diagnose patients' conditions and to monitor progress while under therapy.

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