thermo scientific

A DOSE OF TECHNOLOGY FOR PRECISION MEDICINE

Mass spectrometry workflows for improved healthcare

DISCOVERY | CLINICAL LAB | BEDSIDE

ThermoFisher SCIENTIFIC

INTRODUCTION

With more than 70% of medical decisions now based on clinical lab results, the sooner the diagnosis, the faster the treatment. Answers to complex diseases leveraging mass spectrometry (MS)-based workflows can enable greater productivity and confidence.

This e-book will highlight the trends and pain points in clinical research, and show how MS is helping clinical laboratories around the world find the answers to complex healthcare questions. MS is empowering medical scientists, laboratory directors, and clinicians with more cost effective and confident results to unlock the answers physicians need. Always remember, what you do in clinical research changes the world one life at a time. **Be someone's hero.**

DISCOVERY | CLINICAL LAB | BEDSIDE

TABLE OF CONTENTS

DISCOVERY | CLINICAL LAB | BEDSIDE

Chapter 1
CLINICAL TRANSLATIONAL RESEARCH: TRENDS AND PAIN POINTS

Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in environment, lifestyle and genes.

But choosing the best therapeutics for every individual is often a challenge. For example, in ovarian cancer there are no known driver mutations, such as epidermal growth factor receptor (EGFR) in lung cancer, to help stratify patients to specific therapeutic options.

Therefore, most individuals receive standard-of-care cytotoxic chemotherapy. While many respond initially to standard-of-care therapy, most eventually recur with a chemo-resistant disease. Clinical translational research seeks to better understand the risk factors to enable treatments tailored to prognosis.

Technology Revolution

It's important to understand that disease-related biology does not conform neatly to an isolated approach using scientific disciplines such as molecular biology or biochemistry.

"More than 70% of ovarian cancer patients respond initially, most eventually recur with a chemo-resistant disease."
- Women's Health Advice

The right tools are critical. Many are disappointed in the output of genomics. For example, the US alone has spent billions of dollars developing and using genomics, in the hope that better understanding of the cancer genome would lead to a revolution in the way we treat cancer patients. But so far, the revolution hasn't arrived.

Genomics, however, has taught us a lot about cancer biology, laying bare the complexity of the problem we're facing. Genomics is an important tool, but in cancer research we have seen time and again that one approach will not solve the problem. We need a transdisciplinary approach to analyzing the genome, proteome, and metabolome that views cancer as a system rather than an ensemble of molecules.

The proteotype is the missing link between genotype and phenotype. If we don't have measures at the protein level, we miss this vital link. Today, proteomics is at a similar stage to genomics in the mid-1990s. We're on the verge of revolutionizing clinical research applications that will:

- Provide individualized prognostic information
- Determine who will benefit most from a given therapy
- Identify who can be treated effectively with minimally toxic therapies versus those with potentially lethal pathologies that require intensive and aggressive clinical interventions
- Allow improved and early assessment of therapeutic responses
- Identify potential new drug targets
- Enhance the understanding of how therapies work at the cellular level

Compelling Clinical Questions

Start from a compelling clinical question, then apply or invent the tools to answer it. From discovery to clinical application, the primary goal of most interdisciplinary institutes is to apply proteomic and other technologies and methods to answer compelling clinical questions. Having the clinical and technical know-how to move translational research forward more efficiently is key. To make sure the right questions are being asked, labs need to apply the magic of translational scientists, who have a broad understanding and the confidence to ask questions and generate suitable hypothesis, and finally, to make sure the data is high-quality.

Donor Specimen Quality Importance

The quality of donor specimens is the primary roadblock for many research labs. In a recent 300-specimen study looking at markers of metastasis in endometrial cancer, a lab noted that only 40 percent of the specimens were viable for cancer research – the other 60 percent were either necrotic, didn't contain cancer, or were the wrong cancer type. The research was delayed almost five years until the lab had enough useful specimens to harness the statistical power of the study.

CANCER

14.1M

New cases of cancer worldwide[1]

8.2M

Patient deaths due to cancer globally[1]

440,800

Patient deaths due to adverse drug reactions globally[2]

PER YEAR

[1]Global Cancer Facts and Figures from www.cancer.org
[2]Extrapolated from "Identifying and reporting adverse drug events in oncology," Aleta J. Hong, Matthew J. Fisher, Christina H. Georgopoulos BS, and Charles L. Bennett, MD.

Tackling Variance Early

Clinical labs now need to measure proteins accurately – including all modified forms – at a larger scale than they've done in the past. Researchers also need to carefully consider the extent of biological and pathological variability within the clinical domain being targeted. They must think about what samples should be chosen, and how big the sample bank needs to be to capture the full variability of the healthy versus disease state spectrum and any potential overlaps with other disease states.

In addition, variance can occur in the workflow, everywhere from sample preparation to running and harmonizing mass spectrometers, to how samples are blocked and randomized. By controlling technical variance, researchers can get a better handle on variations in biology.

Implementing "real-time" quality control (QC) for each step in the workflow is key. Similar to the strategies in place in a typical clinical chemistry lab, as samples are analyzed in the mass spectrometer, researchers determine if QC samples are on target. If not, they try to find out what's wrong with the experimental set-up and correct it immediately.

Clinical and Industry Collaboration

Working with a consortium of hospitals providing specimens from both newly diagnosed and recurrent cancer patients is critical to a translational center's success. In order to draw useful research conclusions, samples must be highly qualified, validated for quality, and have a wealth of questionnaire data associated with them.

Instrument manufacturers play a vital role in translational science by developing and scaling the research tools. Without technologically innovative industry partners, translational scientists will likely fall behind the curve. Having partners who are engaged, want a dialog, and actively seek to have their products used for translation, is extremely important to enabling translational research.

"We are measuring expression levels of therapeutically relevant protein biomarkers."
-NantOmics

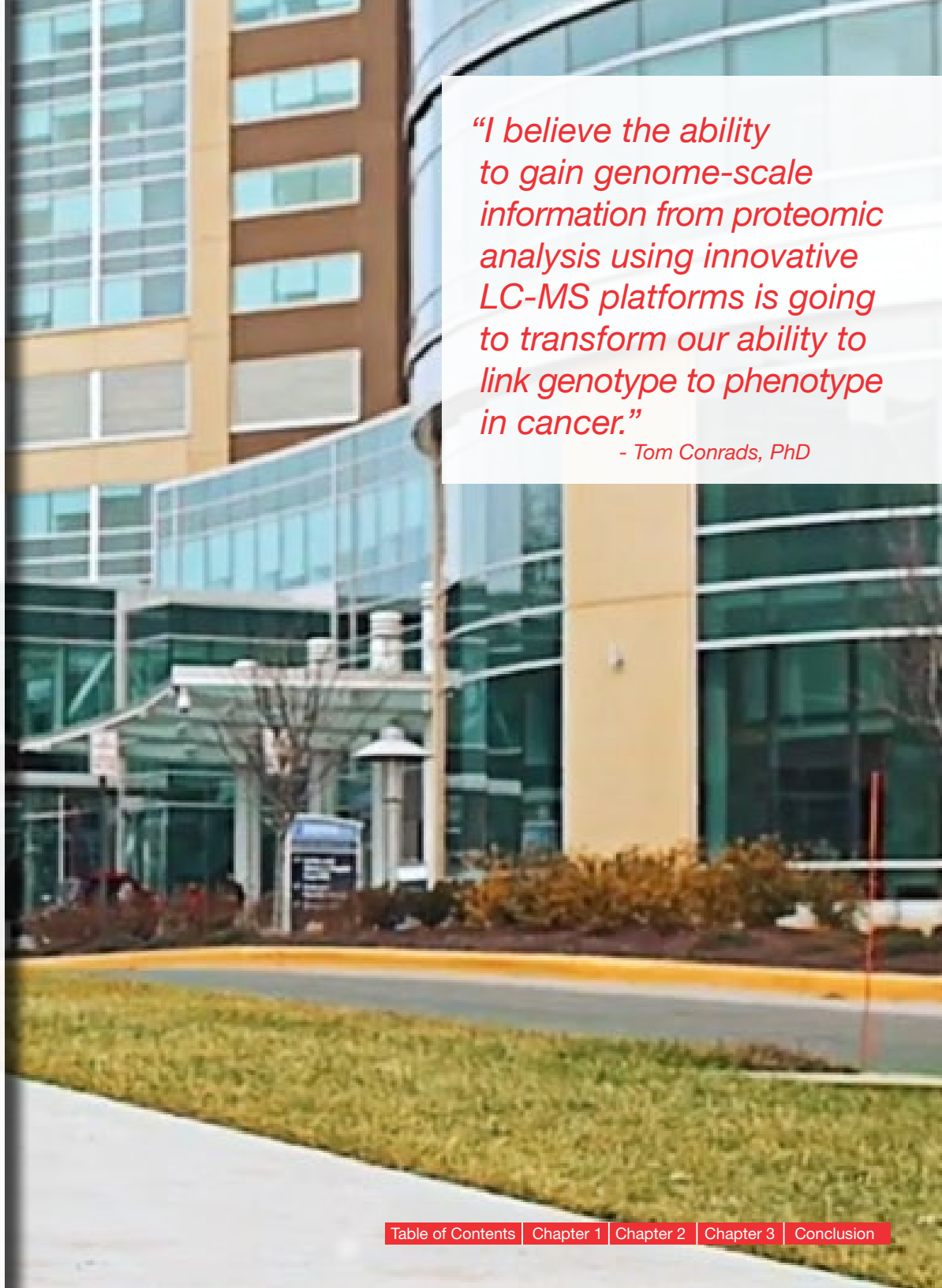
Customer Spotlight:

WOMEN'S HEALTH INTEGRATED RESEARCH CENTER

Women's Health Integrated Research Center is a state-of-the-art research facility established by the Department of Defense Gynecologic Cancer Center of Excellence (GYN-COE) to identify molecular alterations associated with gynecologic cancer and to facilitate future detection, prevention, and treatment strategies for its management.

Advances in MS and separation science are bringing genome-scale proteomic analyses within reach. Thomas Conrads, Associate Director of Scientific Technologies in the Inova Schar Cancer Institute and Chief Scientific Officer of the Women's Health Integrated Research Center at Inova Health System, describes how his lab applies the power of proteomic tools to help women with cancer.

Watch the video



"I believe the ability to gain genome-scale information from proteomic analysis using innovative LC-MS platforms is going to transform our ability to link genotype to phenotype in cancer."

- Tom Conrads, PhD

Customer Spotlight:
VAN EYK LABORATORY

The primary goal of the interdisciplinary Advanced Clinical Biosystems Research Institute is to apply proteomic technologies and methods from discovery to clinical application. The Institute brings together an incredible breadth of knowledge, expertise and skills, to create the right environment for translational research.

The ability to analyze a large number of samples by MS is opening up new insights in discovery and clinical studies. Applying MS-based expertise, the team is working to decipher the precise role that protein expression profiles and modifications play in disease progression.

Jenny Van Eyk, Director of the Advanced Clinical Biosystems Research Institute at Cedars-Sinai Medical Center, shares her vision of their clinical proteomic future.

Watch the video

"Our motto (yes, we have a motto!) is from discovery to patient care."
- Jenny Van Eyk, PhD

WHAT'S NEXT?

Scientists by nature like to tinker with and push the limits of an instrument and worry less about stabilizing a method. But for clinical chemistry, you need reproducible, validated and robust technology from day one to day one thousand. And that is exactly where advances in engineering – driven by instrument manufacturers – is coming to the forefront.

Instrument vendors have made their technology much more stable. In the 1990s, MS systems were mostly sold to a relatively small group of expert labs. But as the technology is stabilized and made suitable for routine use, the potential for its increased utility is enormous.

Chapter 2
MOVING TO THE DIAGNOSTIC LAB: TRENDS AND PAIN POINTS

In the 1990s, gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) technology found their way into clinical laboratories for use in lab developed tests (LDTs). Since 2005, there's been an exponential increase in clinical publications referencing LC-MS. More clinical core testing laboratories are considering or have already implemented LC-MS systems for various lab developed test applications.

The technology offers the flexibility to develop cutting-edge in-house tests for measuring clinically relevant compounds and their metabolites when necessary, with confidence even when a large number of samples are analyzed.

High Quality Results

MS-based systems exhibit superior analytical selectivity for target analytes, as their presence is ascertained via a combination of at least two characteristics – their precursor and product ion mass. MS-based systems also allow for lower detection limits for analytes, such as steroids and therapeutic drugs, when compared to conventional immunological methods e.g. ELISA and RIA.

"The genome, or DNA footprint predicts susceptibility to certain diseases. The proteome shows what's happening in the body in real time, giving researchers answers to critical questions for improved healthcare outcomes in the future."

The Collaborative Center for Translational Mass Spectrometry
Dr. Patrick Pirrotte, Director

Conventional assays used in hospital diagnostic labs have focused mainly on clinical chemistry and immunoassay technology, but both can suffer from several limitations resulting in inconsistencies. These include poor analyte specificity and lot-to-lot variation between assays and reagents. 'Reagent-free' in operation, LC-MS systems minimize waste and have running costs that are one-fifth that of conventional immunoassays.

Technology Expertise

While FDA or locally approved tests may be simpler, more laboratory professionals are shifting to MS-based LDTs because they allow faster CLIA-compliant method development rather than wait for commercially available solutions. Additionally, the lack of standardized reference materials for certain drugs (e.g. immunosuppressants and drugs of abuse) means results may vary from lab to lab.

The healthcare market is accustomed to "push button analyzers," so onboard MS expertise remains a challenge for some institutions. Laboratories continue to prefer FDA or locally approved tests to reduce risk, however market approval continues to be a lengthy endeavor for manufacturers.

Finding trained MS experts will continue to be foundational to technology adoption.

Cost of Ownership

Cost to acquire is always a critical decision. Most labs develop detailed Return on Investment (ROI) analyses to justify acquisition costs. Long-term cost-per-test is a key factor because most labs anticipate reimbursement rates to continually decline. Clinical laboratories are accustomed to continuous workflow optimization to improve test profitability. The fear of workflow downtime can derail adoption decisions.

Laboratory Automation

The majority of clinical laboratories perform separate benchmark throughput requirements—MS-based testing versus non-MS high-throughput, highly-automated workflows. In a recent AACC/MSSS Outlook for Clinical Mass Spec Testing survey, choices for automation and data management were the key areas noted for the adoption of MS instruments in the clinical laboratory.

Industry Perspective:

WHAT MASS SPECTROMETRY OFFERS VS. CLASSICAL CHEMISTRY APPROACHES

While immunoassay methods have dominated clinical analyses, MS-based methods are now providing much more accurate analytical results, rapidly and with less expense because the technology enables a spectrum of analytes to be anlayzed in a single run.

David Harold MD, PhD, UC San Diego, founder of the Mass Spectrometry Applications in the Clinical Lab (MSACL) conference, discusses the utility of MS in helping clinical labs develop better analysis to advance healthcare outcomes with faster, more comprehensive information at a lower cost.

Watch the video

DISCOVERY | CLINICAL LAB | BEDSIDE

Customer Spotlight:
VIAPATH

With a unique partnership of clinical, scientific and operational expertise to transform pathology services in the UK, Viapath provides services for Kings College Hospital, Bedford Hospital and Guy's and St. Thomas' Hospital in London. The goal of the laboratory is to help create better outcomes by giving clinicians the best results possible.

European clinical laboratories increasingly manage samples using total automation systems, or at least a high level of analyzer automation. They're also aware of the advantages MS can offer. One of the biggest issues faced is the large numbers of samples that require testing. It's essential that MS workflows are able to continually produce meaningful data with minimum downtime. Solutions that automate sample cleanup using Thermo Scientific™ TurboFlow™ technology and multi-channel uHPLC maximize MS analysis time, allowing labs to double or quadruple the amount of samples they can analyze.

MS is getting to the point where it is more readily available and more usable. Using multi-channel platforms, with online sample preparation, makes the technology much more suited to high-throughput clinical research labs.

Watch Webinar

Chapter 3

EMERGING TECHNOLOGY AND GUIDANCE RESPONSES

Advanced technology is needed to address today's and tomorrow's clinical challenges. Also needed are guidance documents inclusive of recent technology to ensure safety.

Regulatory Oversight

The FDA regulates in vitro diagnostic devices (IVDs) as medical devices. IVDs analyze human samples such as blood, saliva, tissue and urine. In the past, the FDA did not exercise authority to regulate LDTs that are developed and performed at a single laboratory. Now these tests undergo the same pre-market approval process as other medical devices regulated by the FDA including, in some cases, clinical studies demonstrating that the device is safe and effective for its intended use.

LDTs were traditionally developed by hospitals, researchers and academic medical centers for their own use. However, due to a lack of available tests in certain disease or therapeutic areas, labs were forced to develop in-house tests to help in healthcare efforts. As a result, in the past decade or so, there has been an explosion in the use of LDTs by commercial labs and biotechnology companies.

"The FDA now estimates that there are about 11,000 LDTs offered by 2,000 laboratories."

- Congressional Research Service Report, 2014

Immunoassays versus LC-MS?

While immunoassays have been the gold standard for the past 50 years, especially in the diagnostics arena, that has not meant LC-MS isn't evaluated as an alternative due to the limitations of immunoassays.

MS technology is advancing, and with the clear limitations inherent to immunoassays, LC-MS will play a larger role in the future. In particular, with LC-MS, more confidence in the accuracy of results is obtained. However, for LC-MS to play a greater role, the following needs to occur:

- Easier technology adoption
- Continued performance improvements
- Use acceptance guidelines

New Comprehensive Panel Testing

Prior to 2014, laboratories were paid about $20 per reported drug for quantitative urine drug tests performed by LC-MS methods.[4] This meant that a large, physician-specified panel of tests could yield significant reimbursement. Aggressive promotion by reference laboratories and the growth of physician office labs performing these very profitable panels led to overutilization—and medically unnecessary testing. The Centers for Medicare & Medicaid Services (CMS) and other payers responded to this rise in testing by imposing cuts so severe that small providers may no longer be able to offer LC-MS–based drug testing. With new Healthcare Common Procedure Coding System (HCPCS) codes created by the CMS and Current Procedural Terminology (CPT) codes from the American Medical Association (AMA) which more accurately describe drug testing procedures, restrictive coverage policy is limiting the number of analytes tested for and the frequency of testing.

Clinical researchers are evaluating High-resolution Accurate-mass (HRAM) Thermo Scientific™ Orbitrap™ technology for drugs important to pain management, such as opiates, oxycodone, benzodiazepines and amphetamines, to reduce the cost of testing while potentially providing more clarity to results to determine the need for further tests.

Biological Sample Prep Advancements

For many MS-based tests, HPLC has proven the most versatile form of chromatographic separation in the clinical laboratory by far. The technology emerged in clinical chemistry labs in the 1970s and is ideally suited for separating complex biological samples such as blood, urine and plasma. Today the majority of LDT applications are for the analysis of amino acids, peptides, proteins, carbohydrates, lipids, nucleic acids, vitamins, and hormones.

Coupling HPLC and MS, can offer, in the space of a few minutes separation, identification, and quantification of hundreds of analytes in a complex biological matrix.

For complex biological samples and LC-MS workflow automation, multichannel uHPLC offers several advantages. Operational simplicity and high throughput enable running different methods simultaneously, with or without on-line extraction. Multichannel uHPLC also allows up to 100% utilization of an LC-MS system with consequent improvement in laboratory efficiency.

Thermo Scientific™ TurboFlow™ online extraction improves MS detector response to analytes of interest by removing non-analyte matrix interferences such as phospholipids that can interfere with measuring the analyte of interest. TurboFlow-based methods often save work-flow hours by eliminating several manual steps.

What Are the Next Big Things?

There will be new products that enable MS workflows to meet the demands of clinical core laboratories, while not losing sight of the need to advance clinical and translational research with a path to the clinical routine laboratory.

Simplicity, automation, and point-of-care solutions will continue to be key goals in next-generation product development.

Radical changes will come in the form of simplifying the user experience, reducing complexity, and designing products with the understanding that samples aren't just samples. Behind each sample is a person with hopes, dreams and a life to live.

[4]Challenging times for mass-spectrometry reimbursement, AACC, May 2016

14%

In 2015, clinical labs view mass spectrometry as the main platform in clinical labs[1]

28%

In 2016, LC-MS clinical diagnostics labs say they will invest in LC-MS in the next 1-2 years[2]

41%

In 2020, clinical labs will view mass spectrometry as the main platform[1]

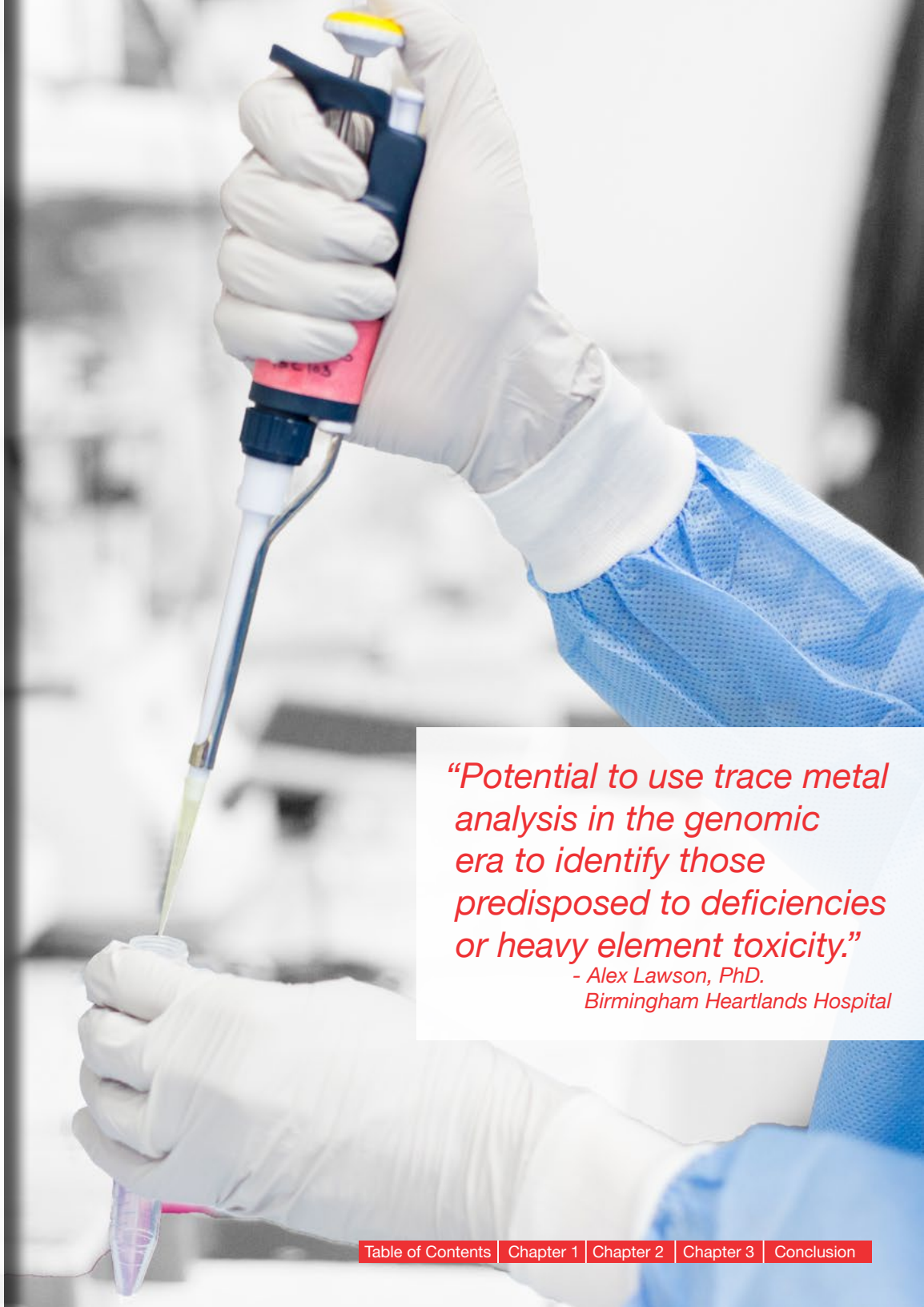
[1]AACC/MSSS Outlook for clinical Mass Spec Testing Survey, 2015
[2]Trends in Clinical Diagnostics Survey, Select Science, May 2016

Customer Spotlight:
BIRMINGHAM HEARTLANDS HOSPITAL

The Department of Toxicology performs clinical research to improve clinical care. Sweat chloride analysis is the gold standard for diagnosis of cystic fibrosis (CF), however, current methods (e.g. coulometry, colourimetry, and ISE) are time-consuming, costly and require large sample volumes relative to the minimum acceptable collection. Researchers have developed a method to measure sweat chloride and sodium using inductively coupled plasma mass spectrometry (ICP-MS). All the information needed can be obtained from just 2 µL of sample in duplication, thereby reducing the need to repeat sweat tests.

Clinical researchers believe using ICP-MS to measure trace elements, such as commonly analyzed co-factors (Zn, Cu), may serve as predictive indicators for a number of disorders and disease in the near future.

Watch the video



"Potential to use trace metal analysis in the genomic era to identify those predisposed to deficiencies or heavy element toxicity."

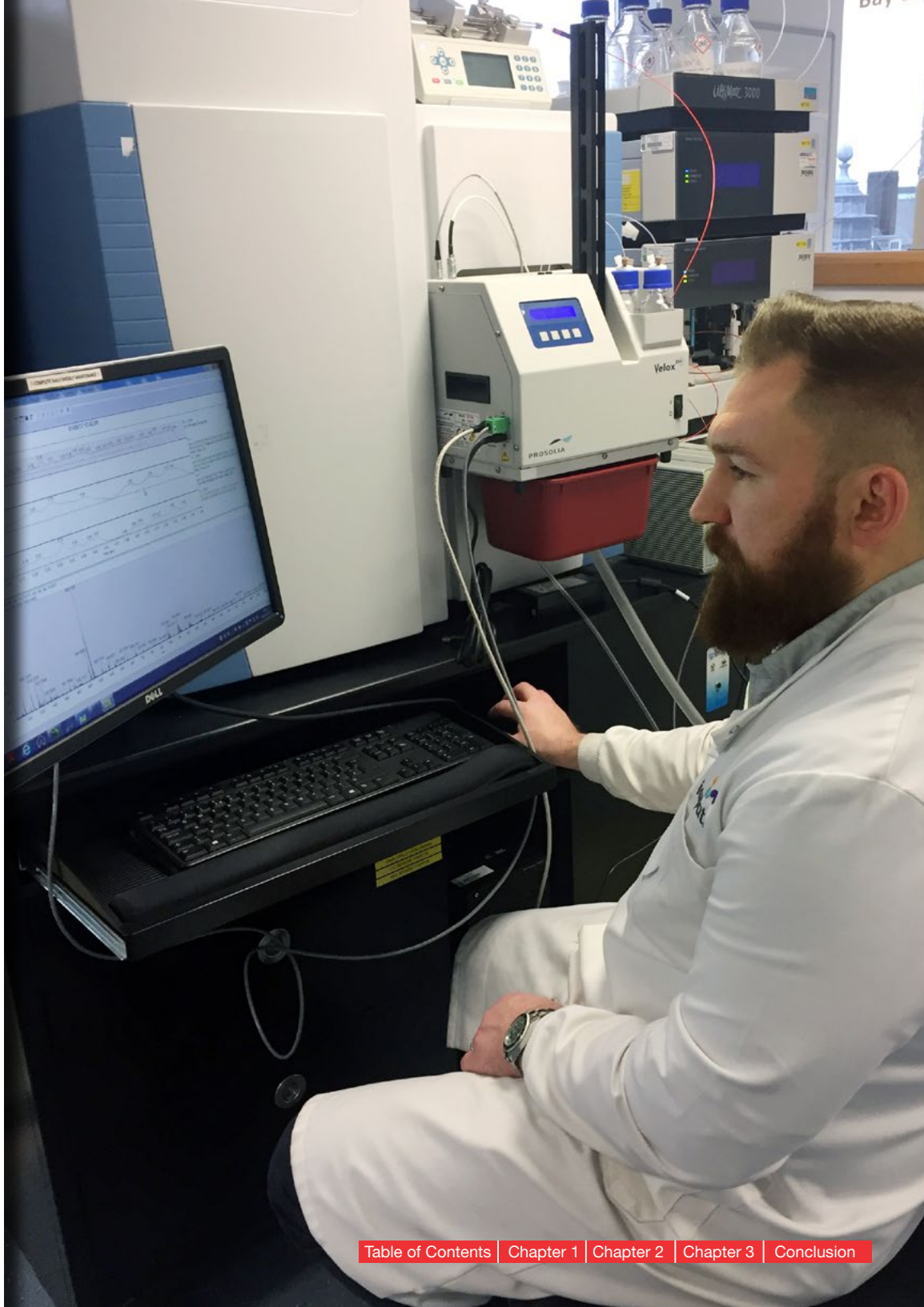
- Alex Lawson, PhD.
Birmingham Heartlands Hospital

Technology Spotlight:
PAPERSPRAY: MODERN SAMPLE PREPARATION

For clinical research applications, the Prosolia Velox 360™ PaperSpray™ ion source eliminates sample preparation steps necessary for LC-MS analysis. Researchers see promise for use with dried bloodspots, a sample type increasingly analyzed in clinical laboratories. An MS-based workflow with PaperSpray uses smaller solvent volumes and produces less solvent waste. The ability to eliminate liquid-liquid extraction sample preparation reduces the need for additional processing steps, such as centrifugation, and manual preparation.

HPLC can be complex and requires proper maintenance. Another common concern associated with HPLC systems is carryover, when high concentration samples contaminate subsequent samples. PaperSpray shows promise in eliminating these problems, as the system uses a fresh, disposable cartridge for each new sample and is significantly more simple than HPLC. PaperSpray removes the LC step so there are no columns or high pressure solvents to replace, reducing overall operational expenses.

For research use only. Not for use in diagnostic procedures.



Customer Spotlight:
GIANNINA GASLINI CHILDREN'S HOSPITAL

The Giannina Gaslini Institute receives samples from thousands of children of 90 nationalities every year. Its Central Laboratory of Analysis performs about 10,000 LC and LC-MS-based tests per year. The analytes of interest are immunosuppressants, antibiotics, antiepileptic's, antimicotics for therapeutic drug monitoring, as well as samples from, catecholamines, vitamins, and sugars.

The institute's clinical research is focused on the development and validation of bioanalytical quantitative methods, and uses triple quadrupole LC-MS/MS to measure drugs in blood and other body fluids. The research is carried out in strict collaboration with hospital clinicians, to define therapeutic protocols in children with the objective of performing more personalized medicine.

An important goal is to optimize therapies for children and to improve the knowledge of the mechanisms of interaction between pharmacokinetics (what the body does to the drug) and pharmacodynamic (what the drug does to the body).

Learn More

"LCMS allows us to give an answer to the needs of the modern pediatrics research and to help improve the treatments for our children."

-Giuliana Cangemi,
Giannina Gaslini Children's Hospital

CONCLUSION

Adopting innovative MS-based workflows and working with suppliers equipped to support your evolving clinical research, today and in the future, is key to obtaining the answers you and your clinicians need while lowering healthcare costs.

You may not wear a cape to work. But what you do day in and day out changes the world one life at a time. Thermo Fisher Scientific is proud to share that quest with you, by providing you with the tools and confidence to improve lives every day.

We both know, the faster the diagnosis, the faster the treatment. So samples to data, knowledge to diagnosis, cancer to Alzheimer's, we never forget those samples aren't just samples. Each is a person. A person for whom your work can make all the difference in the world.

RESOURCES YOU MIGHT ALSO LIKE:

Rapid screening and identification of novel psychoactive substances using PaperSpray interfaced to high resolution mass spectrometry

Authors: Joseph Kennedy et al

Publication: Clinical Mass Spectrometry, Volume 1, November 2016

Download

LC-MS candidate reference methods for the harmonisation of parathyroid hormone (PTH) measurement: a review of recent developments and future considerations

Authors: Lewis Couchman et al

Publication: Clinical Chemistry and Laboratory Medicine (CCLM). April 2014

Download

High-Throughput LC-MS/MS Quantification of 17-Hydroxyprogesterone (17-OHP) in Human Blood Serum for Clinical Research Purposes

Download

BE SOMEONE'S HERO.

What you do changes the world one life at a time. It's that simple, that dramatic. And we share that quest with you, providing the tools and confidence to improve lives every day. Leveraging our years of experience to help advance clinical research to routine testing with the most comprehensive, most innovative mass spectrometry-based workflows on the planet. Lives are very definitely enriched through you and your efforts.

DISCOVERY | CLINICAL LAB | BEDSIDE

Join our Clinical Community

thermo scientific

www.thermofisher.com/ClinicalResearchSolutions

BR64910EN-0117S

ThermoFisher SCIENTIFIC