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Automating LC-MS/MS

The road to improved diagnostic testing

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Dr Victoria Zhang, an expert in clinical mass spectrometry and the Founding Chair of the Mass Spectrometry and Separation Sciences Division (MS^3) from the American Association for Clinical Chemistry (AACC), helps us explore the role of LC-MS/MS in the clinical laboratory, discusses why the lack of automation is holding back progress, and considers how its advancement could be a real game changer in diagnostic testing.

Background information

Mass spectrometry (MS) is a widely used analytical technique, and one that is especially powerful when coupled to liquid chromatography. Based on the separation of particles by their mass-to-charge ratio, MS analysis can be divided into three basic elements:

- Ionization (typically following sample separation by liquid chromatography)
- Mass analysis
- Detection

LC-MS/MS in the clinical laboratory

As such an important analytical tool, LC-MS/MS naturally lends itself as an ideal technique to meet the analytical needs of a wide range of laboratories. For example, it has been applied across several different clinical diagnostic fields over the last few decades. It was first used for the diagnosis of inborn errors of metabolism, before becoming commonplace for forensic and clinical toxicology, and therapeutic drug monitoring applications. Today, it is used across a limited number of clinical specialties, including endocrinology and therapeutic drug monitoring, as well as small molecule, peptide and protein marker analysis.

The use of such a powerful technique brings many advantages to the clinical setting, enabling scientists to analyze multiple analytes with greater specificity than alternative methods (such as immunoassays).

However, it is significant that the technique has not been further adopted across the wider clinical setting, especially given its numerous benefits to clinical diagnostics and patient care. One key barrier preventing more widespread use is the lack of a commercially available automated system. Automating the system and providing a fully integrated solution could help these laboratories eliminate the numerous challenges currently being experienced around the use and implementation of LC-MS/MS, allowing facilities to benefit from its full potential.

LC-MS/MS and its growth in clinical laboratories

Dr Victoria Zhang first used MS technology at graduate school to perform translational research in biomarker discovery and validation. She then gained clinical experience of MS during her fellowship at Harvard Medical School. More recently, as a highly-experienced user of MS, Dr Zhang spearheaded the creation and development of the Mass Spectrometry and Separation Sciences Division (MS^3) under the auspices of the American Association for Clinical Chemistry (AACC), a global scientific and medical organization dedicated to clinical laboratory science and its application to healthcare. Over the last two years, the division has strived to gain recognition of the importance of MS to clinical diagnostics, and is now working to further integrate these technologies within laboratory medicine and patient care. The group serves as a leading resource; explores strategies to eliminate barriers to advancement; develops and presents educational programs; and engages thought leaders in academia, industry and regulatory entities to enhance applications of MS for the betterment of patient care.

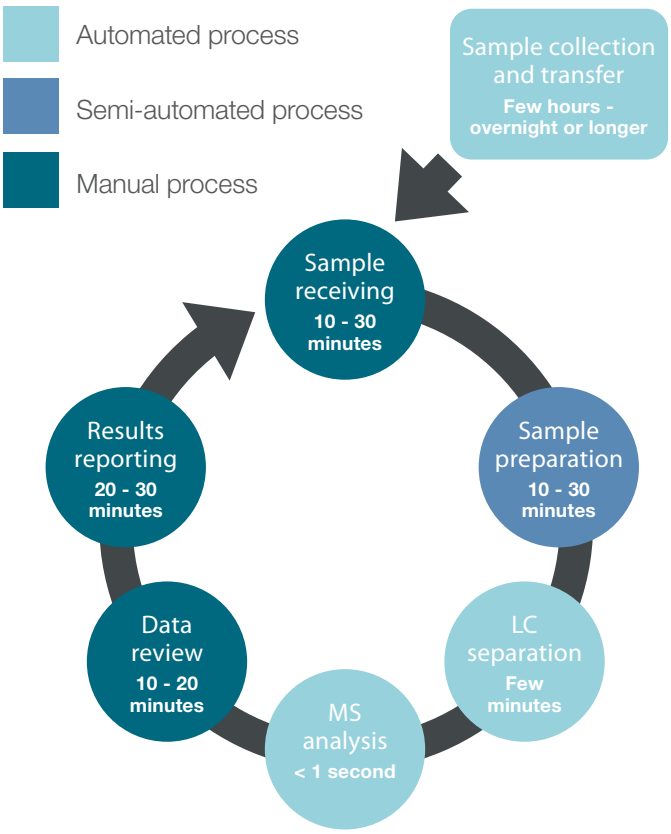
Current challenges with clinical LC-MS/MS

The lack of automated LC-MS/MS has been a bottleneck to the more widespread use of the technique, while also presenting a significant challenge to clinical laboratories under pressure to standardize and harmonize practices, streamline processes, increase productivity and decrease expenditure. The MS analysis step itself is fairly automated, however, as described by Drs Zhang and Rockwood in an authoritative paper discussing the importance of automation in clinical MS, there are numerous pain points experienced during the LC-MS/MS workflow, as many manual processes are still required (Zhang and Rockwood, 2015).

A few key points include:

- Sample acquisition involves the retrieval of samples from a central site/another part of the lab, and their subsequent identification and centrifugation (requiring decapping, aliquoting and labeling). As such, sample retrieval typically takes 10 to 30 minutes
- Sample preparation involves steps to ensure the sample is MS compatible, and the time taken for one 96-well plate to be processed is between 10 and 30 minutes
- LC separation and MS analysis are not actually the rate limiting steps, taking a few minutes for the LC phase, depending on the methods, and a fraction of a second for MS analysis
- Following analysis, results are reviewed manually and adjusted, if needed, before being transferred into the laboratory information system and reported to the electronic health record. Data review and results reporting can take another 10 to 20 minutes for one sample batch

Figure 1. The typical time taken for each step of current LC-MS/MS platform workflows. Times are based on a one-batch sample for a 96-well plate.



In addition to sample preparation is the requirement for manual preparation, aliquoting, storage and maintenance of all consumables, such as reagents, calibrators, blanks and controls. Another consideration when using LC-MS/MS is the need for careful batching and scheduling of runs for the various assays throughout the week, which may make it difficult when offering multiple shifts or a weekend testing service.

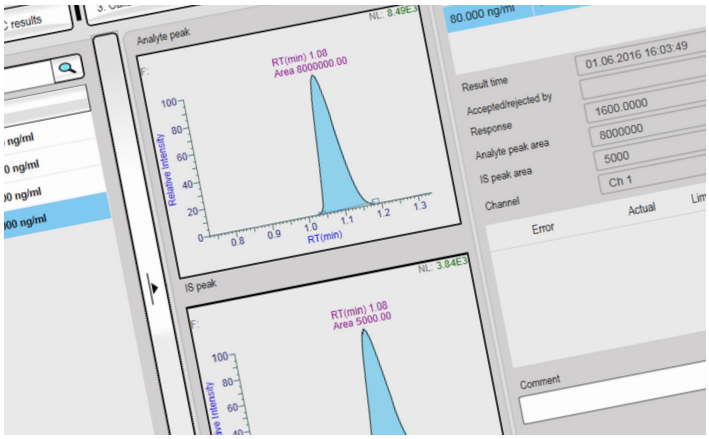
As such, current LC-MS/MS methods do not fit with the working practices of the clinical laboratory, since they are labor intensive and have limited throughput. They require a high level of personnel input and capital expense.

Focusing on just the data reporting step for 25-OH Vitamin D analysis demonstrates the extent of labor required for current LC-MS/MS applications in the clinical laboratory. This method requires two analytes to be measured: 25-OH Vitamin D2 and 25-OH Vitamin D3. For example, a laboratory that regularly analyzes 100 samples per day produces 200 results. If each result has two significant digits, when entered manually, that equates to 10 finger strokes per patient, which escalates to thousands of key strokes per day. Manual input of this scope opens a significant window for human error. To ensure quality, another person is required to validate the results entered before final reporting. This and many other critical results, such as immunosuppressant drug concentrations, can suffer from potential errors, which may lead to incorrect drug doses, treatment decisions and, in extreme cases, even death and injury. The removal of this manual process is essential to ensure quality of clinical results and patient care. Significant efforts have been made and progress achieved in this area, and yet bi-directional interfacing is still a challenge.

Likewise, the importance of reducing medical errors across the full spectrum of patient care has become a priority of many well-respected private, non-profit advisory institutions. A report from the Institute of Medicine (IOM) of the National Academies found that medical errors kill 44,000 people in US hospitals each year, meaning that more people die from medical mistakes annually than from highway accidents, breast cancer or AIDS (To Err is Human: Building a safer healthcare system).

Introducing automation, particularly a complete end-to-end solution, would inherently lead to a reduction in errors, as well as an increase in turnaround times and improvements to working risks by removing the need for repetitive motions. Not only would it increase quality and consistency, but would lead to an increase in job satisfaction and productivity by removing the need to perform highly tedious tasks.

By decreasing the time and manual efforts required to gain quality results through automation, the end reports will be generated faster and without the influence of human error, which has huge implications for patient management. Being able to confidently assess patient samples with a high degree of accuracy in the routine laboratory at a reduced turnaround time will dramatically impact laboratory workflow and patient care for a number of high value assays. It will especially benefit those assays that require more sophisticated sample preparation and involve multiple steps, streamlining those complex processes, while increasing throughputs.



What is the key barrier to LC-MS/MS adoption?

Fewer laboratories have adopted LC-MS/MS than many would have predicted, given the analytical advantages of such a system. The lack of automation is a significant factor in this and impacts on the risk of human error (from repetitive manual labor - pipetting, typing, etc), operating times and costs (managing multiple connected components), slower turnaround times for results, very high personnel education/ training requirements, and limitations on ease of use.

These challenges could effectively be met through the adoption of automated LC-MS/MS and a fully integrated solution, which would enable laboratories to provide a higher throughput of reliable results, and thus increase efficiencies related to patient care. A 2015 paper (Zhang and Rockwood) identifies automation as paramount in breaking through the bottlenecks to increase the appeal of LC-MS/MS for routine use. In addition, a recent survey of more than 100 people, conducted by the MS^3 division from AACC, identified automation as the highest-ranking hurdle to be overcome in the clinical setting (Workshop discussions from AACC/MSSS Mass Spectrometry and Separation Sciences Annual Conference in 2016). The key to overcoming this will not only be the availability of a suitable LC-MS/MS system, but a platform for communication to ensure understanding of the different challenges faced, such as protocols for validation, regulatory adherence and system operation.

LC-MS/MS automation: The road to a better future in healthcare

> "We can have the best cars in the world, and yet we cannot drive very fast without an efficient highway system. Automation to LC-MS/MS is like highways to cars. We have great technologies in LC-MS/MS. But, we need to build a streamlined system and platform to fully utilize its potential in the clinical world. Automation is the solution; it will enable us to use the great tools we already have in place to better serve patients and to take us into a brighter future of healthcare."

Automation will greatly benefit how LC-MS/MS is run, facilitating its implementation in more laboratories. A system that harnesses complete automation would remove the need for repetitive manual tasks. Laboratories not yet taking advantage of clinical LC-MS/MS would be able to access this highly accurate technology without needing to create a new team of highly skilled staff. This overcomes a significant barrier for most laboratories. For those facilities currently performing some clinical LC-MS/MS testing, automation would enable them to better manage their highly trained experts and apply their talents to the development and early implementation of newer, more esoteric, high value analytes – expanding the laboratory's overall service as a result.

Furthermore, while the capital cost of a currently available LC-MS/MS system is high, operational costs related to materials are actually low. If the volume of samples is high enough, then the economy of scale will make cost of ownership comparable to alternative diagnostic methods. With a fully integrated, automated LC-MS/MS system, the operational costs related to materials could be expected to be higher, but the additional costs required to maintain high quality, such as managing multiple manual steps and personnel education/training, would be significantly reduced.

Clinical diagnostics: A snapshot of the future

The future of clinical diagnostics is trending towards fully automated systems. Such technology will have a lower cost of ownership, produce high quality results with less manual effort and broaden the scope for the future of LC-MS/MS applications. A fully integrated, automated LC-MS/MS system will be welcomed by those laboratories not currently using LC-MS/MS methods. However, those labs already performing laboratory developed tests (LDTs) using LC-MS/MS may be more resistant to change. MS assays take a significant amount of time and expertise to develop and validate, and those laboratories that have undertaken this task and already invested in an LC-MS/MS system may be fearful of the impact automation will have on their existing tests. But, LDTs and automation are not mutually exclusive; automation will not be a limiting factor in a laboratory's ability to develop and implement LDTs. Even these facilities can benefit from automation, since it has the potential to:

- Reduce the cost associated with maintaining highly trained staff and needing them to apply themselves to the more mundane, repetitive tasks
- Enable these laboratories to process higher volumes and undertake more routine tests
- Expand their capacity for development and production of more emerging, clinically needed LDTs

> Dr Zhang explains: "LDTs play a crucial role in providing the necessary care and diagnostic tools to serve patient needs while FDA approved assays are not available. It is important for the community to know that the LDTs have been under a tight control of the federal and state regulations to ensure the quality of the results."

Within the clinical community, Dr Zhang is actively working with colleagues and key stakeholders to promote the cause and educate people via workshops, conferences, on-site training, and collaborating with the FDA, the Centers for Disease Control (CDC) and the National Institutes of Health (NIH), to improve general communication amongst academics, the healthcare industry and manufacturers.

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Conclusion

LC-MS/MS has clear benefits within clinical diagnostics, but it is not a technique that has been well adopted in these laboratories to date. We spoke to Dr Victoria Zhang, an expert in clinical MS and author of *Impact of Automation on Mass Spectrometry*, to better understand the barriers to more widespread adoption, and what the industry needs to be able to break down these road blocks. The key issue has been identified as a lack of automation, with currently available LC-MS/MS technology requiring expert operation, and the investment of significant time to ensure compatibility with sample preparation processes and data review and reporting systems. A fully integrated, automated system would alleviate these pain points, enabling clinicians to benefit from quality results at high throughputs, while reducing the need to hire experts and perform repetitive manual tasks. The impact of such a system would benefit the laboratory, helping it to meet its clinical needs by providing faster turnaround times at a lower cost of ownership, while also providing clear benefits in terms of patient care by quickly delivering quality results.

Thermo Fisher Scientific has listened to customers and is addressing the needs of clinical laboratories through the development of the Thermo Scientific™ Cascadion™ SM Clinical Analyzer. This dedicated clinical LC-MS/MS analyzer is accurate, easy-to-use and designed for the clinical laboratory. As a fully integrated system, the Cascadion analyzer will allow clinical laboratories to fully leverage the power of LC-MS/MS technology.

This product is IVD/CE-marked. Product is not 510(k) cleared and not yet available for sale in the U.S.

References

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2. Kohn LT *et al*. To Err is Human: Building a safer healthcare system. Institute of Medicine (US) Committee on Quality of Health Care in America. *National Academies Press (US)* (2000).

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