Easy-to-use, fully automated LC-MS/MS technology

Driving clinical testing forward

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) technology is a very powerful analytical tool, offering high accuracy, precision, sensitivity and specificity. The technology has the potential to transform clinical testing, but it has not yet been widely adopted in clinical laboratories. So why is this? To find out, we spoke to LC-MS/MS expert Dr. Judy Stone to ask her opinion on the growing role of LC-MS/MS technology in the clinical laboratory, why it is not more accessible, and how an easy-to-use, fully automated system may help to overcome these challenges.

Clinical laboratory professional scanning solvents on the Thermo Scientific Cascadion SM Clinical Analyzer for specialty diagnostics

LC-MS/MS: Its future in clinical testing

LC-MS/MS technology is broadly recognized as the 'gold-standard' analytical tool for much clinical chemistry testing. The principle is based on isolating and directly quantitating a target molecule using the mass of the molecule and an electrical charge added to it through an ionization process.

Capable of generating reproducible and reliable results with high accuracy and precision, LC-MS/MS technology is likely to supplant current clinical testing tools, such as immunoassays, for some analytes. However, it is not yet widely adopted, mainly due to the complexity of the methodology and use of differing standards between laboratories. A standardized automated system could further the use of LC-MS/MS technology in clinical testing, directly benefiting laboratories in terms of accuracy, reliability and speed of test results.

Recent improvements in instrumentation have the potential to overcome current challenges. Thermo Fisher Scientific has developed the Thermo Scientific™ Cascadion™ SM Clinical Analyzer for specialty diagnostics*, a fully automated LC-MS/MS analyzer designed for ease-of-use in the clinical laboratory. We asked Dr. Stone about the challenges to introducing LC-MS/MS technology in clinical laboratories and whether the new Cascadion system could overcome them.

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Dr. Judy Stone, trainer for MSACL and LC-MS/MS expert

About Dr. Judy Stone
Dr. Stone is a trainer for Mass Spectrometry Applications to the Clinical Laboratory (MSACL) and is a recognized expert in the field of LC-MS/MS technology, having extensive familiarity with the maintenance and troubleshooting of clinical LC-MS/MS systems. Her professional experience spans a variety of clinical laboratory environments, including automated routine laboratories – hospital laboratories of various sizes and a high volume commercial reference laboratory – as well as clinical LC-MS/MS specialty laboratories. Given her expertise in this field, she deeply understands the challenges of implementing LC-MS/MS technology in a clinical setting. In addition, Dr. Stone participated in the Thermo Fisher Scientific Cascadion Key Operator Training Program, gaining an in depth understanding of the analyzer's features and experiencing the system first hand.

The growing need for LC-MS/MS technology in clinical laboratories

Dr. Stone identifies typical situations where LC-MS/MS technology provides a direct practical advantage over immunoassays:
"Sometimes commercial immunoassays are not available for certain analytes, and for some assays, reagents can be particularly expensive. LC-MS/MS technology is also more reliable for distinguishing between lower molecular weight compounds with similar structures – such as within the steroid hormone family or between drugs and their metabolites."

While the clinical use of LC-MS/MS technology is growing, most laboratories still rely on immunoassay-based methods. However, it is widely accepted that LC-MS/MS technology offers significant advantages over most immunoassays in terms of the accuracy of results. For example, the specificity of immunoassays is generally lower than that of LC-MS/MS technology, and cross-reactivity issues may compromise an immunoassay result. Immunoassays may also be less sensitive than LC-MS/MS. In combination, these factors can limit the utility for particular patient populations and lead to poor agreement between different immunoassays for the same analyte on the same patient sample. The variations among patients and between laboratories makes possible false positive or false negative results for patients, and also creates difficulties in patient follow-up over time.

With its enhanced reliability, specificity and sensitivity over the current norm, and with the technology generally lending itself to more rapid development of new assays as well as the measurement of multiple analytes simultaneously, it would be expected that LC-MS/MS technology would be more widely adopted. However, practical difficulties pose barriers to common use.

Challenges to introducing LC-MS/MS technology: The limitations of conventional systems

Dr. Stone explains the reasons why conventional LC-MS/MS software as well as hardware requires specialists for manual operation:

"These instruments have been designed for use in the research laboratory, where it is an advantage to offer a high level of flexibility, allowing each research team to customize their set-up to meet their specific needs. However, this flexible design is less appropriate for a clinical setting where the focus must be on standardization and reliability."

The main barrier to introducing LC-MS/MS technology to the clinical laboratory has been how difficult it is to use compared to automated clinical chemistry and immunoassay systems. The most significant issue is usually the amount of time and training that is needed for operators to become competent with this specialist technology, which deters laboratories from implementing these systems. Likewise, for laboratories currently using LC-MS/MS technology, expanding its use for assays they would wish to add may be hampered by the limited

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number of technologists with LC-MS/MS competency. Until now, all available LC-MS/MS systems have involved complex workflows with intensively manual sample and information handling. While the time required to perform LC and MS analyses is only a few minutes, there are multiple labor- and time-intensive manual steps, as well as expertise, required for traditional sample preparation and data analysis.

The LC-MS/MS instrument processing itself is sequential, so laboratories need to spend time optimizing batches and scheduling runs, which limits the overall throughput and delays time to reportable results. Additionally, batched LC-MS/MS workflows require significant investment of time and money for calibration and running of controls with each batch. Overall, the batch approach slows turn-around times, with implications for the patient.

Furthermore, the multiple, manual, repetitive processes that current LC-MS/MS systems require introduces the potential for human error. Thus, additional checks and quality assurance protocols are necessary to guarantee the reproducibility of results.

Given these issues, the power and potential of LC-MS/MS technology remains underutilized in clinical testing as the complex manual workflows are difficult to perform and complicate standardization. To address this need, Thermo Fisher Scientific has developed the fully automated, easy-to-use Cascadion system which is specifically designed to unleash the full potential of LC- MS/MS technology within clinical laboratories.

The new Thermo Scientific Cascadion SM Clinical Analyzer

Clinical laboratory professional programing a test run on the Thermo Scientific Cascadion SM Clinical Analyzer for specialty diagnostics

Rapid and easy implementation

For Dr. Stone, the ease of introducing the Cascadion system to the clinical laboratory is a major advantage:

"No big instrument is simple but, in practical terms, the process of implementing the Cascadion system is quite quick and easy. Training for key operators is provided by Thermo Fisher, and then the key operators can train others in the laboratory. This training is of a similar nature and duration as for automated immunoassay analyzers, so there is no need to set aside additional time, and staff should find it easy to develop familiarity with the system."

When deciding whether to introduce a new platform to the clinical laboratory, the first step to consider is the effort and time needed for implementation. A key feature of the Cascadion system is that it is IVD/CE marked as a whole system, including the analyzer and the first assay available – the 25-Hydroxy Vitamin D assay. This means there is no need to invest time or resources into developing assays and meeting the high regulatory standards for validating laboratory-developed tests (LDT). Dr. Stone explains why this feature of the Cascadion system is so important for many clinical laboratories:

"Significant expertise and effort is required for laboratories to validate and maintain an LDT. Labs need to hire people who are able to tinker and frequently work through issues. Laboratory personnel with this type of capability are scarce, and for many laboratories it can be difficult to invest in this sort of continuous activity."

Evidence of ease-of-use from recent beta-trial data

To test how easy it is to integrate the Cascadion system into a clinical laboratory, a beta-trial was carried out at Frimley Park Hospital (Camberley, UK), in a facility where staff had no prior experience with LC-MS/MS technology. The results were encouraging: the team could easily operate the Cascadion analyzer after only five days of training, and the system was well-accepted, with staff reporting that it *"felt just like using a routine immunoassay analyzer."*

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The speed of implementation is another important consideration in terms of operational efficiency. With conventional LC-MS/MS systems, assay implementation from initial development to go-live can take up to 18 months (with a median timeframe of around 6 months). Compared to these platforms, the Cascadion system enables a 70% reduction in the total time required to invest in implementing ready-made assays to routine clinical testing applications.

Read our white paper, titled "Is LC-MS/MS assay development restricting your clinical testing services?" for an expert insight into how the Cascadion system uses complete pre-validated assay kits to accelerate assay implementation of LC-MS/MS technology in clinical laboratories.

The power of automation

Dr. Stone emphasizes the benefits of automation in terms of saving time and improving the accuracy of results:

"Fully automating the process of sample preparation cuts out the need for repetitive manual tasks, which reduces the potential for error and increases confidence in results. For example, technologists will be less likely to mis-identify patient samples which, for the situations that are known, does tend to occur several times a year for conventional LC-MS/MS systems and becomes more likely at higher test volumes. Also, streamlining workflows leads to a significant time saving, which helps free up laboratory resources and also provides a shorter turnaround time to drive more timely clinical decisions."

Given the practical difficulties with the complex manual workflows of conventional LC-MS/MS analyzers, the fully automated Cascadion system offers a major advantage: being as easy to use as an automated immunoassay analyzer and able to be operated by any medical laboratory professional. This means laboratories can be more flexible about staff scheduling, as there is no need for highly trained staff to operate and maintain the system. The minimal user input required also enables laboratories to expand their services by running samples overnight or during the weekend, improving time to first results and turn-around times.

Routine usability and easy maintenance

Dr. Stone highlights the operational benefit of the Cascadion system:

"The software is easy to navigate and is designed with the needs of the clinical laboratory in mind. For example, in contrast to conventional LC-MS/MS systems, the Cascadion system does not require:

1. *Batching – samples can be loaded without waiting for the previous cycle to complete.*
2. *Workflow interruptions – mobile phases can also be added on the fly.*
3. *Manual offline management of tasks – software reminders about tasks and updates make daily operation easier in the busy environment of the clinical laboratory."*

When introducing a new technology into a clinical laboratory, the process is much smoother if the system does not require extensive training. Conventional LC-MS/MS systems will be generally unfamiliar to staff in a clinical setting. Training for quantitative LC-MS/MS is not included or is covered only briefly in programs for clinical laboratory scientists and may or may not be addressed in clinical chemistry fellowship and pathology residency programs.[1]

Evidence of ease-of-use from recent beta-trial data

The ease-of-use related to running and maintaining the Cascadion system in the clinical laboratory was also tested at the Frimley Park Hospital (Camberley, UK) beta-trial site. Laboratory professionals particularly appreciated that system maintenance took only 10 minutes in the morning, consumables could be changed while the instrument was running, and the system was *"exceptionally easy to use."* One participant summed up their experience by describing the Cascadion system as *"the simplest analyzer I have used in my career as a biomedical scientist."*

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The Cascadion system is designed to minimize maintenance and possible delays to the start of patient testing during a shift in the clinical laboratory. Maintenance checks can be scheduled off-hours so that they do not interfere with laboratory throughput. Meanwhile, the daily start-up procedure takes only 20-30 minutes and can be programmed to start just before working hours. This improvement is significant: with conventional LC-MS/MS systems there is usually a requirement to run system suitability testing prior to each run, which can take 1-2 hours, impacting the number of tests that can be run per day.

The ease of troubleshooting is another major advantage. Dr. Stone explains:

"Traditional LC-MS/MS systems require specialist expertise to identify and correct problems, which can happen pretty often and cause delays in the workflow. In contrast, the Cascadion system's software actively monitors performance and uses alarms to flag issues as they arise. The alerts are easy to understand and color-coded, and provide descriptions on how to resolve the problem. This helps non-expert operators feel confident with using and troubleshooting the system."

All these features ensure that operation and maintenance of the Cascadion system are simple and easy. Importantly, the system is well suited to the clinical laboratory, as it is similar to other automated clinical analyzers – specialist knowledge of LC-MS/MS technology is not required.

The benefits of standardization

Standardization is of key importance in clinical testing. For clinicians to monitor individual patients, it is crucial that test results can be compared over time. As a fully integrated and automated solution, the Cascadion system is designed to facilitate standardization. If used in a network of laboratories, the results would be comparable between different locations, which is particularly useful when patients are transferred between hospitals.

Conclusion

The widespread adoption of LC-MS/MS technology could dramatically improve the accuracy and speed of clinical chemistry testing. The major barriers to its introduction have been ease-of-use and lack of standardization, both of which are addressed by the Cascadion system for specialty diagnostics. This new solution combines the ease-of-use of automated immunoassay analyzers with the accuracy, sensitivity and specificity of LC-MS/MS technology.

Dr. Stone describes how the Cascadion system could transform the future of clinical testing:

"With its exceptional ease-of-use, the Cascadion system has great potential to accelerate the use of LC-MS/MS in clinical testing. This new system could allow automated, standardized LC-MS/MS to become commonplace in clinical laboratories."

The Cascadion system could allow laboratories without LC-MS/MS technology to expand their services, and enable those already using the technology to consolidate their resources – if highly trained staff are already employed in running traditional LC-MS/MS systems, introducing the Cascadion system could free up these professionals to expand their laboratory's services by developing new high value analyses. Introducing this new LC-MS/MS system into the clinical laboratory could ultimately increase confidence in results, reduce the need for re-testing and allow for better patient monitoring over time.

References

1. Judith A. Stone, Robert Fitzgerald, Liquid Chromatography-Mass Spectrometry Education for Clinical Laboratory Scientists, Clin Lab Med, Vo. 38, Issue 3, Sept. 2018, PP. 527-537

Find out more at **thermofisher.com/cascadion**

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