

Adoption of high content screening at HTS laboratories

Over the past five years, a majority of HTS laboratories have adopted high content screening (HCS) in their operations. As HTS laboratories have sought more biologically-relevant assays, cell-based assays and high content screening technologies have become more widespread.

HighTech Business Decisions' latest report, (High Content Screening 2013: Expanded Use and Improved Technologies), shows the adoption rate of HCS has increased over the past five years. In 2012, 61% of the HTS laboratories incorporated HCS in their operations, compared to 40% in 2007 (Figure 1). Improvements in throughputs, system capabilities, data handling and analysis have to increase the adoption of HCS. While barriers to adoption remain (eg, costs, throughput, etc), both HTS laboratories and their suppliers continue to dedicate resources to improve HCS technologies.

While HCS adoption has increased over the past five years, its rate of adoption has not been uniform across the various types of organisations that operate HTS laboratories. In order to obtain a better understanding of the adoption of HCS technologies by HTS laboratories, we have segmented the HTS laboratories into three different categories based on the type of organisation to which they belong. For our analysis, the HTS laboratories are categorised into three segments: a) academic or government-sponsored laboratory, b) pharmaceutical and biotechnology companies, and c) contract research organisations. We define academic HTS laboratories as those that operate under either a university or a government entity. Pharmaceutical

and biotechnology HTS laboratories belong to innovative drug companies developing therapeutics or diagnostics. The third segment includes contract research organisations (CRO) that provide fee-for-service screening to clients.

From our study, more than three-quarters of the academic laboratories have adopted HCS technologies, while slightly over half of the pharma/biotech HTS laboratories use HCS technologies in their high throughput screening operations. While a majority of academic and pharma/biotech has adopted some HCS technologies, a minority of contract research organisations uses HCS technologies. From our study, approximately one-quarter of the contract research organisations use HCS technologies in their laboratories (Figure 2).

HCS activities in HTS operations

For the HTS laboratories that have adopted HCS technologies, slightly less than half of those HTS laboratories use HCS in multiple areas of drug discovery (Figure 3). Most HTS laboratories run high content screens for secondary screens or hit validation (84%), while 48% of the HTS laboratories use HCS for primary screening. Other areas where HCS is used include lead optimisation, compound profiling and toxicity studies (Figure 4).

By William Downey
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Screening

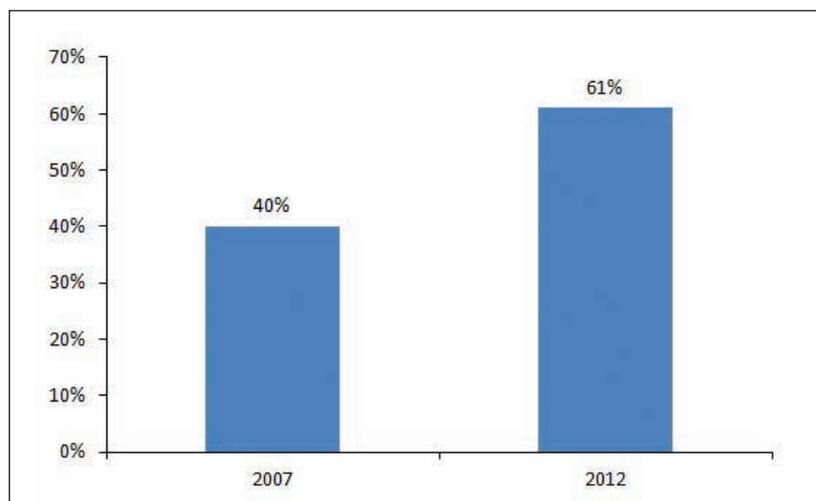


Figure 1: Proportion of HTS laboratories using HCS technologies

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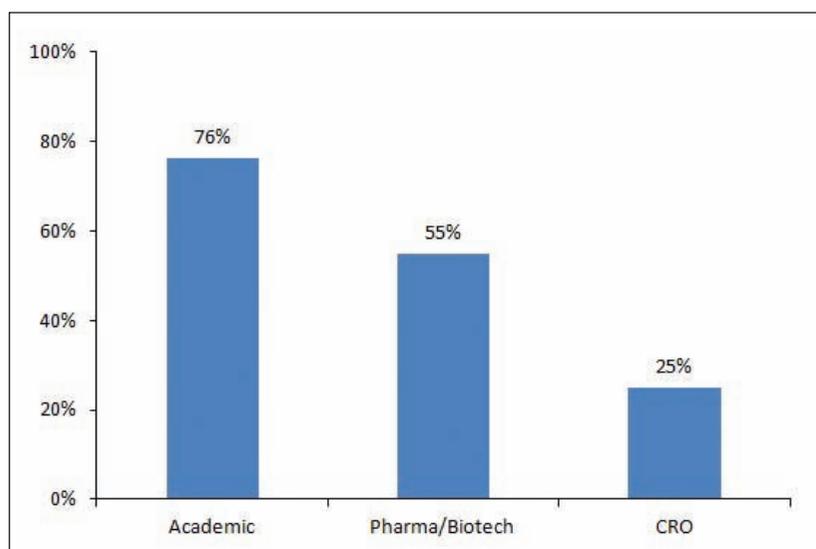


Figure 2: HCS adoption by segment

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For those HTS laboratories using HCS, there has been an increase use of HCS in both primary and secondary screening over the past five years (Figure 5). The proportion of HTS laboratories using HCS technologies for both their secondary and primary screens has increased considerably over the past five years. In 2012, 84% of the HTS laboratories used HCS for secondary screening, compared to 53% in 2007. Similarly, 48% of the HTS laboratories used HCS for primary screening activities in 2012, compared to 27% in 2007.

Below are selected comments from directors at leading HTS laboratories regarding the use of HCS in their operations.

“We use HCS more in the hit validation stage when we want to look at what the compound is doing in more detail. It comprises about 10% of our screening at the moment with secondary and ADME-Tox screening the bulk of the effort. We have all the technology we need and I anticipate we will use HCS more as phenotypic screening increases.”

Pharma/Biotech HTS Lab

“We use HCS in a number of different ways. We have to be careful because it is such a commitment to assay development and image analysis. We don't want to use HCS if we can use something else instead. We use it for follow up of morphology types of assays. They are sensitive for measuring activity in primary and iPS cells. Imaging is a good readout for neuronal cells and T-cells. We use HCS for lead optimisation, follow-up and primary screens of targeted libraries, for example, repurposing FDA-approved drugs. It is not so good for looking for new chemistry. But, is it worth it? The trend in pharma is HCS seems to be going down a little. It needs to be used for the right indication. In the future, what needs to happen is the equipment needs to get cheaper so that it can inundate government and university biology labs so more and better assays can be developed. Then we will finally see more penetration of HCS in drug discovery. We need the biologists to explore this type of capability in disease-relevant cells with better software and processing power.”

Academic AS

“We have used HCS for primary screens as well as secondary assays and for cytotoxicity studies to characterise our library. In the next five to 10 years, we will increase the number of phenotypic assays we do. We are interested in collecting data on a per cell basis and measuring multiple parameters.”

Academic HTS Lab

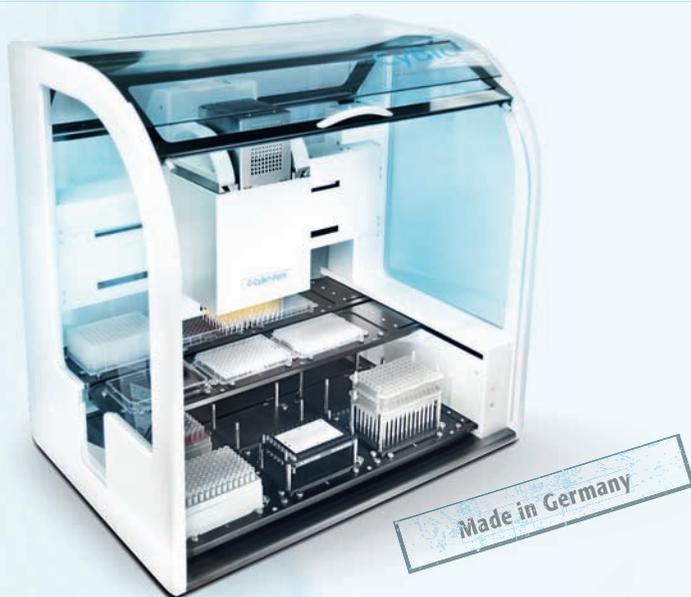
“We only use HCS for secondary assays. Sometimes HCS is the only real readout we can use, we did not have any other method to assay the target. We also use it for different projects outside screening, for example, we will use the microscope to see if we are staining the cells properly.”

Pharma/Biotech HTS Lab

While there is an increase use of HCS, several HTS laboratory directors see barriers to its continued adoption. Most of the barriers associated with the adoption of HCS relate to the costs and benefits of HCS compared to traditional screening technologies. As noted by one HTS Director: “We use

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other options first. High content is only used for secondary screens to show the compound does what it should do in the cell. HCS is important in target discovery. We have just started to use it for some primary screening but it is hard to judge the benefit as of yet. We use HCS to have additional approaches, additional to the target-based approach. We were recently considering acquiring additional capabilities but we made a strategic decision to use what we have, so now if we want a different approach to a target, HCS is the way we will handle it.”

Overcoming barriers

In HighTech Business Decisions’ study, the HTS directors discussed the steps they or their suppliers have taken to overcome the barriers to adopting HCS. Most HTS directors noted improvements in both software and hardware. On the software side, most HTS directors have seen improvements in both data management and analytical methods. On the hardware side, the HTS directors note major improvements in the usability of the equipment and higher screening throughputs. A summary of the steps taken to overcome the barriers to adopting HCS is shown in Table 1.

The industry continues to demand improvements in HCS, and suppliers are working to provide new tools that will further reduce the barriers to adoption of HCS for drug discovery. These improvements encompass equipment, data management and consumables.

For example, Molecular Devices introduced the ImageXpress® Micro XL Widefield System. This new instrument is equipped with a sCMOS camera offering three times the image capture area. “The increase in field-of-view translates to fewer images needed per well and faster imaging speed, said Dr Grischa Chandy, Product Manager, Cellular Imaging at Molecular Devices. “In addition, the system provides a stable solid-state light source plus environmental control and fluidics options, delivering a robust platform that meets the high throughput demands of a screening laboratory.”

Similarly, Thermo Fisher Scientific is looking at new technologies in hardware, software and in informatics which address the coming trends and current bottlenecks in HCS. “We are looking at how to make software more automated and easier to use, but maintain the flexibility and power that High Content can provide,” said Scott Keefer, Manager, Product Management, Cellular Imaging Analysis at Thermo Fisher Scientific. “We are also focused on providing the

most robust and scalable platforms so screening facilities are more productive. The CellInsight NXT provides throughput, assay breadth and the robustness necessary to bring High Content more into primary screening facilities. These tools are all connected by BioInformatics tools that enable users to make decisions about their compounds more rapidly and in the context of other assay data.”

As previously noted, a major barrier to the adoption of HCS technologies has been the management of data and that data management, which has been a major constraint in screening operations. “Historically, analysis and management of HCS images and the resulting data has been the domain of software packages attached to the high content imagers,” said Dr Stephan Heyse, Head of Genedata Screener® Business Unit. “However, such data analysis software bundled with HCS instruments was not designed for higher throughput – it did not keep pace with instrumentation output from automated assays. Additionally, it was not designed to integrate with, for example, other HCS instruments, other image analysis packages, or with corporate screening analysis workflows and data management systems. This created an HCS analysis and data management bottleneck. To address these issues, Genedata Screener® was designed. In 2012, we added support for direct analysis of cell population data as part of the screening data analysis, which enables scientists to interactively define and analyse cell populations for complete screening experiments, which I believe to be an industry first.”

Molecular Devices has also introduced new tools for data management. “On the software front, Molecular Devices launched MetaXpress® Software 5.0 in summer 2012,” said Dr Chandy. “This latest release empowers users to create complex analysis using the Custom Module Editor. The new interface guides users through a step-by-step creation of custom analysis, such as identifying objects within objects, creating morphometric classifiers for shape analysis and analysing transmitted light images. Users can specify which responses to detect and which measurements to report out, saving unnecessary analysis time.”

Other improvements being made in data handling comes from De Novo Software which has released FCS Express™ Flow and Image Cytometry software package with the option for a High Content Analysis add-on. “The HCS add-on allows high content customers to quickly analyse and make sense of their flow and image cytometry

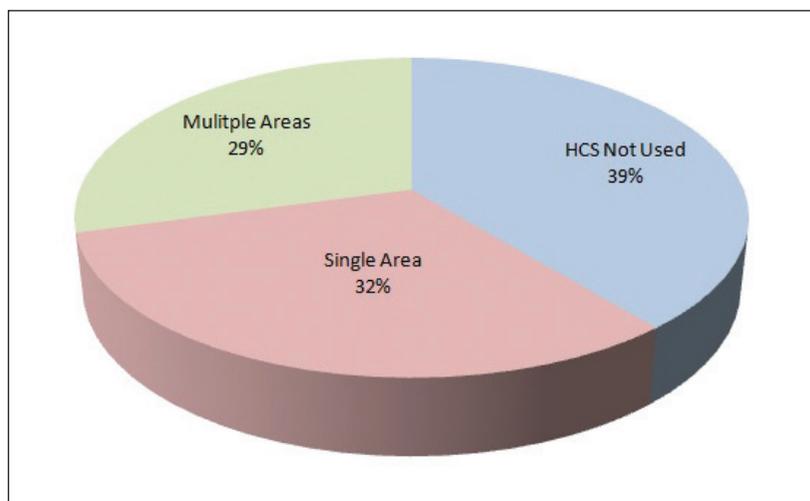


Figure 3: Adoption of HCS
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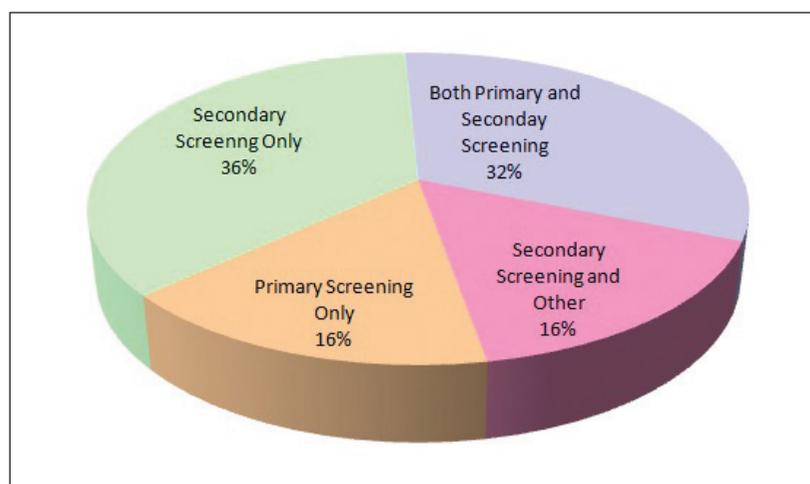


Figure 4: Application of HCS
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data while easily allowing the creation of high quality exports to PowerPoint, Excel and other lab information systems,” said Sean Burke, Product Manager at De Novo Software. “With FCS Express Plus, customers have the added benefit of combining HCS Flow and Image Cytometry analysis in one seamless package.” De Novo Software has also been working with industry leaders such as PerkinElmer, Molecular Devices and Thermo Fisher to provide direct compatibility of imaging data generated by their high content screening devices with FCS Express.

Suppliers are also making improvements in consumables and reagents. For example, Corning has developed microplates that improve HCS imaging and throughput. “At Corning, we continuously

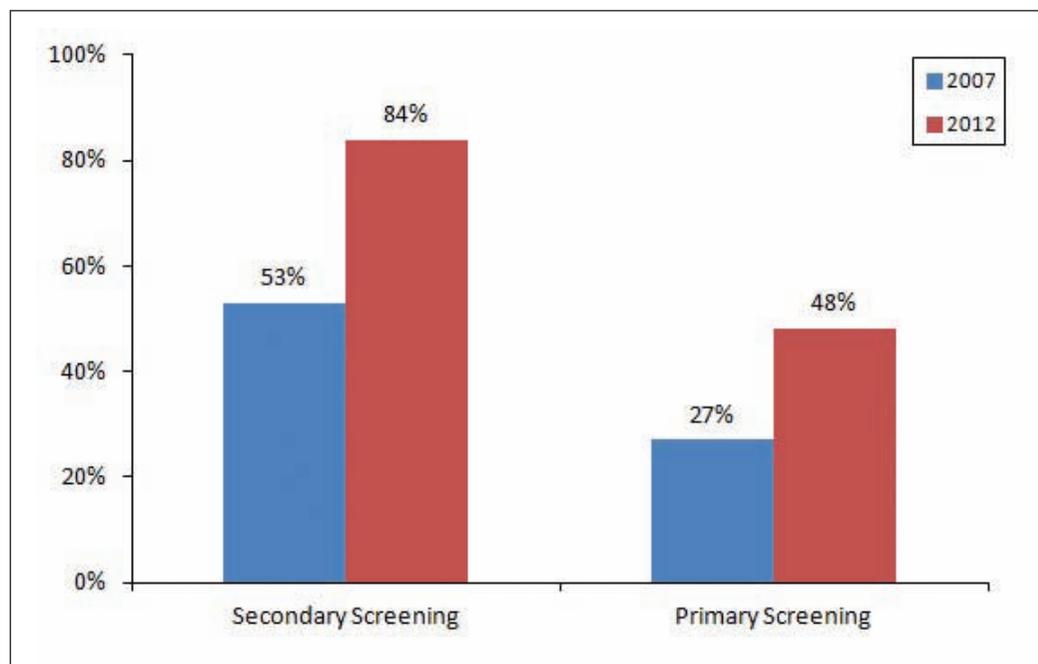


Figure 5: Proportion of HTS laboratories using HCS for primary and secondary screens
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strive towards improving efficiencies and developing new products and technologies for life science researchers,” said Dr Todd Upton, Commercial Technology Manager, Corning Life Sciences. “We have developed and launched two glass bottom microplates (half area 96 well and 384 well) especially designed for HCS applications. The high optical-quality and scratch resistant glass bottom microplates are ideal for performing high-content assays using imaging systems. The glass bottom flatness of <math><50\mu\text{m}</math> ensures planarity for imaging devices, reduces autofocus time and increases throughput. We are now gearing up for a summer 2013 launch of superior quality COC (Cyclic Olefin Copolymer) film-bottom microplates to complement the glass bottom HCS microplate product line. Both glass and COC bottom offer unique advantages of low auto-fluorescence and low diffusion of fluorescent detection; therefore, leading to high signals and low background. These attributes are particularly advantageous in enabling assays that typically have low emission intensity, therefore, expanding the applicability of high content imaging.”

There has also been improvements in the development of reagents for use in HCS. “We have consistently validated new reagents on at least one high-content platform. Examples include CellRox (oxidative stress) and CellEvent (apoptosis). We have also generated data supporting the utility of

established reagents in a high-content setting, for instance Alexa Fluor® labelled phalloidin actin markers,” said Dr Magnus Persmark, Senior Product Manager, Imaging, at Life Technologies.

Future use of HCS

The use of HCS will continue to increase. Forty-four percent of the HTS Directors in our study expect to increase their use of HCS at their laboratories. For HTS laboratories that do not currently use HCS, one-third of the HTS Directors surveyed in our study expect to add HCS in the coming years. Furthermore, the HTS Directors, on average, plan a 13% increase in the number of wells read per week over the next two years. In addition, there continues to be interest in using HCS for primary screens. Selected comments regarding adoption of HCS, as provided by HTS directors surveyed are shown below:

“We don’t have HCS yet, but we are investigating it seriously. We plan to bring in a system within six to 18 months.”

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“We are just starting to be interested in HCS, but have not yet run a screen. We will use HCS as a follow-up to a secondary assay. We will start running HCS primary screens within six months.”

Pharma/Biotech HTS Lab

Table 1: Steps taken to overcome barriers to adopting HCS

STEPS TAKEN	NUMBER OF MENTIONS
Improved data management and storage, IT infrastructure	10
Purchased mature, proven, user-friendly equipment	8
Improved ways to analyse data	6
Improved speed of microscopes	3
Automated process	2
Developing better dyes, kits	2
Considering laser-based instruments to improve throughput	1
Expand instrumentations at high- and low-end	1
Miniaturised to 1536-well to improve speed to read a plate	1
Pooling compounds to increase throughput	1
Relying on external partners	1
No improvements	3

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“We utilise HCS only in secondary screening after primary screening, but as technology improves, costs decrease, and throughput increases, we anticipate moving HCS more to a primary screening mode.”

Pharma/Biotech HTS Lab

tomor loyalty studies for suppliers serving the pharmaceutical and biotechnology industries. The company recently published the report High Content Screening 2013: Expanded Use and Improved Technologies. www.hightechdecisions.com.

“We use HCS in early screening programmes, lead discovery, or hit identification, as just one technology, in addition to other technologies. We anticipate we will expand the amount of HCS in future. Clearly, if we run more phenotypic screens, we will need to run more HCS.”

Pharma/Biotech HTS Lab

Conclusions

The majority of HTS laboratories have adopted HCS technologies into their laboratory operations. HCS is primarily being used in secondary screening operations, but there continues to be a trend toward its use in primary screening. Over the past five years, both HTS laboratories and their suppliers have worked to reduce these barriers to adoption. Yet, for many HTS Directors, there continues to be significant barriers for its continued adoption. Those barriers include costs, the current state of analytical software and data management, throughputs and the quality of antibodies and labels. Despite these barriers, HCS will continue to grow as the number of HTS laboratories continue to adopt HCS technologies and expand its use. **DDW**

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