



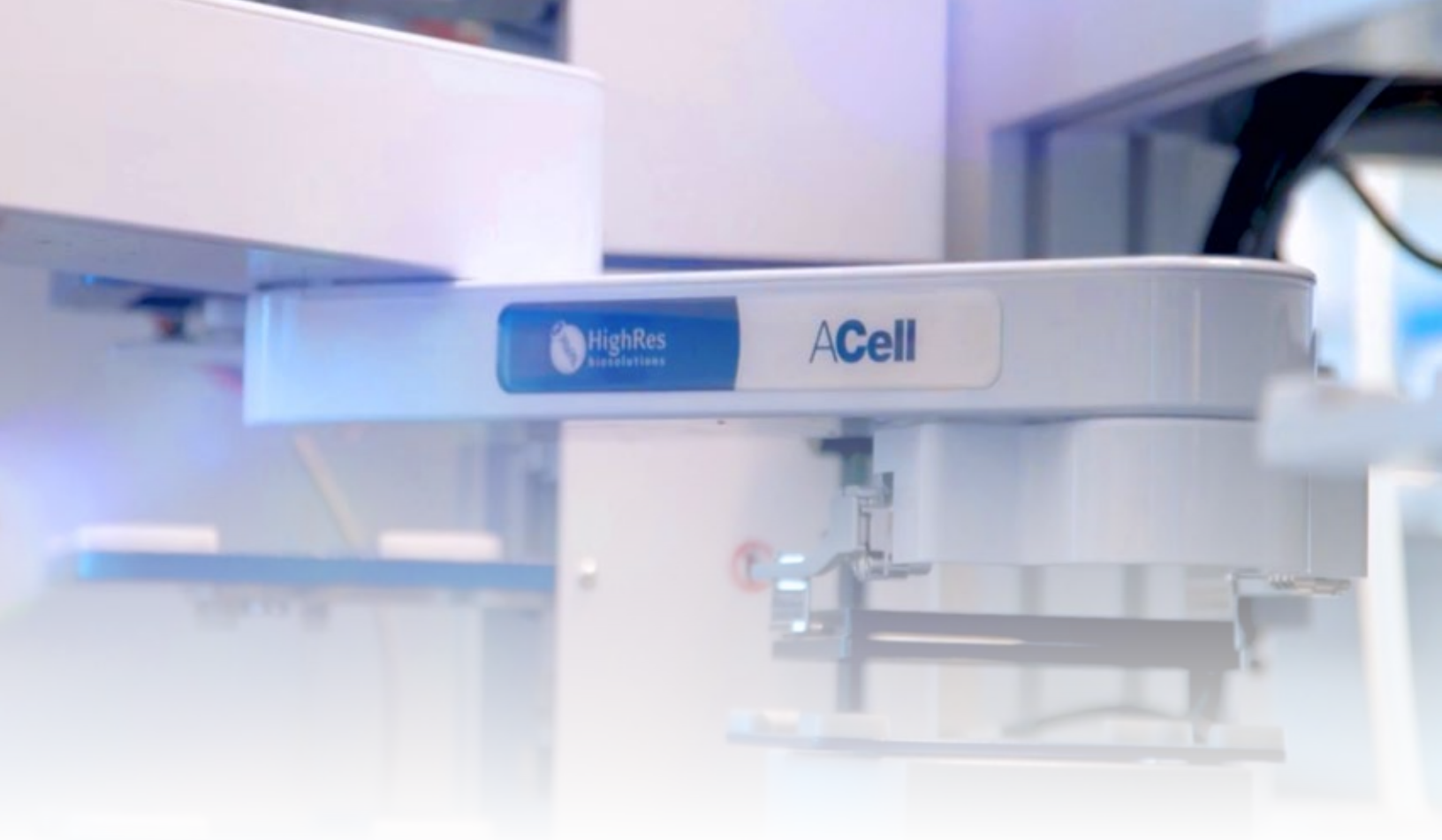
## Customer Journey

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Flexible Automated Lab Design  
for Integrated Drug Discovery





# SYGNATURE DISCOVERY

## Overview

Sygnature Discovery is a world leading contract research organization (CRO) based in the UK, that provides drug discovery and other services ranging from target validation through lead optimization and candidate selection. The Sygnature Discovery high-throughput screening (HTS) program involves developing customer assays as well as testing compound screening libraries against customer assays to determine whether compound lead candidates can be identified. When Sygnature Discovery decided to expand the scope and quality of its services by establishing HTS capabilities in-house, they partnered with HighRes® Biosolutions to create an automated solution that would enable them to adapt and readapt to the changing landscapes of customer need and scientific inquiry.

## Identifying Project Requirements

The screening business at Sygnature Discovery includes both cell-based and biochemical assays, so flexibility in automation was key to project success. The goal was to create an automated HTS workflow to assay many library compounds quickly, reliably, and reproducibly with a minimum of hands-on time, and to monitor processes and correct issues remotely whenever possible. High-precision liquid handling for assay plate preparation was also a critical requirement.

Other key elements of the project included sourcing software for laboratory information management (LIMS) and screening data analysis. A LIMS software interface was needed so that library source plates could be managed, and compound libraries organized for screening campaigns, especially when performing hit compound cherry-picking and associated dose-response assays in an automated fashion. Likewise, data analysis software was required to maximize error-free data handling through seamless integration with other system components, provide intuitive results processing tools, and enable rapid identification of hit compounds.

It was vital that the integration development time for this project be minimized to reduce production disruptions so that delivery lead times to Sygnature Discovery customers stayed on track.

*“When we were starting to design this project, I liked the idea of the whole solution [coming from] industry-leading suppliers used by all of big pharma and our competitors as well. I wanted an established solution for this project.”*

**Denise Swift**  
Senior Principal Scientist,  
HTS Group Leader



## Establishing Industry Partnerships

Sygnature Discovery chose to combine the strengths of HighRes Biosolutions, Titian and Genedata, because each of these industry-leaders have experience working together and could amply meet project expectations.



HighRes Biosolutions was selected to provide the automated robotic hardware powered by Cellario™.



Titian Software, Ltd. was selected to provide Mosaic SampleBank for LIMS and sample management.



Genedata AG was selected to provide Screener software for analyzing and visualizing data.

## The Automated Robotic System

The HighRes Work Cell that was configured for this application leveraged the strengths of HighRes Biosolutions by creating a data factory that connected instrumentation with informatics with a focus on modular components to adapt and readapt to changing scientific, technological, or organizational needs. It included a benchtop affixed ACell robotic arm and a Beckman Coulter Echo® acoustic dispenser as shown in Figure 1. This modular and expandable system can run both cell-based and biochemical assays as well as meeting future needs. Cellario™ software, also by HighRes Biosolutions, enables dynamic scheduling of different types of screening assays as well as adaption to different user requirements for hardware at any given time.

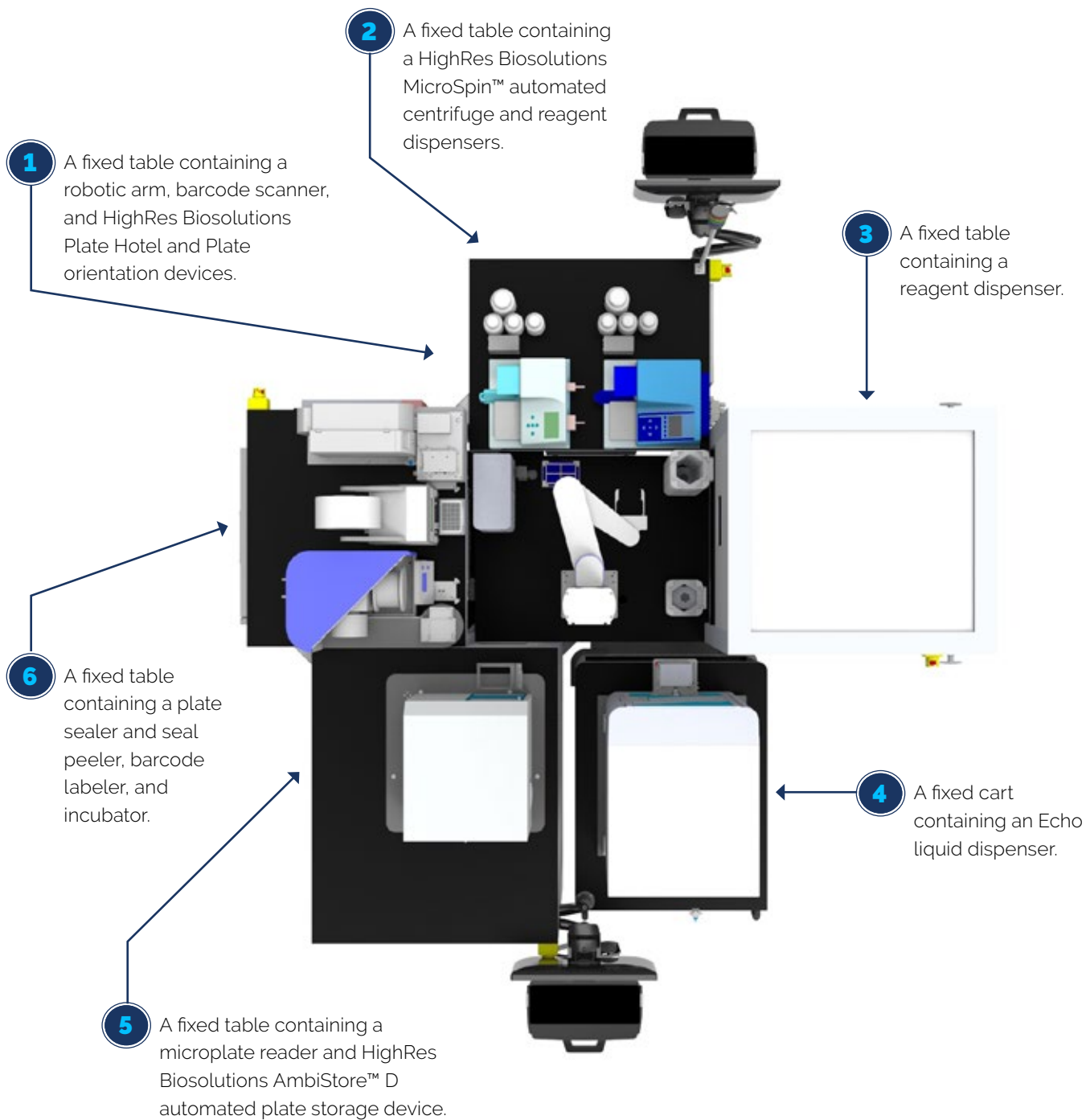
The Sygnature HTS system also includes existing proprietary LeadFinder screening compound library plate sets which are held in environmentally controlled manual stores manufactured by BigNeat, Ltd. This store houses stackers that are used on the HighRes Biosolutions automated Work Cell to ensure minimal human intervention in operations such as plate sorting.

*"We decided to build our own HTS capability after feedback from our customers, especially around compound quality in many historical screening libraries. Having the capability housed within our UK labs, where it can be integrated with our other hit-finding functions, [brings] an enormous amount of additional value to our customers and their drug discovery projects."*

### Colin Sambrook Smith

*Director of Computational Sciences  
& Informatics Sygnature Discovery*

**Figure 1:** The Anatomy of the Sygnature Discovery Work Cell





## The Sample Management System

Mosaic SampleBank software from Titian was chosen to provide seamless inventory tracking, sample ordering and workflow management in one simple package. Mosaic software is well established for compound management and is increasingly being used in screening environments for removing error during the development of assays and in project-driven testing, especially those with wide dilution ranges and multiple reagent types.

SampleBank seamlessly integrated into the HighRes Work Cell, providing real-time data exchange so that assay plate preparations could be scheduled from compound library sources with dynamic inventory updates. Thus, Sygnature Discovery can accurately monitor the quality of its compound library sources as well as inventory stock levels by reporting the plate survey information carried out on compound source plates by the Echo acoustic dispenser. Finally, compound mapping information was made to be directly exported into Genedata Screener for a smooth data flow.

## The Data Analysis System

Genedata Screener software enables analysis, visualization, and management screening data from *in-vitro* screening assay technologies. Sygnature chose Genedata Screener because it is intuitive and straightforward to use, allowing rigorous interrogation of data by plate, batch, or the entire screen. Screener was also fully integrated with the rest of the HTS system so it could combine process data from the HighRes Work Cell with substance identity concentration information from the Mosaic inventory.

## Verifying Automated Workflows

To verify the new automated system, Sygnature ran a pilot screen for mitogen-activated protein kinase kinase kinase kinase 1 (MAP4K1; also known as hematopoietic progenitor kinase 1 or HPK1), an immuno-oncology target involved in negative regulation of T-cell receptor (TCR) signalling.

Sygnature uses target screens such as this one to identify novel chemical starting points from which potent and selective inhibitors of MAP4K1 can be developed. In the assay itself, the intrinsic ATPase activity of MAP4K1 was used to develop fluorescent polarization (FP) via ADP production as shown in Figure 2.

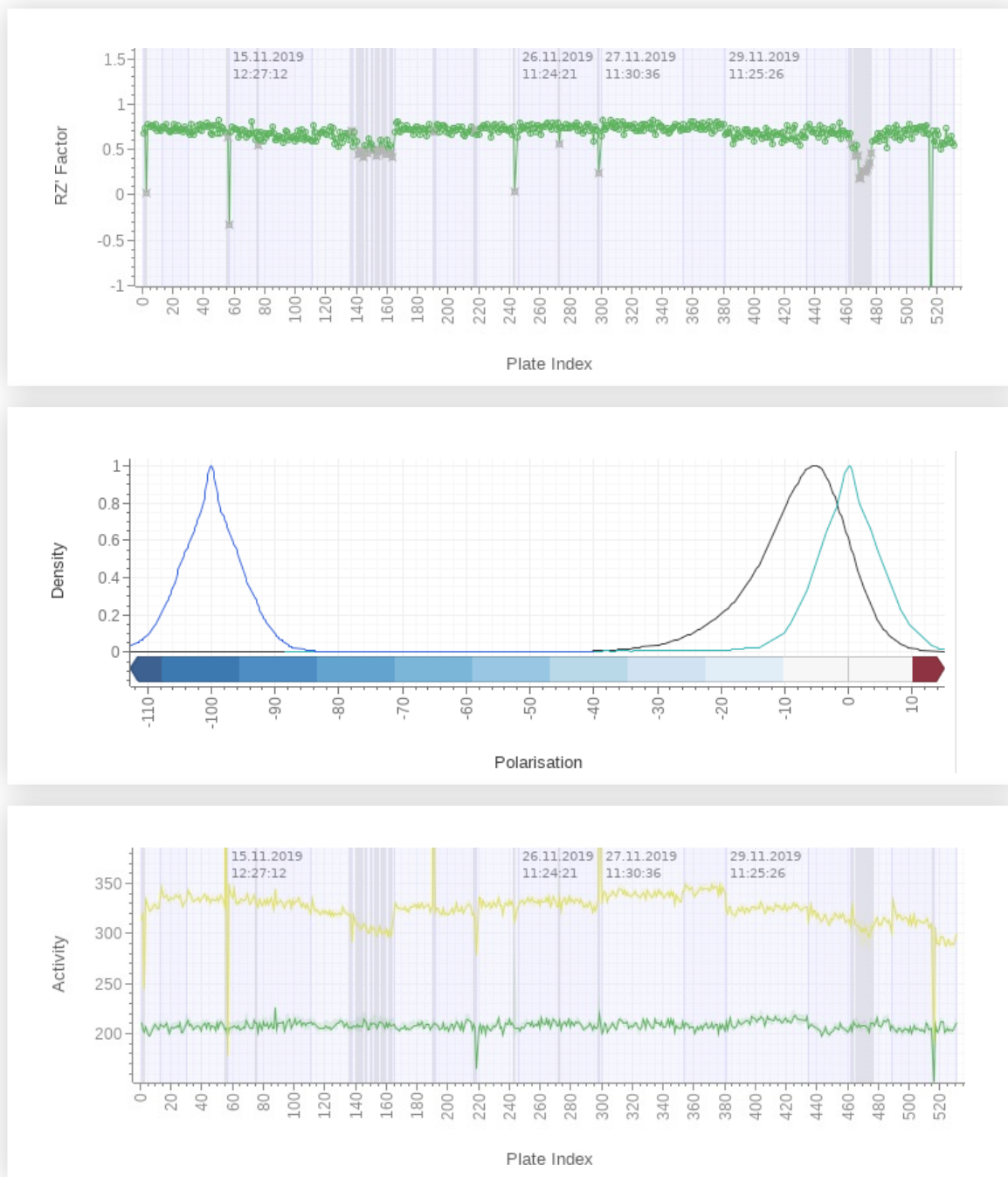


**Figure 2:** The screening assay leverages the ability of MAP4K1 to enable ATP binding, which is involved in several processes, including c-Jun N-terminal kinase (JNK) signaling cascades. Source: National Library of Medicine, National Center for Biotechnology Information, accessed 5/10/22 at 11:34 AM PT [MAP4K1 mitogen-activated protein kinase kinase kinase 1 \[Homo sapiens \(human\)\] - Gene - NCBI \(nih.gov\)](https://pubmed.ncbi.nlm.nih.gov/26511111/)

The MAP4K1 assay took a little more than one workday to complete, and it consisted of the following steps:

- 1 Setup** – Compound orders for assay screening were created in Mosaic software and passed to the HighRes automated Work Cell for execution, with Mosaic automatically writing the necessary control scripts. Source plates, controls and destination plates were loaded and verified on the HighRes Work Cell.
- 2 Compound Management** – Screening-ready sealed assay plates from compound library source plates were automatically prepared over the course of five to nine hours (these can be run unattended overnight).
- 3 Screening** – Fresh assay reagents were used for an automated run which lasted four to seven hours.
- 4 Data Analysis** – Data quality assessment and analysis on the day of screening.

Representative results are shown in Figure 3.



**Figure 3:** Using the new HTS system for the first time, Sygnature was able to screen a 150,000 small molecule library in less than four weeks, with an average Robust Z' > 0.7.

Sygnature Discovery observed good repeatability and reproducibility from its verification efforts. Extensive testing before starting the screen helped to identify processes that caused issues, such as barcoding and the need for liquid dispenser calibration. Issues caused by the transition from test to production data systems also needed to be resolved.





**HighRes**  
biosolutions

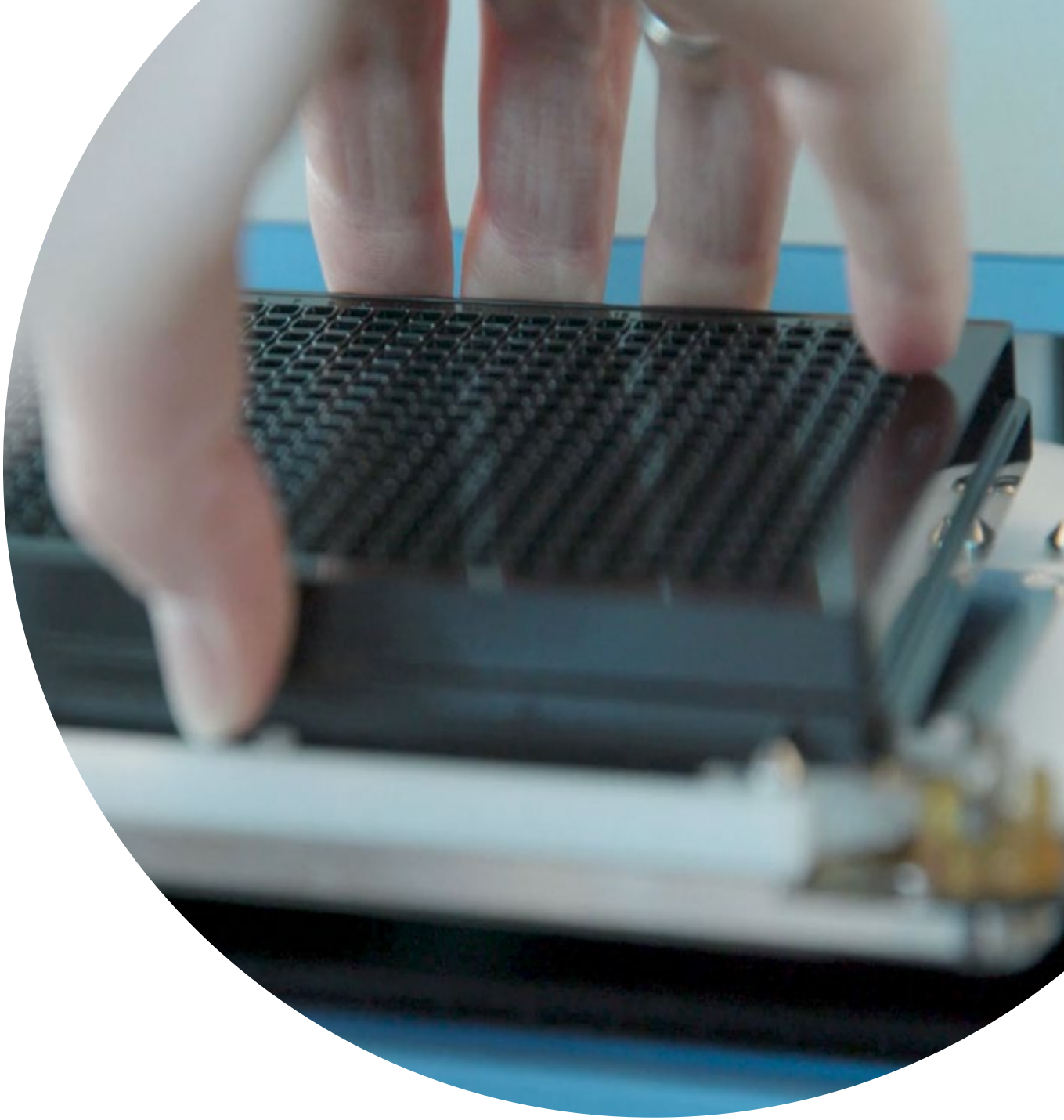


## Lessons Learned

The project moved quickly from product delivery to initial screening in less than six months, and this was in large part to the fact that industry partners had experience with HTS workflows and each other. All the systems were tested extensively before going live, and issues were dealt with rapidly and systematically. Careful planning and preparation for all stages of the project was required, and this included a significant amount of information technology (IT) support as the lab was reconfigured for automation.

In terms of functionality, MAP4K1 verification runs were invaluable in weeding out production issues and shaping operational practices.

Tomorrow-ready automation from HighRes Biosolutions and collaboration with other industry-leading vendors significantly benefitted Sygnature Discovery as they maintained delivery of timely and accurate drug discovery and other service data to their clients.



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