» *Business Case:* optimizing molecular staff utilization in COVID times with FastFinder software for high-throughput Roche FLOW

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Routine diagnostic COVID testing in a high-throughput lab

Like many labs around the world, the lab ramped up to perform ultra-high throughput COVID testing. **Many labs are under stress with lack of personnel, the need to rapidly ramp up junior staff, and unprecedented volume growth**. In this business case, we illustrate how Roche Denmark and Hvidovre Hospital were able to avoid these pitfalls by partnering with UgenTec and implementing its FastFinder software configured for high throughput COVID screening.

Once the pandemic hit, the benefit of freeing up staff resources through software automation rapidly became tangible: FastFinder streamlines routine lab operations to free capacity for pandemic testing, and expert staff can move from time-consuming result review and spreadsheet-based reports to managing the complexity of rapid lab ramp-up.

Hvidovre Hospital uses intelligent software to ease workflow for expert molecular lab personnel, maintain turnaround times and accuracy, and cope with unprecedented test volumes.

- Jan Gorm Lisby, Head physician, Department of Microbiology

What you will learn

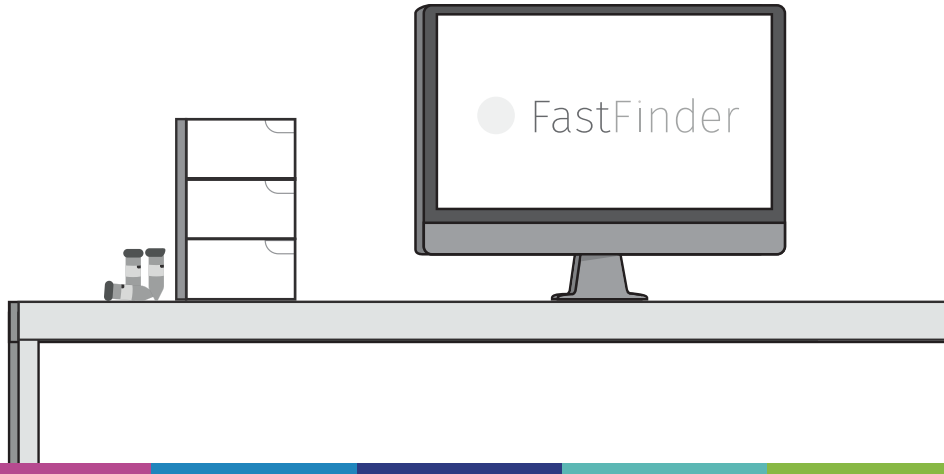
This case study highlights the Business Case Hvidovre Hospital has developed around the adoption of UgenTec FastFinder for its FLOW workflow.

FastFinder is a software platform that employs machine learning to support data analysis and interpretation and automates the post-analytical workflow for PCR assays, **optimizing molecular expert staff utilization, maintaining low error rates** under high-throughput personnel strain, **and ensuring rapid turnaround times with optimal result accuracy.**

Introduction - Hvidovre's pathogen testing workflow

Hvidovre Hospital is one of Denmark's largest hospitals and features an innovative clinical diagnostic lab that has implemented a high-throughput molecular testing pipeline on Roche FLOW™ pre-COVID performing around 500.000 PCR reactions annually and a peak throughput of 900 samples per day. The lab receives samples from a large catchment area and is always keen to evaluate and adopt new technology to drive operational efficiency.

The FastFinder software project, which completes the operational workflow Hvidovre has implemented on Roche's FLOW system, has been configured to automate a number of routine high-throughput assays in the testing menu already. Currently, the COVID workflow, the respiratory panel, and the MRSA assay are implemented. The gastro panel is currently in development, with the ambition to eventually support entire LDT portfolio the lab runs on the FLOW system.



Current approach to pathogen testing

Prior to COVID, the Department of Clinical Microbiology at Hvidovre Hospital examines more than 150.000 clinical patient samples annually for 21+ pathogen targets, generating more than 500.000 analysis results per year.

Hvidovre has multiple diagnostic assays in their diagnostic menu. They rely on Roche FLOW as a key solution to their high-throughput workflow. The FLOW platform provides the required flexibility in instrument configuration and allows them to standardize the wet lab workflow.

With COVID testing ramping up, Hvidovre decided to complement the Roche FLOW workflow with UgenTec's FastFinder software platform, to (a) streamline and automate data analysis, (b) limit the burden on lab staff technicians, especially since adding junior personnel needs to ramp up quickly, and (c) maintain optimal assay accuracy and turnaround times without straining molecular diagnostic experts with increased review and sign-off workloads.

A PCR workflow, from sample to result

Each individual PCR reaction, in 96 well or 384 well format, requires manual inspection of amplification curves before a positive or negative analysis result may be released to the LIS and subsequently to the HIS (EPIC/SP). For some pathogens a positive/negative result is based on a simple one-target detection; for some pathogens, a dual target approach is applied; and for some pathogens, the positive/negative interpretation is more complicated, involving e.g. end-point genotyping or delta Ct for several targets.

Challenges in high throughput: lab bottlenecks to avoid & prevent

» The manual interpretation causes several potential concerns, which Hvidovre decided to address proactively.

	Look at	Issues	Call
One target	C_t	Creeping curves	
Two targets	C_t	Creeping curves	**yes/yes; yes/no; no/yes; no/no**
End-point	2-D coordinate with fluorescence levels compared to controls		
delta C_t	Difference in Ct in a 4-target PCR		

Table 1 - Of the interpretation rules above, only the bold may be performed with assistance from the existing LIS. Automation of the rest of the interpretation tasks is currently not considered possible.

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A first issue is **interpersonal variation**. For all but the clearly positive and clearly negative curves, manual interpretation can vary between operators. Especially for non-standard curves, staff training burden for newly hired operators and interpersonal variation is an issue to be avoided. An example of this is so-called creeping curves, a well-known problem where fluorescence creeps up over cycles and crosses the threshold, triggering a false positive. Borderline and dubious amplification curves have throughout the history of real-time PCR posed a general interpretation problem, and ***manual rules for interpretation are impossible to implement reproducibly in a routine setting***.

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Secondly, with the increased strain on lab personnel and growing reliance on newly hired technicians, labs need to mitigate the risk for **human error**. This isn't necessarily limited to the analysis and interpretation stage but can occur at other operational steps: when having to review a high number of amplification curves and manually enter the interpretation in the LIS, mistakes happen. Unpublished results from a large clinical study in the Department of Clinical Microbiology have documented that ***errors may occur if results are entered manually in the LIS*** (e.g. as is currently necessary for some of the departments dual target assays).

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Thirdly, there is a significant **demand on time resources**. Manual interpretation requires highly skilled staff resources. During the period December 12, 2018 to January 18, 2019, on average 3,1 hours (1,9 – 5,9) were spent on manual interpretation on weekdays. With exceptional volumes for COVID testing, it has become ***essential for labs to avoid this resource strain impacts turnaround times.***

It's key to avoid delays on availability of test results to clinicians. FastFinder helps us remove the manual interpretation steps.

- Jan Gorm Lisby, Head physician, Department of Microbiology

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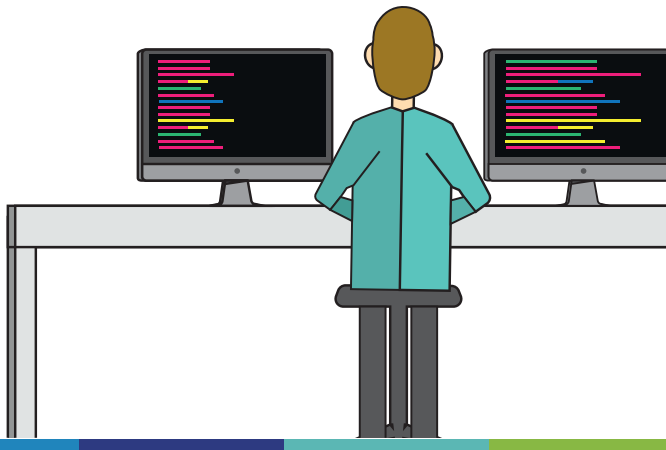
A fourth issue is potential **result delays**. A delayed availability to the clinicians of test results may impact clinical care. The manual interpretation delays the availability of test result in the LIS/HIS by, on average, 36 minutes plus the "lag time" for initiation of the interpretation process after completion of the PCR - an estimated 15 minutes. In total, the delayed availability of test results for the clinicians caused by the manual interpretation process is estimated to be 51 minutes.



Solution: post-analysis workflow automation with FastFinder

UgenTec FastFinder is a software platform that uses **machine learning techniques to automate data analysis and assay interpretation instructions to reduce the time required for manual data review**: only results that don't meet the lab's confidence requirements are flagged for manual review.

Out of the box (i.e. without prior training of the underlying algorithm on representative lab result data), the UgenTec machine learning software is capable of automatically calling >98% of all PCR results without human intervention according to data presented by the supplier. The remaining <2% is flagged by the software and will require manual review. **After training of the software on example data, the performance of automated calling typically rises well above the 99% mark**.

The Roche FLOW is ideal for our high-throughput COVID testing workflow. Adding FastFinder to our workflow allows us to optimize our workflow for massive sample throughput.

- Jan Gorm Lisby, Head physician, Department of Microbiology

Validating the approach: a comparison

In order to validate this approach, initially a more conservative ("doublechecking" mode) approach will be applied by the Department of Clinical Microbiology, flagging 10% of cases (the "top 10%" based upon evaluation by the UgenTec software) for manual interpretation. As these 10% of all Roche Flow analysis results will be the 10% most difficult to interpret, it is estimated that the manual interpretation of these test results will require double the amount of time compared to the average time used for manual interpretation.

Hence, the reduction in time used by the manual interpretation is estimated to be 80%, and overall delayed availability of test results for the clinicians is estimated to be reduced from 51 minutes to 10 minutes i.e., **on average, test result will be available for the clinician 41 minutes faster compared to the current situation.**

Our staff is our key asset. With FastFinder software in their hands, we're confident on result accuracy, turnaround times, while getting new staff members productive in record time.

- Jan Gorm Lisby, Head physician, Department of Microbiology

Conclusion

With FastFinder in place, these key challenges in the high-throughput lab are addressed:

- The **interpersonal variation** is removed because the interpretation is now supported and standardized in a set and documented software algorithm (curve calling, but also automation of the rules on how to deal with controls, how to deal with exceptions, and more - in software-based "decision trees").

- In COVID times, labs are strained to hire new, junior staff. With decision protocols embedded in software instead of in people's minds, errors are avoided, new staff is ramped up quickly, and **molecular experts are freed up** and available for complex, strategic tasks instead of routine data review.

- **The human error risk** is removed because data is transferred automatically, through LIS integration capabilities, automatic reading and 'parsing' of result files, and audit trails on what happens when and why.

- The **demand on the lab staff time resources is significantly reduced** through automation of the entire analytical and interpretation workflow, from instrument readout to report generation, and because only a small fragment of the data needs to be manually reviewed.

- Lastly, **availability to the clinicians of test results is sped up** through automation of interpretation SOPs and integration between IT systems.