

White paper

Maximizing flexibility, efficiency and throughput in research histology with full automation and continuous random access

A comparative workflow analysis for automated chromogenic immunohistochemistry (IHC) and in situ hybridization (ISH) staining



Study materials and methods

Instruments observed for this comparative analysis include:

DISCOVERY ULTRA

- Medical Research University 1
 - Histopathology Research Core Lab 1
 - Histopathology Research Core Lab 2

Leica BOND RX

- Medical Research University 1
 - Histopathology Research Core Lab 3

Biocare IntelliPATH

- Medical Research University 2
 - Histopathology Research Core Lab 1

Dako Autostainer

- Medical Research University 2
 - Histopathology Research Core Lab 2

Based on each staining instrument's capabilities, this study was designed to document platform-specific protocols for IHC, ISH and dual stain/multiplexing:

- Day 1: 30 IHC slides (Vimentin)
- Day 2: 15 dual/multiplex slides* (CD3, CD8, CD68, PDL1) and 15 IHC**
- Day 3: 15 IHC slides (Vimentin) and 15 ISH slides (Alu II)**

* Dual stains only on Dako Autostainer; on Leica BOND RX, dual stains only when using Leica reagents.

** ISH could not be performed/observed on the Dako Autostainer and Biocare IntelliPATH at Research University 2 because the laboratory did not have the additional equipment required to perform ISH experiments on those instruments. (No additional equipment is needed to perform ISH on the DISCOVERY ULTRA system or the Leica BOND RX.)

For a brief overview of similarities and differences between the four advanced staining instruments observed in this study, see Figure 1.

The DISCOVERY ULTRA is for research use only, not for diagnostic purposes.

Cover photo: Slides being removed from the individual slide staining drawers of the DISCOVERY ULTRA system.

Optimizing workflow through automation and individual slide staining

Histology research is essential – it leads to new discoveries that can save and improve lives while helping to create more effective and efficient standards of care and diagnostics. As testing menus become more varied and complex, research laboratories can improve efficiency by adopting full automation with continuous random access.

Many advanced staining instruments are available, though not all are created equal. It is important to understand and assess the differences between semi-automation and full automation, as well as batch mode systems versus individual slide staining. Fully automated systems offer a range of lean workflow benefits, from faster turnaround times to reduced manual activity. These gains, in turn, can lead to higher throughput and productivity.

To evaluate the advantages of full automation and individual slide staining, a workflow consultant from Roche Diagnostics observed and documented the processes involved with two fully automated and two semi-automated staining systems used for histology research at two major research universities in the United States. Of the four instruments studied, one allows continuous random access to individual slide staining drawers; the other three require batching of slides to achieve maximum instrument capacity and throughput. This white paper presents the results of that study, including an analysis of the flexibility and efficiency gains made possible when batching and other manual activities are eliminated from the research histology workflow.

Full automation decreases manual steps for greater efficiency

For laboratories using older, semi-automated technology, there is significant opportunity to streamline operations by adopting full automation for histology staining. As demonstrated through this study, automation decreases time spent on manual, hands-on activities while offering shorter overall run times.

Instrument specifications at a glance

	Fully automated systems		Semi-automated systems	
	DISCOVERY ULTRA	Leica BOND RX	Biocare IntelliPATH	Dako Autostainer
Workflow	Continuous random access	Mini-batch	Mini-batch	Batch
Number of slide drawers (a.k.a. racks or trays)	30	3	5	4
Slides per drawer	1	10	10	12
Ability to run multiplex stains	Yes	Dual stains only*	Yes	Dual stains only
Ability to run IHC, ISH, and multiplex on same run	Yes	Yes**	No	No

* Expanded multiplexing capabilities available only via third-party detection kits.

**Able to complete during the same run but not in the same drawer.

Figure 1: A brief overview of the differences between the four advanced staining instruments observed in this study.

Figure 2 illustrates the timing observed for all steps involved in processing 30 IHC slides per instrument. The DISCOVERY ULTRA system had the shortest total run time for 30 IHC slides, in part because it also required the fewest manual steps. By contrast, the semi-automated systems had longer total run times and required the user to spend nearly two hours on manual activities, compared to 15 minutes or less with full automation. As a result, when compared to semi-automation, the fully automated platforms reduced manual workflow processes by an average of 91% (the DISCOVERY ULTRA system) and 87% (Leica BOND RX).

Full automation reduces manual steps and total run time

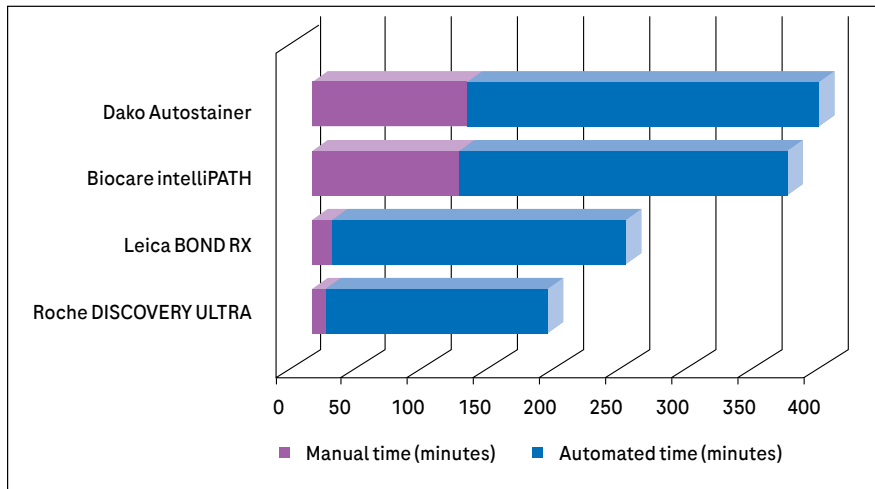


Figure 2: An illustration of total run time for processing 30 IHC slides, broken down by manual versus automated time.

To understand and illustrate where time-savings and efficiencies can be gained by maximizing automation, the Roche workflow consultant objectively classified each step into one of three categories:

1. Automated steps: steps performed automatically by the staining instrument being used;
2. Manual steps: steps that cannot be performed automatically by any staining instrument;
3. Manual steps with automation opportunity: steps that are performed manually due to lack of an automated alternative with the instrument being used, but where other instrumentation does provide an automated, walk-away alternative.

Not surprisingly, the highest percentages of automated activity were associated with fully automated staining. It is notable, however, that even among the two fully automated systems, the difference in the number of “manual steps with automation opportunity” was significant. By eliminating steps associated with batching and sorting, the DISCOVERY ULTRA system delivered an end-to-end process with fewer than half as many overall steps than the Leica BOND RX (12 steps and 25 steps, respectively). Furthermore, only 17% of all steps on the DISCOVERY ULTRA system qualified as manual steps that could be replaced with automation, compared to 40% on the Leica BOND RX.

With semi-automation, the opportunity to streamline with more robust automation is even more pronounced. Of the 30 total steps on the Biocare IntelliPATH and 34 total steps on the Dako Autostainer, roughly three-quarters represented manual activities with automation opportunities (73% and 76.5%, respectively). For more details, see Figures 3, 4 and 6a-6d.

Comparison of manual vs. automated activity by instrument

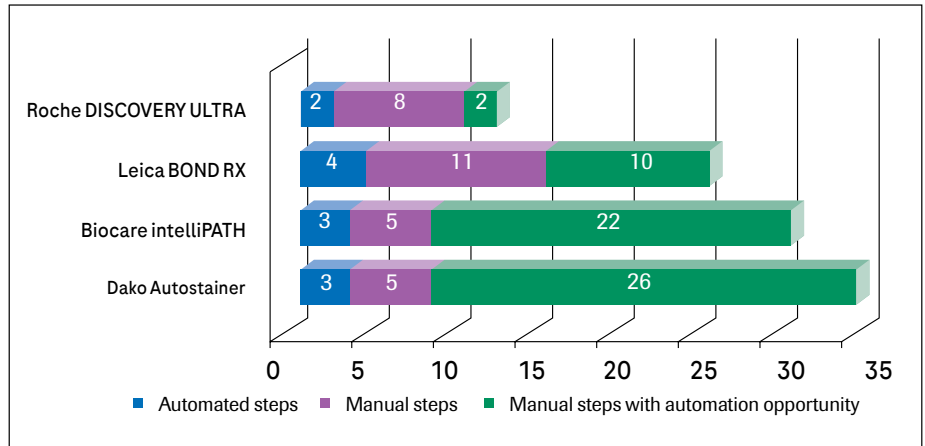
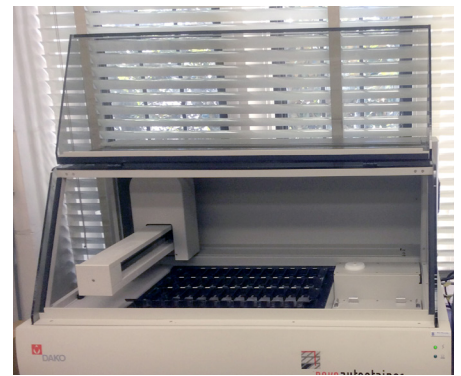
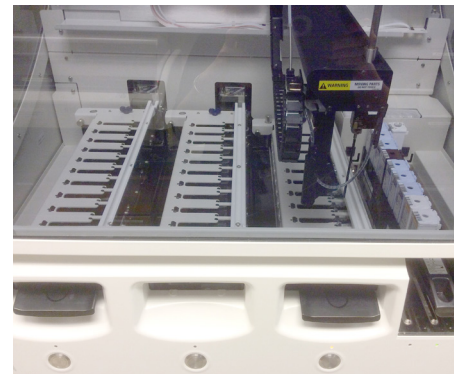
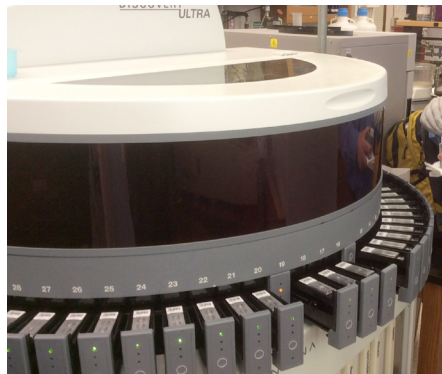
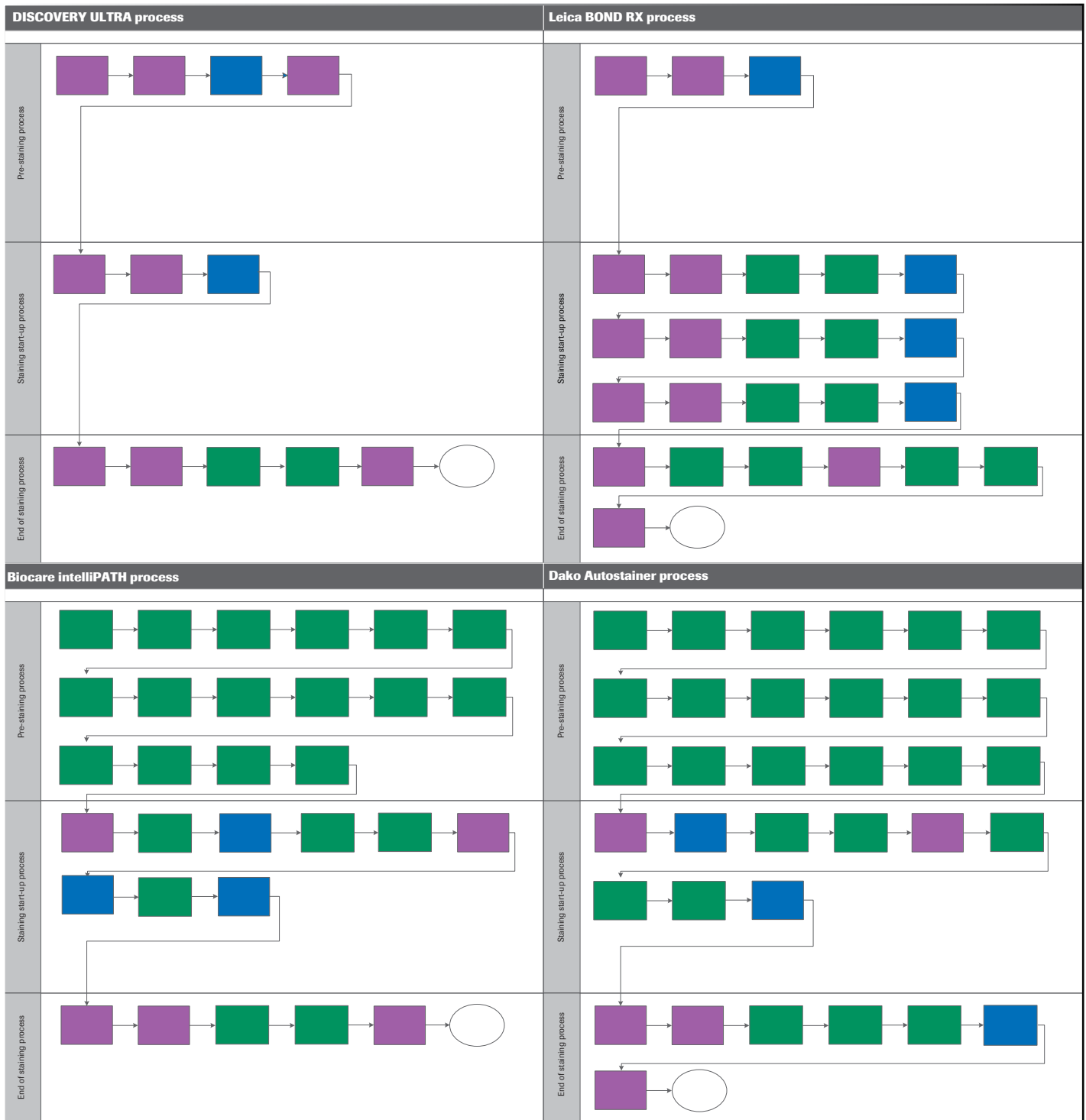


Figure 3: An illustration of total workflow steps involved in IHC staining, broken down by type of activity (automated, manual, and manual with automation opportunity).



The images above illustrate the differences in slide drawer design between the four instruments used in this study – differences that result in a range of workflows, including continuous access, mini-batching and batching. Top left: The DISCOVERY ULTRA system (individual slide drawers for single piece flow and continuous random access); top right: Leica BOND RX (three drawers with 10-slide capacity each for mini-batching); bottom left: Biocare IntelliPATH (five drawers with 10-slide capacity each for mini-batching); bottom right: Dako Autostainer (four drawers with 12-slide capacity each for batching).

Full automation without batching results in the fewest steps, leanest workflow



■ Automated step ■ Manual step ■ Manual step with automation opportunity

Figure 4: A high-level illustration of workflow steps involved for pre-staining, staining start-up, and end of staining processes. For more detailed flow charts, see Figures 6a-6d in the Appendix.

Benefits of continuous random access and individual slide staining

- Allows a wide range of protocols to run simultaneously, eliminating the need to batch and sort.
- Enables technicians to run both manual and fully automated experiments at the same time with no synchronization errors, including FISH, gene and protein IHC/ISH, mRNA ISH, and multiplex assays with any combination of IHC and ISH.
- Enables continuous runs at maximum instrument capacity by allowing the immediate removal and replacement of individual slides with no impact on the slides still processing in the remaining drawers.

Continuous loading in “drawers of one” optimizes efficiency

Where batching instruments were used, a substantial increase was observed in the number of steps performed throughout the process. The most notable increases were associated with the semi-automated processes, though batching led to a significant rise in the number of steps performed at the point of staining startup, regardless of whether the instrumentation was fully automated or semi-automated. Given the workflow inefficiencies associated with batching, laboratories that aim to achieve optimal efficiency and throughput need the ability to continuously load and unload individual slides (also known as “continuous random access”).

Based on the data from this study, continuous access decreased turnaround times for routine IHC stains by an average of 35% when compared to the semi-automated platforms, and by an average of 24% when compared to the fully automated batch mode system.



*The DISCOVERY ULTRA system compared to Leica BOND RX, based on data from this study.

Individual slide drawers enable maximum drawer utilization

When each slide drawer is an independent reaction chamber, a single slide requiring its own protocol does not affect drawer utilization: one slide always equals 100% drawer capacity. By contrast, when batching slides for drawers of ten or 12, one slide in a drawer would represent just 8-10% drawer utilization (see Figure 5).

Although the need to run a separate slide protocol for a single slide was not a factor in this study, the overall analysis supports the notion that individual slide staining is key to maximizing protocol flexibility and daily throughput. For example, consider a situation involving 15 multiplex slides and 15 ISH slides. With 30 individual slide staining drawers, all 30 slides can be completed simultaneously, regardless of their varying detection protocols. However, this same combination of assays requires two separate runs on a system that requires batches of ten or 12 without allowing different detection protocols on a single tray (as was observed with the Leica BOND RX). Generally speaking, with batch mode systems, such a scenario will indeed require either a second run or modifications to the testing setup, which would include more strategic utilization of slides, reagents and instrumentation on the part of the user.



Research histologists using the DISCOVERY ULTRA system.

Individual slide access delivers optimal capacity

Instrument	Drawer utilization for a single slide
The DISCOVERY ULTRA system One slide per drawer (30 drawers)	100%
Leica BOND RX Ten slides per drawer (three drawers)	10%
Biocare IntelliPATH Ten slides per drawer (five drawers)	10%
Dako Autostainer 12 slides per drawer (four drawers)	8%

Figure 5: Individual slide drawers enable maximum drawer and instrument capacity with every slide, allowing continuous loading and unloading of single slides throughout the day. This chart is intended to illustrate the difference in drawer utilization among a sample of instrument designs available in the market and is not directly representational of the findings of this study.

In summary

Laboratories that perform histology research can achieve leaner, more productive operations by choosing advanced staining instrumentation wisely. As these findings illustrate, semi-automated and/or batch mode staining systems require more manual steps and hands-on interaction, whereas fully automated staining instruments offer enhanced workflow, efficiency and productivity that semi-automation cannot match.

Additionally, continuous random access to independent, single-slide reaction chambers maximizes protocol flexibility, allowing technicians to shape the platform to meet varying project requirements while enabling laboratories to operate at full instrument capacity at all times. This is true even when testing becomes more complex and requires various pretreatment methods, retrieval or detection chemistry – factors that require more instruments to complete the same volume of tests when batch mode systems are used.

About this paper

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Appendix

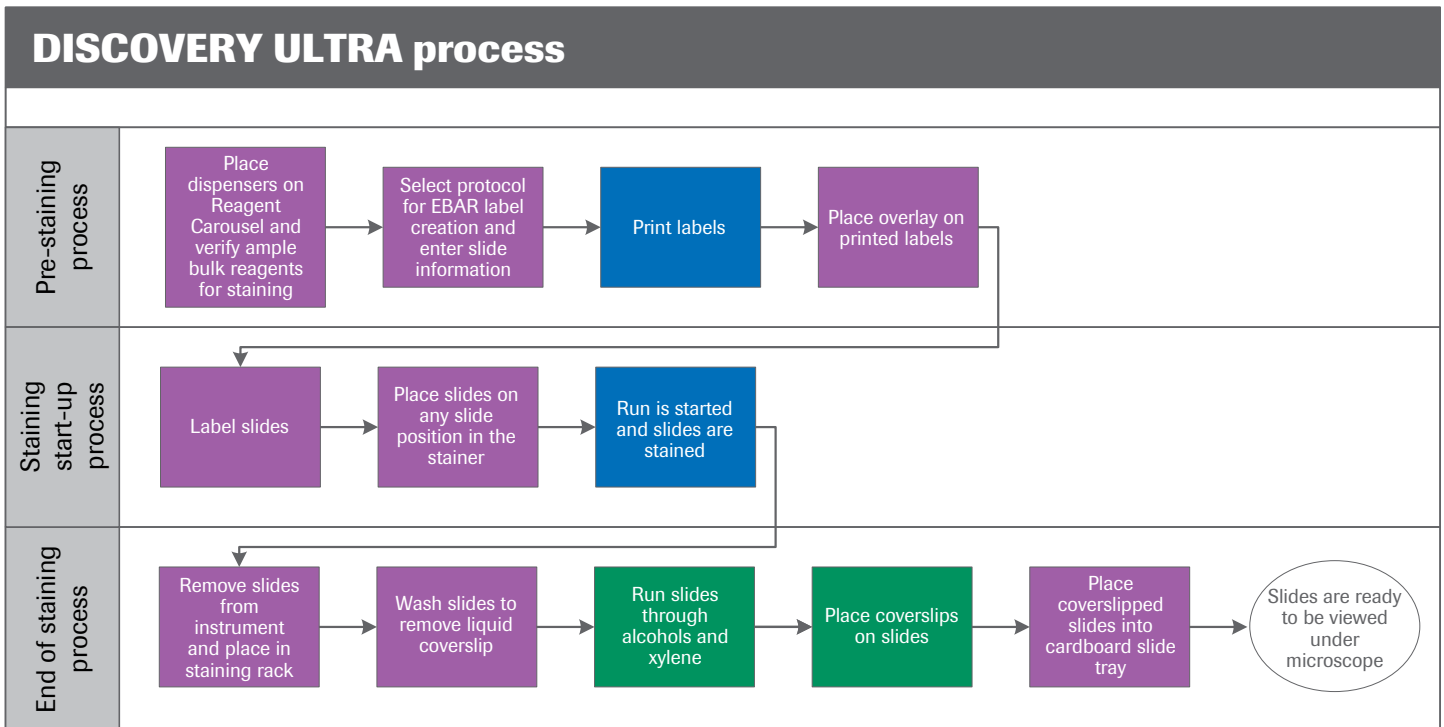
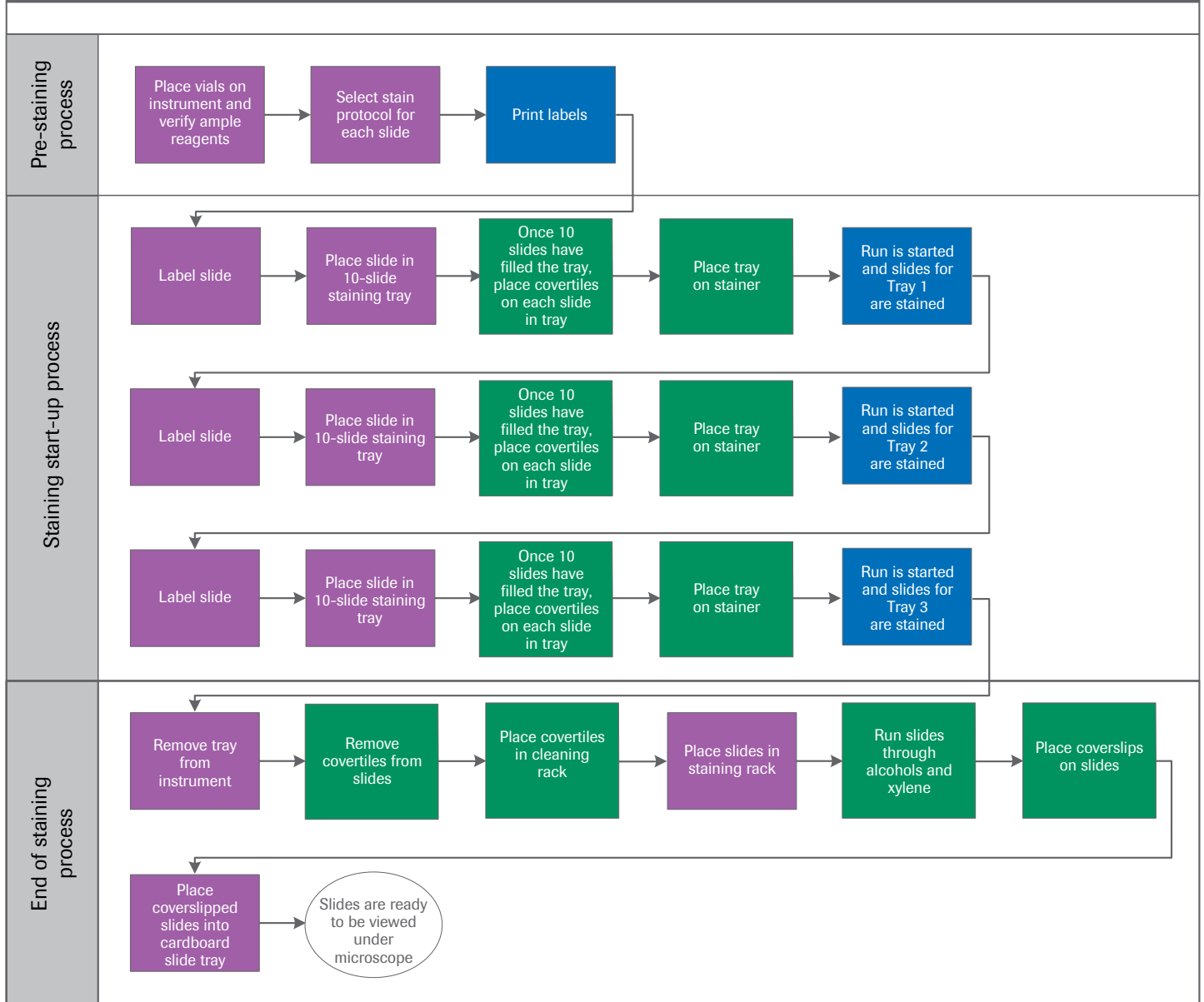


Figure 6a: A detailed flow chart of all steps observed with staining 30 IHC slides on the DISCOVERY ULTRA system. Due to full automation with continuous random access to individual slide staining drawers, this instrument required the fewest steps overall (12 total). Data further indicate that, of the four instruments observed for this study, the DISCOVERY ULTRA system offers the most robust automation: only two activities represent manual steps with automation opportunities.

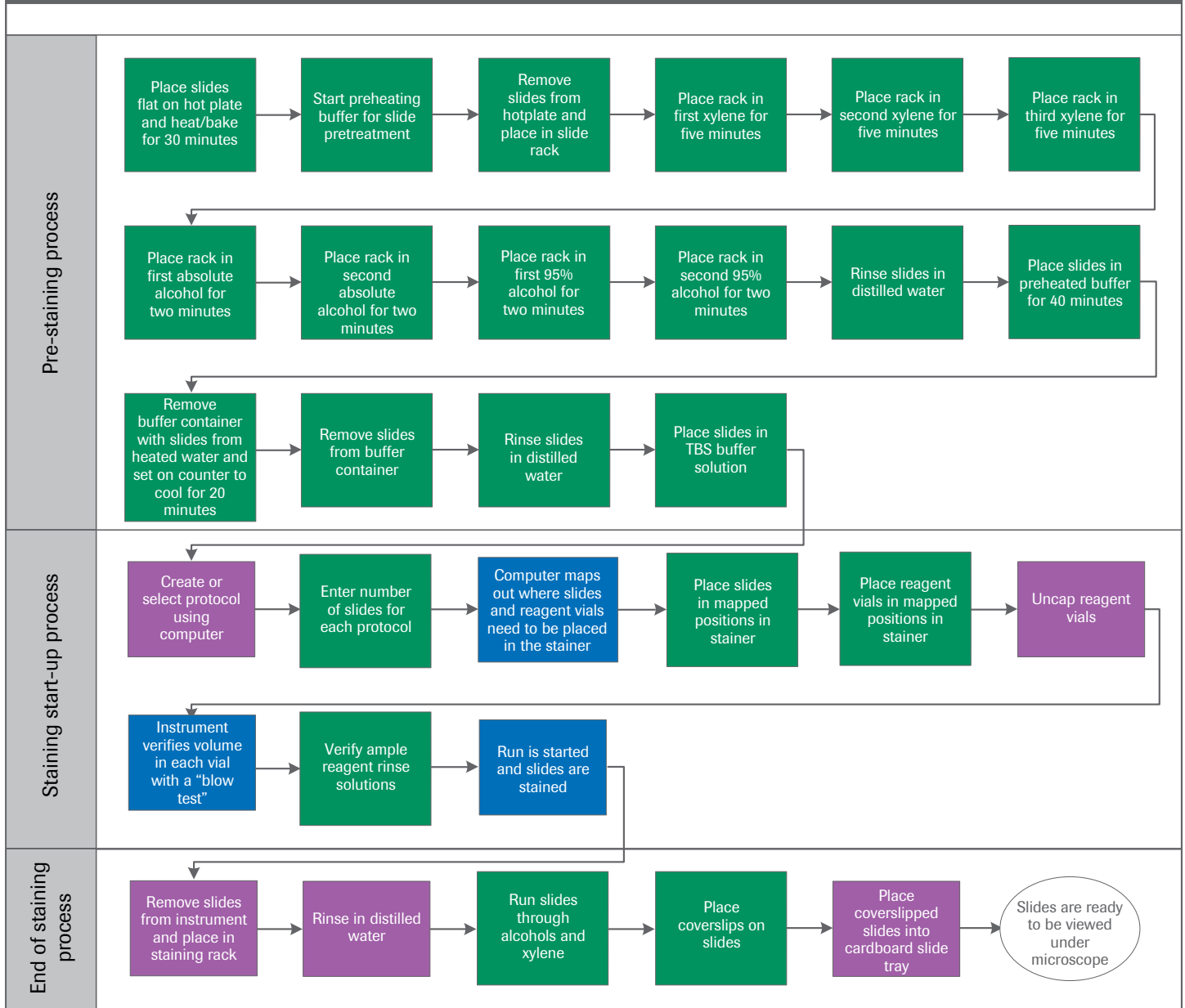
Leica BOND RX process



■ Automated step ■ Manual step ■ Manual step with automation opportunity

Figure 6b: A detailed flow chart of all steps observed with staining 30 IHC slides on the Leica BOND RX. Batching slides in drawers of ten was observed to add numerous steps to the overall process, resulting in 25 total steps. Despite its status as a fully automated instrument, 40% of all steps observed with the Leica BOND RX represent manual steps with automation opportunities (compared to less than 17% on the DISCOVERY ULTRA system).

Biocare IntelliPATH process



■ Automated step ■ Manual step ■ Manual step with automation opportunity

Figure 6c: A detailed flow chart of all steps observed with staining 30 IHC slides on the Biocare IntelliPATH. Because it is a semi-automated instrument that requires batching slides in drawers of ten, this instrument required 30 steps in total, which is 2.5 times more steps than the fully automated DISCOVERY ULTRA system, but only 1.2 times more steps than the fully automated Leica BOND RX. Nearly three out of every four steps (73%) observed on the Biocare IntelliPATH represented manual activities that could be replaced with automation (compared to less than 17% with the DISCOVERY ULTRA system and 40% with the Leica BOND RX).

Dako Autostainer process

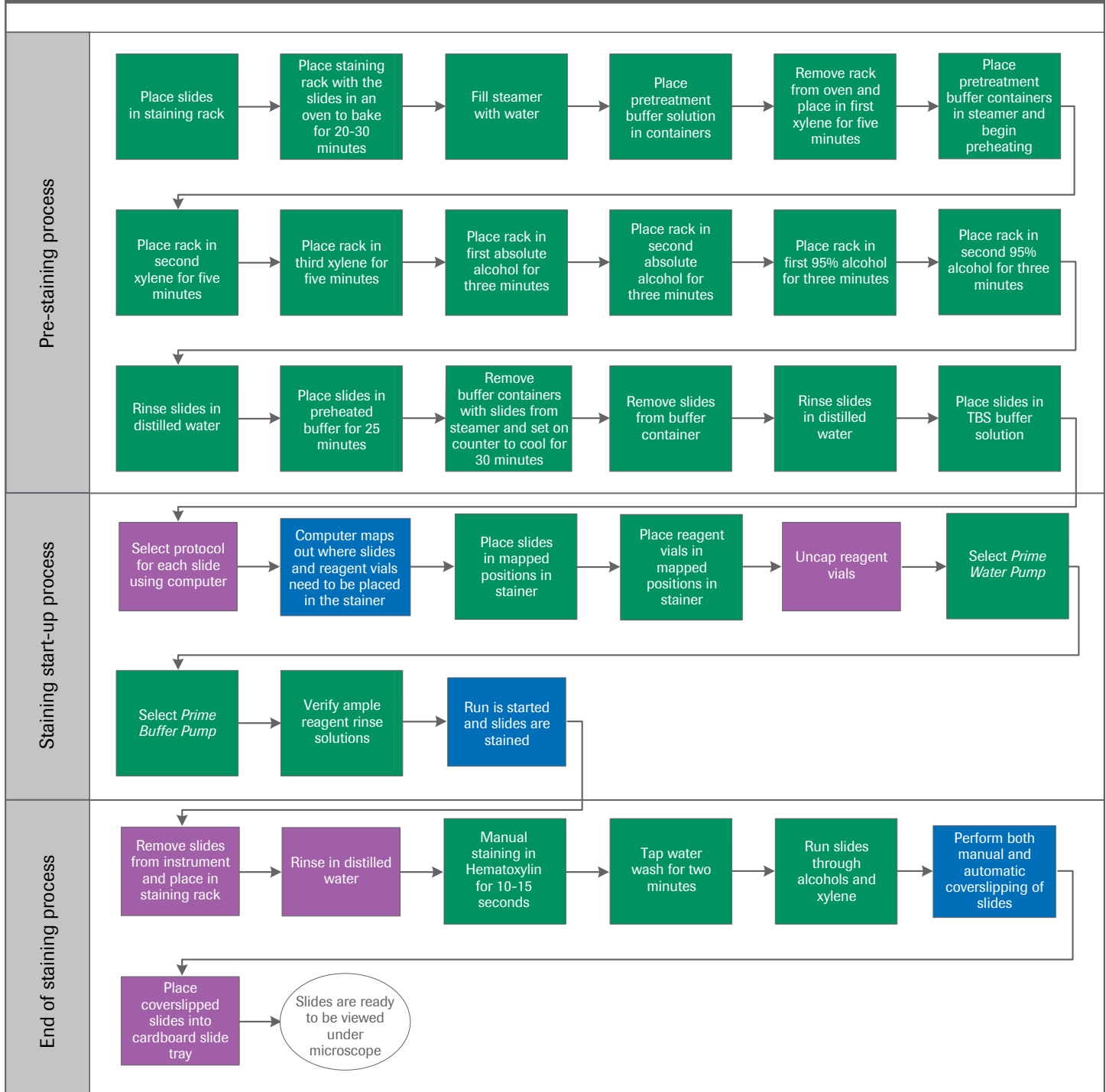
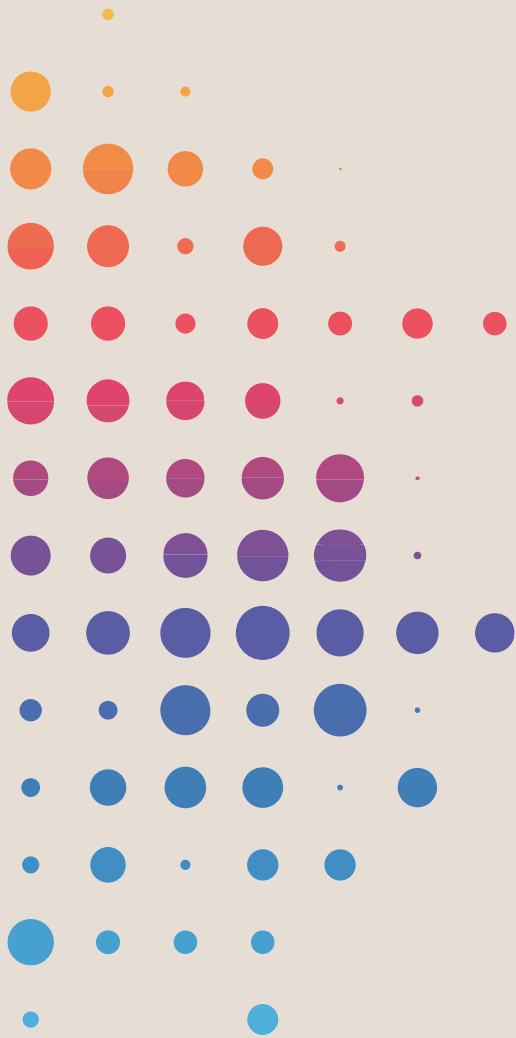


Figure 6d: A detailed flow chart of all steps observed with staining 30 IHC slides on the Dako Autostainer. As a semi-automated instrument that requires batching slides in drawers of 12, this instrument required 34 steps in total (the most among the four instruments studied), which is 2.8 times more steps than the fully automated DISCOVERY ULTRA system but only 1.4 times more steps than the fully automated Leica BOND RX. More than three-quarters (76%) of all steps observed on the Dako Autostainer represented manual activities that could be replaced with automation (compared to less than 17% with the DISCOVERY ULTRA system and 40% with the Leica BOND RX).



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