WHITEPAPER

Automating Your IHC Lab
Key Considerations

BIOCARE MEDICAL

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Abbreviations

Name	Description
H&E	Hematoxylin and eosin
IHC	Immunohistochemistry
ISH	*in situ* hybridization
LIS	Laboratory Information Systems
PAMA	Protecting Access to Medicare Act
TAT	Turnaround time
FTE	Full-time equivalent
ROI	Return on investment
HIER	Heat-induced epitope retrieval
RTU	Ready-to-Use
DAB	3,3'-Diaminobenzidine

Why IHC Automation?

The demand for IHC tests has been increasing since the 1990s as a result of advances in personalized medicine. In conjunction with a standard H&E stain, IHC data provides valuable information for many pathologists in the evaluation of neoplastic diseases. Based on market research data in 2007, it was estimated that about 20% of the slides examined by pathologists were IHC slides; additionally, data as recent as 2016 suggests that this share of volume of IHC tests remained the same if not increased this decade.[1,2] Yet, the pathology community faces many different challenges in their IHC practice:

- The shrinking histotechnologist/histotechnician workforce as a result of fewer training opportunities and retirement.[3]
- Increasing pressure to reduce TAT: a key quality performance indicator for many clinical labs.[4]
- The difficulty in standardization of IHC tests and quality control. IHC is a process subject to substantial variation between different labs with different practices. There is a pressing need for standardization and quality control.[5]
- Reduced reimbursement for clinical labs. Since the implementation of PAMA in 2014 clinical labs face greater financial pressure with an average 35% decrease in reimbursement for most tests from 2018 to 2023.[6] Finding ways to minimize cost and reduce repeat testing will be of paramount importance to sustain the business of clinical labs now and in the years to come.

All these environmental factors could be driving automation of the IHC process, but does it mean this is applicable to your lab? This white paper introduces the process and key factors to review and consider before bringing automation to your lab.

Objectives of IHC Automation

- ✔ Increase daily throughput and volume of samples per technologist/technician.
- ✔ Standardization to reduce variability and to improve staining quality and consistency.
- ✔ Enhance cost effiency - minimize hands-on time and better utilize lab personnel in value-added tasks.
- ✔ Reduced errors through auto-correction, process monitoring and information tracking.
- ✔ Improve TAT as a result of fewer repeats and standardization.

“Based on customer feedback, a daily throughput of 25 slides is the threshold for most laboratories to consider IHC automation.”

Planning for IHC Automation, Workflow Analysis

Workflow analysis provides a clear, data-driven picture of what the lab is doing "right now." The objective data delivers a comprehensive understanding of the strengths and weaknesses of the specific lab workflow and can pinpoint with clarity the exact areas that the lab needs to focus on to provide the biggest impact on efficiency. Workflow analysis also captures the attention of all stakeholders regarding the introduction of a new automation solution.

Pre-analytic Stage	✔ Order verification ✔ Tissue processing and fixation time ✔ Slide-drying time and temperature ✔ Labeling of consumables
Sample Processing and Analysis	✔ Antibody selection and optimization (selection of clones, dilution, incubation time and antigen retrieval method) ✔ Automated stainer vs manual staining (pros and cons)
Post-analytic Stage	✔ Quality control and interpretation ✔ Result reporting

Workflow analysis needs to be done in the context of the entire sample life cycle as shown above.[7,8] Some of these are mundane tasks in pre-analytic/post-analytic stages (e.g. order verification, labeling of consumables, sample storage and data handling and reporting) but perhaps the most important consideration here is in the automation of samples processing and analysis. Nonetheless, in some cases, merely changing the current workflow may provide improved efficiency without the addition of automation. Steps in a typical workflow analysis include:[9,10,11]

1. Workflow mapping to identify functions and steps to be automated.
2. Collect existing process performance data (e.g. TAT, cost) as baseline metrics.
3. By means of quality improvement methods such as Lean Six Sigma:
    a. Identify bottlenecks and roadblocks.
    b. Evaluate simple work modifications and process automation as solutions to eliminate bottlenecks and problems.
    c. Prioritize the potential modifications and automation solutions

After the conclusion of a workflow analysis, there should be no surprise that automation may not be the best solution for every lab. Once the solutions to streamline current workflows and to automate processes have been implemented, the new automated process will be monitored to ensure the intended objectives are attained and to make any necessary adjustments to the new process for maximum performance and throughput.

Considerations for an Investment in IHC Automation

The topic has been reviewed in various literature with comparisons of the different automated IHC platforms in the market.[12,13] It is important to understand that there is no one best IHC system in the market. Rather, a solution applicable to your lab would be an outcome of the interplay between the following factors and each lab will have its own unique challenges and requirements to be considered.

Technical Considerations

There are three important technical factors that a lab manager needs to consider in automating the IHC process:

1. Degree of standardization of the IHC process.
2. How flexible the system would need to be? (Closed vs Open Platforms)
3. Is a fully-automated system the appropriate solution? (Full automation vs Semi-automation)

Standardization

Does the software enable better tracking of sample and order information to minimize errors and the need for repeats? Is connectivity to LIS an important consideration for my lab?

Features such as reagent tracking, volume sensing, bulk liquid detection, and automated error detection/reporting could be important in standardization and ensuring consistency of staining.

Reagent dispensing mechanism (matrix vs rotary platforms) is an important consideration.

Flexibility: Closed vs Open Platforms

Is it necessary for my lab to have a diverse choice of reagents (including antibody, detection) from any source?
Do I need the flexibility to modify different parameters in my protocol (e.g. incubation time, temperature, etc.)?

Do you require new biomarkers in the future? (If yes, an “open” system may offer more advantages)

Availability of RTU reagents so users can have the flexibility to switch to a “closed” system if required.

Is standardization and consistency of staining most important to my lab? How tolerant of error and variability are the current processes in my lab? (Most pertinent for clinical applications where a large menu of RTU reagents may be required)

Do I need to have onboard heating for HIER? (This feature is usually not available in an “open” system)

Full Automation vs Semi-automation

What volume of slides is my lab handling daily? Weekly? Monthly? Do you expect that number to increase?

Do I need to include the entire IHC process from deparaffinization, to coverslipping on one platform? Does it make sense to have some of the steps done separately? (e.g. antigen retrieval, coverslipping - utilize workflow analysis to determine)

Is there any operational constraint (e.g. TAT) that would make a fully automated platform a better choice?

Operational Considerations

Each lab has its own operational needs; the introduction of any new automation platform should evaluate the following:

Volume of Slides and TAT

Capacity of the system and volumes of samples: this is perhaps the most important parameter and will impact the slide management functionalities required such as continuous processing and random slide processing. Slide capacity, batch size, number of positions for reagent containers, multiplexing protocol and incubation time of different reagents will also have a cumulative impact on the throughput of a platform. Most IHC automation platforms have a 30-50 slide capacity, some load slides in trays of 5-10 slides while others are loaded one slide at a time. Every lab will need to find its sweet spot of balancing system capacity, batch size and protocol mix in order to select the right option to achieve the best throughput. How does your lab receive and process slides? All at one time? Do you receive a few slides at a time? Are they all the same test type?

Turnaround time (TAT): another key performance metric and important to clinician satisfaction which may trigger the need for managing STAT requests in the automated IHC platform without impact on in-process slides. The definition of TAT is a matter of debate and there are differences between clinicians and labs. It should be noted that TAT may be intra-laboratory versus total TAT spanning from order placement to the point when the results are available for clinicians.[14,15]

Management of Slides, Reagents and Waste

How many different protocols need to be implemented on the platform and how diverse are these protocols? Is multiplexing required? Is it also necessary to run ISH tests on the platform?

Safety and Waste management: DAB is a hazardous waste requiring special handling and higher disposal cost. The capability to separate DAB waste from other non-hazardous waste will make the disposal easier and more cost-effective as well as minimizing histotechnologists' exposure to hazardous materials.

Software and LIS Capability

How intuitive is the software (notably the user interface)? How easy is it to train the existing lab workforce? Is there a provision (e.g. camera, barcode scanner) to recognize and track reagents and slides through the run?

Additional Considerations

Review technical support and training provided by vendors and how responsive they are; so that instrument downtime is minimized and your automation solution has longevity as a lab workhorse.

Maintenance requirements for instrument include stringent cleaning as any slide staining protocol causes residue build-up which significantly impacts staining quality. A provision of assisted-cleaning capabilities (i.e. part of the routine cleaning tasks can be performed automatically) will be a big plus for any lab, especially for labs handling large volume of samples.

Financial Considerations

One of the key advantages of an automated system will be the better utilization of histotechnologist hands-on time, providing cost-savings as economic justifications for an automated IHC system.[16] Apart from the cost of purchasing the equipment, one will also need to consider the other costs related to the purchase (see table below). In addition, the potential cost savings and revenue associated with the IHC test should also be considered.

Direct Cost	Indirect Cost	Other Costs
Consumables and Reagents Labor: Hourly rate for histotech, QC, equipment installation costs	Administrative costs Facilities costs Utilities Waste management	Depreciation* Service Contract Financing costs**

*Capital Purchase Only **Leasing Only

Instrument Acquisition Options

The table below compares three different instrument acquisition options: capital purchase, leasing (either as a capital lease or operating lease), reagent rental.[17,18,19,20] The financing option could have significant cost implications, and this should be considered in the context of sample volume (see "Financial analysis" below).

Capital Purchase	Reagent Rental	Lease
Upfront Cost		
High upfront cost. Long annual budgeting exercise, limiting purchase time.	Minimal capital outlay and best for cash-flow management. Acquisition of instrument can happen at any time.	Debt financing without the huge capital outlay. Better cash-flow management, However, subject to credit checks.
Contractual Obligations		
No contractual obligation for reagents and consumables purchase. Users can use other reagents and processes (if supported).	Contractual obligation to purchase a set volume or dollar amount of reagents and consumables over a contracted period.	Periodic lease payments, typically lower cash-flow because only paying a portion of the instrument over a fixed period of time.
Instrument Ownership		
Transfer of ownership from manufacturer.	No transfer of ownership (except at the end of the agreement period, dependent on contract terms).	Ownership transferred to lessee for capital lease, but not for operating lease.
Access to Updated Technology		
Lab is stuck with the equipment and so there could be risk of outdated technology.	Flexibility to upgrade to the latest technology / return equipment according to operational needs.	Flexibility to upgrade to the latest technology / return equipment according to operational needs.
Accounting Considerations		
Incur depreciation costs.	All reagents and consumables costs expensed as operating expense.	Capital lease is considered as a liability (debt financing) while operating lease payments are simply operating expenses.

Deciding the Appropriate Acquisition Type

Many labs prefer the reagent rental option as there will be no capital outlay as long as their slide volume is large enough to meet the reagent purchase requirements. On the other hand, there could be benefits in capital purchase given the long useful life of an automated IHC slide stainer and the new tax incentives as a result of the updated section 179 deductions as stipulated in the Tax Cuts and Jobs Acts of 2017.[21,22] A tax professional should be consulted to determine if such tax benefit is applicable to each individual case.

Conduct a Financial Analysis

As discussed, cost savings could be one of the justifications for an IHC automation project.
In order to work out cost savings, the following information will also need to be captured:

- Total volume of anatomic pathology tests performed per day
- Number of FTE performing IHC tests and hands on time required (most notably hourly rate)
- Total volume of IHC tests automated
- Total Cost Per Slide (including all reagents and ancillary items)
- Revenue generated from each IHC test, if applicable

One of the approaches to estimate the unit cost of an IHC test can be summarized below:

Direct Cost
Volume of all IHC tests x direct cost per slide

+

Indirect Cost
Percentage by volume of IHC slides x total lab indirect cost

+

Other Costs
Service contract cost / depreciation cost

=

Total Cost

With the financial analysis complete, one can then determine the total cost and revenue based on the volume of samples processed with automation. With this information, breakeven analysis can be done to determine:

- Pay-back period and ROI for the investment (A)
- Optimize cost savings and see at what throughput reagent rental agreement is more cost-effective than capital purchase (B)
- Increase in revenue as a result decreased FTE/hands-on time and increase samples processed due to automation.
- Optimize cost savings/revenue through estimating an appropriate mix of automated and manual IHC tests; or an appropriate mix of financing options if purchasing more than one instrument is required.

Figure A
Graphical representation of pay-back period as a financial metric for consideration

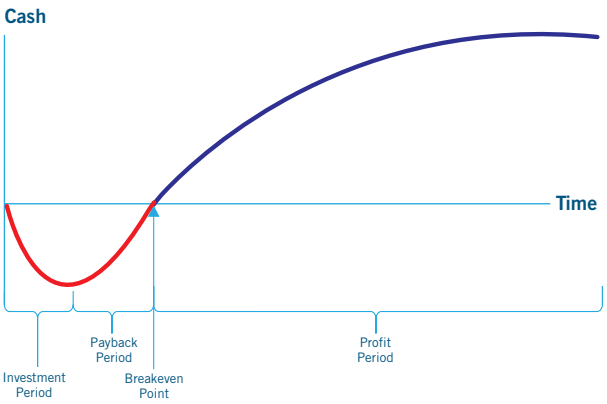
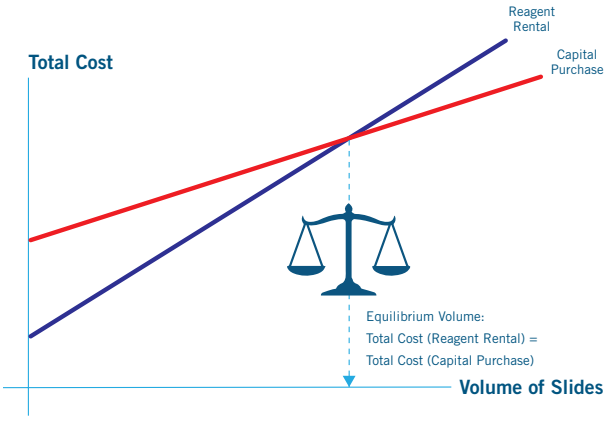
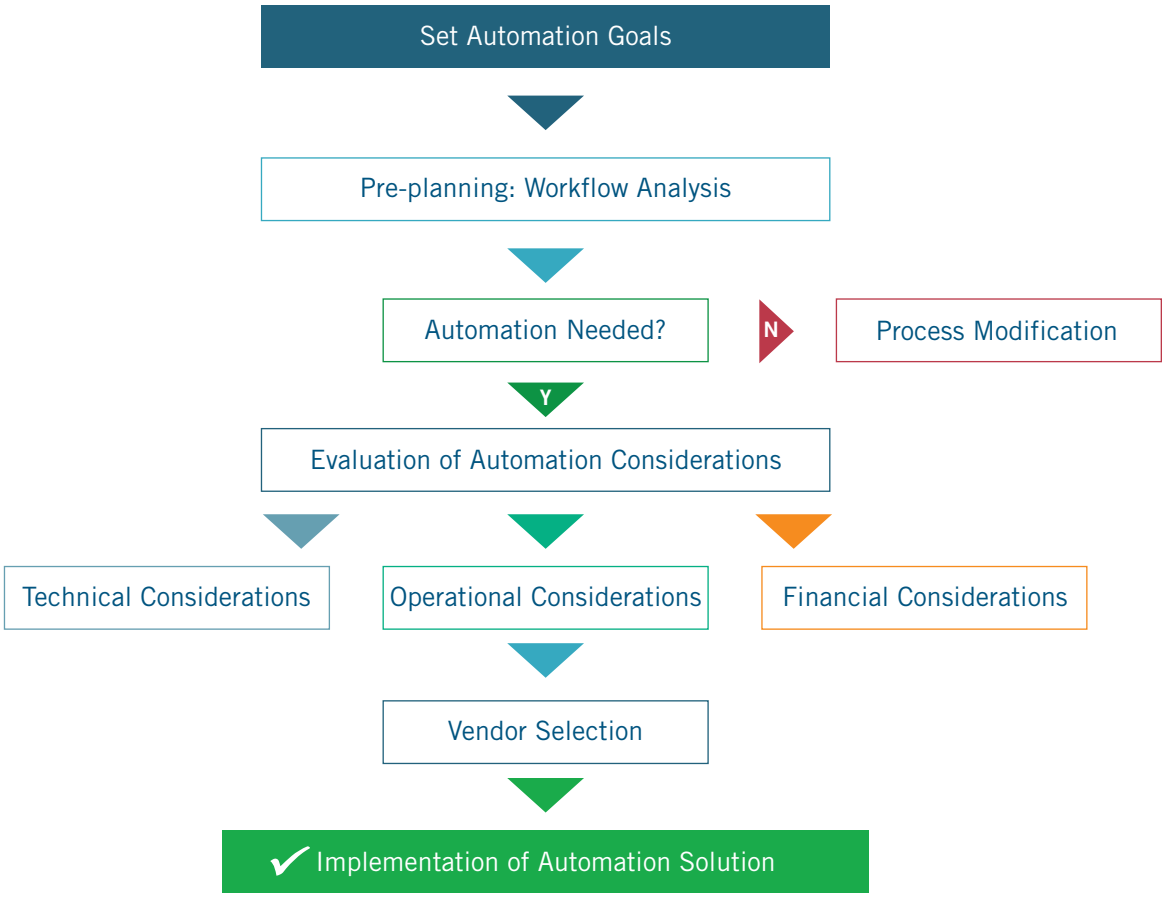


Figure B
An analysis of the volume of IHC slides and two different acquisition options (reagent rental vs capital purchase).



Conclusion

Today, the IHC lab is facing greater challenges to standardize procedures and increase efficiency as pathologists are demanding higher throughput and quality in the era of personalized medicine. IHC automation is considered one of the key improvements to achieve this goal. Based on the above discussion, a high-level outline of how to implement IHC automation solution is depicted below. There is no one perfect standard solution and it is essential for each lab to consider its own constraints and the merits of different options in order to find an optimized solution to meet their unique needs.



About Biocare Medical

Biocare Medical is a global leader in solutions for cancer research and diagnostics, providing world-class reagents, including tissue-conserving simultaneous multiplex antibody cocktails and detections; renowned customer care; and a comprehensive suite of advanced instrumentation for IHC, molecular, and histology testing. Customers include clinical anatomic pathology labs, pharmaceutical companies, CROs, and biotechnology companies as well as academic, government, military, and other non-profit labs. Biocare's reagent portfolio includes primary antibodies, Multiplex IHC, and FISH probes for target indications. Biocare also offers a unique line of polymer detections for clinical, human, and animal research that delivers high sensitivity and exceptionally low background. The Company's advanced platforms of semi and fully-automated instrumentation have been designed to meet every need from high throughput clinical diagnostics to flexible research requirements. Biocare Medical's corporate headquarters and operations are based in the San Francisco Bay Area with a global distribution network.

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