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Your Guide to Digital Pathology

Gain Insights

Safety Assessment

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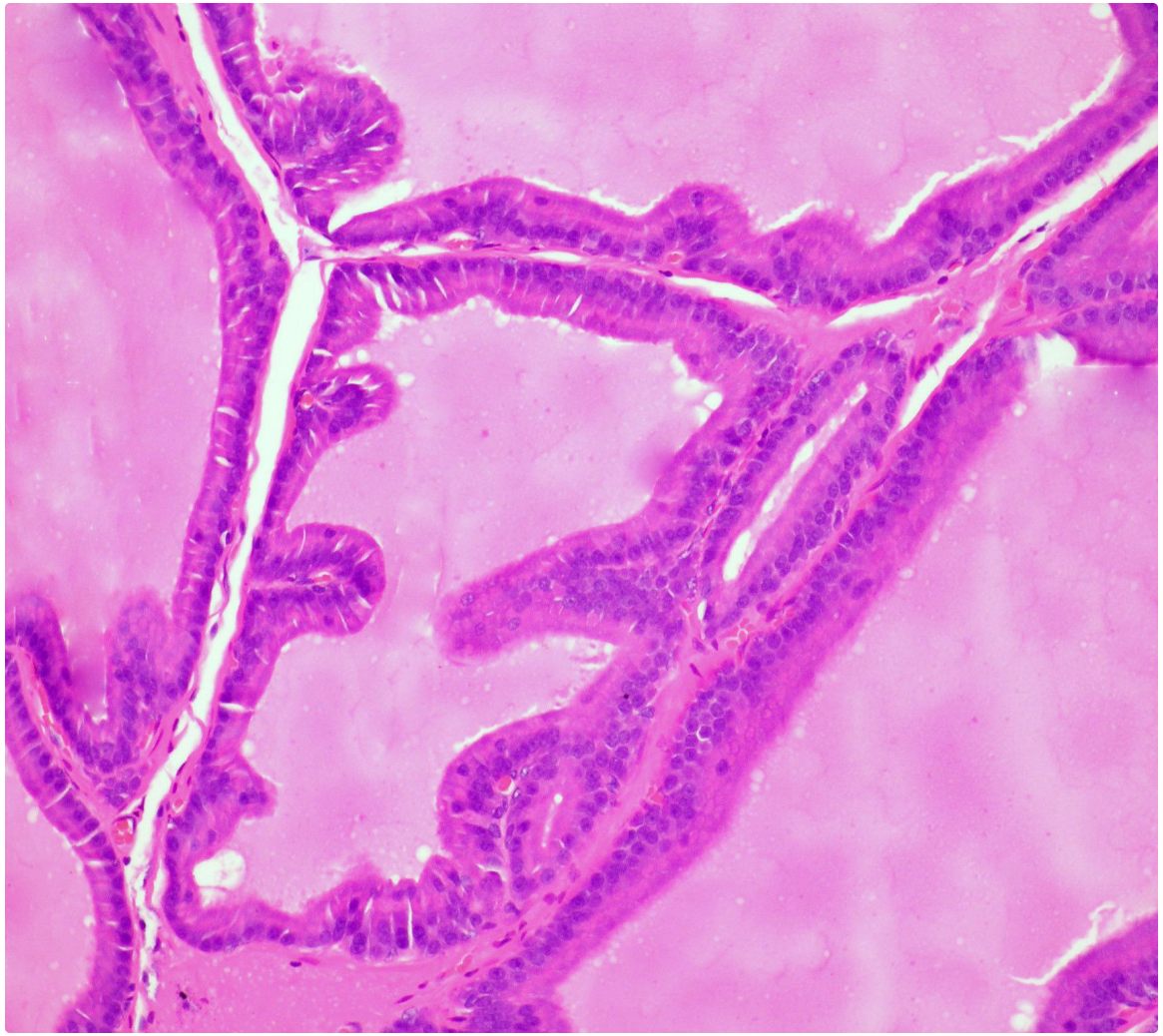
Introduction

It is expected that pathology workflows will be fully digital, from the lab to analysis and reporting, in the near future. Charles River is leading the nonclinical digital pathology transformation and has built a GLP-validated digital workflow that supports the needs of our clients. We have implemented a GLP-validated semi-automated digital workflow from the whole slide scanner, to digital primary and peer review, to archival. Ongoing optimization of this workflow using hardware and software-based automation, Cloud storage and archiving, and Artificial Intelligence (AI)-based methods will result in deployment of an automated digital-first workflow across all Safety Assessment sites by the end of 2027.

Terms and Acronyms to Know

- AI – Artificial Intelligence
- DIA – digital image analysis
- IMS – image management system
- LIMS - laboratory information management system
- Patholytix – licensed IMS from Deciphex
- WSI – whole slide image(s)



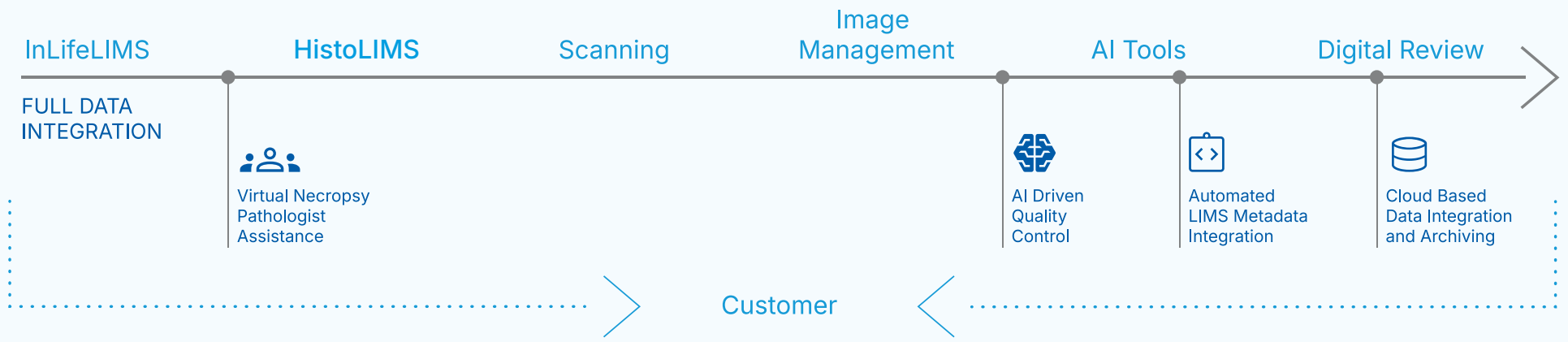
Why It Matters

The new paradigm for pathology is digital; the ability to streamline workflows, unlock deep, data-driven computational insights, and directly access more data than ever before makes digital pathology the future-proof solution to ensuring your competitive edge. Regulatory bodies are moving towards digital pathology via guidelines issuance and compliance requirements. Failing to keep pace is a risk to companies who want to ensure their long-term competitiveness. You need a trusted partner and innovator who enables you to digitize your study material (glass slides), and empowers you to make data-driven, real-time decisions afforded only to those wielding the most cutting-edge drug development technology.

Charles River delivers on this promise not only to our pathology clients, but to every single client via Apollo™, our cloud-based platform that offers real-time data visualization, milestones, documents, and program planning tools.

Questions to Consider

1. How do you manage remote collaborations or consultations with pathologists across different locations?
2. What challenges do you face with a traditional pathology workflow?
3. How do your pathology studies impact your other nonclinical milestones?
4. What pathology data can you access, and how quickly?



The Workflow

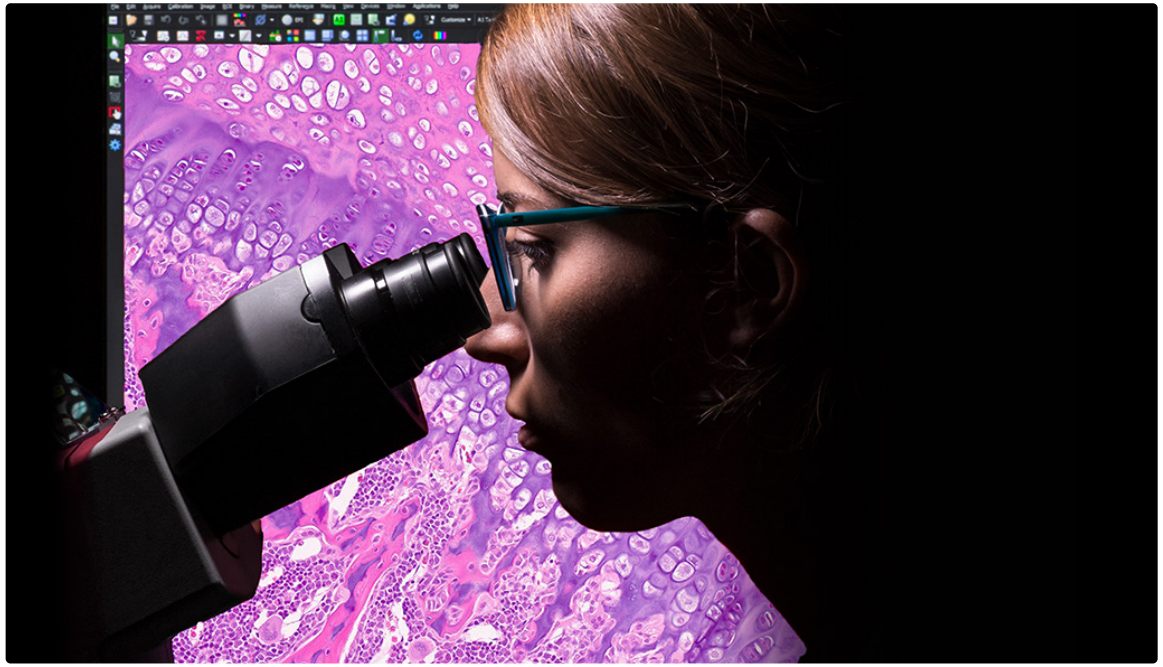
Our workflow for Digital Pathology is SOP-controlled. It begins with digital scanning of the glass slide on a GLP-validated slide scanner at the protocol-defined magnification, usually 40x. Each project undergoes a 100% quality control review of the whole slide images (WSI), and rescanning will be recommended if necessary before ingestion into the Charles River Image Management System (IMS). The metadata (such as animal number, tissue, block, group, etc.) is exported from the laboratory information management system (LIMS, e.g., Prima) and uploaded to the IMS (e.g. Patholytix, or alternate delivery per client request). The study is assigned to appropriate pathologist and/or data scientist, which enables them to download the WSI and associated metadata to their local system for digital review, aided by AI-driven quality control and computational tools. The full GLP Digital Pathology process is largely automated.

Primary Evaluation

The study pathologist performs the primary evaluation of the tissue sections using digital WSIs. The best practice for Charles River Laboratories is to provide the digital WSI and the associated metadata using our GLP-validated digital pathology system to the study pathologist. Our digital pathology system has undergone fit-for-purpose, rigorous testing and validation of all software and hardware components from the digital scanner to the viewer. We interviewed pathologists internally and externally and reviewed current literature to identify a key list of features difficult to characterize histologically and tested the equivalency of WSI and glass slide reviews.

Comparisons were performed of glass slides vs. WSI for features of the full tissue list and standard stains for all animal models, as well as immunohistochemistry sections, in our scientific qualification supporting GLP validation.

A client can review our validation methods and support documentation by requesting a formal audit through their CRL business contact(s).



>990k slides for primary evaluation

>900k slides scanned for digital pathology in 2025

Peer Review

The peer review pathologist performs their review of the study pathologist's primary evaluation of tissue slides using digital WSI. Following the study pathologist's evaluation (either on glass slides or WSI acquired at 40x magnification), the best practice for Charles River Laboratories is to provide the digital 40x magnification WSI and the associated metadata using our GLP-validated digital pathology viewing platform, Patholytix Preclinical (distributed by our partners at Deciphex) to the peer review pathologist. WSI for peer review can also be delivered using other methods (durable media or cloud transfer), with the qualification for intended use being the responsibility of the client. Our GLP-validated digital pathology system incorporates rigorous testing and validation of all software and hardware components from the digital scanner to the viewer. It is recommended that the client match or exceed the specification for the hardware/software used by Charles River to support appropriate validation for intended use.

Benefits

- Eliminate overhead expenses associated with glass slides
- Overcome logistical hurdles such as shipping delays, damage, and international transport permits
- Empower users with direct, self-serve data access
- Enable location-agnostic pathologist collaboration
- Gain efficiencies through AI-enabled decision support tools
- Develop insights and analytics with data-driven computational support

>1.4M slides for peer review

>150 pathologists worldwide

Whole Slide Images

Viewing Software

Charles River Laboratories has adopted the Deciphex Patholytix Preclinical slide-viewing software that uses local caching of WSI for pathology diagnostics (primary evaluation and peer review). This licensed software has been specifically developed for the purpose of digital pathology evaluation in toxicology studies in collaboration with Charles River and other industry pathologists. We also use Patholytix as an image management system (IMS).

Generation

Charles River Laboratories has a global fleet of slide scanners composed primarily of Leica Biosystems (Aperio) GT450 scanners and Hamamatsu S360 scanners. We also have specialty scanner options for fluorescence and biomarker work, which include Zeiss Axioscan, Hamamatsu S60, and Akoya PhenoCyler and PhenoImager. Scanning is performed at 40x magnification unless an alternate magnification is expressly requested. The slide scanning process is fully GLP-validated and WSI can be generated for both GLP and non-GLP studies.

Client Hardware

Using hardware that does not meet these specifications may result in an inferior user experience and puts the client at risk of not supporting the intended use requirements of the digital workflow as tested by Charles River Laboratories. We invite you to contact us to discuss your specific hardware considerations.

Minimum specifications are as follows:

- Dell Mobile Precision 7680 Laptop: i7-13850HX, 16GB RAM, 500GB SSD, with Nvidia RTX A3050 Ada graphics
- 8TB M.2 NVMe Internal Solid-State Drive (SSD) E.g., Crucial CT4000P3PSSD8
- Dell WD19DCS Docking Station
- Minimum 27″ 144 Hz, 2K, 2560 x 1440, QHD, G-Sync, 1MS response E.g., ASUS VG27AQ
- USB-C to DisplayPort cable, 4K, 6′, E.g., Tripp Lite

Mitotic Figures	Eosinophilic Granules	Intracellular Pigments	Microvacuolation
Viral inclusions	Hyaline droplets – renal tubular epithelium	Foreign material (Lung)	Crystals
Intracellular parasites	Intracytoplasmic basophilic granules	Basophilic tubules	Axonal degeneration
Bacteria	Single cell necrosis (GI crypts, liver and neuronal)		

Points of Interest (POI) Examined in Glass Slides vs. WSI Qualification

WSI vs. Glass Slides

Charles River Laboratories has compared and validated glass slides and WSI for tissues examined in each of our main general toxicology nonclinical species. Board-certified pathologists from multiple sites confirmed that all tissue and cell features could be assessed equally when comparing the glass slides and WSI. The documentation of this work is included in our GLP validation. Input from literature and external pathologists was also incorporated into the validation process, with the result being final confirmation that WSI, in a controlled environment, provides a "faithful representation" of the features and Points of Interest (POI) observed on a glass tissue slide.

While there are differences in glass slide evaluation and WSI use, we see light and digital microscopy to be equivalent for the intended use of toxicologic pathology microscopic evaluation. Monitoring of the digital pathology process is ongoing, and pathologists will always have access to the glass tissue slide(s) if deemed necessary for their diagnostics.

Regulatory Status of WSI and Their Archiving

Per regulatory guidance, if WSI are used by the study pathologist to generate diagnostic data that is captured and supports reporting, then these WSI are archived with oversight by an archivist in accordance with Charles River retention policies. Following peer review consensus and/or at the instruction of the study pathologist, the archivist will lock the study WSI in the Deciphex Patholytix Preclinical software. Upon finalization, the study status will be set to “archived” and study WSI and all corresponding metadata are archived to a secure Charles River cloud-based environment. As is the case with glass tissue slides, clients can elect to transfer archival responsibility to their organization or a third party. Peer review is a consultative exercise and WSI associated with a peer review use are not archived under GLP and are deleted from Charles River systems four months from scanning or at study finalization, whichever comes first.

Validation of Digital Pathology for Primary Evaluation and Peer Review

Validation of Deciphex Patholytix Preclinical platform was completed for peer review in 2020 and for primary evaluation in 2022. As of the date of this publication, we have scanned more than 1.4M slides for peer review and over 990k slides for primary evaluation using our validated digital pathology system. The full chain of custody of the images and metadata is in place for the entire workflow. Security, functionality, and compliance standpoints have been tested and documented from image capture (through scanner and image repository validation) to upload and download of images/metadata to Deciphex Patholytix. If a client uses the digital pathology system, to ensure full compliance under current regulations, the hardware and software they use must also be covered by a validation cycle of their own, using the client's processes for these activities in completing the end-to-end validated state. Charles River and Deciphex can provide guidance to clients in the approach and elements required to ensure that GLP compliance can be claimed for the entire chain of custody.

Regulatory Acceptance

As of November 2024, regulators have audited the digital pathology workflow at multiple Charles River sites without findings. We also presented our Digital Workflow to all three review divisions of the FDA in April 2023. As of the date of this publication, approximately 4,600 studies have been digitized for agrochemicals, gene/cell therapy, biologics, and small molecule candidates in different stages of active development (pre-IND to registration). Medical pathologists use similar workflows with comparable scanners under a medical device authorization to complete digital diagnostics. Industry guidelines from the Society of Toxicologic Pathology (STP) and European Society of Toxicologic Pathology (ESTP) highlight key considerations for using digital pathology in nonclinical safety assessments. These methods are informed by regulatory scientists, ensuring that our digital pathology services align with the highest regulatory standards for accuracy and compliance.

GLP-validated Digital Image Analysis

For specialty pathology needs that arise outside of the full digital pathology workflow, Charles River offers 21 CFR Part 11-compliant custom algorithm development for quantitative digital image analysis (DIA). Highly trained and experienced image analysis scientists within our global Safety and Discovery network, spanning sites in the U.S. (Mattawan), Canada (Laval and Senneville), and Europe (Edinburgh and Evreux) are available to assist you in the design of your study to extract the most meaningful data possible from your samples. The Visiopharm platform is utilized to further enhance our existing WSI capabilities with machine and deep learning image analysis.

Our global working group of pathologists and scientists have expertise in developing algorithms that can drive your scientific discoveries and safety evaluations. In-house and partnering computer scientists, statisticians, and other specialists contribute to study design, development, and testing. These sophisticated image analysis algorithms can be applied as decision support tools for pathologists or for producing primary data for-nGLP and GLP studies.

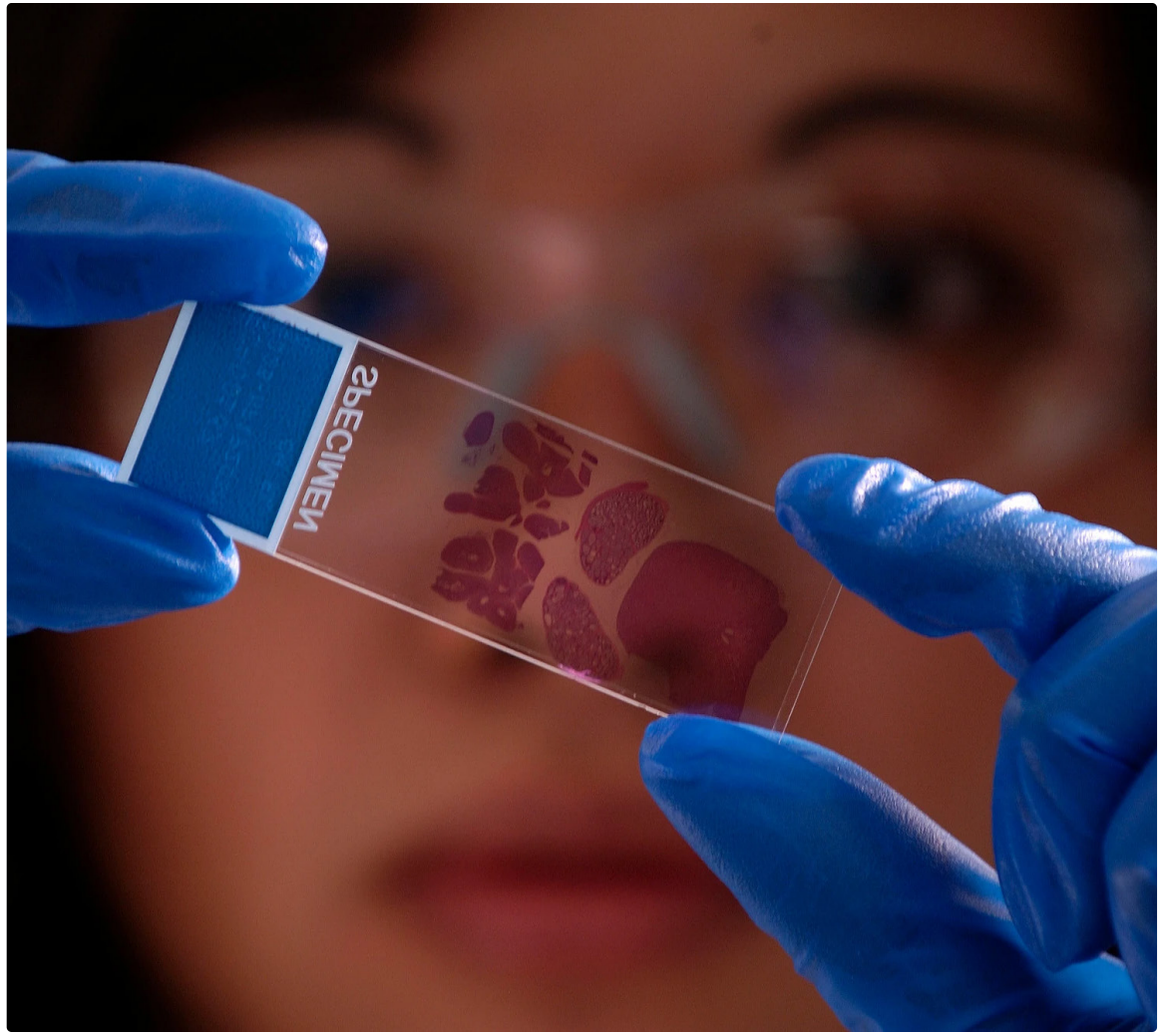
Charles River extends digital pathology capabilities into high-plex spatial pathology and profiling services, enabling simultaneous visualization and quantification of dozens of biomarkers within intact tissue architecture. This approach provides deeper insight into cellular interactions, microenvironment organization, and mechanism of action in both nonclinical and clinical studies.

Beyond the examples listed here, our image analysis experts are ready to help you with a wide range of quantitative measurements for your program, tailored specifically to your needs.

- Quantitative analysis of *in situ* hybridization images to characterize DNA or RNA expression in tissues, providing robust spatial transcriptomics data
- Static and dynamic measurements for musculoskeletal pathology
- Image analysis of immunohistochemically or histochemically stained slides, including number of labeled cells, area of positive staining, and tissue composition analysis
- Determination of cell proliferation index (Ki67, BrdU, PCNA) or apoptotic index (cleaved caspase-3, TUNEL)
- Diameter of stented blood vessels for medical device pathology
- Extent of infarcts in the heart
- Capillary angiogenesis in cutaneous wound defects, including microvascular density quantification
- Goblet cell number in the respiratory tract
- Adult and juvenile rat cerebellar and cerebral measurements for neuropathology
- Myelination index and neuronal G-ratio calculation for neuropathology
- Cell phenotyping and neighborhood analysis, identifying functional cell populations and their interactions

Final Considerations

Conventional approaches to pathology, while still effective, may soon face critical limitations as new digital technologies become the standard. Implementation of digital pathology processes streamlines workflows and affords deeper, more impactful insights than what traditional light microscopy methods can yield, allowing you to de-risk better and earlier. You can increase your probability of success by ensuring your drug development partner has well-trained and experienced scientific staff to conduct these studies using the most advanced technologies, as well as the understanding of regulatory guidelines to perform the required studies to support your regulatory submission. Finally, not only do our digital solutions put your pathology data at your fingertips, but accessibility of your entire drug program data is an important consideration that should not be overlooked. In conjunction with Charles River's Apollo™, you have the power to access and share your nonclinical study-related information in a secure environment while uncovering a new world of speed, insight, and accessibility for more informed decision-making.



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Learn more. Visit criver.com.
Contact us for personalized help.

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