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The status of digital pathology and associated infrastructure within Alzheimer's Disease Centers

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ABSTRACT

Digital pathology (DP) has transformative potential, especially for Alzheimer disease and related disorders. However, infrastructure barriers may limit adoption. To provide benchmarks and insights into implementation barriers, a survey was conducted in 2019 within National Institutes of Health's Alzheimer's Disease Centers (ADCs). Questions covered infrastructure, funding sources, and data management related to digital pathology. Of the 35 ADCs to which the survey was sent, 33 responded. Most respondents (81%) stated that their ADC had digital slide scanner access, with the most frequent brand being Aperio/Leica (62.9%). Approximately a third of respondents stated there were fees to utilize the scanner. For DP and machine learning (ML) resources, 41% of respondents stated none was supported by their ADC. For scanner purchasing and operations, 50% of respondents stated they received institutional support. Some were unsure of the file size of scanned digital images (37%) and total amount of storage space files occupied (50%). Most (76%) were aware of other departments at their institution working with ML; a similar (76%) percentage were unaware of multiuniversity or industry partnerships. These results demonstrate many ADCs have access to a digital slide scanner; additional investigations are needed to further understand hurdles to implement DP and ML workflows.

KEYWORDS: Alzheimer disease, Computational pathology, Deep Learning, Digital pathology, Machine Learning, Quantitative pathology, Slide scanner

INTRODUCTION

Pathology practice has been profoundly transformed (1–3) by the advent of microscope slide scanners and the introduction of whole slide imaging (WSI) technologies more than 2 decades ago (Fig. 1—timeline) (3–14). Although there are extra steps within the workflow (Fig. 2) when incorporating digital pathology (DP), there are significant advantages given the rapid transferability and portability of the resulting digital image files (15, 16). In addition, computer-based interfaces (17) make WSIs accessible to multiple individuals, and this can be simultaneous, even from different geographic locations, thereby enhancing opportunities for education, collaboration, and consultation between persons, particularly in areas in which pathologists are not readily available (15, 18–20). Combining DP with quantitative assessment tools, such as machine learning (ML) algorithms, can bring about paradigm shifts in assessing neuropathology through deeper phenotyping of brain tissue, enabling scalable and more in-depth objective analyses, and enhancing harmonized shareable workflows (21, 22). Publicly available programs such as ImageJ, QuPath, and machine learning algorithms, and software associated with slide scanners, have been used to provide deeper understanding of neuropathology processes associated with Alzheimer disease (AD) and related disorders (ADRDs) (17, 23–28).

Globally, AD is one of the most prevalent neurodegenerative brain diseases and is often associated with other neurodegenerative and vascular features that lead to cognitive impairment and dementia (29). This devastating disease poses a substantial social and economic burden to healthcare worldwide (21, 30). The number of Americans aged 65 years or older who suffer from AD is estimated to be at least 6 million. It is anticipated by 2050, this number will more than double. According to a projection, the cost of managing ADRDs in 2022 will be $325 billion annually. By 2050, these costs could reach nearly $1 trillion (31). Postmortem histopathological evaluation of the brain is the gold standard for definitively diagnosing ADRDs (22). AD is neuropathologically characterized by the presence of extracellular aggregated amyloid β (Aβ) protein in the form of Aβ plaques and aggregated hyperphosphorylated tau protein in the form of neurofibrillary tangles and dystrophic neurites (for review see [32]). Established criteria to assess AD pathological hallmarks are predominantly based on semiquantitative scoring schematics with considerably high interrater variability (33–37). These pathologic features are thought to begin as much as 20 years prior onset of cognitive symptoms. Further they may interact, synergistically or antagonistically to influence onset and progression of the cognitive syndrome (38). Determining how all this may occur and develop is part of the current challenge facing ADRD neuropathology-based investigations. In the past we have focused on persons expressing the cognitive syndrome as "dementia" and then characterizing the pathologic features present. With DP, we will also have a better window through which to observe similar pathologic features among individuals without cognitive symptoms; further we aim to be able to link back these findings to prior clinical and biomarker data collected during life. It would be beneficial to develop tools to provide more objective quantitative measures, facilitating deeper phenotypes that will aid clinical correlations (22, 34, 39). Hence, there is an intensive global research effort to leverage innovative technologies with the overarching goal of better comprehending the mechanisms and heterogeneity of ADRDs and developing solutions for early detection and progression prevention.

Since 1985, the National Institute on Aging (NIA) has variably funded over 33 Alzheimer's Disease Centers (ADCs) within the United States. The mission of the ADCs is to provide individuals with comprehensive clinical evaluations, educational outreach and infrastructure to support cutting-edge research to better address the diagnosis, treatment, and prevention of ADRDs and therefore contribute to a deeper understanding of this devastating disease (40). In the spring of 2019, talks began amongst individuals within the ADC realm, and an email was sent to all ADC Neuropathology Core leaders searching for persons interested in forming a Digital Pathology Working Group. In June of 2019, the first of what became monthly meetings was held, where the overall goals of the group were to: (1) assess the needs and potential uses of digital pathology within ADCs, (2) evaluate feasibility of implementation of technology across ADCs, and (3) develop recommendations for the use of DP by ADC Neuropathology Cores. Although there are established recommendations for adopting WSI systems in pathology departments (41–44), implementation of DP and machine learning workflows can be particularly challenging. Hence, to aid in the goals of the ADC Digital Pathology Working Group to gain a deeper understanding of the current benchmarks in DP and ML across ADCs, a survey was developed, refined, and distributed to ADC directors and Neuropathology Core leaders. The current paper presents the results of the survey and provides a brief discussion of their implications.

MATERIALS AND METHODS

The ADC Digital Pathology Working Group, with the aid of the National Alzheimer's Coordinating Center, produced and disseminated a survey to ADC directors and/or Neuropathology Core leaders in the fall of 2019 to collect baseline data on awareness and use of DP and ML procedures among ADRCs. It is important to note the terminology to define ADCs can also include Alzheimer's Disease Research Centers (ADRC); to maintain the language previously used in the survey the ADC term will be used. The survey assessed topics such as: (1) infrastructure (such as type of digital slide scanners utilized), (2) data management and storage of WSI data (such as size of digital files), (3) knowledge and access to ML workflows, and (4) associated costs/funding. The survey was converted to a digital version using SurveyMonkey.com (Momentive.ai, San Mateo, CA) to facilitate collection of responses (see Supplementary Document for the full survey).

The link to the survey was electronically distributed via email to 35 past and current ADC Neuropathology Core leaders and/or ADC directors in the fall of 2019, and survey responses were compiled in the spring of 2020. Participation was voluntary, responses contained no personally identifiable

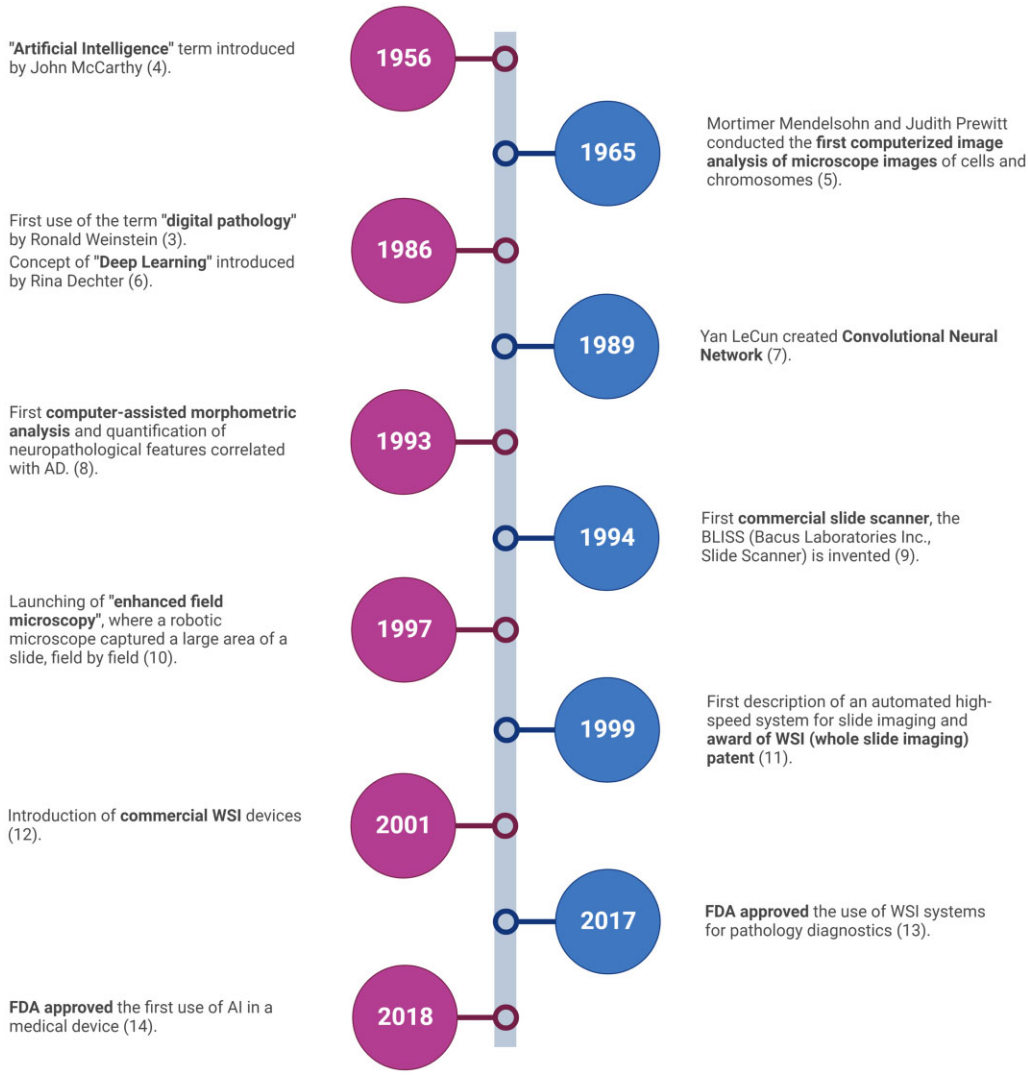

Figure 1. Timeline of select events in the field of digital pathology and artificial intelligence leading to advancement, regulation, and commercialization of WSI systems. AD, Alzheimer disease; AI, Artificial intelligence; FDA, Food and Drug Administration; WSI, whole slide imaging.

information, and results were anonymized. Categorical data are presented as frequencies and percentages. Figures were created using BioRender (BioRender.com).

RESULTS

Survey respondents

A response rate of 94.3% was achieved (33/35 centers), with 32 centers completing all responses. Most of those who completed the survey (75%) were Neuropathology Core leaders, followed by 12.5% who were ADC coinvestigators, 1 (3.1%) ADC director, and 9.3% selected other.

Infrastructure and associated costs/funding

Most respondents (81.2%) reported their ADC had access to a digital slide scanner, with Aperio/Leica being the most common brand (62.9%) and Keyence being the least (3.7%); responses were not mutually exclusive (Fig. 3). The most common file type of scanned slides was SVS (52%), followed by TIFF (16%), CZI (12%), QPTiff (8%), VSI (4%), ISyntax Philips proprietary file (4%) with 28% unsure, 16% reporting other, and no one selected JPEG. Half of respondents (50%) reported there were no fees for service for their ADC to utilize the digital slide scanner, 34.6%. stated yes, and 15.4% were unsure. The 2 most common uses of digital slide scanners were by the ADC (30.7%) and researchers (other than those in the ADC) (38.4%) while clinical (other than those in the ADC) was 23.0%, education (other than those in the ADC) was 3.8%, and 3.8% did not know. Half of the participants stated they had received institutional support to cover the purchase and operation cost of the slide scanner, followed by philanthropic support (15.4%) and NIA funding (11.5%) no respondent listed National Institute of Neurological Diseases and Stroke (NINDS) funding; approximately one-third of respondents (26.9%) were uncertain of the origin of the funding used to purchase the equipment; responses were not mutually exclusive (Fig. 4). Of type of slides scanned for ADC cases, 61.5% were immunohistochemistry-stained slides,

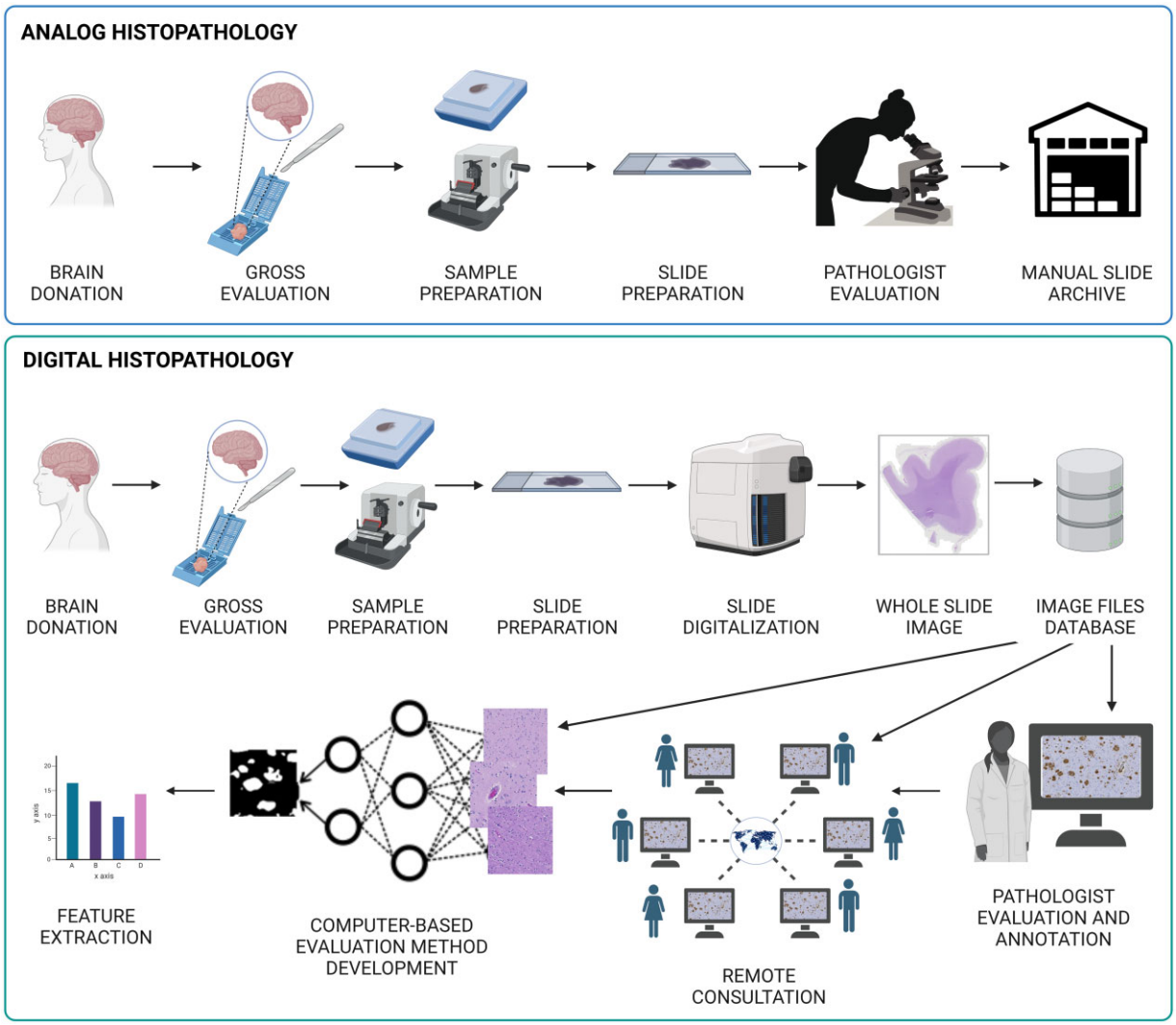

Figure 2. A landscape of the main differences in the workflows of analog and digital histopathology. From whole slide imaging (WSI), image files can be used for various purposes such as diagnosis and annotation, development of tools such as machine learning (ML) algorithms, to assess select features within the image (pathologies, anatomic areas etc.). Experts may use these measures to augment select portions of their annotations/evaluations.

followed by project-specific stains (57.7%) and hematoxylin and eosin (H&E) slides (50%), special stains (such as silver) (26.9%), and 3.8% were unsure. According to 15/24 (62.5%) respondents, less than 10% of their ADC slide inventory was scanned, 6/24 (25%) respondents listed 11%–25%, 2/24 (8.3%) listed 26%–50%, 4.2% were unsure and no respondents listed any number greater than 51% of their current slide inventory had already been digitized. A large percentage (95.6%) of those surveyed responded their ADC and affiliated personnel utilize the scanner to digitalize human tissue, followed by mouse tissue (56.5%) and nonhuman primates (17.4%), dogs (8.7%), other species (4.3%), and no respondents selected rat; responses were not mutually exclusive.

Data management and storage of whole slide imaging

Most respondents (37.0%) were unsure about the average scanned file size after compression, 29.6% denoted the file size to be greater than 1 GB but less than 4 GB, 3.7% reported the file size to be greater than 4 GB, and also 3.7% for both 100 MB or less, 101–500 MB, and 501 MB to 1 GB. Of respondents, 50% did not know the total amount of storage space all compression files occupy, 8.3% reported greater than 1 TB but less than 10 TB, and 4.2% for both greater than 10 TB but less than 20 TB and greater than 20TB but less than 30 TB, 8.3% reported greater than 30 TB but less than 40 TB, and 16.7% reported great than 40 TB. In 34.8% of cases, digital slide storage was maintained locally (on premise) and directly by the ADC; 30.4% of responses denoted onsite storage was handled by an entity other than the ADC; 26.1% denoted slides were saved on an offsite server shared with other departments, 17.4% stated offsite storage directly controlled by a department (i.e. shared departmental server), 17.4% other, and 4.3% reported offsite cloud storage provided by a third-party vendor; responses were not mutually exclusive. With respect to sharing of digital slide files, 50% noted digital slide files were shared outside of the institution; with 28.1% reporting their

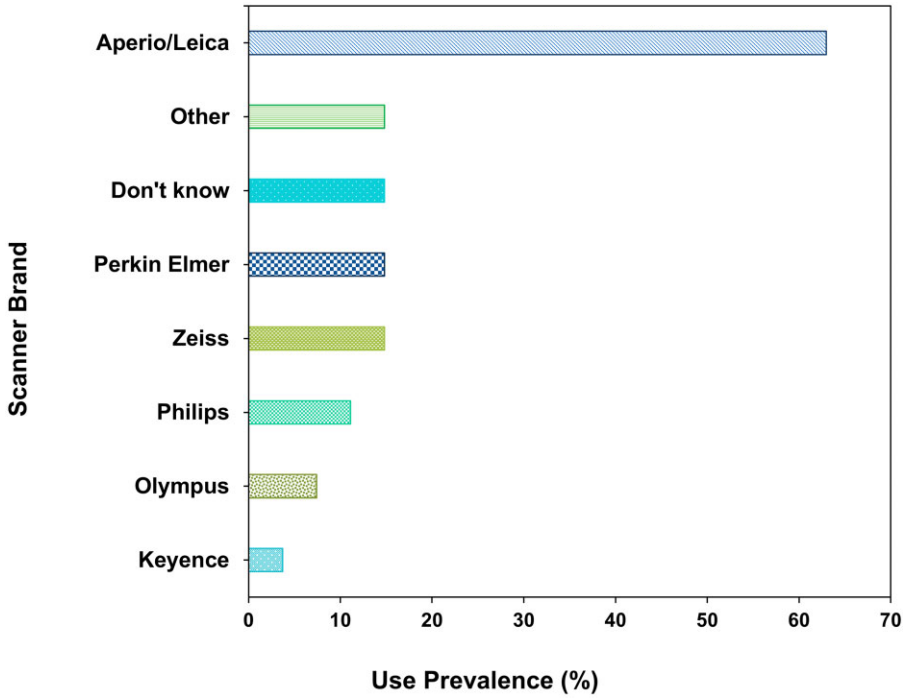

Figure 3. Prevalence of the use of digital scanner brands indicated by ADRCs during the period of the survey (2019) Responses were not mutually exclusive.

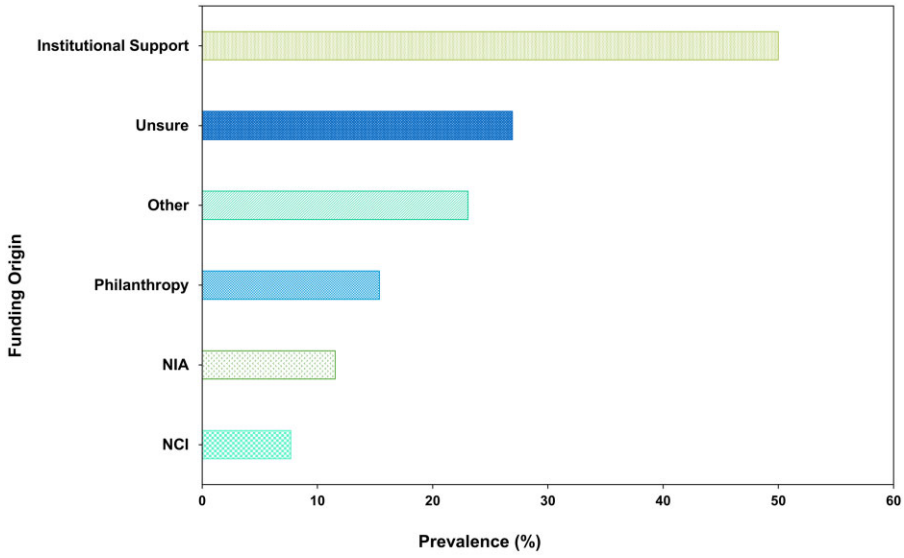

Figure 4. Type of funding utilized by the ADRCs to cover the purchase of WSI systems. Responses were not mutually exclusive. NIA, National Institute of Aging; NCI, National Cancer Institute.

ADC had discussions of digital pathology and related topics with respect to material transfer agreements (MTAs), collaborative agreements and/or IRB within the past year. When sharing slides in the past year, 18.2% reported there were MTA and/or collaborative agreements in place, 21.2% reporting no, 9.1% being unsure, and 54.5% stated the question was not applicable (N/A). Furthermore, with respect to sharing the main methods listed that were used, were web portals (such as eSlide Manager) at 28.1%, file sharing such as Google drive, or box at 12.5%, external hard drives at 12.5%, and 3.1% were unsure.

Slightly over half of respondents (53.1%) agreed a centralized scanner service would benefit the ADC, indicating they would be open to sending slides to one site for scanning. With respect to digital pathology (DP) and/or machine learning (ML) resources supported in any way by the ADC, over

one-third (40.6%) reported there was no resource support, while 31.2% stated there was slide scanner support, 15.6% service contracts for DP equipment, 25% personnel to manage DP infrastructure, 12.5% for GPUs, and 3.1% were unsure. Furthermore, within the past year when asked about the estimated percentage of their ADC budget allocated to DP and/or ML, 46.9% of responders stated none, 28.13% less than 5%, 6.2% between 5% and 10%, 3.1% between 11% and 25%. No respondents reported greater than 25% of their ADC budget was allocated to DP and/or ML while 9.4% were unsure.

Details on information printed on glass slides for identification within the ADRC neuropathology core as well as what information is included in the file name of ADC digitized slides are in Table.

Awareness of digital pathology and machine learning/artificial intelligence

Most respondents (75.8%) were aware of other departments within their institutions working with DP and ML/artificial intelligence (AI). Most respondents (72.7%) were unaware of the existence of multiuniversity partnerships in the field of DP and ML within their organization, and over 80% did not know of any existing collaborations between their institution and industry.

DISCUSSION

Implementing a DP system can enhance workflow efficiency, provide more reliable and consistent data for analysis, and enable the sharing of resources and information worldwide, thereby contributing to a better collective outcome (22, 24, 45–50). The ADC Digital Pathology Working Group is part of an NIA initiative to update the guidance on best practices and resources for new ADCs and centers undertaking new research areas. The purpose of the survey was to provide benchmark data for DP and ML across ADCs.

Despite the increased availability of slide scanners over the past 2 decades, a lagging regulatory process for commercial WSI devices in the United States posed a potential significant hurdle to the widespread adoption of DP in clinical settings (43, 51, 52). Initially, the Food and Drug Administration (FDA) classified WSI systems as class III medical devices, which are deemed "highest risk" medical devices (43). As a result of the collaboration between the Digital Pathology Association task force and the FDA, WSI systems have more recently been cleared for commercialization and reclassified as class II devices, providing manufacturers with a more straightforward route to FDA approval (42). Currently, there are 2 DP solutions available for primary diagnosis approved by the FDA: the Philips IntelliSite Pathology Solution (PIPS)—(approved April 12, 2017)—and the Leica Aperio AT2 DX System—(approved May 29, 2019) (13, 53). Most of the surveyed ADCs reported to have access to Leica/Aperio systems (62.96%), with very few denoting Phillips (11.11%). The reasons for this were not addressed by this survey but are most likely multifactorial and may include items associated with when systems were available, resources needed for implementation (costs), lower image quality, or less flexibility for research applications.

To determine which specific system is likely to be most suitable for one's work/institution, a thorough evaluation of potential stakeholders within the organization/unit should be conducted to correctly inform the decision-making process. A collaborative purchase effort can be initiated by amassing multiple entities (such as departments and/or centers) within the institution (for example, Cancer, Neuroscience, Pathology, Dermatology, Gastroenterology, and/or Telehealth) who would benefit from the resources in addition to contributing to the initial cost and/or service contract, operations, and maintenance. Most polled ADCs indicated they received institutional support for purchasing the WSI system, indicating institutional openness toward support of this technology. The acquisition of imaging equipment involves a substantial initial expense, and additional costs need to be considered, such as the purchase, installation, and maintenance of a file sharing/file storage system; personnel expenses (e.g. a technician assisting with slide scanning and management); an uninterrupted power supply; and adequate space for the equipment. The necessary resources to purchase and set up infrastructure for a digital scanner may be accomplished through a variety of means, including using funding from federal grants (e.g. NIA, NINDS, NCI) in the form of administrative supplements, and/or departmental funds for recruitment, and/or philanthropy.

When choosing a WSI digital slide scanner, the ADC Digital Pathology Working Group recommends compiling a list of potential users/uses to better understanding the scanner features needed to support those purposes. It should be noted each brand may offer a different model and there is no clear indication of which slide scanner is "best" (54). Some details on scanner features to consider should include: (1) load capacity (i.e. how many slides can be loaded and continuously run at a time unattended); (2) brightfield versus immunofluorescent capabilities (scanning of H&E, histochemical, and immunohistochemical stains at a reported 1.0–4.0 minutes/slide [standard size] based on tissue area and objective); (3) compatible objectives (most microscope objectives range from 5× to 40×); (4) slide size (standard slide size supported by all slide scanners is 26 mm×77 mm, with a glass/glass cover thickness of 0.9–1.2 mm in depth); and (5) image file format (i.e. TIFF, JPEG, SVS).

Regarding file-size and storage, some responses indicated they were unsure of average slide file size after compression and about the total space that files occupy. A digital slide derived from one human formalin fixed paraffin embedded 5μm brain section typically ranges between 1.0 and 4.0 GB in size (depending on compression), and if an institution is scanning multiple cases with multiple slides, large amounts of data can be generated quickly. Although scanning onto a computer's internal hard drive (HDD) or onto an external HDD may seem appealing and easy, a long-term storage plan, and a dedicated approach for data management, is highly recommended. Having files directly scanned onto the internal HDD may cause the computer to crash (overburdening local memory), ultimately causing data loss. If the ADC work is internal,

Table. Frequencies of information on glass slides and included in digitized file names (responses are not mutually exclusive)

	Information included on glass slides	Information included in the digitized file name
Globally Unique Identifier (GUID)	0%	0%
Unique deidentified autopsy number	90.32%	24.14%
Barcode	48.39%	12.79%
Patient ID	29.03%	10.34%
Stain	70.97%	17.24%
Date of staining	38.71%	6.90%
Anatomic area	25.81%	13.79%
Unique code corresponding to an anatomic area (e.g. 9 = amygdala)	12.90%	10.34%

the ADC digital pathology working group recommends consulting with the institution's IT department and/or data core personnel about setting up an on-site server. A server/file sharing platform may be a reasonable alternative if the ADC is expanding its collaborative efforts (17). Whenever data transfer is contemplated, it should be noted most slide scanners have a minimum requirement for connectivity (such as 10–100 MB/s) to ensure optimal results. It is critical to verify which specific file-sharing options are permitted at your institution, especially if you are working in a healthcare setting and/or if your slides contain any protected health information. Furthermore, support in advance of and during the initial setup may be required, including ensuring reliable network connectivity (i.e. network speed and manageable firewall rules). A specific recommendation for one service over another cannot be made, but backup power and storage and reliable archiving, along with data loss prevention features, are essential and need to be considered. Overall, involving the IT team in all discussions during the scanner purchase and implementation process is essential, as they have a thorough understanding of the institution's specific system requirements, risk assessments, and limitations.

As slide scanners are adopted more widely, a paradigm shift is occurring in the field of pathology, not merely because of increased efficiency and collaborative opportunities provided by WSI technology (Fig. 2). The digitalization of pathology slides is quickly becoming a major source of big data in medicine, allowing for the development of a vast diversity of image analysis applications based on AI and/or ML processes (55). As the name implies, AI refers to a machine or computer's ability to mimic or imitate human intelligent behaviors and perform tasks in a similar manner to those done by humans (56). ML is an application of AI that enables computers to learn from data without being explicitly programmed or aided by domain expertise (57).

Integration of digital pathology and AI/ML processes can have tremendous potential for neuropathology, particularly the diagnosis and research on ADRDs (22, 50). Our survey results emphasize certain opportunities in AI/ML processes within ADCs. Although most respondents were aware AI/ML workflows in other departments in their institutions, less than a third acknowledge multiuniversity partnerships. Even fewer knew of industry partnerships related to AI/ML with their institution. Of utmost importance, nearly half of those surveyed reported none of their current ADC budget was allocated to AI/ML technology within ADCs. The lack of existing AI/ML specific budget allocations highlights an important opportunity and niche for continuous education and research in this area.

Differences between pathologists' diagnoses commonly occur in clinical practice. In many pathology subspecialties, significant inter and intraobserver variability has been reported (58–60). In addition, most of the world is experiencing a shortage of pathologists, despite the increased demand for histopathological routine diagnostics (61, 62). The results of a recent global survey involving pathologists from 59 countries indicate that most professionals believe integration of AI tools with human input can improve workflow efficiency and significantly reduce human error and rater variability. A noteworthy finding, when questioned about the possibility of AI eventually replacing pathologists, most respondents believed that AI tools might increase the demand for professionals in the future (63).

A significant barrier to the implementation of ML workflows into pathology practice and research is the requirement for a vast quantity of high-quality WSI data in order to develop and train algorithms (64). Many histological materials, such as those collected within ADC neuropathology cores, have been collected over time. Many centers may have their own specific sampling/staining protocols based on the intended use of the sample and sampling guidelines for specific diseases. Furthermore, there have been changes in diagnostic criteria over time, which can lead to changes in staining and sampling procedures. This heterogeneity may be advantageous to take more ML approaches, but also may be problematic due to inadequate standardization. In this regard, harmonizing or implementing standardized protocols especially in a research setting can be challenging because of differences in slide preparation (sectioning, fixation, staining, and mounting), scoring algorithms, and inherent variability among raters (65–67). Slide preparation can also generate artifacts (over- or under-staining, air bubbles, folded tissue, etc.) that if not adequately represented in datasets used to train, validate, and test ML algorithms can produce inaccuracy in resulting ML algorithms (68). When multiple centers collaborate on an ML project, understanding similarities and differences in procedures and quality control methods should be acknowledged as these can be potential sources of adverse results. A single noise element in large pathology datasets can lead to misclassification and alter slide analysis and prediction, which may possibly result in

a substantial number of false positives or negatives (68). Further discussions as to what meta-data to include in whole slide image databases and reporting in published manuscripts, as well as harmonization strategies for historical samples, are imperative.

It is important to note the current neuropathologic diagnostic and staging criteria for ADRDs are based on microscopic assessments of characteristic neuropathologic brain lesions. After the presence of a specific brain lesion is identified microscopically, the lesion may be further scored based on intrinsic properties or its distribution throughout the brain. This is typically performed using a combination of semiquantitative assessments (e.g. CERAD neuritic plaque density) and regional distribution assessments (e.g. Braak neurofibrillary tangle staging) (33–36). Application of the various diagnostic neuropathologic criteria like the ones described above, can be a laborious process. This can be especially challenging when evaluating multiple pathologies and nuances within the same slide/case, in which the application of ML pipelines can be significantly beneficial and many have ventured into algorithm development and validation (24, 45, 47, 48, 69–71). Using supervised ML algorithms based on previously expert-trained models can offer significant improvements and remarkable success in traditional pathology tasks, achieving performance comparable to pathologists especially in the cancer realm (72–75). This innovative methodology is particularly promising to the research field of ADRDs, as ML models can augment the ability of experts, aid standardization, and accelerate quantitative tasks. This ultimately facilitates diagnoses, enhances tissue biomarker analytics, and improves therapeutics development.

CONCLUSION

This survey intended to establish current benchmarks of DP and AI/ML availability within ADCs. Our findings indicate most ADCs have access to a digital slide scanner, predominantly acquired through institutional funding. Most ADCs were unaware of the specifics of file size and storage. Although most respondents were aware of digital pathology and/or AI/ML work at their institution, a significant percentage reported having few resources for supporting research or diagnostic activities. Additional research is needed to better comprehend hurdles and challenges associated with implementing DP and ML workflows within ADCs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this study. The views and opinions expressed in this manuscript are those of the authors and do not necessarily reflect the official policy or position of any public health agency of the states or the United States federal government.

SUPPLEMENTARY DATA

Supplementary Data can be found at academic.oup.com/jnen.

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