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Review Article

Eye tracking in digital pathology: A comprehensive literature review

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ABSTRACT

Eye tracking has been used for decades in attempt to understand the cognitive processes of individuals. From memory access to problem-solving to decision-making, such insight has the potential to improve workflows and the education of students to become experts in relevant fields. Until recently, the traditional use of microscopes in pathology made eye tracking exceptionally difficult. However, the digital revolution of pathology from conventional microscopes to digital whole slide images allows for new research to be conducted and information to be learned with regards to pathologist visual search patterns and learning experiences. This has the promise to make pathology education more efficient and engaging, ultimately creating stronger and more proficient generations of pathologists to come. The goal of this review on eye tracking in pathology is to characterize and compare the visual search patterns of pathologists. The PubMed and Web of Science databases were searched using 'pathology' AND 'eye tracking' synonyms. A total of 22 relevant full-text articles published up to and including 2023 were identified and included in this review. Thematic analysis was conducted to organize each study into one or more of the 10 themes identified to characterize the visual search patterns of pathologists: (1) effect of experience, (2) fixations, (3) zooming, (4) panning, (5) saccades, (6) pupil diameter, (7) interpretation time, (8) strategies, (9) machine learning, and (10) education. Expert pathologists were found to have higher diagnostic accuracy, fewer fixations, and shorter interpretation times than pathologists with less experience. Further, literature on eye tracking in pathology indicates that there are several visual strategies for diagnostic interpretation of digital pathology images, but no evidence of a superior strategy exists. The educational implications of eye tracking in pathology have also been explored but the effect of teaching novices how to search as an expert remains unclear. In this article, the main challenges and prospects of eye tracking in pathology are briefly discussed along with their implications to the field.

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Introduction

The role of a pathologist is complex. Every day, one must assess numerous histopathological samples on a microscopic level and determine whether or not each sample is affected by one or more pathologies. The pathologist must also assess and measure several features (e.g. histological subtype, lymph node involvement, vascular invasion, tumor size, cellular arrangement), all of which will ultimately determine their final diagnostic assessment. For this reason, pathology is a field that requires years of training and immense focus. Insight into the pathologist's thought process and how that relates to their experience level, diagnostic accuracy, and efficiency could be incredibly useful and has been made possible with the use of eye tracking technology. Eye tracking itself is not new as it can be traced back as far as 1879 for use in ophthalmology.[1] Since then, eye-tracking has been deployed in a variety of medical settings ranging from radiology to surgery to psychology.[2–8] The common goal with eye tracking is simple: learn from the user, the skills and techniques used to complete the task at hand. However, the data collected with eye tracking provide insight into the user's thought process, information the user may not be able to articulate well or even be fully aware of. Thus, eye tracking allows one to unlock a deeper level of information that can ultimately be used to better understand and improve the workflow of the clinic.

In general, eye tracking technology uses a set of near infrared or infrared lights shone on the user's eyes to illuminate their pupils. This generates a corneal reflection which is read by one or more cameras found within the eye tracker. The angle of the corneal reflection is then continuously related back to the center of the user's pupils to compute a series of vectors that link real-time eye position to the location in which the user is looking on the screen.[9,10]

Currently, there are no guidelines for how pathologists assess digital whole slide images (WSIs), meaning all pathologists may interpret their slides a little differently. From the eye tracking data of these individuals, one can begin to understand the visual characteristics of certain tissue morphologies that capture the attention of pathologists and those that pathologists devote less attention towards. This information provides insight into the exact features that are associated with the difficulty level of cases and the corresponding interpretation time for such cases. Further, the eye tracking data of pathologists can be used to identify inefficiencies in search patterns, which would serve to improve the interpretation time and/or diagnostic accuracy of the clinical pathology workflow.

Eye tracking in pathology has been enabled by the emergence of digital pathology in the form of WSIs in 1999.[11] With WSIs, the entire glass slide can be converted into a high-resolution digital image which can be viewed on a screen, versus the narrow and confined view of a traditional light microscope. Prior to WSIs, the use of eye tracking in pathology was severely limited by the design of the conventional light microscope. The main limitation is the physical space restriction of a light microscope to include such a technology. Further, as explained above, eye tracking technology works using a series of light reflections off the user's eyes. The use of a light microscope would pollute the data collection with the series of lenses used within the barrel of a light microscope along with the light source itself altering the reflected light off of the pathologist's eyes. Despite these challenges, there are technologies that exist which incorporates eye tracking in a conventional microscope; however, these technologies are not widely used due to their high cost and extensive set up.[12] For these reasons, the introduction of WSIs removed the main barriers between eye tracking and pathology by allowing the eye tracking technology to physically fit between the pathologist and their field of view on the digital image, along with eliminating the series of concave and convex lenses used to display the image to the pathologist.

It is worth noting that telepathology precedes WSIs by approximately 20 years, which originally began as individual screenshots of glass slides that were taken through the view of an optical microscope.[13] These digital images, however, are restricted to a small subset of the glass slide, providing limited opportunities for eye tracking. This comes as any eye tracking data would only be able to reveal the pathologist's eye gaze on a static image, without any information as to how a pathologist navigates the slide. Over the two decades, however, telepathology has evolved to offer pathologists high-resolution video feeds of glass slides as well. Here, the microscopes are remotely operated, and the videos are sent to the consulting pathologist for review.[14] This form of telepathology offers a set up that is more feasible for eye tracking research. This comes as pathologists are given complete remote control of the microscope allowing one to assess their eye gaze as the pathologist navigates the slide, offering a more complete view of the diagnostic process. However, one caveat with this form of telepathology is the effect of lag time when focusing or changing magnification of the microscope. In the context of eye tracking, this means that a pathologist will not be as efficient as they would for digital slides which have minimal lag effects. Therefore, eye tracking in telepathology is possible, but one must consider the inherent effects induced by the remote nature of this field, and the translatability of their results to a non-remote workflow.

On a global scale, pathology is in the midst a digital revolution as many leading countries such as Canada, the United States, Germany, Australia, Europe, Japan, and Korea are converting or have fully converted to a digital pathology workflow.[15–19] In 2017, the United States Food and Drug Association (FDA) approved the use of commercial WSI platforms.[17] With this revolution, the clinical, research, and educational fields of pathology are booming with new possibilities and technologies, one of which is eye tracking. Along with the many advantages that come with digital pathology and WSIs, it is also much easier to track the eye movements of pathologists.

This article provides a comprehensive overview of eye tracking in pathology. The methods and results of previous work in the field are reviewed and assessed to provide the reader with a strong foundation on the current landscape of eye tracking in pathology. Further, this article discusses the applications and implications of this technology for pathology in both the clinical and teaching environments. The current challenges and some prospects for the direction of this field moving forward are also discussed.

Methods

A search query was developed on the PubMed and Web of Science databases for literature on this topic published up to and including 2023. The query string was as follows: (Pathology OR Histopathology OR Histopathological OR whole slide images OR “WSI”) AND (eye-tracking OR eye tracking OR eye tracker OR eye-tracker OR visual search). The selection criteria were to only accept case studies that implemented a form of foveated eye tracking in the assessment of digital histopathologic images (WSIs or telepathology). Studies that tracked the participant's assessment of images solely via viewport tracking were not included. Viewport tracking records the rectangular part of the image that the participant is viewing with respect to the entire specimen, but does not allow the participant's eye movements to be tracked within the viewport. For similar reasons, studies that tracked the participant's assessment of images solely via a “think-aloud” approach were not included.

The two databases provided a total of 3383 studies, 32 of which were duplicates, and 3329 studies were removed from consideration as they did not meet the acceptance criteria. The large number of studies returned in this query versus the number of studies used in this review was due to the inclusion of the generic term "visual search" in the search query, which was required to capture several contextually relevant studies that referred to eye tracking using this term.

The remaining 22 studies were used in this qualitative synthesis and the relationship between each study was assessed to identify 10 topics for thematic analysis: (1) effect of experience, (2) fixations, (3) zooming, (4) panning, (5) saccades, (6) pupil diameter, (7) interpretation time, (8) strategies, (9) machine learning, and (10) education. It is possible for a single study to apply to multiple themes and all data from each study were organized into their respective theme(s). Table 1 offers a brief summary of the 22 studies in this review.

Characteristics of included studies

Each study in this review reported quantitative eye tracking data. Six of these studies also included qualitative data in the form of assessing the participants' difficulty levels, confidence, and reasoning for their diagnoses.[20–25] Unfortunately however, none of these studies correlated their eye tracking and qualitative data, which is an important step in determining the underlying cognitive processes of the participant.[26] Instead, these five studies collected their qualitative data after the participants made their assessments and could no longer view the digital images. This data collection approach relies on each participant's accurate recollection of the digital image and is subject to the participants' abilities to accurately retrospectively recall the specific visual details that led to their assessments; this is particularly difficult where unconscious processing of some images details occurred. Additionally, most of these studies' results were validated by an expert panel of pathologists, except for the studies of Tiersma et al.,[24] Sudin et al.,[27] and Sudin et al.[28] Further, none of the 22 studies used a randomized controlled trial to investigate the effect of eye tracking with respect to their research questions. The closest study to a randomized controlled trial was that of Mariam et al.,[29] who compared the performance of a machine learning algorithm trained on gaze-labeled data to an identical machine trained on hand-labeled data. Although their control group was the machine trained on hand-labeled data, the objectivity of their results was potentially compromised as their ground-truth labels used for both machines were hand-annotated labels. Altogether, 661 observers participated in these studies and 438 digital histopathological specimens were interpreted. It is worth noting that 16 of the 22 studies in this review used breast biopsy specimens,[20,21,27,28,30–41] while the remaining studies used colon, skin, and gynecological specimens.[22–25,29,42] As a result, a common limitation to many of these studies was the possibility of their results being unique to breast tissue. In general, many of these studies were also limited by their small sample sizes, the inability to track para-foveal (peripheral) vision, only viewing one image from each case (which is unrealistic to the true clinical workflow), and a limited variety in study participants.

Effect of experience

It is important to note that "experience" is a subjective term that is not explicitly defined by many of the studies in this review. Of the studies that did, they described an experienced pathologist as one who was an attending or faculty pathologist, or had 10–30 years of experience in pathology.[37,38,42] The remaining studies referred to participants as more or less experienced than the remaining participants in the study. In general, the effect of expertise on diagnostic accuracy is inconsistent across the studies. Three of the more recent studies found that experience is positively associated with diagnostic accuracy.[28,41,42] Meanwhile four previous studies concluded that experience is not associated with diagnostic accuracy.[21,23,31,32] The most likely cause for these inconsistent findings is the variable amount of image-based data used for analysis. Specifically, studies that found a positive association between experience and diagnostic accuracy used 20–48 unique pathology cases. Only 10 unique pathology cases were used for each study that did not find any association between experience and diagnostic accuracy. Other possible explanations for this inconsistency such as participant pool, number of participants, specimen type, technology used, and study design were ruled out after further comparison due to the fact that no significant differences were identified between the two sets of studies.

It is important to note that the number of years of experience may not always provide an accurate representation of the true expertise of an individual. A pathologist who works in a busy practice and assesses many cases daily will be more experienced than one who has been a pathologist for the same number of years, but works in a smaller practice with fewer cases per day.[43] As a result, gauging participants based on their years of experience instead of case level is not always reliable and could be another reason for the discrepancy between the two sets of studies. Another possible reason for the discrepancy between the two study sets could arise from the specialty of the pathologists who participated in the study with respect to the tissue type being assessed. This comes as a pathologist who specializes in lung tissue will differ in experience from a pathologist of the same seniority who specializes in a different field of pathology, such as dermatopathology. Despite both pathologists have the same number of years in their practice, the dermatopathologist will be less familiar with lung tissue as they do not normally review lung cases.

Fixations

A common result amongst several studies was that the number of fixations decreased with increasing experience.[8,21,27,28,31,34–36,40,41] These studies referred to a fixation as the maintenance of one's eye gaze on a single location (Fig. 1). The more digital images a pathologist assesses, the greater their ability to ignore irrelevant information. This in turn improves a pathologist's ability to accurately characterize the regions in which they fixate, making their fixations more efficient.[44] Koh et al.[21] quantified this observation in their study where pathologists were tasked with a five-step diagnostic reporting process to be completed for 10 surgically resected invasive cancer breast specimens. The reporting process had pathologists comment on the overall diagnosis, epithelial proliferation, lymphovascular invasion, invasive components, and grading for each case. This study showed that experienced pathologists had an average of 55.30 fixations compared to an average of 178.90 fixations by less experienced pathologists. However, the opposite effect was observed when counting the number of fixations within the diagnostic region of interest (dROI). Experienced pathologists often had more fixations and longer fixation durations within the dROI than those with less experience.[23,31,40,42] For example, it was found that pathology residents spent 16% less time fixating on dROIs than faculty pathologists.[40] In other words, those with less experience were observed to have many fixations and longer fixation durations in non-dROI areas. This means that pathologists with less experience are more likely to not recognize a dROI when their foveated vision lands in that region, making them more vulnerable to visual distraction by non-dROI features. In support of this, Jaarsma et al.[23] reported their novice participants had difficulty recognizing parts of WSIs of colon tissue and distinguishing abnormal and normal colon tissue. A potential explanation for the difficulties experienced by less-experienced pathologists is that the WSIs shown in pathology courses are often resections presented as a cross-section at an angle that is optimal for demonstrating the tissue structure.[23] This representation, however, is not used in clinical practice for biopsies and could explain why pathologists with less clinical experience are easily distracted by non-dROI features.[23] In general, the study by Brunyé et al.[41] found that those with more fixations and longer fixation durations within the ROI had a higher diagnostic accuracy.

Zooming

A recurrent point of interest amongst many studies was the pathologists' use of zooming to change the magnification of the image. Of these studies,

Table 1
A summary of the studies used in this review.

Study	Sample size	Tissue type	Participants	Eye tracking technology	Screen size (inches)	Study goal	Conclusions
Drew et al. 2023[20]	32	Breast	92	RED-m by SensoMotoric Instruments	24	To test if pupil diameter could be used to identify biopsies that could benefit from a second opinion	Phasic pupil dilation was found to relate to case difficultly level. Tonic pupil dilation indicated arousal differences between pathologists as they interpret their cases
Brunyé et al. 2023[37]	32	Breast	89	RED-m by SensoMotoric Instruments	22	To show the shift between control states (exploration and exploitation) in terms of the Adaptive Gain Theory	Tonic pupil diameter is associated with image difficult ratings and zoom level. Phasic pupil diameter constricted upon zoom-in events and dilated immediately after zooming out
Brunyé et al. 2023[38]	32	Breast	90	RED-m by SensoMotoric Instruments	22	To use a mixed methods approach to isolate the sources of diagnostic error in pathology	Pathology trainees were more likely to use incorrect terminology to describe ROI features than attending pathologists. Failure to accurately describe features was the only factor strongly associated with an incorrect diagnosis
Sudin et al. 2022[28]	20	Breast	5	SmartEyePro	22	To investigate the effect of experience on zooming and panning behaviors, external markers of visual processing capabilities	Greater experience is positively associated with fewer fixations, quicker reading times, and higher diagnostic accuracies
Mariam et al. 2022[29]	4	Oral squamous cell carcinoma	2	GazePoint GP3 HD	26	To explore the viability and timing comparisons of eye gaze labeling compared to conventional manual labeling for training object detectors	Gaze-labeled annotations were faster than free-hand labeled annotations and were used to train machine learning algorithms on simple object detection and classification tasks
Drew et al. 2021[39]	32	Breast	92	RED-m by SensoMotoric Instruments	22	To more quantify the scanning and drilling behaviors and examine associations with diagnostic accuracy	Significant associations between accuracy and scanning rate were found. No such association was found for zooming rate suggesting pathologists gather critical information by scanning on a plane of depth
Brunyé et al. 2021[42]	48	Melanocytic skin	12	RED-m by SensoMotoric Instruments	24	To examine eye movements and diagnostic decision-making of pathologists when briefly exposed (500 ms) to digital whole slide images of melanocytic skin biopsies	The brief viewing time was sufficient to observe rapid shifts of the eyes towards critical abnormalities, high diagnostic sensitivity and specificity, and high accuracy localizing critical diagnostic regions
Sudin et al. 2021[27]	20	Breast	3	SmartEyePro	27	To investigate the visual search behaviors in trainee and expert pathologists, and to identify the parameters that could serve as markers of progress	Experience was positively associated with quicker reading times and fewer fixations. It was observed that the most utilized magnification level was 5 ×
Kimeswenger et al. 2021[25]	9	Skin	4	RED-m by SensoMotoric Instruments	Not disclosed	To study the regions of images that formed the basis for the predictions of the artificial neural network generated for automatic detection of basal cell carcinomas, and compare those with the diagnostically relevant regions outlined by pathologists	Machine learning algorithms rely on different recognition patterns for tumor detection compared to pathologists. Histopathological images can be analyzed by machine learning techniques
Koh et al. 2020[21]	10	Breast	3	SmartEyePro	27	To analyze how pathologists examine digital pathology images of different pathology modalities by using eye-tracking technology	Experience was positively associated with fewer fixations and shorter interpretation times.
Brunyé et al. 2020[40]	32	Breast	92	RED-m by SensoMotoric Instruments	22	To determine if early image viewing behavior is associated with experience level and diagnostic accuracy when pathologists and trainees interpreted breast biopsies	Expert pathologists were found to have a direct and efficient search behavior with early detection and recognition of critical image features
Brunyé et al. 2017[41]	24	Breast	40	RED-m by SensoMotoric Instruments	22	To examine how a pathologist's diagnosis is influenced by fixed case-level factors, their prior clinical experience, and their patterns of visual inspection	Experience was positively associated with diagnostic accuracy for only the atypia and ductal carcinoma in situ cases. It was also found zooming-in lead to a higher rate of over-diagnosis for benign and atypia cases
Brunyé et al. 2016[30]	24	Breast	21	RED-m by SensoMotoric Instruments	22	To determine if using eye tracking to monitor tonic and phasic pupil dynamics may prove valuable in tracking interpretive difficulty and predicting diagnostic accuracy	Tonic pupil diameter was positively associated with case difficulty level. Phasic pupil diameter was influenced by case difficulty and overall agreement with the consensus diagnosis
Jaarsma et al. 2015[22]	7	Colon	38	RED-m by SensoMotoric Instruments	Not disclosed	To study both aspects of expertise and analyses with three main constructs: encapsulations, efficiency, and hypothesis testing	Found encapsulations and efficiency are apparent in both visual and cognitive aspects of expertise. Experts used lower magnification levels and entered diagnostically relevant areas later than those with less experience
Brunyé et al. 2014[31]	10	Breast	7	RED-m by SensoMotoric Instruments	19	To test whether saliency maps can aid in discriminating between novice and expert pathologists' viewing behavior while interpreting digitized breast specimens	Experience was positively associated with fewer fixations and less revisited areas but was not associated with diagnostic accuracy. Found experts and novices followed different search patterns
Jaarsma et al. 2014[23]	10	Colon	38	RED-m by SensoMotoric Instruments	Not disclosed	To find expertise-related differences in the processing of histopathological slides using a combination of eye tracking data and verbal data	Found no association between expertise and diagnostic accuracy, but did find cognitive processing differed according to experience level

Table 1 (*continued*)

Study	Sample size	Tissue type	Participants	Eye tracking technology	Screen size (inches)	Study goal	Conclusions
Krupinski et al. 2013[36]	20	Breast	4	ASL SU4000 Eye-tracker	22.2	To examine and characterize changes in the ways that pathology residents examine digital whole slide images as they progress through the residency training	Experience was associated with quicker interpretation times, fewer fixations, and less examinations of non-diagnostically relevant areas
Raghunathet al. 2012[32]	10	Breast	7	RED-m by SensoMotoric Instruments	19	To evaluate the utility of mouse cursor movement data, in addition to eye-tracking data, in studying pathologists' attention and viewing behavior	Mouse cursor position moderately predicted eye gaze patterns. Mouse cursor movements may be a useful addition to future studies of pathologists' accuracy and efficiency when using digital pathology
Krupinski et al. 2012[33]	20	Breast	4	ASL SU4000 Eye-tracker	22.2	To examine changes in search patterns of pathology residents as they progressed through their residency program to determine when residents start to become more efficient in their search behaviors	With more experience, search times decrease overall, time spent on areas selected as potentially diagnostic that they would want to zoom on for further viewing decreases, and saccades are more efficient
Krupinski et al. 2011[34]	20	Breast	4	ASL SU4000 Eye-tracker	22.2	To examine changes in search patterns of pathology residents as they progressed through their residency program to determine when residents start to become more efficient in their search behaviors	Found total number of fixations generated per slide as a function of year of residency decreased, less time dwelling on the selected ROIs, saccade length increased, saccade distances decreased
Krupinski et al. 2006[35]	20	Breast	9	ASL SU4000 Eye-tracker	22.2	To assess eye movements of medical students, pathology residents, and practicing pathologists examining virtual slides	Experience was positively associated with quicker interpretation times and fewer fixations, fewer saccades, and lower saccade velocity
Tiersma et al. 2003[24]	2	Cervical interepithelial neoplasia	5	EyeCatcher	Not disclosed	To investigate how effectively eye tracking devices can visualize the scanning patterns of pathologists, for application in studies on diagnostic decision making	A scanning style and a selective style of visual search were distinguished, where the scanning pattern varied between observers

it was found that experience was associated with a greater use in magnification changes;[28,41] however, diagnostic accuracy in relation to zooming was inconsistent. Specifically, Drew et al.[39] did not find any evidence that zooming was associated with diagnostic accuracy in breast pathology. Conversely, Brunyé et al.[41] found zooming-in was associated with a higher rate of over-diagnosis for benign and atypia breast pathology cases specifically. In support, a study by Mercan et al.[45] (which was excluded from this review due to their sole use of viewport tracking) came to a similar conclusion with over-interpretation being associated with increased zooming of WSIs of breast pathology. A possible explanation for this discrepancy lies in the amount of data collected from each study. Drew et al.[39] had more than double the participants (and thus, double the data collection) than Brunyé et al.[41] This could have led to a more balanced dataset, canceling out the association between zooming and diagnostic accuracy. Interestingly, it was shown that pathologists (regardless of expertise level) exhibited a preference for 5× magnification, where experts spent more time at low magnification than those with less experience.[22,27,28] Further, Koh et al.[21] studied the early and late visual search patterns of pathologists interpreting digital

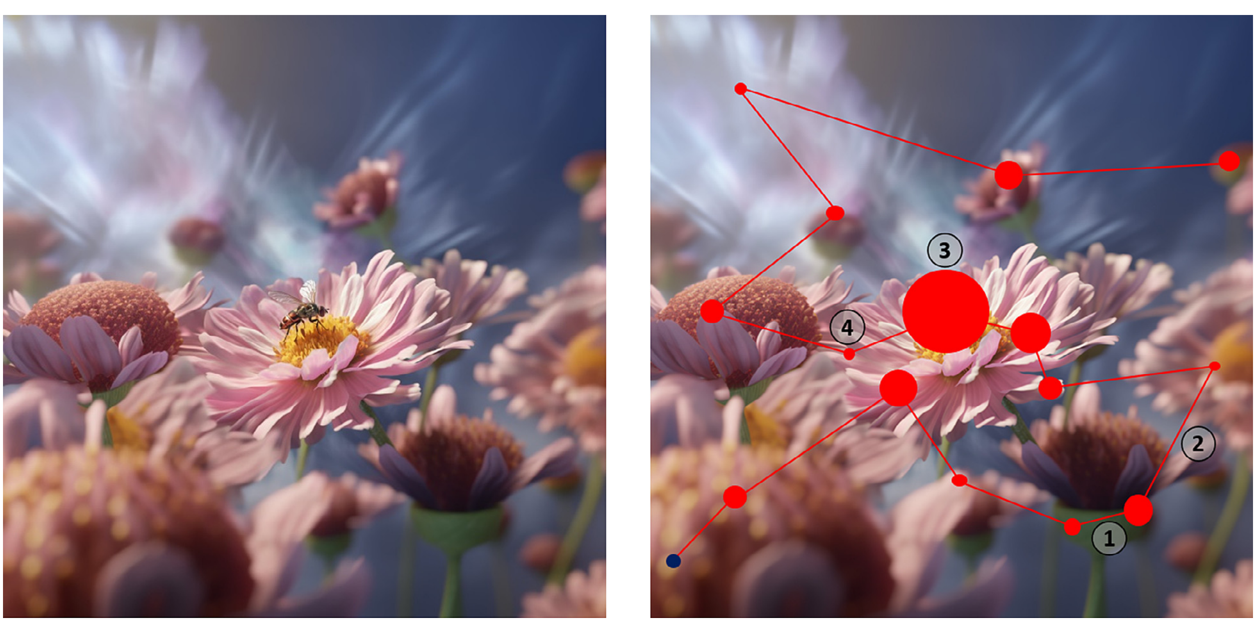

Fig. 1. Fixations and saccades. (Left) Original image. (Right) Sample eye gaze overlayed on image. Blue circle symbolizes initial fixation. The center of each circle represents a fixation point. The larger the circle, the longer the fixation. Lines connecting each fixation point are saccades amplitudes. The longer the line, the larger the saccade amplitude. (1) Short saccade amplitudes, (2) long saccade amplitudes, (3) long fixations, and (4) short fixations. Image was generated using Midjourney©. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

WSIs of surgically resected breast specimens.[21] They discovered that experienced pathologists used a higher magnification in the first 20 s of assessment, whereas those with less experience used a higher magnification after 40 s. One possible explanation is that it takes those with less experience more time to find a potential ROI that they wish to further examine.

It is worth noting, however, that none of the studies in this review explicitly discuss the relation of eye tracking to the use magnification changes for a digital image. A possible reason for this knowledge gap is the difficulty associated with correlating real-time eye tracking data with real-time magnification changes and the associated interpretation and analysis of the data. This is in comparison to the much simpler case of eye tracking data collected for a single magnification level. However, as eye tracking and digital pathology technologies continue to improve, it is expected that studies in the near future focusing on eye tracking in digital pathology will be able to fill this knowledge gap in the field to gain insight into the relationship between eye gaze and magnification change.

Panning

From this review, only 3 of the 22 studies briefly considered how pathologists scan and pan through image sections to assess the image at a fixed magnification; where panning is used to change the visible section of the image in the viewing window and scanning is used to assess the features of that image section by transitioning their foveated vision to different areas on the image. Drew et al.[39] suggested that scanning is a technique used by pathologists to gather critical information at a given magnification level and panning location. It was found that scanning rate was positively associated with diagnostic accuracy, where scanning rate was defined as the number of instances where an observer transitioned their foveated vision to a different area of the image, per second. Further, a common consensus amongst the studies was that experienced pathologists make fewer panning movements than those with less experience.[22,28] This demonstrates that experienced pathologists are more efficient at collecting and interpreting visual information in a given field of view than those with less experience. Interestingly, the underlying results of these studies demonstrate that the combination of eye tracking and image panning allows one to gain insight into the effect of peripheral vision in image analysis. This comes as peripheral vision serves to guide one's foveated vision by influencing the direction of their saccades and thus, the direction and rate of panning. Introducing the panning motion in eye tracking increases the complexity of the data analysis as both the digital image and the pathologist's eye gaze are in motion; however, this complexity offers an enriched insight into the pathologist by engaging their motor and cognitive skills simultaneously.

Saccades

Saccades are rapid eye movements that abruptly change the point of fixation.[46] The extent of these movements can be described in terms of amplitude and velocity. Saccade amplitude is a measure of the distance between fixation points. For example, small saccadic amplitudes are used for reading while large saccadic amplitudes are used to look around a room (Fig. 1).[47] Saccade velocity refers to the speed at which the eyes move between fixation points.[46] Eye tracking can also be used to quantify the saccadic patterns of pathologists when interpreting digital pathology images. It was found that saccade velocities decrease as a function of experience level, with greater experience leading to slower saccade velocities.[33–35,48] It was also found that fewer saccades and longer saccadic amplitudes were associated with more experience, with Drew et al.[39] relating longer saccade amplitudes to higher diagnostic accuracy.[34,35,39,40,48] A more in-depth analysis into saccadic patterns was done by Brunyé et al.[40] who assessed the early (before first magnification change) and late (after first magnification change) visual search patterns of pathologists assessing breast biopsy specimens. Results indicated that saccade amplitude was not associated with experience level during the early viewing period; however, it was in the late viewing period where the positive association between experience and saccade amplitude was observed, agreeing with the previous studies. The switch of saccadic pattern between early and late viewing is also indicative of experience level. This comes as experienced pathologists are more likely to perform a directed search towards the dROIs first, and then do a broad sweep of the image to exclude other possible ROIs and gather additional diagnostic information to support their initial assessment.[40] Conversely, Jaarsma et al.[22] was unable to identify the same relationship and concluded that experience level has no effect on saccade amplitude. This discrepancy could be due to differences in the tissue types being studied. Specifically, all five studies who reported a positive association between experience and saccade amplitude used breast biopsy specimens, whereas Jaarsma et al.[22] used colon biopsy specimens.

Pupil diameter

An interesting application of eye tracking in pathology is measuring the pupil diameter of participants as they interpret a digital pathology image. This line of research was inspired by the multitude of studies reported in literature dating as far back as 1960 in how pupil dilation can offer meaningful and reliable insight into one's cognitive processes.[20,30,49–55] The pupil can undergo two responses when stimulated: phasic and tonic.[56] A phasic pupil response is associated with task-related activities.[20] With this, it is believed that phasic pupil changes are sensitive to the constant fluctuations that occur in response to task-related stimuli.[53] Conversely, tonic pupil responses are associated with ongoing activities that allow the pupil diameter to change over time.[56] It is believed that tonic pupil diameter increases with an increase in mental effort or cognitive load related to the task. For this reason, tonic pupil diameter is associated with one's general attentional state associated with a task.[20,52] In general, it is important to keep in mind that both phasic and tonic pupillary responses can also be caused in part by the sympathetic response of the participant due to the experimental environment and their level of anxiety towards the experiment.

Three of the 22 studies in this review explored pupil diameter and how it relates to a pathologist's assessment of digital pathology images.[20,30,37] It is worth noting that all three studies used breast biopsy specimens as their tissue type and each participant was asked to rate their perceived diagnostic difficulty for each case. Further, all three studies conducted their experiments in a private conference room with dim lighting to minimize noise in the data collection due to pupillary response to lighting conditions. It is worth noting, however, that only one of the three studies specifically accounted for the effect of image magnification changes on pupillary response where a transient pupil dilatory effect was observed immediately following a transition from high to low magnification levels.[37] Generally, the consensus amongst the studies was that larger tonic pupil diameter was observed for the subjectively higher rated difficulty cases. This is supported by previous literature in the belief that tonic pupil diameter is associated with increased mental effort when presented with a difficult task.[30,50] Regarding the phasic response, each study explored slightly different characteristics. Drew et al.[20] discovered that the phasic response immediately after fixating on a dROI varied as a function of perceived case difficulty. Meanwhile, Brunyé et al.[37] studied the effect of zooming on pupillary response to find that phasic pupil diameter decreases (constricts) and increases (dilates) immediately following zoom-in and zoom-out events, respectively. In contrast, Brunyé et al.[30] discovered that phasic pupil diameter reflects the pathologist's level of diagnostic agreement with the reference diagnosis validated by an external expert panel. Interestingly, this study observed a strong decrease in the overall pupil diameter of a pathologist who gave a different diagnosis than the expertly validated reference. One possible reason for this response can be explained by the work done by Usher et al.[57] in pupillary response in relation to cognitive interpretation. Specifically, if the pathologist's eye gaze passes over a dROI, but they fail to interpret the area as relevant, their pupil diameter will subsequently decrease. This in turn leads to insufficient processing of valuable visual details and a less accurate diagnosis.[30,57]

Overall, despite pupillary response providing a unique set of information about the pathologist, it has not been found to be significantly associated with diagnostic accuracy.[20] Thus, the usefulness of pupillometry in the clinical pathology setting towards improving diagnostic outcomes is unclear. One main challenge uniquely faced by these studies was the effect of lighting conditions on data collection. Specifically, interpretations of pupil diameter variation needed to consider such variations were caused in part by one's cognitive processes and in part by the ambient and focal lighting conditions of the environment.[20]

Interpretation time

Studies show experienced pathologists have shorter interpretation and reporting times than those with less experience.[21,22,28,31–33,35,39,40,48] Specifically, reporting times ranged from 84.16 s to 4 min amongst the studies.[21,27] An outlier result, however, was reported by Raghunath et al.[32] who found viewing times differed according to the difficulty level of the case, but not according to the expertise level of the participants.[32] This inconsistency is possibly due to participants chosen for this study, where four of the seven participants were experienced faculty pathologists. This imbalance in expertise level in the participant group, along with the consideration that expertise based on years in the field is an unreliable measure of skill, could explain this discrepancy. On a similar note, the study by Drew et al.[39] assessed whether time devoted to a breast biopsy case was related to diagnostic accuracy but did not find such a relationship. However, this observation may be specific to breast pathology as Brunyé et al.[42] discovered increased viewing time improved the diagnostic specificity of melanocytic skin biopsies.

Strategies

Although it is difficult to characterize the search preferences of all pathologists, Brunyé et al.[31] and Drew et al.[39] refer to four general search strategies observed from their participants. These preferences may help identify new and existing search strategies of pathologists moving forward as eye tracking becomes more prominent in pathology and is thus included in this review. The first strategy is the detect-then-search process. Here, diagnostically relevant features are detected quickly, followed by a brief search to confirm the absence of other relevant features.[31] Conversely, the search-then-detect process is where one conducts a thorough visual search of multiple features after which the diagnostically relevant features are identified. This strategy is also referred to as the search-then-rule-out approach.[31] The third and fourth strategies loosely relate pathologists to “scanners” and “drillers”, respectively. These terms were coined for characterizing the visual search strategies of radiologists for lung nodule detection on chest computed tomography (CT) scans, which are three-dimensional volumes of image data.[6] With this, scanners were radiologists who slowly moved through the depth of the image and searched the entire plane of the lung before moving to the next plane in depth. Conversely, drillers were radiologists who would quickly scroll through the planes in depth while maintaining eye gaze on a small region of the lung.[6] In relation to pathology, Drew et al.[39] defined scanners as pathologists who mostly used panning movements to assess the entire image plane at a given magnification level, with minimal magnification changes. Meanwhile, drilling pathologists were identified as those who quickly moved through the magnification planes of the image by zooming in and out, while maintaining focus on a small region of the image.

There is currently no evidence that supports one search preference (or combination of preferences) is better than another in terms of diagnostic accuracy and efficiency. There is, however, one observation made by Brunyé et al.[31] that experienced pathologists often use a detect-then-search approach while those with less experience often use a search-then-detect approach. Further, the study by Drew et al.[39] found that clinicians often maintained a consistent strategy (whichever strategy that may be) across cases. It is important to emphasize that a consistent strategy was observed from pathologists when assessing multiple pathology images of the same tissue type. These study results provide no indication that a single search strategy would be effective for multiple tissue types. Interestingly, the idea of scanning and drilling patterns in pathology was loosely discovered by Tiersma et al.,[24] more than 10 years before these terms were coined for radiology and the subsequent pathology research study was conducted.[6,23,24] In this study, it was found the participating pathologists used one of two scanning patterns: a scanning type of search where pathologists briefly focused on many points in the image, and a selective type of search where pathologists restricted their gaze to within a lesion for long periods of time.[24] The former is indicative of scanning while the latter is indicative of drilling. It is worth noting that the time at which this study was conducted had very restrictive eye tracking technology in which the participants were unable to make magnification changes to the digital pathology image. Despite this, pathologists who restricted their regions of fixation on images embody the characteristics of a drilling strategy.

An interesting consideration to have regarding strategies amongst all reported studies in this review is the effect of the chosen tissue type for the experiment and the corresponding diagnostic questions asked. Specifically, as previously mentioned, 16 of the 22 studies in this review used breast biopsy specimens. A possible reason for the bias towards the use of this tissue type is that breast biopsies often have a consistent shape and the corresponding diagnostic questions asked to pathologists are fairly routine. Therefore, it would be reasonable to assume that the search strategies used for this breast biopsy task may be similar amongst the group of pathologists. Conversely, it would be expected that changing the tissue type or diagnostic questions asked would in turn alter the search strategy applied by pathologists as this changes their task. Therefore, the characterization of search strategies in digital pathology must also be considered in tandem with the specific task at hand along with factors such as worked experience.

Overall, it is important to keep in mind that the design and goal of an eye tracking study may lead to different search strategies. The difference in strategies may not indicate one is better than another for a given task; however, these strategies serve to offer insight into the important visual features of an image and biases inherent with a specific diagnostic process.

Machine learning

An interesting application of eye tracking in pathology is to train and test machine learning models to better understand and possibly improve the workflow of pathology. Two such studies were found in literature and are included in this review. The first study was conducted by Kimeswenger et al.[25] who implemented an artificial neural network (ANN) for detection of basal cell carcinomas (BCCs) and compared the differences in recognition patterns and relevant diagnostic features between machine leaning algorithms and expert pathologists. The ANN architecture itself was composed of a feature constructor convolutional neural network (CNN) and a classification ANN. The sensitivity and specificity of the ANN was 0.965 and 0.910, respectively. Interestingly, this study found that ANNs and pathologists identify BCCs using different recognition patterns. ANNs assessed the entire digital image equally, whereas pathologists often focused on individual areas within the image. These results highlight, at least in the case of BCCs, that pathologists are trained to fixate on structures with high contrast and color intensity, whereas ANNs are trained to consider all region types.[25]

The second study by Mariam et al.[29] explored the viability of gaze-based labeling in place of hand-based labeling for training object detectors in machine learning algorithms. Briefly, two deep CNNs were developed and separately trained on gaze-labeled data and hand-labeled data. It was found that gaze labeling can be used to train machine learning algorithms for simple object detection and classification tasks. However, gaze-based labeling is limited as it cannot outline shapes as accurately as hand-based labeling and thus is limited to the detection of simple oval and circular shaped ROIs.[29] Despite this, gaze-based labeling was found to save a considerable amount of time. Specifically on average, gaze-based labeling required 57.6% less time per label compared to the bounding box hand-labeling technique, and 85% less time per label compared to the freehand labeling technique.[29]

Education

In the teaching environment, eye tracking offers information that benefits both the teacher and the student. The teacher gains insight into how well the students are progressing and allows for personalized lesson plans aimed at helping each student with the particular aspects they may be struggling with. As for the student, eye tracking information from an expert in their field can help solidify the student's understanding by giving them a visual guide that maps how to assess a digital WSI. This in turn will help students excel in their field, reaching the level of an expert sooner. Currently in pathology, this information can flow in only one direction, from teacher to student, in the form of a multi-headed microscope.[58] Multi-headed microscopes allow for the teacher to share what they are seeing, and correctly position and focus a glass slide while verbally annotating the important features in the field of view. It is also possible to display digital WSIs on a screen to allow the teacher to verbally annotate the WSI. These methods of teaching, although helpful, rely on the teacher's ability to effectively articulate their search and thought processes. Further, the teacher's understanding of the student's progression is subject to hidden misinterpretations that, although may give the same diagnostic result in training, may lead to diagnostic inaccuracies in clinical practice. For example, a student may correctly identify a specimen as being cancerous, not because they are looking at the cancer cells, but instead are looking at the adjacent cells reacting to the cancer. The danger in this is that this generalization of cellular reaction to cancer is not uniformly true and may lead to false diagnostic reports. Another common example in which a student's hidden misinterpretations can propagate into inaccurate diagnoses is the identification and quantification of a mitotic figure. Specifically, mitotic figures are cells that are in the process of dividing and can be distinguished from non-mitotic figures based on the cell's shape and structure. It is common practice for pathologists to count the number of mitotic figures within a given tissue sample to make a diagnosis of cancer and grade the malignancy of cancer.[59,60] This task, however, heavily relies on a pathologist's ability to accurately distinguish between the characteristics of cell shape and structure. Any misinterpretation with regards to what indicates a mitotic figure may lead a pathologist to under- or over-quantify the mitotic activity in a tissue sample, leading to inaccurate diagnostic reports.

Generally, studies have shown that providing medical trainees with the eye movements of experts over cases is beneficial in learning which features are most important for their task.[44,61] Eye tracking use in pathology training research settings have shown that pathology residents become more efficient at searching digital pathology slides as they progress through their residency program, which in turn has led to their improved ability to render a diagnosis in a timely manner.[21,31,33,34,36,40] Several studies by Krupinski et al. between 2011 and 2013 showed that with each successive year of residency, the visual search of residents became more efficient in terms of decreased search times, larger saccade amplitudes, decreased saccade velocities, and less non-dROI fixations.[33,34,36] For example, one longitudinal study followed a set of residents throughout their 4 years of residency and found that the total number of fixations per slide decreased from a high of 129.64 in the first year to a low of 24.63 in the fourth year of residency.[34] Additionally, Brunyé et al.[40] found early and late visual search patterns showed a 10% and 2% increase respectively in the odds of fixating on the dROI for breast biopsy WSIs with each year of residency. Overall, these trends in residency progression move towards those of experts as previously discussed in this review. Further, Krupinski et al.[36] identified two general points within residency where improvements in search and efficiency are most noticeable: between the first and second year, and between the third and fourth year of residency. It is important to note that a resident at the completion of their fourth year does not resemble the characteristics of an expert; however, these studies show that with continued clinical exposure, new pathologists will continue to improve and eventually become experts.

In a slightly different approach, Brunyé et al.[38] used eye tracking and the corresponding pathology reports of participants to determine pathology residents were more likely to use incorrect terminology to describe ROI features compared to expert pathologists. As such, a strong association between inaccurate feature descriptions and incorrect diagnoses was identified.[38] This information can then be used by educators to adjust the pathology curriculum to focus more on accurate feature detection, which could help improve the diagnostic accuracy of their residents.

Challenges

One of the main challenges with eye tracking technology is the cost of the technology itself. Currently, screen-based eye trackers are the most cost-effective eye-tracking systems and are priced anywhere from $2000 to $50,000 USD. It is worth noting that even in the most cost-effective scenario, adding eye tracking technology to the pathology workflow would double the cost for each workstation alone. For this reason, the expense of this technology is a major challenge for research and its implementation in the clinic.

Another challenge unique to eye tracking is the inability to track parafoveal (peripheral) vison. The results of several previous studies have supported theories of holistic image processing for medical images suggesting that physicians, at least in part, scan diagnostic images parafoveally to guide their search path.[40,42,62–69] For example, experienced radiologists were able to detect lung nodules from chest X-rays up to 15 degrees away from their foveated vision.[62] More recently in pathology, Brunyé et al.[42] found that an image viewing time of 500 ms was sufficient to provide the participant's visual processing system with enough goal-relevant information to guide their eye movements towards that location. Thus, it is possible that a diagnostician's interpretive process occurs, at least in part, through their parafoveal vision. For this reason, solely tracking the foveated eye gaze may not provide a complete representation of one's cognitive processes.

Additionally, a major challenge of eye tracking in pathology is the proper design of experiments, recruitment of participants, choice of eye tracking device, the analysis of large and relevant datasets, as well as a fair understanding of vision and cognitive sciences. It is crucial that the experimental setup and the eye tracking technology are carefully selected as these factors will determine the quality and quantity of data collection. Specifically, not all eye trackers are made the same, which is why there is quite a large price range for their purchase. Some eye trackers are more sensitive, precise, accurate, or robust than others, and each eye tracker will have their own strengths and weaknesses in each of these categories. It is up to the researcher to determine which eye tracking technology they require for their study and how their experimental setup may affect the data collection (e.g., environmental lighting). Additionally, the recruitment of participants for eye tracking in digital pathology studies may pose a barrier for small research centers and/or busy pathologists. Along with these considerations, the validity and quality of an eye tracking experiment in digital pathology heavily relies on the analysis of the collected data. As eye tracking is a relatively new field for digital pathology, there are not many standardized tests available in the literature that researchers can refer to. As a result, a variety of analysis techniques are being used by researchers across this field, making it difficult to compare results between studies. Further, the eye tracking element of digital pathology now requires researchers to have an understanding of vision and cognitive sciences to provide context and insight into the quantitative results of these studies. Overall, the challenges of experimental design, technology selection, and analysis methods indicate that the field of pathology is migrating towards a more interdisciplinary field that requires expertise in diagnostic pathology, mechanical engineering, and cognition and perception fields to fully assess the data from an eye tracking experiment in digital pathology.

Briefly, the last main challenge associated with eye tracking in digital pathology is the learning curve associated with the use of this new technology and the change in a pathologist's workflow. This comes as pathologists will need to first learn how to properly setup and use the eye tracker. This is in conjunction with learning what to do with the data collected from the eye tracker and what conclusions one can draw from it to improve diagnostic assessment or clinical workflow. As such, it is expected that a training period would be required for all pathologists engaging in research studies involving eye tracking.

Prospects

With information technology spending projected to increase by 11% and 13% from 2023 to 2024 for device and software development respectively,[70] it is expected that eye tracking technology will become more accurate and precise within the coming years. As a result, a multitude of new eye tracking studies in pathology are expected to add to the body of work summarized in this review and explore new avenues of research in pathology.

Additionally, recent developments in smartphone technology have made smartphone-based eye tracking a possibility for simple research studies.[71–73] With the continued development of small-scale high-quality cameras, the use of affordable smartphones in place of traditional remote eye tracking devices can be a reality in the coming decades. The implications of this would make eye tracking in pathology widely assessable, regardless of geographic region, and allow eye tracking-related research to be fully exploited to advance the field.

Limitations

Despite doing an extensive literature search, this review may not have captured all existing literature that concerns foveated eye tracking in pathology. Given that eye tracking in pathology is a relatively new field of research, all relevant studies were included in this review regardless of the year in which they were published. Further, the search was restricted to pathology to provide a comprehensive review of this emerging field. It is possible that some of the findings referenced in this review apply to other non-pathology related fields; however, the transferability of results cannot be confirmed and is outside the scope of this review.

Conclusion

The literature to date has focused on the relationship between rudimentary search patterns, biometrics, and expertise level with diagnostic accuracy for specific pathology tasks. There are only a few studies that have examined these systems in the context of assistive tools such as machine learning. Thus, there is significant room for exploration in this area as studies embrace these emerging technologies moving forward. The rise in adoption of digital pathology workflows into clinical practice increases the opportunity to use these systems to address important clinical questions and enhance our understanding of pathologic processes.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Matthew Cecchini reports a relationship with Merck that includes: board membership, funding grants, and speaking and lecture fees. Matthew Cecchini reports a relationship with AstraZeneca Pharmaceuticals LP that includes: board membership, funding grants, and speaking and lecture fees. Matthew Cecchini reports a relationship with Eli Lily that includes: board membership, funding grants, and speaking and lecture fees. Matthew Cecchini reports a relationship with Amgen that includes: board membership, funding grants, and speaking and lecture fees. Matthew Cecchini reports a relationship with Need that includes: consulting or advisory and equity or stocks. Matthew Cecchini reports a relationship with Tenomix that includes: equity or stocks. Matthew Cecchini has patent pending to Tenomix Inc.

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