Artificial intelligence-supported digital microscopy diagnostics in primary health care laboratories: a scoping review protocol

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Table of Contents

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Abstract

Background: Digital microscopy combined with artificial intelligence (AI) is increasingly being implemented in health care, predominantly in advanced laboratory settings. However, AI-supported digital microscopy could be especially advantageous in a primary health care setting since the methods could improve access to diagnostics via automation and a decreased need for experts on-site. To our knowledge no scoping or systematic review had been published on the on the use of AI-supported digital microscopy within primary health care laboratories when this scoping review was initiated. A scoping review can guide future research by offering insights to help navigate the challenges of implementing these novel methods in primary health care laboratories.

Objective: The objective of this scoping review is to map available studies on AI-supported digital microscopy in primary health care laboratories in order to generate an overview of the subject.

Methods: A systematic search of the databases PubMed, Web of Science, Embase, and IEEE will be conducted. Only articles in English will be considered and no limit on publication year will be applied. The concept inclusion criteria in the scoping review are studies that have applied AI-supported digital microscopy with the aim of achieving a diagnosis on the subject level. In addition, the studies must have been performed in the context of primary health care laboratories as defined by the criteria of not having a pathologist on site and using simple sample preparations. The proposed methodology is in accordance with the JBI methodology for scoping reviews.

Results: The results will be presented in a table developed by the researchers, including information on investigated diseases, sample collection, preparation and digitization, AI-model used and results. Furthermore, the results will be described narratively to provide an overview of the studies included. The finalized scoping review is expected to be finalized by the end of 2024.

Conclusions: The findings of this scoping review will provide a comprehensive overview of studies published in English on implementing AI-supported digital microscopy in primary health care laboratories. Clinical Trial: Open Science Framework DOI:10.17605/OSF.IO/YZ67T; Available from: https://osf.io/yz67t/

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Abstract

Background: Digital microscopy combined with artificial intelligence (AI) is increasingly being implemented in health care, predominantly in advanced laboratory settings. However, AI-supported digital microscopy could be especially advantageous in a primary health care setting since the methods could improve access to diagnostics via automation and a decreased need for experts on-site. To our knowledge no scoping or systematic review had been published on the on the use of AI-supported digital microscopy within primary health care laboratories when this scoping review was initiated. A scoping review can guide future research by offering insights to help navigate the challenges of implementing these novel methods in primary health care laboratories.

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Trial registration: Open Science Framework DOI:10.17605/OSF.IO/YZ67T; Available from: https://osf.io/yz67t/

Key words:

Diagnosis; Machine learning; Pathology; Whole slide images; Artificial intelligence; AI; Primary health care; Deep learning

Introduction

Artificial intelligence (AI) in the form of machine learning has successfully been applied to image-based diagnostics within several medical fields [1]. Deep learning is a machine-learning method that utilizes artificial neural networks (ANNs) that mimic the neurons of the brain and enables computers to learn and represent complex patterns in data. Convolutional neural networks (CNNs) and vision transformers are currently the most commonly used ANNs for image classification and interpretation [2]. Implementing AI-based diagnostics into the workflow has the potential to automate processes, increase productivity in laboratories and improve diagnostic accuracy [3]. Multiple AI-based diagnostic systems have been approved by the U.S. Food and Drug Administration (FDA) or corresponding authorities in Europe (notified bodies for CE-marking), for example for cervical cancer screening and prostate cancer diagnostics [3–5]. Most diagnostic systems in use utilize high-end digital imaging instruments, so called whole-slide scanners, and require access to advanced laboratory infrastructure, and may, therefore not be optimal for use in primary health care (PHC) laboratories [3,4]. However, the development of cheaper, portable digital microscope scanners has enabled research on the use of AI-supported diagnostic systems suitable for PHC-laboratories [6,7].

The World Health Organization (WHO) has emphasized the importance of providing diagnostics near the patient in PHC settings, to enhance the accuracy and timeliness of diagnoses, improve clinical decision-making, and reduce the risk of diagnostic errors. [8,9]. A PHC-laboratory, also known as a tier 1 laboratory, can be defined as a laboratory primarily serving outpatients by providing point-of-care tests, slide microscopy for simple preparations, and preparing fine needle aspirations and other simple tissue specimens later dispatched to a tier 2 laboratory for analysis. The tier 1 laboratories work with a small budget compared to more advanced laboratories and are generally managed by a laboratory technician supervised by a pathologist from distance [9].

The implementation of AI-supported diagnostic systems could be particularly advantageous

at PHC-laboratories. To begin with, since a PHC-laboratory do not have access to expertise in the form of a pathologist, appliance of AI could enable for further analyses being performed on-site, consequently, increasing the availability of diagnostics [9]. In addition, a systematic review showed the implementation of AI-supported diagnostics for microscopy increased the effectivity of laboratory personnel [3]. Henceforth, implementation of AI could potentially lower the costs of diagnostics. Furthermore, moving diagnostics from advanced laboratories to PHC-laboratories has the potential to enable faster diagnostics.

Studies have been performed investigating AI-supported microscopy in PHC-settings in diagnostics for different diseases, such as, studies investigating oral and cervical cancers [6,10]. Furthermore, studies have been performed targeting different parasitic infections, for example, schistosomiasis and infections caused by soil transmitted helminths [11,12]. Although the targeted diseases differed in these studies, it appears that the researchers faced similar challenges because of the commonalities in the methodologies applied. Challenges observed when comparing these studies include, first, the sample preparation method needs to be simple enough to be easily performed in PHC-laboratories, while maintaining sufficient sample quality to enable AI-analysis of the digitized sample. Second, the sample digitization instrument needs to be cost-efficient and easy to use in a PHC environment. Third, the AI algorithms need to be reliable and feasible to implement in the diagnostic workflow in a way that provides robust and accurate diagnostics.

A preliminary search of the databases PubMed and Cochrane was performed to investigate whether any scoping or systematic review had been performed investigating AI-supported digital microscopy in PHC-laboratories. Some similar reviews were found. A systematic review of AI diagnostics for oral cancer [13] has some overlap with our proposed review but because it investigates a single disease it does not provide an overview of the development of AI-supported digital microscopy in PHC-laboratories. A systematic review evaluating the application of AI to whole slide images (WSI) of tissue samples stained with hematoxylin and eosin (H&E) was also identified [14]. This article presents the current state of knowledge on AI implementation in pathology in high-end laboratories, highlighting different approaches regarding datasets, pre-processing of images, and different approaches to image analysis. However, to our knowledge, no scoping review has been performed to compile the present knowledge and evidence on AI-supported digital microscopy diagnostics in PHC-settings.

A scoping review performed on this subject is of value because multiple challenges exist

that needs to be mapped and addressed to successfully implement a diagnostic system with AI-supported digital microscopy in PHC-laboratories. Such a review can also provide knowledge regarding what approaches have been applied so far and guide future research towards a potential implementation of AI-supported digital microscopy in PHC-laboratories.

This scoping review aims to systematically review published studies that have been performed related to AI-supported digital microscopy in PHC-laboratories. The scoping review will specifically address the following questions: I) In which diseases has AI-based microscopy been applied for diagnostics within PHC-laboratories; II) What methods have been used in acquiring microscopy images to train and analyze AI-models for diagnostics; III) What AI models and training approaches have been applied; and IV) How has the AI-supported diagnostic system performed compared to expert microscopists with regards to diagnostic accuracy?

Review question

What studies have been conducted in implementing AI-supported digital microscopy in PHC-laboratories? What methods have been used when doing so, regarding acquiring images and training AI-models?

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [15]. A protocol has been published in the Online Science Framework (OSF) [16]. The inclusion and exclusion criteria can be found in Table 1.

Table 1. Inclusion and exclusion criteria for identified studies.

Study CHARACTERISTIC	Inclusion criteria	Exclusion criteria
LANGUAGE		
	-English	-Non-English
Study design		
	-Diagnostic test accuracy studies	-Not diagnostic test accuracy studies
Population		
	-Humans	-Studies performed on animals
Concept		

	- Artificial Intelligence techniques applied as a diagnostic tool on microscopy -Final slide-level diagnosis was performed and compared to a standard microscopist -Outcome valuable for clinicians	- Studies that applied AI-algorithms on images not classically analyzed in microscopy -No final slide diagnosis
Context		
	-Performed at primary health care laboratory (tier 1 laboratory) - No pathologist needed on site - simple sample preparation, such as, stool sample preparation or simple tissue preparations such as fine needle aspirations	- Studies performed in an advanced laboratory setting

Eligibility criteria

Participants

This scoping review will consider studies on human subjects. No exclusion will be performed based on age, sex, economic status, or nationality.

Concept

The studies to be included in this scoping review will have to fulfill three concept criteria. First, the studies need to have been performed on images gathered with an imaging instrument built to automatically capture microscopy sample areas large enough for diagnostic purposes. Further, the imaging instrument used must be operated in a way that does not require human expertise to determine what areas of the slide should be captured.

Microscopy was defined as deploying a light source, optical lenses, and a digital camera to acquire a magnified image of a biological sample, generating an image conventionally interpreted by a microscopist.

Second, the studies need to have utilized AI when analyzing the microscopy images. AI was defined as a computer system that is trained to perform a task that typically requires human intelligence. This analysis of the microscopy images can be performed on-site or in a remote cloud environment.

Third, the studies must have compared the AI-supported diagnostic system to a standard diagnostic system. A diagnostic system was defined as all the steps included in the diagnostic process, from sample collection to the acquisition of results. The result needs to be sufficient to reach a diagnosis at the subject level.

Context

The included studies must have been performed in a PHC-laboratory setting. To be defined as a PHC-laboratory, also known as a tier 1 laboratory, the laboratory should fulfill two criteria. First, regarding staffing, the laboratory should be run by a laboratory technician, and thus, not require a pathologist on site. Second, the sample preparations should not exceed the capabilities of a PHC-laboratory, that is, stool or urine sample preparations, cytological samples such as blood, oral, and cervical smears or tissue samples obtained through fine needle aspirations [9].

Types of sources

All types of diagnostic test accuracy studies (DTA) will be included. Because DTAs can be both retrospective and prospective, studies using either approach will be included. Additionally, studies using both paired and random designs for reference standards will be included [17]. The included studies must be published in English.

Search strategy

The search strategy was designed to identify peer-reviewed published articles. An initial limited search of PubMed and Cochrane was undertaken to identify articles on the topic. Search blocks were created for the final search based on terms used in the identified articles. The search blocks were developed to find articles containing the two concepts, microscopy, and AI as well as the context specification of being in a PHC-setting, with one block created for each. For a detailed description of the search strategy see the appendix

(Appendix I). The reference lists of all included articles will be reviewed for additional studies and duplicates. In addition, all the articles citing the included articles will be reviewed. The databases to be searched are PubMed, Web of Science, Embase, and IEEE.

Study/Source of Evidence Selection

Following the search, all identified articles will be compiled in a reference management software system *(Zotero 6.0.20 (January 13, 2023, opensource)* and duplicates removed. Following a pilot test, titles and abstracts will be screened by two independent reviewers for assessment against the inclusion criteria of the review. After the exclusion based on abstracts, the full text of the remaining studies will be assessed in detail against the inclusion criteria by two independent reviewers. The reasons for exclusion during the full-text screening will be recorded and reported. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion between the reviewers and an additional researcher. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram [18].

Data Extraction

Data will be extracted from studies included in the scoping review by two independent reviewers using a data extraction tool developed by the reviewers, which can be found in the appendix (Appendix II). Any disagreements that arise will be solved through discussion between the reviewers and an additional researcher.

Critical Appraisal of Results

To investigate the bias of the included studies the QUADAS-2 tool will be applied. This tool was developed to assess the risk of bias for primary diagnostic accuracy studies in four areas: patient selection, index test, reference standard, and flow and timing [19]. The results will be presented in a table in the Results section and the specific form for each article will be found in the Appendix (Appendix III).

Results

The findings will be presented narratively and additionally in a table format based on the extraction tool developed beforehand by the researchers. The table will have seven columns; 1: the study name, year of publication and authors, 2: what disease the study investigated, 3: the dataset preparation, 4: AI model and training, 5: quadas-2 risk of bias, 6: results and 7: additional comments. The column of dataset preparation will contain sample collection and preparation as well as digitization procedure. The column of AI model and training will contain training dataset, the training procedure, and the structure of the AI-model. The narrative presentation of the results will aim to provide an overview of the results. The protocol was initiated in January 2022 and the scoping review is expected to be finalized by the end of 2024. The results of the scoping review will be disseminated through publication in a peer-reviewed journal.

Discussion

This study will map studies implementing AI-supported digital microscopy in PHC-laboratories, collating what diseases AI has been applied to and what methodological approaches have been used when doing so. To the best of our knowledge no scoping or systematic review has been conducted on this topic at the initialization of this scoping review.

Our proposed methodology for the scoping review has several potential strengths. First, only studies that contain complete diagnostic systems will be considered thus excluding studies investigating single objects (e.g., cancer cells or parasite eggs) or studies containing samples gathered in an artificial setting. By doing this the results presented in this scoping review will be more applicable to real world settings. Second, by collating the knowledge gathered from studies performed on a multitude of diseases, this scoping review will provide a comprehensive overview of the published literature on implementing AI-supported digital microscopy in PHC-laboratories.

This scoping review has some limitations, most significantly regarding the definition of PHC-laboratories since laboratory capabilities can vary significantly within PHC-settings. To minimize bias a definition was chosen based on Fleming et al description of PHC-laboratories, excluding studies in laboratories with a pathologist on-site and advanced sample preparation[9]. By opting for a broad definition of PHC-laboratories it is anticipated

that more studies will be included. This was deemed advantageous as the purpose of the scoping review is to provide an overview of the entire field, however, the settings in which the studies have been performed will probably vary to a greater extent, making comparison between studies increasingly intricate.

It is relevant to map these studies because large-scale implementation of AI-supported digital microscopy in PHC-laboratories has not been achieved; however, the possibility of constructing such a system has increased with technical advancements [7,20]. Multiple studies have investigated different ways to implement AI-supported digital microscopy in PHC-laboratories [6,10]. By producing an overview of these studies, it has the potential to guide further research towards the implementation of these diagnostic systems.

Acknowledgements

Joar von Bahr conceived and designed the study, wrote the manuscript, and developed the search strategy. Johan Lundin conceived and designed the study, assisted in writing the manuscript and developing the search strategy. Nina Linder conceived and designed the study, assisted in writing the manuscript and developing the search strategy. Vinod Diwan conceived and designed the study and assisted in writing the manuscript. Andreas Mårtensson assisted in designing the study and in writing the manuscript. This study is funded by the Erling-Persson Family Foundation. Additionally, it was supported by The Swedish Research Council, Finska Läkaresällskapet r.f. and Medicinska Understödsföreningen Liv och Hälsa r.f. We would like to acknowledge the support of the Karolinska Institute's Library for guidance in developing a satisfactory search strategy. Paperpal Preflight was used when writing the manuscript for a grammar check. Additionally, ChatGPT4 (GPT-4, OpenAI's large-scale language-generation model) was used for evaluating sentences in grammatical correctness and coherence. ChatGPT4 was not used for writing parts of the manuscript.

Conflicts of interest

Dr J. Lundin reported receiving personal fees from Aiforia Technologies Oy and serving as cofounder and co-owner of Aiforia Technologies Oy outside the submitted work; in addition, Dr J. Lundin reported having a patent for Mobile Microscope pending (no. WO2017037334A1; the invention is related to the use of fluorescence imaging filters combined with inexpensive plastic lenses; all rights are with the University of Helsinki) and having a patent for a slide holder for an optical microscope pending (no. WO2015185805A1; related to motorization of regular microscopes). No other disclosures were reported.

Abbreviations

AI - Artificial intelligence
ANNs - Artificial neural networks
CNN - Convolutional neural network
FDA - U.S. Food and Drug Administration
PHC – Primary health care
WHO - World Health Organization
WSI - Whole slide images
H&E - Hematoxylin and Eosin
JBI - Joanna Briggs Institute
OSF - Online Science Framework
DTA - Diagnostic test accuracy
PRISMA-ScR - Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
QUADAS-2 - Quality Assessment of Diagnostic Accuracy Studies-2

Appendices

Appendix I: Search strategy

PubMed: (((artificial intelligence[Title/Abstract] OR machine learning[Title/Abstract] OR deep learning[Title/Abstract] OR neural network[Title/Abstract] OR artificial neural network[Title/Abstract] OR convolutional neural network[Title/Abstract] OR generative adversarial network[Title/Abstract] OR transfer learning[Title/Abstract] OR convolution neural network[Title/Abstract] OR CNN[Title/Abstract] OR AI[Title/Abstract]) OR (ai artificial intelligence[MeSH Terms])) AND ((microscop*[Title/Abstract] OR whole slide image[Title/Abstract] OR Cytology[Title/Abstract] OR Histology[Title/Abstract] OR digital pathology[Title/Abstract]) OR (microscopy[MeSH Terms]))) AND (((point of care[Title/Abstract] OR low-cost[Title/Abstract] OR cost effective[Title/Abstract] OR resource-constrained[Title/Abstract] OR low-resource[Title/Abstract] OR primary

care[Title/Abstract] OR Field based[Title/Abstract] OR Affordable[Title/Abstract] OR on-site[Title/Abstract] OR easy-to-use[Title/Abstract]) OR (point of care system[MeSH Terms])) OR (care, primary health[MeSH Terms]))

Web of Science: TS=(“artificial intelligence” OR “machine learning” OR “deep learning” OR “neural network” OR “artificial neural network” OR “convolutional neural network” OR “generative adversarial network” OR “transfer learning” OR “convolution neural network” OR “CNN” OR “AI”) AND TS=(microscop* OR “whole slide image” OR Cytology OR Histology OR digital pathology) AND TS=(“point of care” OR “low-cost” OR “cost effective” OR “resource-constrained” OR “low resource” OR “primary care” OR “Field based” OR Affordable OR “On-site” OR “easy-to-use”)

IEEE: (((("All Metadata": artificial intelligence OR machine learning OR deep learning OR neural network OR artificial neural network OR convolutional neural network OR generative adversarial network OR transfer learning OR convolution neural network OR CNN OR AI) OR ("Index Terms": artificial intelligence)) AND (("All Metadata": microscop* OR whole slide image OR Cytology OR Histology OR digital pathology) OR ("Index Terms": microscopy)) AND (("All Metadata": point of care OR low-cost OR cost effective OR resource-constrained settings OR primary care OR Field based OR affordable OR On-site OR easy-to-use) OR ("Index Terms": Point of care) OR ("Index Terms": Primary health care))))

Embase: ('artificial intelligence':ab,ti OR 'machine learning':ab,ti OR 'deep learning':ab,ti OR 'neural network':ab,ti OR 'artificial neural network':ab,ti OR 'convolutional neural network':ab,ti OR 'generative adversarial network':ab,ti OR 'transfer learning':ab,ti OR 'convolution neural network':ab,ti OR cnn:ab,ti OR ai:ab,ti OR 'artificial intelligence'/exp) AND ('microscopy'/exp OR microscop*:ab,ti OR 'whole slide image':ab,ti OR cytology:ab,ti OR histology:ab,ti OR 'digital pathology':ab,ti) AND ('point of care':ab,ti OR 'low cost':ab,ti OR 'cost effective':ab,ti OR 'resource constrained':ab,ti OR 'primary care':ab,ti OR 'field based':ab,ti OR affordable:ab,ti OR 'on-site':ab,ti OR 'easy-to-use':ab,ti OR 'point of care testing'/exp OR 'primary medical care'/exp)

Appendix II: Data extraction instrument

Title, author, year	Target disease	Dataset preparation	AI model and training	Quadas-2 risk of bias	Results	Additional comments

		How the samples were collected, prepared, and scanned	How the model was trained, the number of samples, the structure of AI		Number of samples and endpoints and what it was compared to	

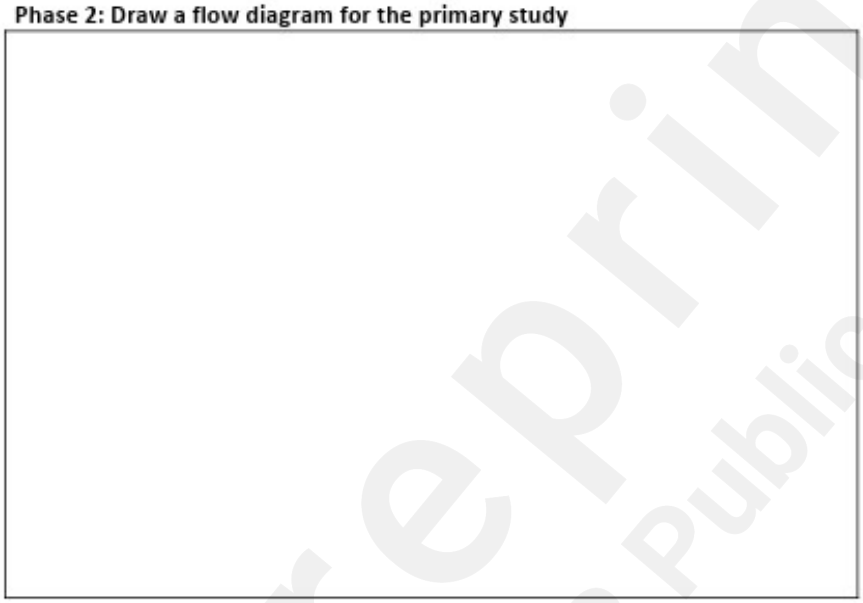
Appendix III: Quadas2-tool

QUADAS-2

Phase 1: State the review question:

Patients (setting, intended use of index test, presentation, prior testing):
Index test(s):
Reference standard and target condition:

Phase 2: Draw a flow diagram for the primary study



Phase 3: Risk of bias and applicability judgments

QUADAS-2 is structured so that 4 key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:

- ❖ Was a consecutive or random sample of patients enrolled? Yes/No/Unclear
- ❖ Was a case-control design avoided? Yes/No/Unclear
- ❖ Did the study avoid inappropriate exclusions? Yes/No/Unclear

Could the selection of patients have introduced bias? **RISK: LOW/HIGH/UNCLEAR**

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):

Is there concern that the included patients do not match the review question? **CONCERN: LOW/HIGH/UNCLEAR**

DOMAIN 2: INDEX TEST(S)

If more than one index test was used, please complete for each test.

A. Risk of Bias

Describe the index test and how it was conducted and interpreted:

- ❖ Were the index test results interpreted without knowledge of the results of the reference standard? Yes/No/Unclear
- ❖ If a threshold was used, was it pre-specified? Yes/No/Unclear

Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question? **CONCERN: LOW /HIGH/UNCLEAR**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted:

- ❖ Is the reference standard likely to correctly classify the target condition? Yes/No/Unclear
- ❖ Were the reference standard results interpreted without knowledge of the results of the index test? Yes/No/Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question? **CONCERN: LOW /HIGH/UNCLEAR**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):

Describe the time interval and any interventions between index test(s) and reference standard:

- ❖ Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear
- ❖ Did all patients receive a reference standard? Yes/No/Unclear
- ❖ Did patients receive the same reference standard? Yes/No/Unclear
- ❖ Were all patients included in the analysis? Yes/No/Unclear

Could the patient flow have introduced bias? **RISK: LOW /HIGH/UNCLEAR**

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Supplementary Files

Multimedia Appendixes

Search strategy.
URL: http://asset.jmir.pub/assets/3258cc560fc7fb5869983557d581cbe7.docx

Results table.
URL: http://asset.jmir.pub/assets/eec27b67be0e09008b9dc1f6ef5ad132.docx

Quadas2 tool.
URL: http://asset.jmir.pub/assets/9e9bac9ca4b45bdb0aa1ab02ee50d03e.docx