COLLEGE of AMERICAN PATHOLOGISTS

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Laboratory Workup of Amyloidosis

Guideline From the College of American Pathologists

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GUIDELINE DEVELOPMENT METHODS

Panel Composition

The College of American Pathologists (CAP) convened an expert and advisory panel (EP/AP) consisting of members with expertise in hematopathology, neuropathology, cytopathology, clinical pathology, renal pathology, and community pathology. Members included practicing pathologists, a cardiologist, a contracted methodologist, and two patient advocates. The CAP approved the appointment of the project chair(s) and panel members.

The roles of each panel are described in the Evidence-based Guideline Development Methodology Manual (Methodology Manual).[1]

Conflict of Interest (COI) Policy

Prior to acceptance on the expert or advisory panel, potential members completed the CAP conflict of interest (COI) disclosure process, whose policy and form require disclosure of material financial interest in, or potential for benefit of significant value from, the guideline's development or its recommendations 24 months prior through the time of publication. The potential members completed the COI disclosure form, listing any relationship that could be interpreted as constituting an actual, potential, or apparent conflict. A complete description of the COI policy is available in the online Methodology Manual.

Everyone was required to disclose conflicts prior to beginning and continuously throughout the project's timeline. EP members' disclosed conflicts are listed in the appendix of the manuscript. The CAP provided funding for the administration of the project; no industry funds were used in the development of the guideline. All panel members volunteered their time and were not compensated for their involvement, except for the contracted methodologist.

Project Scope and Outcomes of Interest

The EP approved the following scope to develop evidence-based recommendations for appropriate laboratory testing to detect amyloidosis and identify the specific amyloidogenic protein.

According to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, it is important for clinical guideline panels to review a comprehensive list of outcomes.[2] As a result, the EP was polled to collect information on which outcomes should be included in the PICO (Population, Intervention, Comparator, Outcome(s)). These outcomes included: accuracy of diagnosis, completeness of diagnosis, early diagnosis, overall survival, diagnostic test characteristics, concordance between pathologists, number needed to detect amyloid.

Using the GRADE approach for defining the importance of outcomes, the EP was polled to rate each initially identified outcome in terms of importance for decision making. The EP voted on a scale of 1–9: outcomes rated 1-3 were defined as "of limited importance"; outcomes rated 4-6 as "important, but not critical"; and outcomes rated 7-9 were "critical for decision making". The outcomes are listed in Supplemental Table 1.

Systematic Evidence Review

The objective of the systematic evidence review (SER) was to identify articles that provided data to inform the recommendations for the workup of amyloidosis. If of sufficient quality, findings from this review would provide an evidence-base to support the recommendations of the guideline. The scope of the SER and the key questions (KQs) with the PICO elements (Population, Intervention, Comparator, Outcome(s)) were established by the EP in consultation with the methodologist prior to beginning the literature search.

Detailed key questions including the PICO are included in Supplemental Table 1.

Search and Selection

Detailed literature searches were constructed using controlled vocabulary and keywords for concepts derived from the PICO elements defined at the onset of the project based upon the key questions. All search strategies were reviewed by a second medical librarian using the Press Review of Electronic Search Strategies (PRESS) statement for systematic reviews.[3] All search results were deduplicated using reference management software following published methods.[3] The literature search strategies and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram are included as Supplemental Figures 1 and 2.

Selection at all levels was based on the predetermined inclusion/exclusion criteria which are detailed in the manuscript.

Data Extraction & Management

The data elements from an included article/document were extracted by methodologist into standard data formats and tables developed using the systematic review database software, DistillerSR (DistillerSR Inc., Ottawa, Canada); a second reviewer confirmed accuracy and completeness. Any discrepancies in data extraction were resolved by discussion between the co-chairs. A bibliographic database was established in EndNote (Clarivate, Overland Park, KS) to track all literature identified and reviewed during the study.

Assessing Quality and Risk of Bias

An assessment of the quality of the evidence was performed for all retained studies following application of the inclusion and exclusion criteria. Using this method, studies deemed to be of low quality would not be excluded from the systematic review but would be retained, and their methodological strengths and weaknesses discussed where relevant. To define an overall study quality rating for each included study, validated study-type specific tools were used to assess the risk of bias, plus additional important quality features were extracted. Specific details for each study type are outlined below.

- Single-arm non-randomized phase I and II clinical trials (NRCTs), prospective cohort studies (PCS), prospective-retrospective cohort studies (PRCS), retrospective cohort studies (RCS), and case-control studies (CCS) were assessed using the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) tool.[4]

- Diagnostic studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[5]

In the following sections, the quantity of the evidence as determined by the number of studies that met our inclusion criteria and were retained, the evidence type as determined by study design,

the quality of that evidence as determined by the quality assessment, and its consistency are all reported, both as individual studies and in totality, statement by statement. Definitions of the certainty of evidence are presented in Supplemental Table 2.

A total of 32 studies comprised the final body of studies included in the SER. Supplemental Figure 1 displays the results of the literature review. All articles were available as discussion or background references. All members of the EP participated in developing draft recommendations, reviewing open comment feedback, finalizing and approving the final recommendations, and writing/editing of the manuscript.

For an explanation of the Quality assessment methods and the ROB assessment, refer to the Methodology Manual.

Evidence-to-Decision Framework

In addition to the panel discussion of the net benefits and harms for each guideline statement, the EP members rated each recommendation using the GRADE evidence-to-decision framework. This allows for a systematic way to document panel members' judgement for each of the recommendations.[6]

Open Comment Period and Organizational Review

A public, open access comment period was held from March 13 through April 3, 2024 on the CAP Web site, www.cap.org, for any interested stakeholder to provide feedback on the draft recommendations. Seven draft recommendations, demographic questions, and questions to assess feasibility were posted for peer review. An announcement was sent to the following societies deemed to have interest.

Medical societies:

- American College of Chest Physicians (CHEST)
- American College of Medical Genetics and Genomics (ACMG)
- American Society for Clinical Oncology (ASCO)
- American Society of Hematology (ASH)
- American Society of Clinical Pathology (ASCP)
- American Society of Cytopathology (ASC)
- American Society for Investigative Pathology (ASIP)
- Amyloid Research Consortium
- Association for Molecular Pathology (AMP)
- Association of Community Cancer Centers (ACCC)
- Association of Directors of Anatomic and Surgical Pathology (ADASP)
- Association of Pathology Chairs (APC)
- Canadian Association of Pathologists (CAP-APC)
- European Society for Medical Oncology (ESMO)
- International Society of Amyloidosis
- National Society for Histotechnology (NSH)
- United States & Canadian Academy of Pathology (USCAP)
- Society for Cardiovascular Society for Pathology
- International Kidney and Monoclonal
- International Myeloma Foundation (IMF)

- International Society for Heart and Lung Transplantation
- Renal Pathology Society
- American Heart Association (AHA)
- American College of Cardiology (ACC)
- International Myeloma Working Group (IMWG)
- Association for Diagnostics & Laboratory Medicine (ADLM)
- Heart Failure Society of American (HFSA)

Patient advocacy groups:

- American Cancer Society
- American Heart Association
- Amyloidosis Support Group
- Cancer Leadership Council
- Cancer Research and Prevention Foundation

Government and other stakeholders:

- US Food and Drug Administration (FDA)
- Centers for Medicare & Medicaid Services (CMS)
- Centers for Disease Control and Prevention (CDC)
- European Medical Agency/ EMEA
- CFDA

"Agree" and "Disagree" responses were captured for every proposed recommendation. The EP reviewed all the comments. Resolution of all changes was obtained by majority consensus of the panel using nominal group technique (discussion at an in-person meeting, rounds of teleconference webinars, email discussion and multiple edited recommendations) amongst the panel members. The final recommendations were approved by the EP with a formal vote. Neither formal cost analysis nor cost effectiveness models were performed.

Organizational review was instituted to review and approve the guideline. An independent review panel (IRP) representing the Council on Scientific Affairs was assembled to review and approve the guideline for the CAP. The IRP was masked to the expert panel and vetted through the COI process.

Dissemination Plans

The CAP hosts a resource page which includes a link to the manuscript and supplement; a summary of the recommendations, a teaching PowerPoint (Microsoft Corporation, Redmond, WA), a frequently asked question (FAQ) document, and an algorithm along with other additional tools such as case studies and webinar recordings as applicable. The guideline is promoted and presented at various society meetings and distributed to the societies listed in the peer review.

Recommendation Statements

Statement 1. In patients with suspected systemic amyloidosis, pathologists may screen cytology specimens (conventional smears and/or cell blocks) of aspirated abdominal fat for detection of amyloid.

Note: **Best preparation methods should be determined and optimized by individual laboratories and ancillary testing technique should be validated on cytologic material.**

Note: **If cytologic smears only are prepared in the absence of a cell block, this limits the ability for further testing including subtyping.**

The evidence base for this statement includes five diagnostic accuracy studies.[7,8-11] Identified studies reported on overall survival rates diagnostic test characteristics of cytology specimens when used to detect amyloidosis. The certainty of evidence was low based on an aggregate very serious risk of bias (Supplemental Tables 5) across studies, but evidence was not further downgraded for any domain (Supplemental Table 6).

The benefits of screening using cytology specimens were large based on ease of use, low morbidity and mortality when compared to organ biopsies, and the fact that the sample can be completed in clinic. After discussions, EP members defined the harms as moderate. The harms included the inability to subtype amyloid on smears and the potential of both variability in staining and interobserver agreement. However, the large benefits of screening using cytology specimens outweighed the harms. It is anticipated that this guidance could increase patient equity as cytology smears require less patient down-time and come at a lesser cost. Similarly, there is an anticipated moderate savings based on the smaller resources required for screening using cytology specimens. Acceptability of the guidance is expected to be variable and dependent on the experience of personnel within an individual laboratory. Adoption of the practice is feasible however, and it is expected acceptability will increase as personnel become more comfortable.

Statement 2. When evaluating specimens for the presence of amyloid, pathologists should use Congo red staining method.
Note: **Laboratories may use other methods but should validate against Congo red or electron microscopy and must show equivalency.**

The evidence base for this statement includes two prospective cohort studies[12, 13] and two retrospective cohort studies.[14, 15] Two identified studies reported on the diagnostic test characteristics of Congo red for detection of amyloidosis when compared to a prior amyloidosis diagnosis[14] or a clinical diagnosis.[12] The other two studies compared Congo red to electron microscopy and reported on the rate of positivity for both methods in amyloidosis positive samples.[13, 15] The certainty of evidence was low for both outcomes of interest based on an aggregate very serious risk of bias (Supplemental Tables 3,4) across studies informing both outcomes, but evidence was not further downgraded for any domain (Supplemental Table 6).

The benefits of Congo red staining methods were large based on ease of use, the availability of automated platforms, and the ubiquity of the stain. However, the harms of the methodology are variable as Congo red is a difficult stain both to perform and to interpret and this can lead to high interobserver variability. After a lengthy discussion, the EP believes that the balance of effects favors the use of Congo red, and it is currently standard of care. It is expected that this guidance will be acceptable to most key stakeholders and feasible to implement. Implementation of this guidance is expected to have no impact on health equity.

Statement 3. When assessing Congo red histochemistry, pathologists may add fluorescence microscopy with the tetramethylrhodamine isothiocyanate/Texas red filter to increase sensitivity for amyloid detection, if available.

The evidence base for this statement includes four diagnostic accuracy studies[16-19] and one retrospective cohort study.[20] Identified studies compared fluorescent microscopy to polarized light

microscopy when interpreting Congo red stained slides and reported on diagnostic test characteristics[16-19] or the rate of an accurate amyloid diagnosis.[20] The certainty of evidence was low for both outcomes of interest. The four diagnostic accuracy studies that reported on the diagnostic test characteristics were limited by an aggregate serious risk of bias (Supplemental Table 5). Additionally, two of the studies included a prior diagnosis of amyloidosis as the reference standard and although this is an adequate standard, the studies reported on specificity and/or negative predictive value (NPV) after testing solely amyloid positive cases. The evidence was downgraded for imprecision as these estimates are very likely inaccurate (Supplemental Table 6). The one retrospective cohort study that reported on rate of accurate diagnosis was limited by a very serious risk of bias (Supplemental Table 4), but evidence was not further downgraded in any domain (Supplemental Table 6).

The benefits of adding evaluation using fluorescence microscopy with a tetramethylrhodamine isothiocyanate (TRITC)/Texas red filter were large based on increased sensitivity for amyloid detection. The harms were defined as small and included the reduced performance ability when used on aspirates. The EP had a lengthy discussion around access to fluorescent microscopes. It is recognized that not all laboratories currently have access to these microscopes and laboratories will not have the resources to obtain a fluorescent microscope solely for Congo red slides. Guidance language was specifically drafted to suggest use only in those with access. If laboratories intend to obtain a fluorescent microscopy, moderate costs would be associated. Similarly, training on the microscope and operating costs would need to be considered. In laboratories who already have access to a fluorescent microscope, the guidance is expected to be acceptable to key stakeholders and feasible to implement.

Statement 4. In patients with amyloidosis being considered for therapy to optimize diagnostic yield and tissue utilization, pathologists should use mass spectrometry to identify the fibril protein type.
Note: **In renal amyloidosis, amyloid fibril typing may often be successfully accomplished by immunofluorescence, although reflex to mass spectrometry-based proteomics should be performed in difficult or equivocal cases.**

The evidence base for this statement includes two prospective cohort studies[21, 22] one diagnostic accuracy study,[23] and one retrospective cohort study.[24] Identified studies reported on assay concordance between mass spectrometry and immunohistochemistry when identifying fibril protein type. The certainty of evidence was low based on an aggregate very serious risk of bias (Supplemental Tables 3-5) across studies, but evidence was not further downgraded for any domain (Supplemental Table 6).
When compared to immunohistochemistry, the benefits of subtyping with mass spectrometry were large based on the ability of mass spectrometry to detect all amyloid types in one assay with high sensitivity and specificity. Although no harms were defined, the balance of effects was judged as probably favors mass spectrometry. This was due to scenarios or situations where other in-house assays can be successfully accomplished. Since mass spectrometry is only performed in a limited number of laboratories, there are moderate costs associated with this guidance. However, the EP weighed the resources required for the assay against the harms of treating with patients for the wrong type of amyloidosis if a less robust methodology was employed. It is anticipated that this guidance will probably be acceptable to most key stakeholders and feasible to implement as most laboratories are already sending out samples for analysis using mass spectrometry.

Supplemental Table 1. Key Questions and PICO Elements

<table>
<tr><td colspan="3">KQ1. In patients with suspected systemic amyloidosis (ATTR, AA, and AL), does fat pad aspiration/biopsy, salivary gland biopsy, and rectal biopsy all provide adequate diagnostic sensitivity?</td></tr>
<tr><td colspan="3">Population:</td></tr>
<tr><td colspan="3">Biopsies from patients with suspected amyloid – symptomatic patients; most minimally invasive means</td></tr>
<tr><td>Intervention</td><td>Comparator</td><td>Outcomes</td></tr>
<tr><td>• Fat pad biopsies (surgical and cytology)</td><td>• Tongue biopsy
• Suction rectal biopsy
• Single arm</td><td>Critical
• Accuracy of diagnosis
• Diagnostic test characteristics

Important
• Early diagnosis
• Overall survival
• Pathologist concordance</td></tr>
<tr><td colspan="3">KQ2. When screening fat pad biopsies for amyloidosis, can cytology samples be used as an alternative to surgical pathology samples (FFPE blocks)?</td></tr>
<tr><td colspan="3">Population:</td></tr>
<tr><td colspan="3">Preparations from patients with suspected amyloid</td></tr>
<tr><td>Intervention</td><td>Comparator</td><td>Outcomes</td></tr>
<tr><td>• Cytology samples</td><td>• Surgical pathology samples
• Single arm</td><td>Critical
• Accuracy of diagnosis
• Diagnostic test characteristics

Important
• Early diagnosis
• Overall survival
• Pathologist concordance</td></tr>
<tr><td colspan="3">KQ3. In patients with suspected amyloidosis, what method most accurately and reproducibly detects amyloid?</td></tr>
<tr><td colspan="3">Population:</td></tr>
<tr><td colspan="3">Tissue sections or cytologic preparations (including FNAs, aspirations, washings, synovial fluid) from patients with suspected amyloid

Subgroups (if data allows)
1. Renal
2. Neuro (this may include Alzheimer’s but these patients excluded)
3. Cardiac
4. Dermatology
5. Other sites</td></tr>
<tr><td>Intervention</td><td>Comparator</td><td>Outcomes</td></tr>
<tr><td>Thioflavin T/S
Sulphated alcian blue (SAB)
Crystal violet
Amyloid P IHC stain
Sirius red
Methyl violet
Electron microscopy</td><td>• Congo red with or without fluorescence
• And other intervention</td><td>Critical
• Accuracy of diagnosis
• Diagnostic test characteristics

Important
• Early diagnosis
• Overall survival
• Pathologist concordance</td></tr>
</table>

<table>
<tr><td colspan="3">KQ4. When using Congo red stain on slides from patients with suspected amyloidosis, does the addition of fluorescence microscopy to polarized light microscopy provide increased sensitivity and reproducibility for the detection of amyloid?</td></tr>
<tr><td colspan="3">Population:</td></tr>
<tr><td colspan="3">Slides from patients with suspected amyloid undergoing staining with Congo red</td></tr>
<tr><td>Intervention</td><td>Comparator</td><td>Outcomes</td></tr>
<tr><td>• Fluorescence microscopy</td><td>• Light microscopy w/ polarizer</td><td>Critical
• Accuracy of diagnosis
• Diagnostic test characteristics

Important
• Early diagnosis
• Overall survival
• Pathologist concordance</td></tr>
<tr><td colspan="3">KQ5. When performing protein subtyping on a case with confirmed amyloid deposition in a paraffin block, what is the diagnostic accuracy of immunohistochemistry when compared with mass spectrometry, and is this dependent on amyloidosis type or biopsy site?</td></tr>
<tr><td colspan="3">Population:</td></tr>
<tr><td colspan="3">Patients with confirmed amyloid deposit identified by special stain

Subgroups:
1. Amyloidosis type
2. Biopsy site (those included in KQ3 subgroups)
3. Biopsy type (those included in KQ1)</td></tr>
<tr><td>Intervention</td><td>Comparator</td><td>Outcomes</td></tr>
<tr><td>• Immunohistochemistry (≥4 panel)</td><td>• Mass spectrometry</td><td>Critical
• Accuracy of diagnosis
• Diagnostic test characteristics
• Completeness of diagnosis (includes misdiagnosis)

Important
• Early diagnosis
• Overall survival
• Pathologist concordance</td></tr>
<tr><td colspan="3">KQ6. When performing protein subtyping on a case with a confirmed amyloid deposition in frozen tissue (i.e. renal, cardiac biopsy), what is the diagnostic accuracy of immunofluorescence when compared with mass spectrometry?</td></tr>
<tr><td colspan="3">Population:</td></tr>
<tr><td colspan="3">Patients with confirmed amyloid deposit identified by special stain</td></tr>
<tr><td>Intervention</td><td>Comparator</td><td>Outcomes</td></tr>
<tr><td>• Immunofluorescence</td><td>• Mass spectrometry</td><td>Critical
• Accuracy of diagnosis
• Diagnostic test characteristics
• Completeness of diagnosis (includes misdiagnosis)

Important
• Early diagnosis
• Overall survival
• Pathologist concordance</td></tr>
</table>

Abbreviations: PICO, population, intervention, comparator, outcomes

Supplemental Table 2. Grades for Certainty of Evidence

Designation	Description
High	There is high confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect.
Moderate	There is moderate confidence that available evidence reflects true effect. Further research is likely to have an important impact on the confidence in estimate of effect and may change the estimate.
Low	There is limited confidence in the estimate of effect. The true effect may be substantially different from the estimate of the effect.
Very Low	There is very little confidence in the estimate of effect. The true effect is likely to be substantially different from the estimate of effect. Any estimate of effect is very uncertain.

Data derived from Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group materials.[2]

Supplemental Table 3. Risk of Bias Assessment of Included Prospective Cohort Studies

Study	ROBINS-I Assessment								Additional Quality Features		
	Confounding	Patient selection	Intervention classification	Deviation from intended intervention	Missing data	Outcome measurements	Selection of reported outcomes	Overall Risk of Bias	Adequately powered	Reported funding sources	Industry funded
Fernández de Larrea et al,[12] 2015	MR	MR	LR	LR	MR	MR	LR	MR	NS	N	U
Yamamoto et al,[13] 2023	MR	LR	LR	LR	LR	MR	LR	MR	NS	Y	N
Mollee et al,[22] 2016	MR	MR	LR	MR	SR	MR	LR	SR	NS	Y	N

Abbreviations: LR, low risk; MR, moderate risk; N, no; NS, no statistical analysis: SR, serious risk; U, unclear; Y, yes.

Supplemental Table 4. Risk of Bias Assessment of Included Retrospective Cohort Studies

Study	ROBINS-I Assessment								Additional Quality Features		
	Confounding	Patient selection	Intervention classification	Deviation from intended intervention	Missing data	Outcome measurements	Selection of reported outcomes	Overall Risk of Bias	Adequately powered	Reported funding sources	Industry funded
Clement et al,[20] 2014	MR	CR	LR	LR	MR	CR	MR	CR	NS	N	U
Abe et al,[24] 2021	MR	CR	LR	SR	SR	MR	LR	CR	NS	Y	N
Barreca et al,[25] 2021	MR	CR	LR	MR	MR	MR	MR	CR	NS	N	U
Chen et al,[14] 2022	MR	CR	LR	LR	MR	MR	LR	CR	Y	Y	N
Suzuki et al,[26] 2016	MR	CR	LR	MR	MR	LR	LR	CR	NS	Y	N
Luigetti et al,[15] 2020	MR	CR	LR	MR	MR	SR	MR	CR	NS	Y	N
Pinton et al,[27] 2023	MR	CR	LR	LR	MR	LR	LR	CR	NS	Y	N

Abbreviations: CR, critical risk; LR, low risk; MR, moderate risk; N, no; NS, no statistical analysis: SR, serious risk; U, unclear; Y, yes.

Supplemental Table 5. Risk of Bias Assessment of Included Diagnoastic Cohort Studies

Study	QUADAS-2							Additional Quality Features				
	Risk of Bias				Applicability Concerns							
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard	Study Design	Specimen Collection	Adequately powered	Reported funding	Industry funded
Abildgaard et al,[28] 2020	HR	HR	HR	LR	LR	HR	HR	RSA	AT, NPT	NS	Y	N
Cohen et al,[29] 2020	HR	LR	HR	HR	LR	LR	LR	RC	AT, DRS	Y	N	U
Fernández Fuertes et al,[7] 2017	LR	LR	HR	HR	LR	HR	HR	PSA	RT	NS	N	U
Fine et al,[30] 2014	LR	LR	LR	HR	LR	LR	LR	RC	AT, DRS	N	N	U
Gilbertson et al,[21] 2015	LR	LR	LR	HR	LR	LR	LR	PC	RT	N	N	U
Hansen et al,[8] 2021	LR	LR	LR	HR	LR	LR	LR	PC	RT	NS	Y	N
Kimmich et al,[9] 2017	LR	LR	HR	HR	LR	LR	LR	PC	RT	NS	N	U
Lee et al,[16] 2021	HR	LR	LR	LR	LR	LR	LR	RC	AT, DRS	NS	N	U
Lee et al,[31] 2023	HR	LR	LR	LR	LR	LR	LR	RC	AT, DRS	N	Y	N
Li et al,[32] 2017	HR	LR	LR	LR	LR	LR	LR	RC	AT, DRS	NS	N	U
Lopes et al,[33] 2021	HR	HR	HR	HR	LR	LR	HR	RSA	AT, NPT	NS	N	U
Miyazaki et al,[10] 2015	HR	LR	LR	HR	LR	LR	LR	RC	AT, DRS	NS	N	U
Muchtar et al,[34] 2017	HR	LR	HR	HR	LR	LR	LR	RC	AT, DRS	NS	N	U
Nishi et al,[35] 2022	UR	LR	HR	HR	LR	LR	LR	PC	RT	NS	Y	N
Paulsson et al,[36] 2020	HR	HR	LR	HR	LR	HR	LR	RSA	RT, DRS	NS	Y	N
Quarta et al,[11] 2017	LR	LR	LR	HR	LR	LR	LR	PSA	RT	NS	Y	N
Rezk et al,[23] 2019	LR	LR	LR	HR	LR	LR	LR	PC	RT	NS	Y	N
Shehabeldin et al,[17] 2022	HR	LR	LR	LR	LR	LR	HR	RC	AT, DRS	NS	Y	N
Vrana et al,[37] 2014	LR	LR	HR	LR	HR	LR	LR	PC	RT	NS	Y	N
Wu et al,[38] 2021	HR	LR	LR	LR	LR	LR	LR	RSA	AT, DRS	N	N	U
Cazzaniga et al,[18] 2023	HR	LR	LR	LR	LR	LR	LR	RC	AT, DRS	NS	Y	N
Pinedo Pichilingue et al,[19] 2023	HR	LR	LR	LR	LR	LR	LR	RC	AT, DRS	NS	Y	N

Abbreviations: AT, archived tissue; DRS, prospective diagnosis defined as reference standard; HR, high risk; LR, low risk; N, no; NPT, no prior or unrelated testing on specimen; NS, no statistical analysis; PC, prospective comparative; PSA, prospective single arm; RC, retrospective comparative; RSA, retrospective single arm; RT, specimens collected, processed, and assayed in real time; U, unclear; UR, unclear risk; Y, yes.

Supplemental Table 6. GRADE Certainty of Evidence Assessment

Number of studies and Study Design	Aggregate Risk of bias	Inconsistency	Indirectness	Imprecision	Other [A]	Certainty	Outcome Importance
RECOMMENDATION 1 In patients with suspected systemic amyloidosis, pathologists may screen cytology specimens (conventional smears and/or cell blocks) of aspirated abdominal fat for detection of amyloid. *Note:* Best preparation methods should be determined and optimized by individual laboratories and ancillary testing technique should be validated on cytologic material. *Note:* If cytologic smears only are prepared in the absence of a cell block, this limits the ability for further testing including subtyping.							
Diagnostic Test Characteristics							
5 DAS Fernández Fuertes, et al,[7] 2017, Hansen et al,[8] 2021, Kimmich et al,[9] 2017, Quarta et al,[11] 2017, Miyazaki et al[10] 2015	Very serious [B]	Not serious	Not serious	Not serious	None	Low	CRITICAL
RECOMMENDATION 2 When evaluating specimens for the presence of amyloid, pathologists should use Congo red staining method. *Note:* Laboratories may use other methods but should validate against Congo red or electron microscopy and must show equivalency.							
Diagnostic Test Characteristics							
1 PCS Fernández de Larrea et al,[12] 2015, 1 RCS Chen, J et al,[14] 2022	Very serious [B]	Not serious	Not serious	Not serious	None	Low	CRITICAL
Accurate Diagnosis							
1 PCS Yamamoto et al,[13] 2023 1 RCS Luigetti et al,[15] 2020	Very serious [B]	Not serious	Not serious	Not serious	None	Low	CRITICAL
RECOMMENDATION 3 When assessing Congo red histochemistry, pathologists may add fluorescence microscopy with the tetramethylrhodamine isothiocyanate/Texas red filter to increase sensitivity for amyloid detection, if available.							
Diagnostic Test Characteristics							
4 DAS Lee et al[16] 2021, Shehabeldin et al[17] 2022, Cazzaniga et al,[18] 2023,	Serious [C]	Not serious	Not serious	Serious [D]	None	Low	CRITICAL

Pinedo et al[19] 2023							
Accurate Diagnosis							
1 RCS Clement et al,[20] 2014	Very serious [B]	Not serious[E]	Not serious	Not serious	None	Low	CRITICAL
RECOMMENDATION 4 In patients with amyloidosis being considered for therapy to optimize diagnostic yield and tissue utilization, pathologists should use mass spectrometry to identify the fibril protein type. *Note:* In renal amyloidosis, amyloid fibril typing may often be successfully accomplished by immunofluorescence, although reflex to mass spectrometry-based proteomics should be performed in difficult or equivocal cases.							
Assay Concordance							
2 PCS Gilbertson, et al,[21] 2015, Mollee et al[22] 2016, 1 RCS Abe et al,[24] 2021, 1 DAS Rezk et al[23] 2019	Very serious [B]	Not serious	Not serious	Not serious	None	Low	CRITICAL

Abbreviations: DAS, diagnostic accuracy study; PCS, prospective cohort study; RCS, retrospective cohort study; TRITC, tetramethylrhodamine isothiocyanate.

Footnotes

A. Other category includes assessment for detection of publication bias, large effect, and confounding.
B. Based on aggregate risk of bias assessment of critical-risk using ROBINS-I for cohort studies and high-risk using QUADAS-2 for diagnostic accuracy studies.
C. Based on aggregate risk of bias assessment of high-risk using QUADAS-2 for diagnostic accuracy studies.
D. Two studies included *a prior* diagnosis of amyloidosis as the reference standard. Although this is an adequate standard, studies reported on specificity and/or NPV after testing only amyloidosis positive studies. These estimated values are likely inaccurate, and evidence was downgraded.
E. As only one study reported on this outcome, the assessment of inconsistent results across studies is limited.

Supplemental Table 7. Diagnostic Test Characteristic of Congo Red and Electron Microscopy for Detection of Amyloid using Fat Pad Biopsy Recommendation 2

Study	Sample Size	Reference Standard	Amyloid Type	Detection Method	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Fernandez de Larrea et al,[12] 2015	n=745	Clinical evaluation	Systemic	Congo red with polarized light	79.0%; 74.7-82.7	79.7%; 74.4-84.2	71.6%; 66.2-76.4	85.4%; 81.4-88.7
				Electron microscopy	76.1%; 71.7-78.0	100%; 98.4-100	74.0%; 69.2-78.2	100%; 98.4-100
			AL (n=320)	Congo red with polarized light	80.9%; 76.1-85.0	NR	NR	NR
				Electron microscopy	79.4%; 74.4-83.6	NR	NR	NR

			AA (n=69)	Congo red with polarized light	76.8%; 64.8-85.8	NR	NR	NR
				Electron microscopy	76.8%; 64.8-85.8	NR	NR	NR
			ATTR (n=30)	Congo red with polarized light	66.7%; 47.1-82.1	NR	NR	NR
				Electron microscopy	43.3%; 26.0-62.3	NR	NR	NR

Abbreviations: AA, amyloid A; AL, immunoglobulin light chain; ATTR, amyloidosis derived from transthyretin; CI, confidence interval; NR, not reported.

Supplemental Table 8. Positivity Rate of Amyloid Detection using Congo Red and Electron Microscopy[A]
Recommendation 2

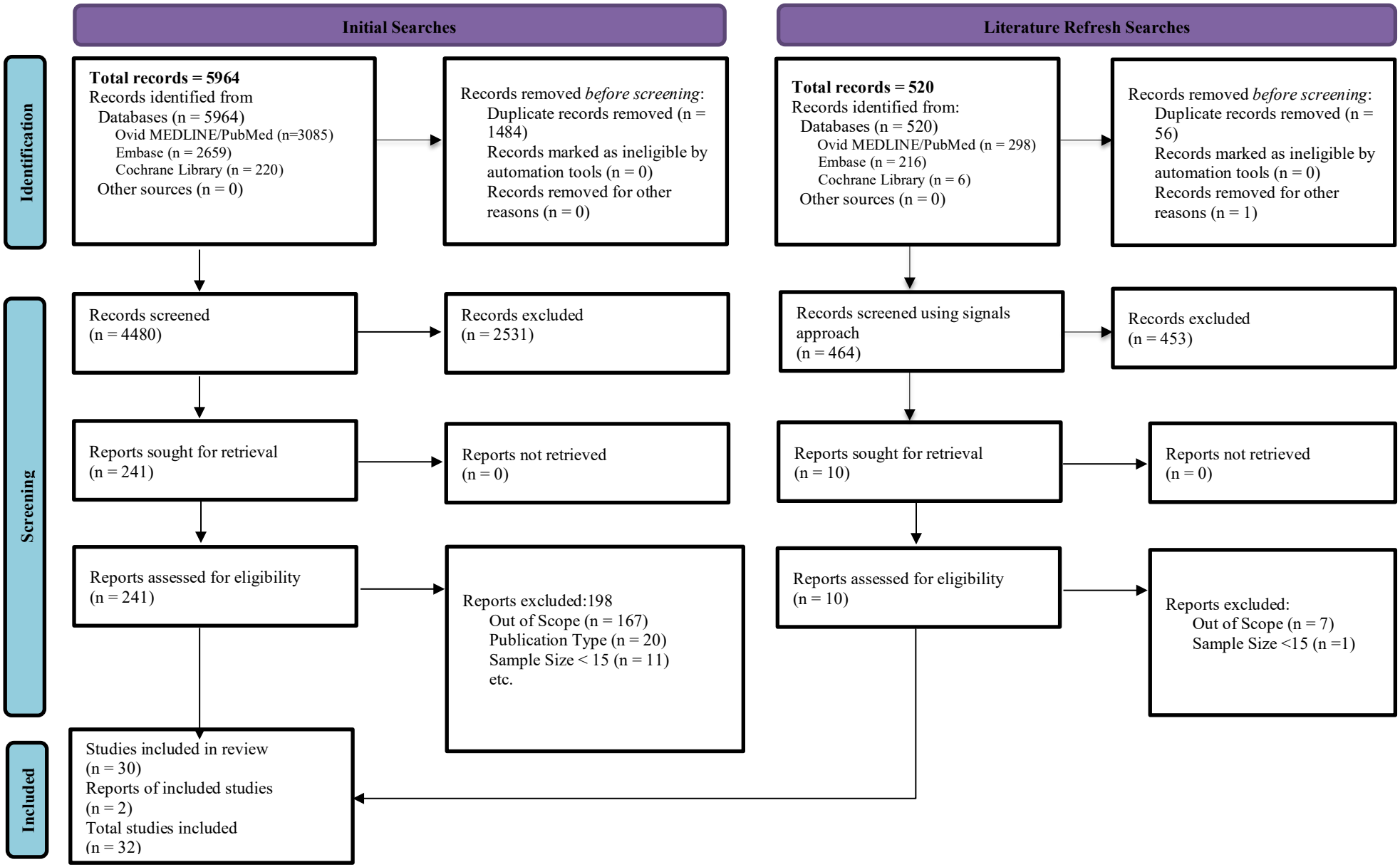
Study	Sample Size	Amyloid Type	Reference Standard	Biopsy Type	Detection Method	Positivity Rate
Luigetti et al,[15] 2020	n=69	Hereditary ATTR	Medical record	Sural nerve (n=69)	Congo red (n=69)	72.5%, n=50/69
				Fat pad (n=20)	Congo red (n=20)	40.0%, n=8/20
				Amyloid deposit (n=34)	Electron microscopy	32.3%, n=11/34
Yamamoto et al,[13] 2023	n=18	Cardiac amyloid	Clinical diagnosis	Endomyocardial	Congo red	94.4%, n=17/18
					Electron microscopy	100%, n=18/18

Abbreviations: ATTR, amyloidosis derived from transthyretin.

Footnotes

A. Chen et al,[14] 2022 included in the evidence base for this recommendation, but data is not included in the table as the study did not compare Congo red and electron microscopy.

Supplemental Figure 1: Systematic Literature Review Flow Diagram



Adapted From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Supplemental Figure 2: Database Search Strings

PubMed Search Run on 2/17/23 and 3/11/24

("Amyloidosis"[Mesh] OR amyloidosis[tiab] OR "Amyloid"[Mesh] OR amyloid[tiab] OR "Amyloidogenic Proteins"[Mesh])

AND

("Biopsy"[Mesh] OR heart biopsy[tiab] OR renal biopsy[tiab] OR endomyocardial biopsy[tiab] OR nerve biopsy[tiab] OR "fine needle"[tiab] OR "skinny needle"[tiab] OR "core needle"[tiab] OR "Bone Marrow"[Mesh] OR bone marrow[tiab] OR "Adipose Tissue"[Mesh] OR fat pad biopsy[tiab] OR fat pad biopsies[tiab] OR fat pad aspiration[tiab] OR "Specimen Handling"[Mesh] OR tissue section[tiab] OR tissue sample[tiab] OR "Cytodiagnosis"[Mesh] OR "Cytological Techniques"[Mesh] OR "Pathology, Surgical"[Mesh] OR "Coloring Agents"[Mesh] OR "Staining and Labeling"[Mesh] OR stain*[tiab] OR "Congo Red"[Mesh] OR Congo Red[tiab] OR Thioflavin T/S[tiab] OR Thioflavin S[tiab] OR Thioflavine[tiab] OR ThT dye[tiab] OR Sulphated alcian blue[tiab] OR Crystal violet[tiab] OR Sirius Red[tiab] OR Methyl violet[tiab] OR methyl violet[tiab] OR "Microscopy, Electron"[Mesh] OR fluorescence[tiab] OR fluorescent[tiab] OR immunofluorescence[tiab] OR "Microscopy"[Mesh] OR microscopy[tiab] OR Immunohistochemistry[tiab] OR "Immunohistochemistry"[Mesh] OR immunohistochemi*[tiab] OR IHC[tiab] OR immunocytochem*[tiab] OR "Mass spectrometry"[Mesh] OR "Proteomics"[Mesh] OR proteomics[tiab] OR histopathology[tiab] OR histopathologic[tiab])

AND

("Early Diagnosis"[Mesh] OR early diagnosis[tiab] OR "Missed Diagnosis"[Mesh] OR missed diagnosis[tiab] OR "Diagnosis"[Mesh] OR diagnos*[tiab] OR diagnostic concordance[tiab] OR "Diagnostic Techniques and Procedures"[Mesh] OR "Diagnosis, Differential"[Mesh] OR accura*[tiab] OR "Sensitivity and Specificity"[Mesh] OR sensitiv*[tiab] OR specific*[tiab] OR detect*[tiab] OR reliab*[tiab] OR "Predictive Value of Tests"[Mesh] OR positive[tiab] OR negative[tiab] OR "False Negative Reactions"[Mesh] OR "Survival Rate"[Mesh] OR "Survival Analysis"[Mesh] OR "Survival"[Mesh] OR "overall survival"[tiab])

AND

#1 AND #2 AND #3 Filters: **English**

#4 NOT ("Case Reports"[Publication Type] OR "Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Letter"[Publication Type]) Filters: **English MEDLINE**

#5 NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

#6 NOT (animal[tiab] OR "cell line"[tiab] OR feline[tiab] OR dog[tiab] OR mouse[tiab] OR "in vitro"[tiab])

#7 NOT Alzheimer*

Embase Search String Run on 2/17/23 and 3/11 24

#1. 'amyloidosis'/exp OR amyloidosis OR amyloidosis:ti,ab OR 'amyloid'/exp OR amyloid OR amyloid:ti,ab OR 'amyloidogenic proteins'/exp OR 'amyloidogenic proteins'

#2. 'biopsy'/exp OR 'heart biopsy':ti,ab OR 'renal biopsy':ti,ab OR 'endomyocardial biopsy':ti,ab OR 'nerve biopsy':ti,ab OR 'fine needle' OR 'skinny needle' OR 'core needle' OR 'bone marrow'/exp OR 'bone marrow':ti,ab OR 'adipose tissue'/exp OR 'fat pad biopsy':ti,ab OR 'fat pad biopsies':ti,ab OR 'fat pad aspiration':ti,ab OR 'specimen handling'/exp OR 'tissue section' OR 'tissue sample' OR 'cytodiagnosis'/exp OR 'cytological techniques'/exp OR 'pathology, surgical'/exp OR 'coloring agents'/exp OR 'staining and labeling'/exp OR stain* OR 'congo red'/exp OR 'congo red':ti,ab OR 'thioflavin t'/de OR 'thioflavin s' OR thioflavine OR 'tht dye' OR 'sulphated alcian blue' OR 'crystal violet' OR 'sirius red' OR 'methyl violet' OR 'microscopy, electron'/exp OR fluorescence OR fluorescent OR immunofluorescence OR 'microscopy'/exp OR microscopy OR immunohistochemistry OR 'immunohistochemistry'/exp OR immunohistochemi* OR ihc OR immunocytochem* OR 'mass spectrometry'/exp OR 'proteomics'/exp OR proteomics OR histopathology OR histopathologic

#3. 'early diagnosis'/exp OR 'early diagnosis' OR 'missed diagnosis'/exp OR 'missed diagnosis' OR 'diagnosis'/exp OR diagnos* OR 'diagnostic concordance' OR 'diagnostic techniques and procedures'/exp OR 'diagnosis, differential'/exp OR accura* OR 'sensitivity and specificity'/exp OR sensitiv* OR specific* OR detect* OR reliab* OR 'predictive value of tests'/exp OR positive OR negative OR 'false negative reactions'/exp OR 'survival rate'/exp OR 'survival analysis'/exp OR 'survival'/exp OR 'overall survival'

#4. #1 AND #2 AND #3

#5. #4 NOT ('alzheimer disease'/exp OR 'alzheimer

disease' OR alzheimers)
#6. #5 AND ([article]/lim OR [article in press]/lim)
AND [english]/lim AND [2013-2023]/py
#7. #6 AND medline
#8. #6 NOT #7
#9. #6 NOT #7 AND [2013-2023]/py
#10 #9 NOT ('animals'/exp NOT 'humans'/exp)
#11 #10 NOT case AND report
#12 #10 NOT #11

Cochrane Search Run on 2/17/23 and 3/11/24

1 (([mh Amyloidosis] OR amyloidosis:ti,ab OR [mh Amyloid] OR amyloid:ti,ab OR [mh "Amyloidogenic Proteins"])):ti,ab,kw (Word variations have been searched)
#2 (([mh Biopsy] OR "heart biopsy":ti,ab OR "renal biopsy":ti,ab OR "endomyocardial biopsy":ti,ab OR "nerve biopsy":ti,ab OR "fine needle" OR "skinny needle" OR "core needle" OR [mh "Bone Marrow"] OR "bone marrow":ti,ab OR [mh "Adipose Tissue"] OR "fat pad biopsy":ti,ab OR "fat pad biopsies":ti,ab OR "fat pad aspiration":ti,ab OR [mh "Specimen Handling"] OR "tissue section" OR "tissue sample" OR [mh Cytodiagnosis] OR [mh "Cytological Techniques"] OR [mh "Pathology, Surgical"] OR [mh "Coloring Agents"] OR [mh "Staining and Labeling"] OR stain* OR [mh "Congo Red"] OR "Congo Red":ti,ab OR [mh ^"Thioflavin T"] OR "Thioflavin S" OR Thioflavine OR "ThT dye" OR "Sulphated alcian blue" OR "Crystal violet" OR "Sirius Red" OR "Methyl violet" OR "methyl violet" OR [mh "Microscopy, Electron"] OR fluorescence OR fluorescent OR immunofluorescence OR [mh Microscopy] OR microscopy OR Immunohistochemistry OR [mh Immunohistochemistry] OR immunohistochemi* OR IHC OR immunocytochem* OR [mh "Mass spectrometry"] OR [mh Proteomics] OR proteomics OR histopathology OR histopathologic):ti,ab,kw (Word variations have been searched)
#3 (([mh "Early Diagnosis"] OR "early diagnosis" OR [mh "Missed Diagnosis"] OR "missed diagnosis" OR [mh Diagnosis] OR diagnos* OR "diagnostic concordance" OR [mh "Diagnostic Techniques and Procedures"] OR [mh "Diagnosis, Differential"] OR accura* OR [mh "Sensitivity and Specificity"] OR [mh "Predictive Value of Tests"] OR sensitiv* OR positive OR negative OR [mh "False Negative Reactions"] OR [mh "Survival Rate"] OR [mh "Survival Analysis"] OR [mh Survival] OR overall survival)):ti,ab,kw (Word variations have been searched)
#4 #1 AND #2 AND 3
#5 ([mh "Alzheimer Disease"] OR "Alzheimer disease" OR Alzheimer’s)
#6 #4 NOT #5

1. Pathologists CoA. Evidence-based guideline development methodology manual. Pathology and laboratory quality center for evidence-based guidelines; 2020.
2. Guyatt G, Oxman AD, Akl EA et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-94. doi:10.1016/j.jclinepi.2010.04.026.
3. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol*. 2016;75:40-6. doi:10.1016/j.jclinepi.2016.01.021.
4. Sterne JA, Hernán MA, Reeves BC et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Bmj*. 2016;355:i4919. doi:10.1136/bmj.i4919.
5. Whiting PF, Rutjes AW, Westwood ME et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-36. doi:10.7326/0003-4819-155-8-201110180-00009.
6. Alonso-Coello P, Schünemann HJ, Moberg J et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *Bmj*. 2016;353:i2016. doi:10.1136/bmj.i2016.
7. Fernández Fuertes J, Rodríguez Vicente Ó, Sánchez Herráez S, Ramos Pascua LR. Early diagnosis of systemic amyloidosis by means of a transverse carpal ligament biopsy carried out during carpal tunnel syndrome surgery. *Med Clin (Barc)*. 2017;148(5):211-214. doi:10.1016/j.medcli.2016.10.046.
8. Hansen CT, Møller HEH, Rojek AM, Marcussen N, Beck HC, Abildgaard N. Combined Subcutaneous Fat Aspirate and Skin Tru-Cut Biopsy for Amyloid Screening in Patients with Suspected Systemic Amyloidosis. *Molecules*. 2021;26(12). doi:10.3390/molecules26123649.
9. Kimmich C, Schönland S, Kräker S et al. Amyloid in bone marrow smears in systemic light-chain amyloidosis. *Amyloid*. 2017;24(1):52-59. doi:10.1080/13506129.2017.1314959.
10. Miyazaki K, Kawai S, Suzuki K. Abdominal subcutaneous fat pad aspiration and bone marrow examination for the diagnosis of AL amyloidosis: the reliability of immunohistochemistry. *Int J Hematol*. 2015;102(3):289-95. doi:10.1007/s12185-015-1827-8.
11. Quarta CC, Gonzalez-Lopez E, Gilbertson JA et al. Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis. *Eur Heart J*. 2017;38(24):1905-1908. doi:10.1093/eurheartj/ehx047.
12. Fernández de Larrea C, Verga L, Morbini P et al. A practical approach to the diagnosis of systemic amyloidoses. *Blood*. 2015;125(14):2239-44. doi:10.1111/ejh.13458.
13. Yamamoto M, Sato K, Murakoshi N et al. Additional diagnostic value of electron microscopic examination in endomyocardial biopsy in patients with suspected non-ischemic cardiomyopathy. *J Cardiol*. 2023;81(2):236-243. doi:10.1016/j.jjcc.2022.09.012.
14. Chen J, Yang H, Xu Z et al. Diagnosis of Primary Cutaneous Amyloidosis by Rapid 4,6-Diamidino-2-Phenylindole Staining. *Dermatology*. 2022;238(2):368-376. doi:10.1159/000518082.
15. Luigetti M, Romozzi M, Bisogni G et al. hATTR pathology: Nerve biopsy results from Italian referral centers. *Brain Sciences*. 2020;10(11):1-12. doi:10.3390/brainsci10110780.
16. Lee AYS, Bayly A, Lin MW. Evaluation of Polarized Light and Fluorescence Microscopy of Congo Red Stain in the Diagnosis of Renal Amyloidosis. *Lab Med*. 2021;52(6):574-577. doi:10.1093/labmed/lmab022.

17. Shehabeldin A, Hussey C, Aggad R, Truong L. Increased Diagnostic Specificity of Congo Red Stain for Amyloid. *Arch Pathol Lab Med*. 2022. doi:10.5858/arpa.2021-0512-OA.

18. Cazzaniga G, Bolognesi MM, Stefania MD et al. Congo Red Staining in Digital Pathology: The Streamlined Pipeline for Amyloid Detection Through Congo Red Fluorescence Digital Analysis. *Lab Invest*. 2023;103(11):100243. doi:10.1016/j.labinv.2023.100243.

19. Pinedo Pichilingue A, Thayyil A, Dai DF, Rastogi P. Diagnostic performance of fluorescence microscopy with a tetramethylrhodamine isothiocyanate filter in identifying renal amyloidosis. *Histopathology*. 2023;83(5):722-732. doi:10.1111/his.15014.

20. Clement CG, Truong LD. An evaluation of Congo red fluorescence for the diagnosis of amyloidosis. *Hum Pathol*. 2014;45(8):1766-72. doi:10.1016/j.humpath.2014.04.016.

21. Gilbertson JA, Theis JD, Vrana JA et al. A comparison of immunohistochemistry and mass spectrometry for determining the amyloid fibril protein from formalin-fixed biopsy tissue. *J Clin Pathol*. 2015;68(4):314-7. doi:10.1136/jclinpath-2014-202722.

22. Mollee P, Boros S, Loo D et al. Implementation and evaluation of amyloidosis subtyping by laser-capture microdissection and tandem mass spectrometry. *Clinical Proteomics*. 2016;13(1):1-6. doi:10.1186/s12014-016-9133-x.

23. Rezk T, Gilbertson JA, Mangione PP et al. The complementary role of histology and proteomics for diagnosis and typing of systemic amyloidosis. *J Pathol Clin Res*. 2019;5(3):145-153. doi:10.1002/cjp2.126.

24. Abe R, Katoh N, Takahashi Y et al. Distribution of amyloidosis subtypes based on tissue biopsy site - Consecutive analysis of 729 patients at a single amyloidosis center in Japan. *Pathol Int*. 2021;71(1):70-79. doi:10.1111/pin.13041.

25. Barreca A, Bottasso E, Veneziano F et al. Immunohistochemical typing of amyloid in fixed paraffin-embedded samples by an automatic procedure: Comparison with immunofluorescence data on fresh-frozen tissue. *PLoS One*. 2021;16(8):e0256306. doi:10.1371/journal.pone.0256306.

26. Suzuki T, Kusumoto S, Yamashita T et al. Labial salivary gland biopsy for diagnosing immunoglobulin light chain amyloidosis: a retrospective analysis. *Ann Hematol*. 2016;95(2):279-85. doi:10.1007/s00277-015-2549-y.

27. Pinton S, Vacchi E, Chiaro G et al. Amyloid detection and typing yield of skin biopsy in systemic amyloidosis and polyneuropathy. *Ann Clin Transl Neurol*. 2023;10(12):2347-2359. doi:10.1002/acn3.51924.

28. Abildgaard N, Rojek AM, Moller HE et al. Immunoelectron microscopy and mass spectrometry for classification of amyloid deposits. *Amyloid*. 2020;27(1):59-66. doi:10.1080/13506129.2019.1688289.

29. Cohen OC, Sharpley F, Gilbertson JA et al. The value of screening biopsies in light-chain (AL) and transthyretin (ATTR) amyloidosis. *Eur J Haematol*. 2020;105(3):352-356. doi:10.1111/ejh.13458.

30. Fine NM, Arruda-Olson AM, Dispenzieri A et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. *Am J Cardiol*. 2014;113(10):1723-7. doi:10.1016/j.amjcard.2014.02.030.

31. Lee HJ, Kim JS, Mun YC, Lee JK. Ultrasound-guided percutaneous core needle biopsy of abdominal subcutaneous fat for diagnosing amyloidosis: comparison with bone marrow biopsy. *Acta Radiol*. 2023:2841851231151369. doi:10.1177/02841851231151369.

32. Li T, Huang X, Cheng S et al. Utility of abdominal skin plus subcutaneous fat and rectal mucosal biopsy in the diagnosis of AL amyloidosis with renal involvement. *PLoS One*. 2017;12(9):e0185078. doi:10.1371/journal.pone.0185078.

33. Lopes AI, Machado-Neves R, Honavar M, Pereira PR. The role of minor salivary glands' biopsy in the diagnosis of Sjögren's syndrome and other systemic diseases. *Eur J Intern Med*. 2021;94:69-72. doi:10.1016/j.ejim.2021.07.012.

34. Muchtar E, Dispenzieri A, Lacy MQ et al. Overuse of organ biopsies in immunoglobulin light chain amyloidosis (AL): the consequence of failure of early recognition. *Ann Med*. 2017;49(7):545-551. doi:10.1080/07853890.2017.1304649.

35. Nishi M, Takashio S, Morioka M et al. Extracardiac Biopsy Sensitivity in Transthyretin Amyloidosis Cardiomyopathy Patients With Positive (99 m)Tc-Labeled Pyrophosphate Scintigraphy Findings. *Circ J*. 2022;86(7):1113-1120. doi:10.1253/circj.CJ-22-0118.

36. Paulsson Rokke H, Sadat Gousheh N, Westermark P et al. Abdominal fat pad biopsies exhibit good diagnostic accuracy in patients with suspected transthyretin amyloidosis. *Orphanet J Rare Dis*. 2020;15(1):278. doi:10.1186/s13023-020-01565-8.

37. Vrana JA, Theis JD, Dasari S et al. Clinical diagnosis and typing of systemic amyloidosis in subcutaneous fat aspirates by mass spectrometry-based proteomics. *Haematologica*. 2014;99(7):1239-47. doi:10.3324/haematol.2013.102764.

38. Wu B, Pak DM, Smith KD, Shinohara MM. Utility of abdominal skin punch biopsy for detecting systemic amyloidosis. *J Cutan Pathol*. 2021;48(11):1342-1346. doi:10.1111/cup.14070.