COLLEGE of AMERICAN PATHOLOGISTS

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Laboratory Detection and Initial Diagnosis of Monoclonal Gammopathies

Guideline From the College of American Pathologists in Collaboration With the American Association for Clinical Chemistry and the American Society for Clinical Pathology

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GUIDELINE DEVELOPMENT METHODS

Panel Composition

The College of American Pathologists (CAP) along with its collaborators, the American Association for Clinical Chemistry (AACC), American Society for Clinical Pathology (ASCP), American Society for Hematology (ASH), and the International Myeloma Foundation's International Myeloma Workgroup (IMWG), convened an expert panel (EP) consisting of members with experience and expertise in the diagnosis and treatment of monoclonal gammopathies and the laboratory procedures used for their initial detection to develop evidence-based recommendations for the laboratory procedures for the initial detection of monoclonal proteins. Members include practicing pathologists, hematologists, clinical chemists, guideline methodologist, and laboratory scientists from the from the United States and Canada. The CAP approved the appointment of the project co-chairs and panel members. The role of the EP members was to identify key questions, perform a systematic review of the literature, review the evidence base, draft recommendations, and author the manuscript.

An advisory panel (AP) of pathologists, hematologists, and clinical chemists was also formed. The role of the AP members was to provide feedback on the key questions for the literature search, vet the draft guideline statements prior to the public comment period, and to review and provide feedback for the manuscript and supplemental digital content (SDC). They did not vote on the recommendations.

Conflict of Interest (COI) Policy

Prior to acceptance on the expert or advisory panel, potential members completed the collaborative conflict of interest (COI) disclosure process, whose policy and form (effective November 2017) 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 12 months post-publication. The potential members completed the COI disclosure form, listing any relationship that could be interpreted as constituting an actual, potential, or apparent conflict. Each potential EP member's disclosures were assessed by a COI review committee and categorized as:

No Relevant Conflicts of Interest**:** Individuals with no relevant COI are approved for full participation including determining the scope and questions to be addressed, reviewing and discussing the evidence, formulating and grading recommendations, voting on recommendations, and writing the document. Research funding that is free of direct or indirect industry funding or control, such as that provided by a government program or a non-profit organization that does not receive industry funding and uses an award mechanism and oversight that is independent of industry, is not regarded to be a conflict of interest. Service on a data and safety monitoring board for such research is also not regarded as a conflict of interest. Finally, industry funded research unrelated to the content of the *Joint Recommendations* is not regarded as a conflict of interest.

Manageable Conflicts of Interest: Individuals with manageable conflicts must disclose their conflicts to the whole guideline panel. They may participate in discussions about the evidence, but must excuse themselves or be recused from decision-making, including formulating, voting on, writing, and grading recommendations related to their COI (i.e., recommendations addressing a product of the commercial entity with which they have a relationship or addressing a product of a competitor of the commercial entity with which they have a relationship). COI that require management include:

A. Research funding from an industry grant that is paid to the participant's institution and related to the content of the *Recommendations*;
B. Research funding from a government program or non-profit organization that receives funding from industry with business interests in the content of the *Recommendations*;
C. Participation on a data and safety monitoring board concerned with research that is relevant to the content of the *Recommendations* and is funded by an industry with business interests in the content of the *Recommendations*, or by a government program or non-profit organization that receives funding from industry with business interests in the content of the *Recommendations*.

D. Participation in scientific advisory board or consultant activities that are exclusively scientific in nature (ie, does not involve any activities that could be perceived as promotional) related to the subject matter of the *Recommendations.*
E. Participation in industry-funded research, scientific advisory committees, consulting roles, non-promotional speaking engagements, or expert testimony on matters that are unrelated to the subject matter of the *Recommendations*, but the company involved is known to have business interest in the subject matter;
F. Delivery of non-promotional talks in which the speaker has full control of the content and is either unpaid or paid by a third party that is responsible for ensuring that the event is free of influence of relevant industry (ie, if the event has industry financial support, all planning and content must be free of industry influence, and any payment of expenses and honoraria must occur through a third party, such as the medical society or institution sponsoring the event, or an event manager acceptable to them, rather than directly by a commercial entity with an interest in guideline subject matter or its agent);
G. Professional roles or activities (ie, roles and activities performed as part of an individual's profession, whether reimbursed or not) that place an individual in a position to personally gain or lose depending upon the recommendations.

Disqualifying Conflicts of Interest: Disqualifying conflicts of interest include the following:

A. Any current professional relationship with or investment in a company involved in the manufacture or distribution of monoclonal gammopathy assays.
B. A direct financial relationship with a relevant commercial entity that has an interest in the content of the Recommendations, exclusive of the research, data safety monitoring board activities, and scientific advisory board and consultant activities noted above. Such direct financial relationships include the following, whether paid to or held by the individual directly or issued to another entity at the direction of the individual (such as to a panelist's institution):
    i. Payment of wages, consulting fees, honoraria, or other payments (in cash, in stock or stock options, or in kind) by a relevant company as compensation for the individual's services or expertise, exclusive of the research and data safety monitoring board activities noted above. Examples of such services are: participation on scientific advisory committees or consulting that is, in full or in part, promotional in nature; non-CME speaking engagements and inclusion in speaker bureaus where control of material is held by industry; expert testimony on matters related to guideline content provided on behalf of a relevant company or a law firm representing a relevant company; employment by a relevant commercial entity (such as a relevant pharmaceutical or medical device company or a third party payer exclusive of commercial laboratory employment that has financial interests in the content of the Recommendations).
    ii. Investments in relevant companies by the panelist or the panelist's spouse or life partner (exclusive of general mutual funds).
C. A patent or other intellectual property that is relevant to the Recommendations' subject matter and has resulted or could result in payments to the panelist or the panelist's institution.

All panel members were required to disclose conflicts prior to beginning and continuously throughout the project's timeline.

Disclosures of interest judged by the oversight group as manageable conflicts are listed in the manuscript. Appendix 1 in the manuscript also includes a table of all disclosed interest of the expert panel members/authors during the development of the guideline for complete transparency.

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Funding
The CAP provided funding for the administration of the project; no industry funds were used in the development of the guideline.

Expert Panel Responsibilities
The EP met a total of 8 times during the guideline development process. The EP met in person on December 17, 2017 to prioritize outcomes and finalize the scope and key questions. The EP met again in person on April 21–22, 2018 to draft recommendations. The EP met 6 times through teleconference and all additional work was completed via electronic mail.

All EP members participated in the systematic evidence review (SER). Each level of the SER (title-abstract screening, full-text review, and data extraction) was performed in duplicate by two members of the EP or one member of the EP and a methodologist. All EP members and a methodologist performed adjudication of the conflicts. All EP members participated in the writing, editing, and reviewing of the manuscript and are listed as authors.

Project Scope
The EP approved the following scope to develop evidence-based recommendations to address the overarching question “What are the specimen requirements and appropriate tests needed for the initial laboratory detection of monoclonal immunoglobulin proteins (M-proteins)?”

The EP approved the following key questions for the systematic evidence review:

1. What specimens are useful in the detection of M-proteins?
2. What are the appropriate tests needed to accurately detect M-proteins?
3. What are the appropriate tests needed to accurately quantify M-proteins?

In addition, the EP approved the following key questions for discussion which will not require a systematic evidence review:

1. What reporting elements should be included in the pathology report?
2. Is there an optimal testing sequence, strategy, or approach for the initial detection of M-proteins?

Systematic Evidence Review (SER)
The objective of the SER was to identify articles that provided data to inform the recommended testing for the workup of monoclonal gammopathies. 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 is included in Supplemental Table 1.

Outcomes Ranking and Selection
According to the GRADE approach, it is important for clinical guideline panels to review a comprehensive list of outcomes.[1] The EP was polled to collect information on which outcomes should be included in the PICO. These outcomes included, but were not limited to, accuracy in diagnosis (specificity, sensitivity, positive and negative predictive values), change in patient management, cost, optimal and adequacy of specimen selection, patient preference, quality of life, rates of adverse reactions, survival rates, test/assay utility, and timely communication to the clinicians.

In consideration of the limited scope and resources, the EP ranked the outcomes used in the PICO. Using the GRADE approach[1] of considering the relative 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 EP finalized the outcomes after a discussion during the first in-person meeting.

Outcomes of Limited Importance:

- These outcomes not used for decision making
  1. Survival rates
  2. Treatment response rates

Important Outcomes

1. Patient experience and quality of life
2. Complication rates based on unnecessary diagnostic procedures (false positive [FP]) and delayed treatment (false negative [FN])
3. Turn-around times

Critical Outcomes

1. Accuracy of diagnosis
2. Diagnostic test accuracy
3. Risk stratification
4. Test utilization

Search and Selection

An initial systematic literature search for relevant evidence in Ovid MEDLINE and Elsevier Embase was completed on January 31, 2018, using controlled vocabulary and keyword terms for the concepts of MGs, specimen type, diagnosis, and ancillary testing. Limits were set for human studies (using the Cochrane search filter) published in English between the dates of January 1, 2008 through January 31, 2018. Limits were also set to exclude the following publication types: case reports, commentaries, editorials, and letters. Database searches were supplemented with a search for unpublished (grey) literature, including a review of clinical trials via ClinicalTrials.gov and a search for existing relevant guidelines, protocols, or standards on guideline repository websites. Guidelines were included if they were published in English since January 1, 2008.

After deduplication, 4,487 unique citations were identified during the initial literature search process. Systematic review searches (including targeted searches) were repeated on January 29, 2019 to identify new evidence published since the initial searches were run. 712 unique citations were identified by the literature refresh searches. In total, 5,199 unique citations were identified across all literature searches.

The PRISMA diagram outlining the outcome of the systematic literature review is included as Supplemental Figure 1. Detailed search strategies are included as Supplemental Figure 2. Selection at all levels was also based on the predetermined inclusion/exclusion criteria.

Included:

1. Study population must consist of patients with clinical features raising consideration for monoclonal gammopathies (MG), including MGUS, MG of renal significance, light chain multiple myeloma, non-secretory multiple myeloma, smoldering multiple myeloma, heavy chain disease, AL amyloidosis, Waldenström Macroglobulinemia, solitary plasmacytoma, or polyneuropathy, organomegaly, endocrinopathy, monoclonal plasmaproliferative disorder, skin changes (POEMS) syndrome.
2. Studies must evaluate either:
   a. The use of serum or urine for accurate diagnosis of monoclonal gammopathy;
   b. The ability of ancillary testing to diagnose and/or risk stratify patients with monoclonal gammopathy.
3. Studies must include one of the following as primary outcomes:
   a. Accuracy of diagnosis, including detection of monoclonal immunoglobulins, risk stratification, rate of appropriate treatment, time to appropriate treatment;
   b. Diagnostic test accuracy, including diagnostic sensitivity, specificity, positive predictive value, and negative predictive value;
   c. Patient survival outcomes, patient experience, quality of life outcomes, or complication rates;
   d. Concordance between intervention and the standard of care;

   e. Appropriate utilization of samples, correct test selection, testing efficiency, or test turn-around-time.
4. Studies must be peer-reviewed full-text articles

Excluded:

- Letters
- Commentaries
- Editorials
- Narrative reviews
- Case reports
- Studies in animal models
- *In vitro* studies
- Consensus documents
- Articles not in the English language
- Meeting abstracts
- Less than 30 patients per study arm
- Less than 10 confirmed MG cases

Data Extraction & Management

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

Quality Assessment Methods

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 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.

Systematic Reviews (SRs) and Meta-analyses

- The following questions were assessed as per the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) 8 tool[2] using Yes or No:
  1. Was an ‘a priori’ design provided?
  2. Was there duplicate study selection and data extraction?
  3. Was a comprehensive literature search performed?
  4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
  5. Was a list of studies (included and excluded) provided?
  6. Were the characteristics of the included studies provided?
  7. Was the scientific quality of the included studies assessed and documented?
  8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
  9. Were the methods used to combine the findings of studies appropriate?
  10. Was the likelihood of publication bias assessed?
  11. Was the COI included?
- Additional assessed items included and were assessed as Yes, No, or Unclear:
  1. Reporting of funding sources.

Prospective Cohort Studies (PCS) and Retrospective Cohort Studies (RCS)

- The following domains were assessed using the Risk of Bias in Non-Randomized Studies – of Intervention (ROBINS-I)[3] tool using low risk, moderate risk, serious risk, critical risk, or unclear:

1. Confounding
2. Patient selection (selection bias)
3. Intervention classification (performance bias)
4. Deviation from intended intervention (performance bias)
5. Missing data (reporting bias)
6. Outcome measurements (detection bias)
7. Selection of reported outcomes (detection bias)

- Additional assessed items included and were assessed as yes, no, or unclear:
  1. Adequately powered statistical analysis
  2. Reporting of funding sources
  3. Industry funding

Diagnostic Accuracy Studies (DAS)

- The following domains were assessed using the QUADAS-2 tool.[4] For domains related to risk of bias, an assessment of low risk, high risk, or unclear was used. For domains related to applicability to the Key Questions, an assessment of low concern, high concern, or unclear concern was used.
  1. Risk of bias – patient selection
  2. Applicability – patient selection
  3. Risk of bias – index test(s)
  4. Applicability – index test(s)
  5. Risk of bias – reference standard
  6. Applicability – reference standard
  7. Risk of bias – flow and timing
- Additional assessed items included and were assessed as yes, no, or unclear:
  1. Study design (prospective or retrospective)
  2. Adequately powered statistical analysis
  3. Reporting of funding sources
  4. Industry funding

Assessing the Strength of Recommendations and Considered Judgement

The central question that the panel addressed in developing the guideline was: What are the specimen requirements and appropriate tests needed for the initial laboratory detection of M-proteins?

Development of recommendations required that the panel review the identified evidence and make a series of key judgments:

1. What are the significant findings related to each KQ or outcome? Determine any regulatory requirements and/or evidence that support a specific action.

2. What is the overall strength of evidence supporting each KQ or outcome? Strength of evidence is graded as High, Moderate, Low, and Very Low, based on published criteria (Supplemental Table 2). Strength of evidence is a key element in determining the strength of a recommendation.

3. What is the strength of each recommendation? The strength of recommendations is designated as Strong or Conditional. There are many methods for determining the strength of a recommendation based on the strength of evidence and the magnitude of net benefit or harm. According to the GRADE approach, the strength of a recommendation demonstrates the extent to which an EP is "confident that the desirable effects of an intervention outweigh undesirable effects".[5] For each statement, the panel rated each GRADE evidence to decision framework (EtD)[6] domain. With a strong recommendation designation, the EP judgements will mostly be favoring the right or left of the framework and indicate high confidence that the desirable effects of the guidance statement outweigh the undesirable effects. With a conditional recommendation, the EP judgements will be more towards the center of the framework or with a dispersed pattern indicating lower confidence. Supplemental Table 3 provides a summary of the Grades for the Strength of Recommendations.

Evidence-to-Decision Framework (EtD) Domains

1. Problem Priority
    - Is the problem a priority and is a recommendation needed to address it?
    - Are there consequences that are serious if the problem is not addressed?
2. Benefits and Harms
    - Are the desirable anticipated effects large?
    - Are the undesirable anticipated effects small?
    - Are the desirable effects large relative to undesirable effects?
3. Values and preferences of stakeholders:
    - Is there certainty of how stakeholders (patients, clinicians) value the outcomes?
    - Is there variability on how patients and clinicians value the outcomes?
    - Will there be different decisions from key stakeholders because of the different values placed on the outcomes?
4. Resources Required:
    - If the Recommendation is made, how large are the resource requirements?
5. Health Equity
    - Are there groups or settings that might be disadvantaged in relation to the Recommendation being considered?
    - Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the Recommendation or the importance of the problem for disadvantaged groups or settings?
    - Are there important considerations that should be made when implementing the Recommendation in order to ensure that inequities are reduced, if possible, and that they are not increased?
6. Feasibility
    - Is the option (or recommendation) feasible to implement?
    - Is the Recommendation sustainable? Are there important barriers that are likely to limit the feasibility of implementing the Recommendation? If yes, do these barriers require consideration when implementing the Recommendation?
7. Acceptability
    - Is the option acceptable to key stakeholders?
    - Are there key stakeholders that would not accept the distribution of the benefits, harms or costs?
    - Are there key stakeholders that would not accept the costs or undesirable effects in the short term for desirable effects (benefits) in the future?

Statements not supported by evidence (i.e., evidence was missing or insufficient to permit a conclusion to be reached) and made based on consensus expert opinion will be included as Good Practice Statements.[7]

Articulation of Recommendations

In order to articulate statements that were clearly written and easy to implement, the EP followed GLIDES (Guidelines Into Decision Support) and accompanying BridgeWiz software (Yale University, New Haven, CT) guidance on the wording of recommendations.[8] Statements should clearly address “who is doing what to whom”, meaning the “actor” is defined within the statement to perform a specific action or intervention to a patient or population. The GLIDES program prioritizes the use of active voice because using the passive voice may lack the clarity and transparency of the statement. However, in some situations, the person responsible for ensuring guidance is implemented is dependent on the organization of the clinic and/or laboratory. To ensure clarity of guidance in these situations, the EP may use passive language to emphasize the recommended action. The guideline uses a two-tier system to rate the strength of recommendations (Supplement Table 3). Supplement Table 2 summarizes the level of evidence and considered judgement, as well as obligatory language that was used for each of the recommendation types.

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Peer Review

An open comment period was held from January 30, 2019–February 22, 2019 on the CAP web site www.cap.org. Thirteen draft statements, 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 Society for Clinical Pathology (ASCP)
- American Society of Hematology (ASH)
- International Myeloma Workgroup (IMWG)
- American Association for Clinical Chemistry (AACC)
- Association for Molecular Pathology (AMP)
- American Society for Clinical Oncology (ASCO)
- Association of Directors of Anatomic and Surgical Pathology (ADASP)
- Association of Pathology Chairs (APC)
- Canadian Association of Pathologists (CAP-APC)
- United States & Canadian Academy of Pathology (USCAP)
- Quality Initiative in Interpretive Pathology (QIIP)
- Society to Improve Diagnoses in Medicine (SIDM)
- European Society for Medical Oncology (ESMO)
- American Association for Cancer Research (AACR)
- European Society of Pathology (ESP)
- Japanese Society of Medical Oncologists (JSMO)
- Canadian Association of Medical Oncology
- Royal College of Pathologists
- Association of Community Cancer Centers (ACCC)
- National Comprehensive Cancer Network (NCCN)

Patient advocacy groups:

- American Cancer Society
- International Myeloma Foundation
- Partnership Against Cancer
- Cancer Research and Prevention Foundation
- Cancer Leadership Council
- Leukemia and Lymphoma Society
- Union for International Cancer Control
- Canadian Partnership Against Cancer

Government and other stakeholders:

- US Food and Drug Administration (FDA)
- Centers for Medicare & Medicaid Services (CMS)
- Centers for Disease Control and Prevention (CDC)
- Veteran's Affairs (VA) and Department of Defense (DOD)
- European Medical Agency

"Agree as written", "Agree with suggested modifications", "Disagree", and "Does not pertain to my area of expertise or practice" responses were captured for each draft recommendation statement. The website received over 344 written comments. Ten draft statements achieved more than 90% agreement and 3 draft statements received more than 80% agreement. All draft recommendation statements have agreements that range between 83.1%–98.8%. The EP was divided to small groups of 2 members each and each group was assigned 2 draft recommendation statements for which members reviewed the comments and provide suggestions to the entire panel to: keep original draft language, edit with minor changes for clarity, or edit with major changes. After consideration of the comments, a total of 9 final

recommendations were included in the guideline: 4 draft recommendations were maintained with the original language; 4 were revised with minor edits for clarity; 3 draft recommendations were combined into 1 statement; and one draft recommendation was edited with a major revision. Resolution of all changes was obtained by majority consensus of the panel using nominal group technique (discussion during teleconference webinars, email discussion, and multiple edited recommendations) amongst the panel members. The final recommendations were approved by the EP with a formal vote.

The panel considered efficiency and feasibility throughout the entire EtD and considered judgment process. The public was split about the feasibility of the entire set of recommendation statements. Over 62% (99 of 158) responded that all of the draft statements were feasible to implement, 36.7% (58 of 158) responded that parts of it were feasible, and less than 1% (1 of 158) responded that none of it was feasible. The respondents identified that barriers may impede the adoption of the final guideline. These barriers include: disagreement with the draft recommendations; disagreement with how the guideline was developed; guideline is too burdensome; possible lack of support from the administration and members of the medical team; lack of resources; and not wanting to give up personal autonomy to follow the guideline. Neither formal cost analysis nor cost effectiveness models were performed.

Document Review and Approval

An independent review panel (IRP) was assembled to review and approve the guideline on behalf of the CAP Council on Scientific Affairs. The IRP was masked to the EP and to each other and were vetted through the COI process.

Dissemination Plans

The CAP plans to host a Laboratory Detection and Initial Diagnosis of Monoclonal Gammopathies resource webpage which will include 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 infographic along with other additional tools such as webinar recordings as applicable. The guideline will be promoted and presented at various society meetings.

Quality Assessment Results

A total of 25 studies identified by our systematic review informed the recommendations. This body of evidence comprised 1 systematic review, 4 PCSs, 10 RCSs and 10 DASs. The quality assessment for the systematic review is detailed in Supplemental Table 4, while the quality assessment for the PCSs are included in Supplemental Table 5, the RCSs in Supplemental Table 6, and the DASs in Supplemental Table 7.

Overall, the body of evidence included in this CPG represents a methodologically rigorous and representative summary of the available evidence with an overall quality of high to very low. Of the 25 studies informing recommendation statements, one was assessed as high quality, three as intermediate quality, five as intermediate-low quality, nine as low quality, and seven as very low quality (Supplement Tables 4-7).

Recommendation Statements

Statement 1. Clinical care providers should order both serum protein electrophoresis (SPEP) and serum free light chains (sFLC) for the initial detection of M-protein in all patients with suspected MG. *Strong Recommendation.*

The strength of evidence to support this guideline statement is moderate. The evidence for this statement comprises five studies[9-13] that evaluated the diagnostic test characteristics of SPEP and sFLC in the initial detection of monoclonal proteins. This included a high-quality systematic review,[9] an intermediate quality diagnostic accuracy study,[10] one low quality diagnostic accuracy study[12] and two very low-quality diagnostic accuracy studies.[11, 13] The diagnostic accuracy studies were assessed as intermediate through very low quality based on a high or unclear risk of bias in terms of patient selection,[11-13] conduct or interpretation of the index tests,[10, 11] selection, conduct or interpretation of the

reference standard[11, 13] and patient flow.[11-13] There were no concerns surrounding the applicability of the patients, index tests, or reference tests when compared with the Key Questions. None of the studies were found to have methodological flaws that would raise concerns about the findings. The aggregate risk of bias across all 5 studies was serious but the evidence was not further downgraded for any domain (Supplemental Table 8).

Although the EP members believed the associated harms of conducting both assays in the initial detection of monoclonal proteins ranged from large to trivial, majority of the members (87.5%) believed the moderate to large benefits outweighed these harms. Additionally, although the majority of EP members agreed that there would be a moderate cost increase when using both assays, all members felt the recommendation would be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 9 for a complete summary of the EtD framework.

Statement 2. Laboratorians should confirm a SPEP abnormality suspicious for a presence of a M-protein with additional testing by serum immunofixation electrophoresis (sIFE) or alternative method with similar sensitivity. *Strong Recommendation.*

The strength of evidence to support this guideline statement is moderate. The evidence base supporting this recommendation comprises 5 studies which all employed sIFE as a reference standard when determining diagnostic test characteristics of SPEP.[12, 14-17] All five studies were of a diagnostic accuracy design and assessed as intermediate,[14] intermediate low,[15] low,[12, 16] and very low[17] quality. Studies were limited by high or unclear risk of bias in patient selection,[12, 15, 17] conduct or interpretation of the index tests,[14, 15, 17] selection, conduct or interpretation of the reference standard,[17] and patient flow domains.[12] There were no concerns surrounding the applicability of the patients, index test, or reference tests when compared with the Key Questions in four studies;[12, 14-16] however, in one study,[17] the patient population included all serum samples with requests for SPEP, raising concerns surrounding the applicability of these samples when compared with our target population. None of the studies were found to have methodological flaws that would raise concerns about the findings. The aggregate risk of bias across the included studies was serious. Although the identified evidence did not provide diagnostic test characteristic for sIFE, the evidence was not downgraded for indirectness (Supplemental Table 8). In current practice sIFE is the gold standard and studies assessing the test characteristics of sIFE were published prior to our search inception.

Although the identified evidence did not directly provide diagnostic test characteristics for sIFE, this is believed to be a consequence of these studies having been published prior to our search inception. In current practice, sIFE is the gold standard. Based on the available evidence and the use of sIFE as usual practice, all EP members believed that the large benefits of increased specificity using sIFE for confirmation outweighed the small to trivial harms of an additional test. The EP discussed the use of alternative assays which have demonstrated similar sensitivities when compared with sIFE.[18-24] Again, some of the studies comparing the sensitivity and specificity of sIFE versus other assays, such as immunosubtraction were published prior to our inclusion dates. Although recent work with mass spectrometry for detection and confirmation of M-proteins indicates that it is at least as sensitive as sIFE, the literature is sparse at the present time.[25] As such, although the systematic review did not provide current evidence for comparable sensitivities for other assays, the EP is comfortable recommending the use of assays with known sensitivity similar to sIFE. All EP members felt that this recommendation would be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 9 for a complete summary of the EtD framework.

Statement 3. Laboratorians and/or clinical care providers should follow-up an abnormal sFLC ratio for the presence of a M-protein with a serum IFE or alternative method with similar sensitivity. *Conditional Recommendation.*

The strength of evidence to support this guideline statement is low. The evidence base for this recommendation comprises six studies that evaluated sFLC.[12, 26-30] The evidence base includes one prospective cohort study assessed as intermediate-low quality,[27] three retrospective cohort studies assessed as low quality,[28-30] and two diagnostic accuracy studies assessed as intermediate-low[26] and

low[12] quality. The cohort studies suffered from risk of bias in selection,[12, 26-30] performance,[12, 30] reporting,[12, 27, 29, 30] and detection[28-30] domains. The two diagnostic accuracy studies were limited by unclear risk of bias in patient selection in one,[12] and unclear risk of bias in conduct or interpretation of the index tests, and selection, conduct or interpretation of the reference standard in the other.[26] Both were limited by high risk of bias in patient flow,[12, 26] but there were no concerns surrounding the applicability of the patients, index test, or reference tests when compared with the Key Questions in either. Additionally, two studies reported that sFLC reagents were supplied by the manufacturer, but the study was not funded by the manufacturer,[12, 26] and three studies did not report on funding sources.[27-29] None of the studies were found to have methodological flaws that would raise concerns about the findings. The aggregate risk of bias across the evidence base was serious and evidence was further downgraded for inconsistency of results; however, evidence was again not downgraded for indirectness (Supplemental Table 8).

As was discussed in the previous recommendation, although the identified evidence did not directly provide diagnostic test characteristics for sIFE, this is believed to be a consequence of sIFE being historically defined as the gold standard. Based on the available evidence and the use of sIFE as usual practice, majority of EP members (87.5%) believed that the moderate to large benefits of increased specificity using sIFE for confirmation of M-protein presence outweighed the harms of an additional test. The remaining EP members (12.5%) felt that there was balance between the benefits and harms of sFLC confirmation by sIFE based on the possible discrepancy between sFLC and sIFE which may cause patient anxiety and prolonged workup. Although there was disagreement surrounding weighing of the benefits and harms, all EP members still felt that this recommendation would be acceptable to key stakeholders and feasible to implement. However, the recommendation is conditional based on the lower strength of evidence and EtD domains. Refer to Supplemental Table 9 for a complete summary of the EtD framework.

Statement 4. Clinical care providers should order SPEP, sFLC, serum IFE, and urine IFE (uIFE) for the initial detection of M-protein in all patients with suspected amyloid light chain (AL) amyloidosis. *Strong Recommendation.*

The strength of evidence to support this guideline statement is moderate. The evidence supporting this statement comprises an intermediate quality diagnostic accuracy study[31] and a very low quality diagnostic accuracy study,[13] both showing increased diagnostic sensitivity in AL amyloidosis patients when SPE, sFLC, and both sIFE and uIFE are conducted. The intermediate quality study[31] employed a prospective design and was limited by unclear risk of bias in conduct or interpretation of the index tests and selection, conduct or interpretation of the reference standard, while the very low quality study[13] employed a retrospective design and suffered from high risk of bias in patient selection, patient flow, and selection, conduct or interpretation of the reference standard domains. There were no concerns surrounding the applicability of the patients, index test, or reference tests when compared with the Key Questions for either study. Neither of the studies were found to have methodological flaws that would raise concerns about the findings. The aggregate risk of bias across the two studies was serious but evidence was not further downgraded for any domain (Supplemental Table 8).

Based on the available evidence, the EP believed the benefits of using all four assays ranged from small to large and the harms ranged from trivial to moderate. However, all members still believed that the benefits outweighed the harms and the recommendation was feasible to implement. There was disagreement amongst the EP in relation to clinician and patient values and preferences, with 12.5% believing there would be variability in how patients and clinicians valued the main study reported outcomes, 25% feeling there would probably be variability, 12.5% believing there would be neutrality, 25% feeling there would probably be no variability, and the final 25% believing there would be no variability. This was further reflected in a minority of EP members (12.5%) feeling this recommendation would probably not be acceptable to all key stakeholder and would probably result in reduced health equity. Refer to Supplemental Table 9 for a complete summary of the EtD framework.

Statement 5. Clinical care providers should NOT order heavy/light chain isotype assay (HLC) for initial detection of M-protein in patients with suspected MG. *Strong Recommendation.*

The strength of evidence to support this guideline statement is low. The evidence base informing this statement includes three low quality studies[32-34] which all compared HLC with sIFE or SPEP. Of the three studies, two were prospective cohort studies[32, 33] which carried a moderate[33] or serious[32] risk of selection bias, and a moderate[32] or serious[33] risk of both reporting and detection bias. Additionally, one study was supported by industry funds,[32] while the other did not report on funding sources.[33] The remaining study was a retrospective cohort study[34] limited by critical risk of selection bias, as well as moderate risk of reporting and detection bias. None of the studies were found to have methodological flaws that would raise concerns about the findings. In addition to a very serious risk of bias across the included studies, the evidence was further downgraded for serious inconsistency of results (Supplemental Table 8).

Based on the identified evidence, the EP decided to draft a strong statement against the use of HLC. The EP believed that harms of using the assay greatly outweighed any benefit that may be incurred with its use. Majority of the EP (87.5%) felt that this recommendation would be acceptable to key stakeholders and all members felt it would be feasible to implement. Refer to Supplemental Table 9 for a complete summary of the EtD framework.

Statement 6. Clinical care providers should NOT use total/intact light chains for the quantitation of M-proteins in patients with suspected myeloma. *Strong Recommendation.*

The strength of evidence to support this guideline statement is *low*. The evidence base supporting this statement includes one retrospective cohort study that evaluated the utility of quantitation using intact and total light chains.[28] This study was assessed as low quality based on a moderate risk of detection bias, a critical risk of selection bias, and no reporting of study funding.[28] However, the study was not found to have methodological flaws that would raise concerns about the findings. Since the evidence base included one study, the strength of evidence was determined by the risk of bias carried by the individual study (Supplemental Table 8).

Although the strength of evidence supporting this statement is low, the EP proposes a strong recommendation against the use of total/intact light chains based on substantial harms to patients when the assay is used. All EP members felt this guidance would be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 9 for a complete summary of the EtD framework.

Statement 7. In patients with intact M-proteins outside the gamma region by SPEP, laboratories should use total immunoglobulin (IgA, IgG, or IgM) for the quantitation of the M-proteins; quantitation of a band in the beta region by SPEP can be performed if the M-protein is distinguished from background normal protein bands. *Conditional Recommendation.*

The strength of evidence to support this guideline statement is *very low*. The evidence base comprises three retrospective cohort studies which evaluated quantification using total immunoglobulin.[34-36] In addition to being limited by selection bias based on their retrospective design, these cohort studies were also limited by performance,[35] reporting,[34-36] and detection,[34-36] bias. None of the studies were found to have methodological flaws that would raise concerns about the findings. The aggregate risk of bias across the evidence base was very serious and evidence strength was further downgraded for inconsistency and indirectness (Supplemental Table 8).

All EP members considered this problem to be a priority. Although the benefits were considered to range from small to large, all EP members believed the benefits outweighed the small to trivial harms. When discussing resource use, majority of the EP members (75%) believed the costs to be negligible, while the minority (25%) felt quantitation using total immunoglobulin would carry a moderate cost. Irrespective of the potential increase in resources, all EP members felt this statement would be acceptable to key stakeholders and feasible to implement. Refer to Supplemental Table 9 for a complete summary of the EtD framework.

Statement 8. Laboratorians should report both quantitative levels of free kappa and free lambda and the kappa/lambda ratio when the sFLC assay is performed. *Strong recommendation.*

The strength of evidence to support this guideline statement is *very low*. The evidence base supporting this statement includes one low quality retrospective cohort study.[30] This study was limited by a moderate risk of performance and detection bias, a serious risk to reporting bias, and a critical risk of selection bias. However, the study was not found to have methodological flaws that would raise concerns about the findings. Since the evidence base included one study, the strength of evidence was determined by the risk of bias carried by the individual study (Supplemental Table 8).

Although the strength of evidence supporting this statement is very low, the EP proposed a strong recommendation for reporting of both quantitative levels and kappa/lambda ratio when sFLC is performed based on substantial harms to patients if only one element is reported. The EP discussed the necessity of the ratio for diagnosis and the quantification level for monitoring response to therapy and relapse. The EP's strong recommendation is based on the need to normalize serum free light chains when the total immunoglobulin concentration is abnormal, such as with immunosuppression, polyclonal gammopathy, and renal disease. In these conditions, the ratio provides additional information. Although a minority of EP members felt reporting both elements would result in a moderate cost increase (12.5%), majority of members (87.5%) felt the resource use would be negligible. All EP members felt this recommendation would be acceptable to key stakeholders, with 75% of members believing it be acceptable and 25% believing it to be probably acceptable. Similarly, 87.5% of members felt this statement to be feasible to implement and 12.5% felt it would probably be feasible. Refer to Supplemental Table 9 for a complete summary of the EtD framework.

Statement 9. Clinical care providers may use rFLC, IgM isotype, M-protein >1.5 g/dL, and immunoparesis as risk factors for progression to MM or a B-cell lymphoproliferative disorder. *Conditional Recommendation.*

The strength of evidence to support this guideline statement is *low*. The evidence base supporting these risk factors is comprised of five studies.[37-41] Three studies evaluated the association between isotype and risk of progression.[37, 38, 41] Four studies evaluated both abnormal sFLC ratios and intact M-protein concentrations,[37-40] and one evaluated risk associated with immunoparesis.[38] The five studies included one prospective cohort study assessed as intermediate-low quality,[37] three retrospective cohort studies assessed as low quality,[38, 39, 41] and one retrospective cohort study assessed as very low quality.[40] The included cohort studies suffered from risk of bias in selection,[37-41] reporting,[37-39] and detection[37, 38, 40] domains. None of the studies were found to have methodological flaws that would raise concerns about their findings. The aggregate risk of bias across the studies was very serious and for the non-IgM isotype risk factor evidence was further downgraded for serious inconsistency of results (Supplemental Table 8).

The EP completed EtD frameworks for each risk factor included in this recommendation statement. Refer to Supplemental Table 9 for a complete summary.

<u>FLC Ratio outside the Reference Interval</u>
Although all EP members felt that defining a cut-off for an abnormal sFLC ratio for risk stratification was a priority, there was substantial variability in responses across the ETD for this statement. Forty-three percent of EP members believed the benefits of the intervention to be moderate, 28.5% of members felt the benefits to be small and 28.5% felt the benefits were large. When considering harms, 75% of members believed the harms to be trivial, while 25% believed them to moderate or small. Based on this variability, 62.5% of members believe the benefits outweigh the harms, while 25% felt the benefits only probably outweighed the harms, and 12.5% felt that the benefits probably did not outweigh the harms. A range of responses was also observed when the panel was discussing values and preferences of clinicians and patients. Although 62.5% of the panel believed there to be no (or probably no) variability in how patients and clinicians would value the reported outcomes, 12.5% believed there probably would be variability, and 25% believed there would be neutrality. Irrespective of the other ETD domains, all EP members believe the statement to be acceptable to key stakeholders and feasible to implement.

<u>IgM Isotype</u>
Based on the available evidence, the EP believes that the use of the IgM isotype as a risk factor for progression carries small to large benefits and small to trivial harms. Due to the range in perceived

benefit, 37.5% of members felt the benefits outweighed the harms, 37.5% felt the benefits probably outweighed the harms, and 25% felt there was a balance between benefits and harms. All EP members believed the statement was both acceptable to key stakeholders and feasible to implement, and that there would probably be no impact on health equity following implementation of the guidance.

Quantitative Immunoglobulin Range

Although all EP members felt that defining a cut-off for a high-risk quantitation of immunoglobulins was a priority, there was substantial variability in responses across the ETD for this statement. Forty-three percent of EP members believed the benefits of the intervention to be moderate, 28.5% of members felt the benefits to be small and 28.5% felt the benefits were large. When considering harms, 75% of members believed the harms to be trivial, while 25% believed them to moderate or small. Based on this variability, 62.5% of members believe the benefits outweigh the harms, while 25% felt the benefits only probably outweighed the harms, and 12.5% felt that the benefits probably did not outweigh the harms. A range of responses was also observed when the panel was discussing values and preferences of clinicians and patients. Although 62.5% of the panel believed there to be no (or probably no) variability in how patients and clinicians would value the reported outcomes, 12.5% believed there probably would be variability, and 25% believed there would be neutrality. Irrespective of the other ETD domains, all EP members believe the statement to be acceptable to key stakeholders and feasible to implement.

Immunoparesis

Based on the identified study, the EP believed that the use of immunoparesis as a risk factor for progression carried small to large benefits and small to trivial harms. Due to the range in perceived benefit, 37.5% of members felt the benefits outweighed the harms, 37.5% felt the benefits probably outweighed the harms, and 25% felt there was a balance between benefits and harms. Although all EP members felt that the recommendation would be acceptable to key stakeholders, a minority of members (12.5%) felt that the statement was probably not feasible to implement, while 50% of members believed the statement was feasible and 37.5% felt it was probably feasible.

Good Practice Statements

According to the GRADE approach, good practice statements (GPS) are recommendations panels may consider important but are not appropriate to be formally rated for quality of evidence.[7] In addition to the set of key questions formulated *a priori* for the SER, the EP decided to draft GPSs, which reflect expert consensus opinions supported by a limited number of studies and data that were not formally included in the evidence-base nor systematically rated and assessed for quality. The EP wanted to address the following questions:

- What reporting elements should be included in the pathology report?
- Is there an optimal testing sequence, strategy, or approach for the initial detection of M-proteins?

The EP co-chairs followed a framework to review the questions for the good practice statements (Supplemental Figure 3). A targeted literature search was performed based on these questions. The EP co-chairs reviewed the available literature and incorporated data collected in a pre-guideline development practice survey to arrive at the GPSs.

1. To ensure completeness of the reporting of the M-protein, the EP recommends that laboratories report test results for M-protein using the template in guideline table 7, which recommended reporting elements.
2. To promote test sequence standardization in initial analysis of suspected MGs, the EP recommends laboratories consider the test algorithm in manuscript figure 1.
3. To promote the harmonization of the nomenclature used for the diagnosis of MGs, the EP recommends the use of the term M-proteins when pertaining to monoclonal immunoglobulin proteins (ie, paraproteins, M-components, monoclonal protein).[42-44]
4. To promote harmonization, the term immunosubtraction is used when pertaining to immunotyping and immunodisplacement.

Laboratory Detection and Initial Diagnosis of Monoclonal Gammopathies
Supplemental Digital Content

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<table>
<tr><th colspan="3">Supplemental Table 1. Key Questions and PICO Elements</th></tr>
<tr><td colspan="3">KQ1. What specimens are useful in the detection in the detection of monoclonal gammopathies?</td></tr>
<tr><td colspan="3">Phase: Pre-Analytical</td></tr>
<tr><td colspan="3">Population: Patients with suspected monoclonal gammopathies or plasma cell disorders</td></tr>
<tr><td colspan="3">Patients with suspected monoclonal gammopathies or plasma cell disorders</td></tr>
<tr><td>Interventions:</td><td>Comparator:</td><td>Outcomes:</td></tr>
<tr><td>Serum
Urine – 24hr collection
Urine – early morning void</td><td>Single arm studies
OR
Comparator defined by study</td><td>Critical: Accuracy of diagnosis (surrogates: survival rates, appropriate treatment); diagnostic test accuracy – sensitivity, specificity, NPV, PPV; risk stratification
Important: Patient experience; QoL; complication rates (eg, diagnostic procedures [FP] and delayed treatment [FN])</td></tr>
<tr><td colspan="3">KQ2a. What are the appropriate tests needed to accurately detect monoclonal gammopathies?</td></tr>
<tr><td colspan="3">Phase: Analytical</td></tr>
<tr><td colspan="3">Population: specimens from patients with suspected monoclonal gammopathies</td></tr>
<tr><td>Interventions:</td><td>Comparator:</td><td>Outcomes:</td></tr>
<tr><td>Serum protein electrophoresis (SPEP) – gel-based method (AGE)
SPEP – capillary method (CZE)
Urine protein electrophoresis (UPEP) – gel-based method
UPEP – capillary method
Gel-based immunofixation (IFE)
Capillary electrophoresis-based immunosubtraction/ immunotyping
Free light-chain assessment (FLC)
mass spectrometry isotype characterization</td><td>SPEP + IFE + FLC

OR

Comparator defined by study</td><td>Critical: Diagnostic test accuracy (eg, sensitivity, specificity, NPV, PPV, detection of monoclonal immunoglobulin); Test utilization (eg, efficiency, under-utilization)
Important: Turn-around time; QoL; complication rates (eg, unnecessary diagnostic procedures [FP] and delayed treatment [FN])</td></tr>
<tr><td colspan="3">KQ2b. What are the appropriate tests needed to accurately quantify monoclonal gammopathies and determine risk stratification?</td></tr>
<tr><td colspan="3">Phase: Analytical</td></tr>
<tr><td colspan="3">Population: Specimens from patients with suspected monoclonal gammopathies</td></tr>
<tr><td>Interventions:</td><td>Comparator:</td><td>Outcomes:</td></tr>
<tr><td>SPEP
• AGE method OR
• CZE method
UPEP using AGE
• 24h collection OR
• Random urine sample
UPEP using CZE</td><td>Serum: SPEP + FLC

Urine: UPEP + FLC

OR

Comparator defined by study</td><td>Critical: Accuracy of diagnosis (surrogates: survival rates, appropriate treatment); risk stratification</td></tr>
</table>

• 24h collection OR • Random urine sample		
Capillary electrophoresis-based immunosubtraction/ immunotyping		
Free light-chain assessment (FLC)		
Heavy light chain analysis		
Urine protein-creatine ratio		
Included Monoclonal Gammopathy Types		

• MGUS
• Multiple myeloma
  ○ Light chain multiple myeloma
  ○ Non-secretory multiple myeloma
  ○ Smoldering multiple myeloma
• Heavy chain disease
• AL Amyloidosis
• Waldenström Macroglobulinemia
• Solitary plasmacytoma
• POEMS syndrome
• MG of renal significance (MGRS)		

Abbreviations: AGE, agarose gel electrophoresis; CZE, capillary zone electrophoresis; FN, false negative; FP, false positive; KQ, key questions; NPV, negative predictive value; PICO, population, intervention, comparator, outcomes; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasmaproliferative disorder, skin changes; PPV, positive predictive value; QoL, quality of life

Supplemental Table 2: Strength 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. Included studies will be of high or intermediate quality.
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. Included studies will be of intermediate or low quality.
Low	There is limited confidence in the estimate of effect. The true effect may be substantially different from the estimate of the effect. Included studies will be of low quality.
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. Included studies will be of low or very low quality.

Data derived from Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group materials.[5]

Supplemental Table 3: Grades for Strength of Recommendations

Designation	Recommendation	Evidence to Decision Judgement
Strong Recommendation	Recommend for or against a particular practice (can include "must" or "should")	Supported by assessment with the GRADE EtD framework showing EP consensus of judgements directed to the far right or far left poles of the framework
Conditional Recommendation	Recommend for or against a particular practice (can include "should" or "may")	Supported by assessment with the GRADE EtD framework showing EP consensus of judgements directed towards the center of the framework or with a dispersed pattern

Abbreviation: EP, expert panel; EtD, Evidence-to-decision framework

Data derived from Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group materials.[5, 6]

Supplemental Table 4. Quality Assessment of Included Systematic Reviews

Study		Rao[9] 2012
AMSTAR Assessment	A priori design	Y
	Duplicate study selection and data extraction	Y
	Comprehensive literature search	Y
	Publication status as inclusion criterion	Y
	List of included and excluded studies	Y
	Characteristics of included studies	Y
	Study quality assessment conducted	Y
	Quality assessment used in formulating conclusions	Y
	Appropriate methods to combine findings	Y
	Publication bias assessment	N
	Conflict of interest reported	Y
Reported funding sources		Y
Study Quality		High

Abbreviations: N, no; Y, yes.

Supplemental Table 5. Quality Assessment of Included Prospective Cohort Studies

Study		Kraj[27] 2015	Kyle[37] 2018	Prokaeva[33] 2016	Kraj[32] 2011
ROBINS-I Assessment	Confounding	SR	MR	MR	MR
	Patient selection	LR	MR	MR	SR
	Intervention classification	LR	LR	LR	LR
	Deviation from intended intervention	MR	LR	LR	LR
	Missing data	LR	SR	SR	MR
	Outcome measurements	LR	MR	SR	MR
	Selection of reported outcomes	LR	MR	MR	MR
	Overall Risk of Bias	SR	SR	SR	SR
Adequately powered		Y	Y	Y	NS
Reported funding sources		N	Y	N	N
Industry funded		U	N	U	U
Study Quality		Int-Low	Int-Low	Low	Int-Low

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

Supplemental Table 6. Quality Assessment of Included Retrospective Cohort Studies

Study		Dejoie[36] 2016	Dispenzieri[30] 2010	Dispenzieri[39] 2008	Katzmann[34] 2015	Landgren[40] 2009	Ludwig[35] 2013	Murray[41] 2012	Turesson[38] 2014	Korpysz[28] 2014	Korpysz[29] 2012
ROBINS-I Assessment	Confounding	MR	MR	MR	MR	MR	MR	MR	MR	MR	MR
	Patient selection	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR
	Intervention classification	LR	MR	LR	LR	LR	LR	LR	LR	LR	LR
	Deviation from intended intervention	LR	LR	LR	LR	LR	MR	LR	LR	LR	LR
	Missing data	MR	SR	MR	MR	LR	SR	LR	MR	LR	SR
	Outcome measurements	MR	MR	LR	MR	CR	SR	LR	MR	MR	LR
	Selection of reported outcomes	MR	SR	LR	LR	SR	SR	LR	MR	MR	MR
	Overall Risk of Bias	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR
Adequately powered		NS	Y	Y	Y	Y	Y	Y	Y	Y	N
Reported funding sources		Y	Y	Y	Y	Y	Y	Y	Y	N	N
Industry funded		N	N	N	N	N	Y	N	N	U	U
Study Quality		Low	Very Low	Low	Low	Very Low	Very Low	Low	Low	Low	Very Low

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

Supplemental Table 7. Quality Assessment of Included Diagnostic Accuracy Studies											
Study		Bakker[10] 2009	Park[11] 2012	McTaggart[12] 2013	Katzmann[13] 2009	Poisson[14] 2012	Korpysz[15] 2013	McCuddden[16] 2008	Smith[17] 2018	Bochtler[26] 2008	Palladini[31] 2009
QUADAS-2 Assessment	RoB – patient selection	LR	HR	UR	HR	LR	UR	LR	UR	LR	LR
	Applicability - patients	LR	LR	LR	LR	LR	LR	HR	UR	LR	LR
	RoB – index test	UR	UR	LR	LR	UR	UR	LR	UR	UR	UR
	Applicability - index test	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
	RoB – reference standard	LR	HR	LR	HR	LR	LR	LR	UR	UR	UR
	Applicability - reference standard	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
	RoB – patient flow	LR	HR	HR	HR	LR	LR	LR	HR	HR	LR
Design		PS	RS	RS	RS	PS	PS	RS	RS	PS	PS
Adequately powered		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Reported funding sources		N	Y	Y	Y	N	N	N	Y	Y	Y
Industry funded		U	N	N	N	U	U	U	N	N	N
Study Quality		Int	Very Low	Low	Very Low	Int	Int-Low	Low	Very Low	Int-Low	Int

Abbreviations: HR, high risk; Int, intermediate; LR, low risk; N, no; PS, prospective design; RoB, risk of bias; RS, retrospective design; U, unclear/unsure; UR, unclear risk; Y, yes.

Supplemental Table 8. Strength of Evidence (SOE) Assessment

Number of Studies and Design	Aggregate Risk of Bias	Inconsistency	Indirectness	Imprecision	Other[a]	SOE Grade
Statement 1						
1 SR, 4 DAS	Serious	Not serious	Not serious	Not serious	None	Moderate
Statement 2						
5 DAS	Serious	Not serious	Not serious	Not serious	None	Moderate
Statement 3						
1 PCS, 3 RCS, 2 DAS	Serious	Serious	Not serious	Not serious	None	Low
Statement 4						
2 DAS	Serious	Not serious	Not serious	Not serious	None	Moderate
Statement 5						
2 PCS, 1 RCS	Very serious	Serious	Not serious	Not serious	None	Low
Statement 6						
1 RCS	Very serious	Not serious	Not serious	Not serious	None	Low
Statement 7						
3 RCS	Very serious	Serious	Serious	Not serious	None	Very Low
Statement 8						
1 RCS	Very serious	Not serious	Serious	Not serious	None	Very Low
Statement 9						
1 PCS, 4 RCS	Very serious	Not serious	Not serious	Serious[b]	None	Low

Abbreviations: DAS, diagnostic accuracy study; PCS, prospective cohort study; RCS, retrospective cohort study; RCT, randomized controlled trial; SR, systematic review.
[a]Other category includes assessment for detection of publication bias, large effect, and confounding.
[b]Statement 10 includes four risk factors for progression. Studies evaluating the IgM isotype were downgraded for imprecision, but the entire evidence base was not downgraded.

Supplemental Table 9. Evidence-to-Decision Framework

Statement 1. Clinical care providers should order both serum protein electrophoresis (SPEP) and serum free light chains (sFLC) for the initial detection of M-protein in all patients with suspected MG.
Strength of Recommendation: Strong; Strength of Evidence: Moderate

Is the problem a priority?	No	Probably No		Probably Yes	Yes
					••••••••
How substantial are the benefits?	Trivial	Small		Moderate	Large
				••	•••
How substantial are the harms?	Large	Moderate		Small	Trivial
	•	•		••	••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
	•	••		••••	•
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
			•	••••	•••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		•••••	•••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			••••••••		
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••••	••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				••	••••••

Statement 2. Laboratorians should confirm a SPEP abnormality suspicious for a presence of a M-protein with serum immunofixation electrophoresis (sIFE) or alternative method with similar sensitivity.
Strength of Recommendation: Strong; Strength of Evidence: Moderate

Is the problem a priority?	No	Probably No	Probably Yes	Yes

		•		•	••••••
How substantial are the benefits?	Trivial	Small		Moderate	Large
				•	••••••
How substantial are the harms?	Large	Moderate		Small	Trivial
				•••	••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
	•			•••••	
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
				••	••••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		••••	••••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			••••••••		
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••	••••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
					••••••••

Statement 3. Laboratorians and/or clinical care providers should follow-up an abnormal sFLC ratio for the presence of a M-protein with a serum IFE or alternative method with similar sensitivity.
Strength of Recommendation: Conditional; Strength of Evidence: Low

Is the problem a priority?	No	Probably No		Probably Yes	Yes
	•			•••	••••
How substantial are the benefits?	Trivial	Small		Moderate	Large
				•••	••••
How substantial are the harms?	Large	Moderate		Small	Trivial
	•			•••	•••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
	•			•••	••••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
			•	•••	••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		••••	••••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			•••••••	•	
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••••	•••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				••	•••••

Statement 4. Clinical care providers should order SPEP, sFLC, serum IFE, and urine IFE for the initial detection of M-protein in all patients with suspected amyloid light chain (AL) amyloidosis.
Strength of Recommendation: Strong; Strength of Evidence: Moderate

Is the problem a priority?	No	Probably No		Probably Yes	Yes
				••	•••••
How substantial are the benefits?	Trivial	Small		Moderate	Large
		••		••	••••
How substantial are the harms?	Large	Moderate		Small	Trivial
		•		•••	••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
	•	•••		••	••
	No	Probably No	Balance	Probably Yes	Yes

Do the benefits outweigh the harms?				••••	••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		••••	••••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
		•	••••••	•	
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
		•		•••	••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
	•			•••	••••
Statement 5. Clinical care providers should NOT order heavy/light chain isotype assay (HLC) for initial detection of M-protein in patients with suspected MG. *Strength of Recommendation: Strong; Strength of Evidence: Low*					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
	••	•••			•••
How substantial are the benefits?	Trivial	Small		Moderate	Large
				••	••••••
How substantial are the harms?	Large	Moderate		Small	Trivial
				••	••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		••		••	••••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
				•	•••••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
			•••	•••••	
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			••••••••		
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
		•		••	•••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				•••	•••••
Statement 6. Clinical care providers should NOT use total/intact light chains for the quantification of M-proteins in patients with suspected myeloma. *Strength of Recommendation: Strong; Strength of Evidence: Low*					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
	•	•		••	••••
How substantial are the benefits?	Trivial	Small		Moderate	Large
	•	••		••	•••
How substantial are the harms?	Large	Moderate		Small	Trivial
		••			••••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		••		••	••••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
			•	••	••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
			••••••	••	
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
		•	•••••••		
	No	Probably No		Probably Yes	Yes

Is the intervention acceptable to key stakeholders?			•••	•••••
Is the intervention feasible to implement?	No	Probably No	Probably Yes	Yes
			••	••••••

Statement 7. In patients with intact M-proteins outside the gamma region by SPEP, laboratories should use total immunoglobulin (IgA, IgG, or IgM) for the quantification of the M-proteins; quantitation of a band in the non-gamma region by SPEP can be performed if the M-protein is distinguished from background normal protein bands.
Strength of Recommendation: Conditional; Strength of Evidence: Very low

Is the problem a priority?	No	Probably No		Probably Yes	Yes
				••••	••••
How substantial are the benefits?	Trivial	Small		Moderate	Large
		••		••••	••
How substantial are the harms?	Large	Moderate		Small	Trivial
				•	••••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		••		•••	•••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
				•••	•••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		••	••••••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			••••••••		
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				•••	•••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				•	•••••••

Statement 8. Laboratorians should report both quantitative levels of free kappa and free lambda and the kappa/lambda ratio when the sFLC assay is performed.
Strength of Recommendation: Strong; Strength of Evidence: Very low

Is the problem a priority?	No	Probably No		Probably Yes	Yes
	•	••		•••••	
How substantial are the benefits?	Trivial	Small		Moderate	Large
		•		••	••••
How substantial are the harms?	Large	Moderate		Small	Trivial
					•••••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		•		•••	••••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
			•	••	•••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		•	•••••••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			••••••	••	
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••	•••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				•	•••••••

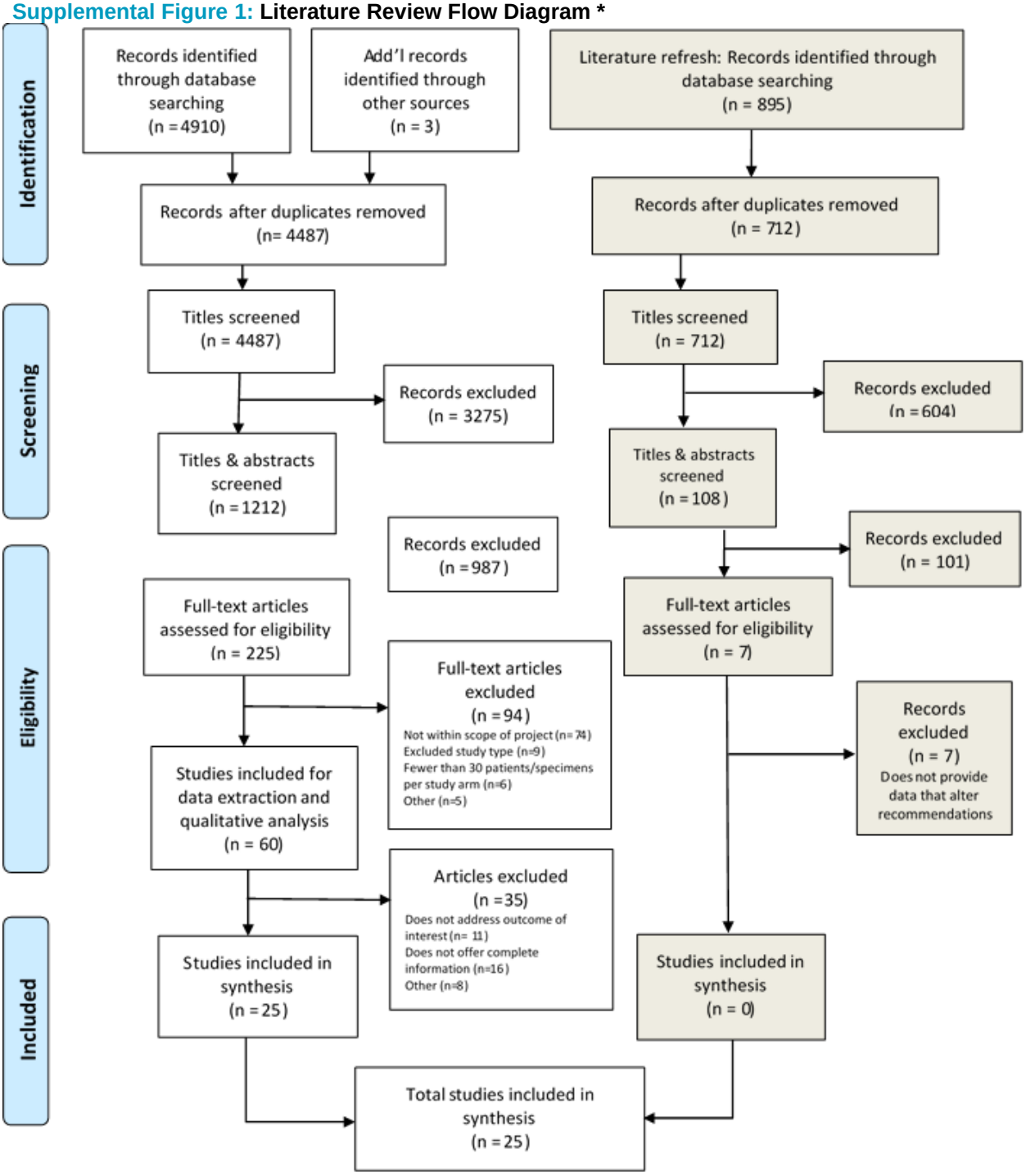
Statement 9. Clinical care providers may use rFLC, IgM isotype, M-protein >1.5 g/dL, and immunoparesis as risk factors for progression to MM or a B-cell lymphoproliferative disorder.

Note: The following ETD is for "Increased risk for rFLC outside the reference interval" *Strength of Recommendation: Conditional; Strength of Evidence: Low*					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
				••••	•••
How substantial are the benefits?	Trivial	Small		Moderate	Large
		••		•••	••
How substantial are the harms?	Large	Moderate		Small	Trivial
		•		•	••••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		••		••	••••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
		•		••	•••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		•	•••••••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			••••••	••	
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••••	••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				••	••••••
Statement 9. Clinical care providers may use rFLC, IgM isotype, M-protein >1.5 g/dL, and immunoparesis as risk factors for progression to MM or a B-cell lymphoproliferative disorder. *Note:* The following ETD is for "Increased risk for IgM Isotype" *Strength of Recommendation: Conditional; Strength of Evidence: Low*					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
				••••	•••
How substantial are the benefits?	Trivial	Small		Moderate	Large
		••		•••	••
How substantial are the harms?	Large	Moderate		Small	Trivial
				•	•••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		•		••••	••••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
			••	•••	•••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		•	•••••••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			••••••••		
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				•••	••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				••	••••••
Statement 9. Clinical care providers may use rFLC, IgM isotype, M-protein >1.5 g/dL, and immunoparesis as risk factors for progression to MM or a B-cell lymphoproliferative disorder. *Conditional Recommendation.* *Note:* The following ETD is for "Increased risk for quantitative immunoglobulin >1.5 g/dL" *Strength of Recommendation: Conditional; Strength of Evidence: Low*					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
				••••	•••
How substantial are the benefits?	Trivial	Small		Moderate	Large
		•		••	••••

How substantial are the harms?	Large	Moderate		Small	Trivial
		•		•	••••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		••		••	••••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
		•		••	•••••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		•	•••••••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			••••••	••	
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••••	••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
				••	••••••
Statement 9. Clinical care providers may use rFLC, IgM isotype, M-protein >1.5 g/dL, and immunoparesis as risk factors for progression to MM or a B-cell lymphoproliferative disorder. *Conditional Recommendation.* *Note:* The following ETD is for "Increased risk for decrease in noninvolved isotypes below the reference intervals (immunoparesis)" *Strength of Recommendation: Conditional; Strength of Evidence: Low*					
Is the problem a priority?	No	Probably No		Probably Yes	Yes
				••••••	••
How substantial are the benefits?	Trivial	Small		Moderate	Large
		•		••••••	•
How substantial are the harms?	Large	Moderate		Small	Trivial
				•	•••••••
Is there variability in how clinicians and patients value the main outcome?	Yes	Probably Yes		Probably No	No
		••		••	••••
Do the benefits outweigh the harms?	No	Probably No	Balance	Probably Yes	Yes
			••	•••	•••
How large are the costs?	Large Cost	Moderate Cost	Negligible	Moderate Savings	Large Savings
		•	•••••••		
What would be the impact on health equity?	Reduced	Probably Reduced	Probably No Impact	Probably Increased	Increased
			••••••••		
Is the intervention acceptable to key stakeholders?	No	Probably No		Probably Yes	Yes
				••••	••••
Is the intervention feasible to implement?	No	Probably No		Probably Yes	Yes
		•		•••	••••

Abbreviations: EtD, evidence-to-decision framework; MG, monoclonal gammopathy
Each individual vote by expert panel members is represented by • during the evidence-to-decision (EtD) discussions.

Supplemental Figure 1: Literature Review Flow Diagram *



*Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.

Laboratory Detection and Initial Diagnosis of Monoclonal Gammopathies
Supplemental Digital Content

Supplemental Figure 2: Database Search Strings

Ovid: ((((Paraproteinemias/ or Paraprotein?emia?.ti,ab,kf. or M-protein?emia?.ti,ab,kf. or Cryoglobulinemia/ or Cryoglobulin?emia?.ti,ab,kf. or Heavy Chain Disease/ or Heavy Chain Disease?.ti,ab,kf. or (amyloidosis adj3 (AL or light chain or primary)).ti,ab,kf. or Monoclonal Gammopathy of Undetermined Significance/ or gamm#path*.ti,ab,kf. or MGUS.ti,ab,kf. or MGRS.ti,ab,kf. or monoclonal immunoglobulin*.ti,ab,kf. or Schnitzler Syndrome/ or Schnitzler* syndrome.ti,ab,kf. or Multiple Myeloma/ or Multiple Myeloma?.ti,ab,kf. or Myeloma-Multiple?.ti,ab,kf. or Monoclonal myeloma?.ti,ab,kf. or POEMS Syndrome/ or POEMS.ti,ab,kf. or (polyneuropathy and organomegaly and endocrinopathy and (monoclonal or m-component or m-protein) and skin).ti,ab,kf. or Smoldering Multiple Myeloma/ or SMM.ti,ab,kf. or Waldenstrom Macroglobulinemia/ or Macroglobulin?emia.ti,ab,kf. or immunocytoma?.ti,ab,kf. or Lymphoplasmacyt* Lymphoma?.ti,ab,kf. or Plasmacytoma/ or plasmacytoma?.ti,ab,kf. or (plasma cell adj2 (malignan* or cancer? or neoplas* or tumo?r? or leuk?emia? or myeloma? or dyscrasia? or disorder? or disease?)).ti,ab,kf. or light chain deposition disease.ti,ab,kf.) AND (Urine/ or urine.ti,ab,kf. or urinary.ti,ab,kf. or urine.fs. or Blood/ or blood.fs. or blood.ti,ab,kf. or Serum/ or serum?.ti,ab,kf. or sera.ti,ab,kf.) AND (Diagnosis/ or diagnos*.ti,ab,kf. or diagnosis.fs. or detect*.ti,ab,kf.)) OR ((Paraproteinemias/ or Paraprotein?emia?.ti,ab,kf. or M-protein?emia?.ti,ab,kf. or Cryoglobulinemia/ or Cryoglobulin?emia?.ti,ab,kf. or Heavy Chain Disease/ or Heavy Chain Disease?.ti,ab,kf. or (amyloidosis adj3 (AL or light chain or primary)).ti,ab,kf. or Monoclonal Gammopathy of Undetermined Significance/ or gamm#path*.ti,ab,kf. or MGUS.ti,ab,kf. or MGRS.ti,ab,kf. or monoclonal immunoglobulin*.ti,ab,kf. or Schnitzler Syndrome/ or Schnitzler* syndrome.ti,ab,kf. or Multiple Myeloma/ or Multiple Myeloma?.ti,ab,kf. or Myeloma-Multiple?.ti,ab,kf. or Monoclonal myeloma?.ti,ab,kf. or POEMS Syndrome/ or POEMS.ti,ab,kf. or (polyneuropathy and organomegaly and endocrinopathy and (monoclonal or m-component or m-protein) and skin).ti,ab,kf. or Smoldering Multiple Myeloma/ or SMM.ti,ab,kf. or Waldenstrom Macroglobulinemia/ or Macroglobulin?emia.ti,ab,kf. or immunocytoma?.ti,ab,kf. or Lymphoplasmacyt* Lymphoma?.ti,ab,kf. or Plasmacytoma/ or plasmacytoma?.ti,ab,kf. or (plasma cell adj2 (malignan* or cancer? or neoplas* or tumo?r? or leuk?emia? or myeloma? or dyscrasia? or disorder? or disease?)).ti,ab,kf. or light chain deposition disease.ti,ab,kf.) AND (exp Electrophoresis/ or electrophoresis.ti,ab,kf. or immunoelectrophoresis.ti,ab,kf. or immunofixation.ti,ab,kf. or Immunosubtraction.ti,ab,kf. or Immunosubtyping.ti,ab,kf. or SPE.ti,ab,kf. or UPE.ti,ab,kf. or SPEP.ti,ab,kf. or UPEP.ti,ab,kf. or exp Immunoglobulin Light Chains/ or light chain?.ti,ab,kf. or exp Immunoglobulin Heavy Chains/ or heavy chain?.ti,ab,kf. or Bence Jones Protein/ or Bence Jones.ti,ab,kf. or SFLC.ti,ab,kf. or (M-spike? or (monoclonal adj3 spike)).ti,ab,kf. or Freelite.ti,ab,kf. or Pentavalent.ti,ab,kf. or IFE.ti,ab,kf. or Hevylite.ti,ab,kf.))) NOT (comment/ or editorial/ or case reports/ or (letter/ not clinical study/) or (exp animals/ not humans/))) limit to (english language and yr="2008 - Current")

Embase: ((((('paraproteinemias'/exp OR 'paraproteinemias' OR paraprotein$emia$:ti,ab,kw OR ‘m protein$emia$‘:ti,ab,kw OR 'cryoglobulinemia'/exp OR 'cryoglobulinemia' OR cryoglobulin$emia$:ti,ab,kw OR 'heavy chain disease'/exp OR 'heavy chain disease' OR ‘heavy chain disease$’:ti,ab,kw OR 'al amyloidosis'/exp OR 'al amyloidosis' OR ((amyloidosis NEAR/3 (al OR 'light chain' OR primary)):ti,ab,kw) OR 'gammopathy'/exp OR 'gammopathy' OR gamm?path*:ti,ab,kw OR mgus:ti,ab,kw OR mgrs:ti,ab,kw OR 'monoclonal immunoglobulinemia'/exp OR 'monoclonal immunoglobulinemia' OR 'monoclonal immunoglobulin*':ti,ab,kw OR 'schnitzler syndrome'/exp OR 'schnitzler syndrome' OR 'schnitzler* syndrome':ti,ab,kw OR 'multiple myeloma'/exp OR 'multiple myeloma' OR ‘multiple myeloma$’:ti,ab,kw OR ‘myeloma multiple$’:ti,ab,kw OR ‘monoclonal myeloma$’:ti,ab,kw OR 'poems syndrome'/exp OR 'poems syndrome' OR poems:ti,ab,kw OR (polyneuropathy:ti,ab,kw AND organomegaly:ti,ab,kw AND endocrinopathy:ti,ab,kw AND (monoclonal:ti,ab,kw OR ‘m component$’:ti,ab,kw OR ‘m protein$’:ti,ab,kw) AND skin:ti,ab,kw) OR 'smoldering multiple myeloma'/exp OR 'smoldering multiple myeloma' OR smm:ti,ab,kw OR 'waldenstroem macroglobulinemia'/exp OR 'waldenstroem macroglobulinemia' OR macroglobulin$emia:ti,ab,kw OR 'immunocytoma'/exp OR 'immunocytoma' OR immunocytoma$:ti,ab,kw OR ‘lymphoplasmacyt* lymphoma$’:ti,ab,kw OR 'plasmacytoma'/exp OR 'plasmacytoma' OR plasmacytoma$:ti,ab,kw OR (('plasma cell' NEAR/3 (malignan* OR cancer$ OR neoplas* OR tumo$r$ OR leuk$emia$ OR myeloma$ OR dyscrasia$ OR disorder$ OR disease$)):ti,ab,kw) OR 'light chain deposition disease':ti,ab,kw) AND ('diagnosis'/exp OR diagnos*:ti,ab,kw OR detect*:ti,ab,kw) AND ('urine'/de OR urine:ti,ab,kw OR urinary:ti,ab,kw OR 'blood'/de OR blood:ti,ab,kw OR 'serum'/de OR

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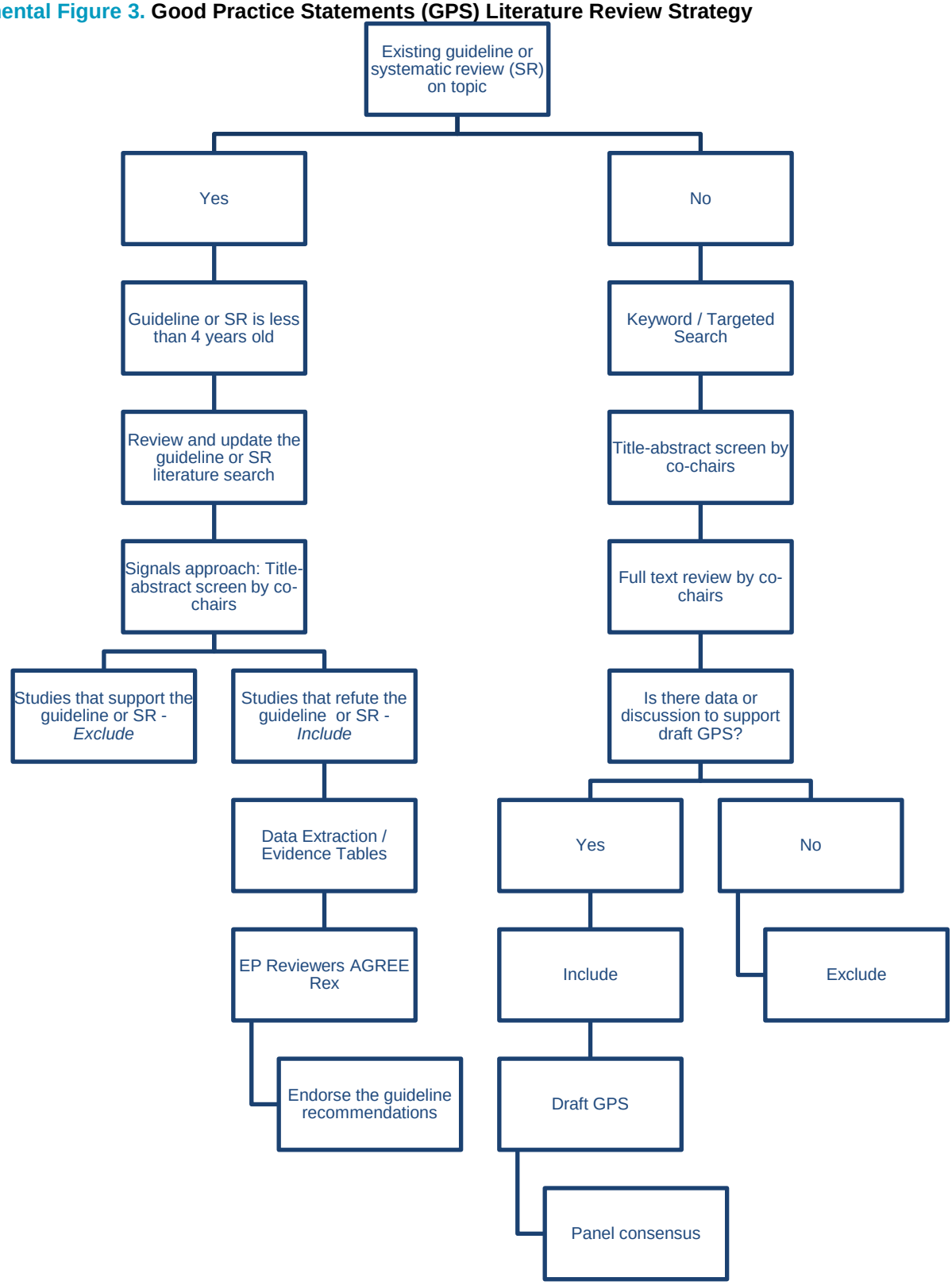
Supplemental Figure 3. Good Practice Statements (GPS) Literature Review Strategy



Glossary

Acceptability—Acceptability reflects who benefits (or is harmed) and who pays (or saves); and when the benefits, adverse effects, and costs occur (and the discount rates of key stakeholders; eg, politicians may have a high discount rate for anything that occurs beyond the next election). For the Evidence to decision (EtD) framework, the expert panel considered target users of the guideline. The less acceptable an option is to key stakeholders, the less likely it is that it should be recommended, or if it is recommended, the more likely it is that the recommendation should include an implementation strategy to address concerns about acceptability.

Accuracy—The degree of correctness or true values of a given laboratory result comparing to a gold standard. Accuracy also implies freedom from error.

Advisory Panel—Group established to provide additional expertise needed outside of the expert panel. Their primary role is to review the draft guideline during key stages of development however they do not hold any formal decision-making capabilities or have voting rights. Advisory Panel members generally do not author the guideline; however, these decisions may be made on a case-by-case basis, as determined by the primary authors, subject to the conflict of interest (COI) disclosures and policies of the publishing journals. Advisory Panel membership may include individuals with professional expertise from other vested organizations including but not limited to a patient advocate among others.

AMSTAR (Assessing the Methodological Quality of Systematic Reviews)—A validated quality assessment tool for systematic reviews.

Amyloid Light-chain (AL) Amyloidosis—Most common form of systemic amyloidosis. Results in deposit of misfolded amyloid protein deposits in and around tissues, nerves, and organs (ref amyloidosis.org).

Autologous Stem cell transplantation (ASCT)— A transplantation of healthy blood stem cells from a patient' own body to replace their diseased or damaged bone marrow. Also called autologous bone marrow transplant.

Benefit—A valued or desired outcome. In EtD, the expert panel considers both the magnitude of the benefits as well as the importance of that benefit to both clinicians and patients.

Concordance—The degree of agreement between two quantitative methods or assays.

Confidence Interval (CI)—The 95% confidence interval is a range of values that we can be 95% certain contains the point statistic.

Conflict of Interest (COI)—A divergence between an individual's private interests and his or her professional obligations such that an independent observer might reasonably question whether the individual's professional actions or decisions are motivated by personal gain, such as financial, academic advancement, clinical revenue streams, or community standing. This includes financial and intellectual relationships that may impact an individual's approach a scientific question with an open mind.

Cost—In this guideline, the discussion on cost pertains to the use of resources for an intervention or a recommendation.

Disease-free survival—The measure of time after treatment during which no sign of disease is found.

Equity—Health equity is the attainment of the highest level of health for all people. For the EtD, the EP deliberated any advantages or disadvantages for any group or setting in relation to the recommendation being considered. The EP considered any differences in baseline conditions across groups or settings

that affect the absolute effectiveness of the recommendation or the importance of the problem for disadvantaged groups or settings. The EP discussed any important considerations that should be made when implementing the recommendations in order to ensure that inequities are reduced or eliminated.

Evidence-to-decision framework (EtD)—The purpose of this framework is to help panels developing guidelines move from evidence to recommendations. It is intended to inform panel members' judgements about the pros and cons of each intervention that is considered; ensure that important factors that determine a recommendation are considered; provide a concise summary of the best available research evidence to inform judgements about each criterion; help structure discussion and identify reasons for disagreements; and make the basis for recommendations transparent to guideline users[1]

Expert Panel—Group established to approve key questions as defined by the guideline co-chairs, assist in the systematic review of the evidence, develop the draft recommendations, and write the final recommendations including full manuscript. The expert panel is overseen by the co-chairs, holds authorship attribution on the final guideline manuscript and is usually comprised of multidisciplinary topic experts. Expert Panel membership may include individuals with professional expertise from other vested organizations.

Feasibility—The capability of an intervention or an action to be accomplished or implemented. The less feasible an option is, the less likely it is that it should be recommended. For the EtD, the EP considered barriers that are likely to limit the feasibility of implementing the recommendation.

Free Light Chain—Immunoglobulin light chains (Bence Jones proteins) that are not bound to heavy chains.

Good Practice Statement—Guidance statements that guideline panels feel are important to provide but are not appropriate for formal ratings of strength of evidence.

Grading of Recommendations Assessment, Development and Evaluation (GRADE)—An internationally accepted and validated approach to grading quality of evidence and strength or recommendations.

Harmonization—Process of ensuring that the results of different laboratories using different clinical laboratory test methods at different times for a given substance are equivalent within clinically meaningful limits.[45]

Harms—A risk or injury occurring as a result of an intervention. In EtD, the expert panel considers both the magnitude of the harms as well as the importance of that harm to both clinicians and patients.

Hypogammaglobulinemia—An immune disorder characterized by a reduction in all types of gamma globulins.

Immunoparesis—Reduction below the normal lower limit of at least one uninvolved immunoglobulin.

Immunodisplacement or Immunosubtraction (ISUB)—Immunotyping using capillary electrophoresis.

Imprecision—A domain of the GRADE strength of evidence assessment. Imprecision results when evidence carries a wide confidence interval around the estimate of effect.

Inconsistency—A domain of the GRADE strength of evidence assessment. Inconsistency refers to an unexplained heterogeneity of results across studies informing a guidance statement.

Indirectness—A domain of the GRADE strength of evidence assessment. Indirectness refers to evidence that does not directly inform the PICO elements.

Interobserver Agreement—The degree to which two or more independent observers report the same values after measuring the same events.

Free Kappa/Free Lambda ratio – The ratio of two types of immunoglobulin light chains (kappa and lambda) when not bound to immunoglobulin heavy chains. It is used to assess risk of harboring a monoclonal protein and its likelihood for progression.

Meta-Analysis (MA) —Statistical procedure for combining data from multiple studies. Outcomes from a meta-analysis may include a more precise estimate of the effect of treatment or risk factor for disease, or other outcomes, than any individual study contributing to the pooled analysis.

M-component—see monoclonal immunoglobulin protein.

Monoclonal Gammopathy—A condition in which monoclonal immunoglobulin proteins circulate in the blood.

Monoclonal gammopathy of undetermined significance (MGUS) —The most common category of monoclonal gammopathy, which is asymptomatic and requires no intervention in the vast majority of cases.

Monoclonal Immunoglobulin Protein (M-protein) —Immunoglobulin proteins produced by monoclonal plasma cells.

Multiple Myeloma—A cancer of plasma cells. Multiple myeloma caused the plasma cells to accumulate in the bone marrow and crowd out the healthy blood cells.

Monoclonal Protein—see monoclonal immunoglobulin protein.

M Spike or M-Spike—This refers to the narrow, isosceles triangle appearance of the monoclonal immunoglobulin protein seen on protein electrophoresis.

Negative Predictive Value (NPV) —The predictive value of a negative result. This value corresponds to the percentage of true negative patients among those given a negative test result.

Overall Survival (OS)—The length of time from either the date of diagnosis or the start of treatment to death from any cause.

Outcomes—Outcomes are the potential benefits or harms. Outcomes that are considered to be important to those affected by the intervention, and which are important to making a recommendation or decision. Consultation with those affected by an intervention (such as patients and their caretakers) or other members of the public may be used to select the important outcomes. A review of the literature may also be carried out to inform the selection of the important outcomes. The importance (or value) of each outcome in relation to the other outcomes should also be considered. This is the relative importance of the outcome.

Paraproteins—see monoclonal immunoglobulin protein

PICO—A validated approach to developing guideline research questions that frames the population of interest (P), interventions (I) under consideration, possible comparisons (C), and relevant research outcomes (O).

POEMS—Rare multisystem disorder characterized by (P) polyneuropathy, (O) organomegaly, (E) endocrinopathy, (M) monoclonal gammopathy, and (S) skin abnormalities.

Problem—In the EtD framework, the EP considered the priority of the problem a recommendation is addressing. The EP considered if the consequences of the problem are serious and if addressing the problem is urgent. Serious problems are more likely that an option which addresses the problem should be a priority (e.g., diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.

Progression-Free Survival (PFS)—The length of time from treatment to disease progression or death.

Prospective Cohort Study (PCS) —Study design that enrolls a cohort of subjects and watches those subjects over a time period. A prospective study watches for outcomes during the study period and relates those outcomes to prior exposure or clinical characteristic.

Positive Predictive Value (PPV)—The predictive value of a positive result. This value corresponds to the percentage of true positive patients among those given a positive test result.

Randomized Controlled Trial (RCT)—Study design that randomly assigns subjects into an experimental group or a control group. Subjects are followed to determine effectiveness of the experimental intervention with outcomes measured at specific time-points.

Recurrence-Free Survival (RFS)—The length of time from treatment to disease recurrence or death.

Retrospective Cohort Study (RCS)—Study design that enrolls a cohort of subjects based on a known outcome and looks backwards to correlate prior exposure or clinical characteristic to that outcome.

Risk of Bias—The risk of systematic error or deviation from the truth within a scientific study.

ROBINS-I (Risk of Bias In Non-Randomized Studies – of Intervention)—A validated quality assessment tool for observational studies.

Sensitivity—The probability that a diagnostic test identifies patients who are in fact positive for a disease. The value corresponds to the percentage of true positive results demonstrated by an assay among those who are truly positive.

Smoldering Multiple Myeloma—An early precursor to multiple myeloma.

Specificity—The probability that a diagnostic test identifies patients who are in fact negative for a disease. The value corresponds to the percentage of true negative results demonstrated by an assay among those who are truly negative.

SPEP (Serum Protein Electrophoresis)—A laboratory test that uses the migration of serum proteins in an electrical field to identify and measure specific proteins in blood.

Systematic Review (SR) —A systematic review summarizes the results of available carefully designed healthcare studies and provides a high level of evidence on the effectiveness of healthcare interventions. Judgments may be made about the evidence and inform recommendations for healthcare.

Time to Recurrence—The length of time from treatment to disease recurrence.

UPEP (Urine Protein Electrophoresis)—Laboratory test that uses the migration of urine proteins in an electrical field to identify and measure specific proteins in urine.

Waldenström Macroglobinemia (WG)—A rare type of non-Hodgkin lymphoma in which cancer cells produce large amounts of macroglobulins.