International Guideline for Idiopathic Inflammatory Myopathy-Associated Cancer Screening: an International Myositis Assessment and Clinical Studies Group (IMACS) initiative

Authors
Alexander G.S. Oldroyd [1, 2, 3, 4], Jeffrey P. Callen [5], Hector Chinoy [1, 2, 3], Lorinda Chung [6, 7], David Fiorentino [8], Patrick Gordon [9], Pedro M. Machado [10, 11, 12, 13], Neil McHugh [14], Albert Selva-O'Callaghan [15], Jens Schmidt [16], Sarah L. Tansley [14, 17], Ruth Ann Vleugels [18], Victoria P. Werth [19, 20], International Myositis Assessment and Clinical Studies Group Cancer Screening Expert Group* and Rohit Aggarwal [21,†]

Affiliations
1 National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, University of Manchester, Manchester, UK
2 Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK
3 Centre for Musculoskeletal Research, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
4 Centre for Epidemiology Versus Arthritis, University of Manchester, Manchester, UK
5 Division of Dermatology, Department of Medicine, University of Louisville School of Medicine, Louisville, KY, USA
6 Division of Immunology and Rheumatology, Department of Medicine and Dermatology, Stanford University, Stanford, CA, USA
7 Palo Alto Health Care System, Palo Alto, CA, USA
8 Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, USA
9 Department of Rheumatology, King's College Hospital NHS Foundation Trust, London, UK
10 Centre for Rheumatology, Division of Medicine, University College London, London, UK
11 Department of Neuromuscular Diseases, Division of Medicine, University College London, London, UK
12 National Institute for Health Research University College London Hospitals Biomedical Research Centre, University College London Hospitals National Health Service Trust, London, UK
13 Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK
14 Department of Life Sciences, University of Bath, Bath, UK
15 Systemic Autoimmune Diseases Unit, Vall D'Hebron General Hospital, Medicine Department, Universitat Autonoma de Barcelona, Barcelona, Spain
16 Department of Neurology, Neuromuscular Centre, University Medical Centre Göttingen, Göttingen, Germany
17 Royal National Hospital for Rheumatic Diseases, Royal United Hospitals NHS Foundation Trust Bath, Bath, UK
18 Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
19 Department of Dermatology, University of Pennsylvania, Philadelphia, PA, USA

20 Division of Dermatology, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA
21 Myositis Center and Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

*A list of authors and their affiliations appears at the end of the paper.

[†]e-mail: aggarwalr@upmc.edu

Abstract

Adult-onset idiopathic inflammatory myopathy (IIM) is associated with an increased cancer risk within the 3 years preceding and following IIM onset. Evidence- and consensus-based recommendations for IIM-associated cancer screening can potentially improve outcomes. This International Guideline for IIM-Associated Cancer Screening provides recommendations addressing IIM-associated cancer risk stratification, cancer screening modalities and screening frequency. The international Expert Group formed a total of 18 recommendations via a modified Delphi approach using a series of online surveys. First, the recommendations enable an individual patient's IIM-associated cancer risk to be stratified into standard, moderate or high risk according to the IIM subtype, autoantibody status and clinical features. Second, the recommendations outline a 'basic' screening panel (including chest radiography and preliminary laboratory tests) and an 'enhanced' screening panel (including CT and tumour markers). Third, the recommendations advise on the timing and frequency of screening via basic and enhanced panels, according to risk status. The recommendations also advise consideration of upper or lower gastrointestinal endoscopy, nasoendoscopy and ^{18}F-FDG PET–CT scanning in specific patient populations. These recommendations aim to facilitate earlier IIM-associated cancer detection, especially in those who are at high risk, thus potentially improving outcomes, including survival.

[H1] Introduction

Idiopathic inflammatory myopathy (IIM, commonly termed 'myositis') is a chronic multisystem autoimmune condition with a range of manifestations, including muscle inflammation, skin involvement and interstitial lung disease (ILD)[1,2]. Adult-onset IIM is associated with an increased risk of cancer, particularly within the 3 years prior to and the 3 years after IIM onset[3]. Evidence suggests that up to one in four people with IIM are diagnosed with cancer within 3 years of IIM onset[4]. Various cancers have been reported, including lung, ovarian, colorectal, lymphoma, breast and nasopharyngeal cancers among the most common forms [5]. Cancer remains the leading cause of death in adults with IIM[4,6–8], likely due in part to delayed diagnosis. IIM-associated cancers are overwhelmingly diagnosed at an advanced

stage; a cohort study identified that 83% of IIM-associated cancers were stage III or IV at the time of diagnosis and were associated with a cancer remission rate of only 17%[5].

Early detection of cancer is key to improving outcomes. Consensus-based recommendations, based on the available evidence, will inform screening for malignancy in patients with IIM and standardize practices across health systems, particularly for patients managed outside specialist IIM centres.

The International Myositis Assessment and Clinical Studies Group (IMACS), the largest international multi-disciplinary group for IIM scientific studies, sponsored a project to develop evidence- and consensus-based cancer screening recommendations for patients with IIM. The first component of the project involved conducting a meta-analysis, which aimed to identify IIM-associated cancer risk factors, and a systematic review, which aimed to compile evidence on screening modalities[9]. The second component of work involved forming an international multidisciplinary Expert Group with expertise in IIM and cancer screening, with the aim of developing evidence-based consensus recommendations on screening for IIM-associated cancer, specifically addressing cancer risk stratification, screening modalities and screening frequency. Herein, we present the methodology and consensus-based recommendations for IIM-associated cancer screening developed by the large multi-disciplinary international Expert Group derived from members of IMACS. These recommendations have been scientifically reviewed by the IMACS Scientific Committee and have been endorsed by the International Myositis Society. They will be revised and endorsed periodically.

[H1] Methods

The recommendation formation process was guided by a Steering Committee (A.G.S.O., J.P.C., H. C., L.C., D.F., P.G., P.M.M., N.M., A.S.-O., J.S., S.L.T. , R.A.V., V.P.W. and R.A.), formed by IIM specialists affiliated with IMACS, led by R.A. and A.G.S.O.

Evidence collation was carried out via a systematic literature review (SLR) to update the meta-analysis and systematic review published in 2019 [ref. [9]] using the same methodology (with regard to study selection, data extraction, quality assessment and data synthesis) and adhering to PRISMA guidelines[10] (see Acknowledgements section for details of the individuals who provided input on the SLR and meta-analysis). Evidence published prior to 1st April 2022 was included.

An international Expert Group with expertise in IIM and cancer screening was convened. Eligibility criteria for the Expert Group included: clinical expertise in IIM with ≥10 years' experience, or one or more publications focused on clinically translational aspects of IIM-associated cancer, or clinical and/or research expertise in non-IIM-associated cancer screening. The Expert Group comprised 75 individuals, including members of the Steering Committee but excluding the process leads R. A. and A.G.S.O.. The Expert Group comprised 46 rheumatologists, 12 neurologists, nine dermatologists, three oncologists with expertise in cancer screening, two pulmonologists with a special interest in IIM, two researchers with expertise in cancer screening implementation and one paediatric rheumatologist, from 22 countries across five continents (North America, South America, Europe, Asia and Australia)

(see Supplementary Table 1 for the composition of the Expert Group by specialty and geographical location). The full list of members of the International Myositis Assessment and Clinical Studies Group Cancer Screening Expert Group is included at the end of the article.

The recommendation formation process followed a modified Delphi Method approach using a series of online surveys. Expert Group members were advised to review the evidence contained within the updated SLR and the published meta-analysis[9] prior to completing the first survey. The first survey, created by A.G.S.O and R.A. and amended by the Steering Committee, aimed to identify the opinion of the Expert Group regarding IIM-associated cancer risk factors (that is, factors that are associated with increased cancer risk compared with the wider IIM population), 'protective factors' (that is, factors that are associated with reduced cancer risk compared with the wider IIM population) and appropriate use of cancer screening modalities. The questions comprising the first survey are detailed in Supplementary Tables 2–4. The Steering Committee created draft recommendations based on responses from the first survey.

Members of the Expert Group were asked to consider individualized cancer risk stratification in comparison with the wider IIM population only, not the general population.

Subsequent surveys asked members of the Expert Group to rate their level of agreement with each draft recommendation on a 1–9 numerical rating scale (with 1 indicating 'complete disagreement' and 9 'complete agreement'). The median vote rating for each draft recommendation was calculated and defined a priori as 'disagreement' (median vote of 1–3), 'uncertainty' (median vote of 4–6) or 'consensus' (median vote of 7–9). Expert Group members were able to provide feedback to A.G.S.O. and R.A. on each recommendation. Draft recommendations were amended according to vote ratings and the feedback provided by Expert Group members, and were then re-presented to the Expert Group via an online survey. A total of three recommendation voting surveys, in addition to the preliminary survey, were carried out before consensus was reached (see Supplementary Tables 5–8).

Each recommendation was assigned a strength of recommendation of strong (1) or conditional (2); 'strong' recommendations were made where the benefits are deemed to clearly outweigh the risks, whereas 'conditional' recommendations were made when the benefits are more balanced with the risks.

Each recommendation was assigned a quality of supporting evidence via the Scottish Intercollegiate Guidelines Network (SIGN)[11], thus summarizing the quality of the body of evidence for each recommendation as high (A), moderate (B), low (C) or very low (D), according to Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology.

Three patient partners with adult-onset IIM provided written feedback on the acceptability of the final recommendations and co-authored the final manuscript, although they were not involved in the voting proces. (one patient partner chose to remain anonymous and not be included as a co-author).

The project and final manuscript were reviewed and approved by the IMACS Scientific Committee.

[H1] Recommendations

A total of 18 final recommendations were formed, which address IIM-associated cancer risk stratification (compared with the wider IIM population, not the general population), use of screening modalities and screening frequency. The recommendations are discussed below and summarized in Table 1. The statement for each recommendation is followed by details relating to the strength of recommendation, quality of the supporting evidence (GRADE level A–D), the number of votes and the median vote rating with the inter-quartile range (IQR). Regarding strength of recommendation, 13 recommendations are strong and five are conditional. The quality of supporting evidence was moderate (B) for eight recommendations, low (C) for four recommendations and very low (D) for three recommendations; three further recommendations had no corresponding evidence base and were formed via expert consensus only. No recommendation had high (A) quality of supporting evidence. The evidence corresponding to each recommendation is available in Supplementary Table 9.

[H2] Recommendation 1. Screening for IIM-associated cancer is not routinely required in patients with juvenile-onset IIM.

- Strong recommendation.
- Evidence level: B.
- Voting: 62 votes, median vote rating 8 (IQR 8–9).

Current evidence indicates that cancer risk is not increased in patients with juvenile-onset IIM in comparison with the general population [12–18]. Therefore, routine cancer screening in this patient group was not deemed necessary by the Expert Group. Clinicians should, however, be vigilant for features suggestive of underlying cancer in patients with juvenile-onset IIM, including abnormal complete blood count, unexplained weight loss, fevers, and splenomegaly and/or lymphadenopathy.

[H2] Recommendation 2. Screening for IIM-associated cancer is not routinely required in patients with verified inclusion body myositis.

- Strong recommendation.
- Evidence level: B.
- Voting: 62 votes, median vote rating 8 (IQR 7–9).

Existing evidence indicates that inclusion body myositis (IBM) is not associated with an increased risk of cancer[4,19]. In particular, a nationwide Norwegian-based cohort study by Dobloug et al calculated a cancer standardised incidence rate of 1.0 (95% confidence interval (CI) 0.6–2.1) in 100 cases of IBM, indicating a cancer risk similar to that of the general population[4]. However, emerging evidence suggests a potential association between IBM and T cell large granular lymphocytic leukaemia[20,21]; ongoing research could further delineate this association and potentially inform the need for screening.

[H2] Recommendation 3. All patients with IIM, irrespective of cancer risk, should continue to participate in country- or region-specific age- and sex-appropriate cancer screening programmes.

- Strong recommendation.
- Evidence level: B.
- Voting: 64 votes, median vote rating 9 (IQR 9–9).

It is imperative that all patients with IIM, including those with juvenile-onset IIM and IBM, continue to participate in population-level cancer screening programmes, such as mammography for breast cancer, pelvic exam and/or cervical screening (smear test) for cervical cancer and low radiation dose chest CT scanning for lung cancer, as available in their country or region according to their age and sex[22]. These recommendations aim to facilitate the detection of IIM-associated cancers above and beyond the general population screening guidelines. Moreover, these recommendations are not tailored to detect cancers that might occur due to non-IIM-associated risk factors for which certain countries or regions might have instigated screening programmes.

[H2] Recommendation 4. All adult patients with new-onset IIM should be tested for myositis-specific autoantibodies and myositis-associated autoantibodies to assist stratification of cancer risk.

- Strong recommendation.
- Evidence level: B..
- Voting: 64 votes, median vote rating 9 (IQR 8–9).

Myositis-specific autoantibodies (MSA) can aid risk stratification for IIM-associated cancer, diagnosis and prediction of clinical manifestations and aid management decisions. A variety of methods are available for MSA detection and clinicians should interpret the results of such tests in the context of potential limitations, especially false positivity or negativity.

[H2] Recommendation 5. Underlying cancer risk of patients with adult-onset IIM should be stratified according to IIM subtype, autoantibody status and clinical features.

- Strong recommendation.
- Evidence level: B.
- Voting: 52 votes, median vote rating 8 (IQR 7–9).

The Expert Group identified IIM subtypes, autoantibodies and clinical features associated with high, intermediate and low risk of IIM-associated cancer.

[H3] 'High risk' factors

- Dermatomyositis

- Anti-transcription intermediary factor 1γ (anti-TIF1γ) antibody positivity
- Anti-nuclear matrix protein 2 (anti-NXP2) antibody positivity
- Age >40 years at the time of IIM onset
- Features of persistent high disease activity despite immunosuppressive therapy (including relapse of previously controlled disease)
- Dysphagia (moderate to severe)
- Cutaneous necrosis or ulceration

[H3] 'Intermediate risk' factors

- Clinically amyopathic dermatomyositis (CADM)
- Polymyositis
- Immune-mediated necrotizing myopathy (IMNM)
- Anti-small ubiquitin-like modifier-1 activating enzyme (anti-SAE1) antibody positivity
- Anti-3-hydroxy 3-methylutaryl coA reductase (anti-HMGCR) antibody positivity
- Anti-Mi2 antibody positivity
- Anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody positivity
- Male sex

[H3] 'Low risk' factors

- Anti-synthetase syndrome (ASSD)
- Overlap IIM–connective tissue disease-associated myositis
- Anti-signal recognition protein (anti-SRP) antibody positivity
- Anti-Jo1 antibody positivity
- Non-Jo1 ASSD antibody positivity
- Myositis-associated antibody positivity (anti-PM-Scl, anti-Ku, anti-RNP, anti-SSA/Ro, anti-SSB/La antibodies)
- Raynaud phenomenon
- Inflammatory arthropathy
- Interstitial lung disease

[H2] Recommendation 6. Patients with adult-onset IIM who have two or more 'high risk' factors (subtype, autoantibody or clinical feature) should be considered to have 'high risk for IIM-related cancer'.

- Strong recommendation.
- Evidence level: B.
- Voting: 67 votes, median vote rating 8 (IQR 8–9).

[H2] Recommendation 7. Patients with adult-onset IIM who have two or more 'intermediate risk' factors (subtype, autoantibody or clinical feature) or only one 'high risk' factor (subtype, autoantibody or clinical feature) should be considered to have 'moderate risk for IIM-related cancer'.

- Strong recommendation.

- Evidence level: B.
- Voting: 67 votes, median vote rating 7 (IQR 7–9).

[H2] Recommendation 8. Patients with adult-onset IIM who do not fulfil the 'high' or 'moderate' risk definitions as outlined in recommendations 6 and 7 should be considered to have 'standard risk for IIM-related cancer'.
- Strong recommendation.
- Evidence level: B.
- Voting: 67 votes, median vote rating 8 (IQR 7–9).

These recommendations have been formed to enable clinicians to stratify an individual patient's risk of IIM-associated cancer. The Expert Group formed an initial recommendation that identifies IIM subtypes, autoantibodies and clinical features associated with 'high', 'intermediate' and 'low' risk of IIM-associated cancer (see Box 1). The Expert Group also formed three subsequent recommendations that enable clinicians to assign an individual patient as having an overall 'high', 'moderate' or 'standard' risk of IIM-associated cancer, on the basis of their IIM subtype, autoantibody status and clinical features. It is important to note that these risk categories are in comparison to the overall IIM population, not the general population; indeed, those with 'standard' risk of IIM-associated cancer will likely have an increased risk of cancer compared with the general population. Empirical comparison of cancer risk between the standard risk group and the general population has not yet been carried out and is clearly warranted.

[H3] Factors associated with high risk for IIM-related cancer.
The Expert Group identified seven 'high risk' factors (one subtype, two autoantibodies and four clinical features). Dermatomyositis is consistently associated with the highest cancer risk, compared with other IIM subtypes; our 2019 meta-analysis identified a risk ratio (RR) of 2.21 (95% CI 1.78–2.77), indicating that the risk of cancer with dermatomyositis is more than double that with other IIM subtypes[9]. A large number of observational studies exist that detail cancer risk for each IIM subtype. A large body of evidence has characterized the high cancer risk associated with anti-TIF1γ antibody positivity, hence its inclusion as a high risk factor with a RR of 4.68, indicating that the risk of cancer is over four times higher for adults with anti-TIF1γ antibody positive IIM compared with those with anti-TIF1γ antibody negative IIM. Anti-NXP2 antibody positivity has also been associated with an increased risk of cancer; however this risk is considered lower than that associated with anti-TIF1γ antibody positivity. It is important to note that a number of studies associating anti-NXP2 antibody positivity with an increased risk of cancer employed the general population, not an IIM cohort, as a comparator group[23,24]. Our 2019 meta-analysis, which employed the wider IIM cohort as a comparator group, identified no association of anti-NXP2 antibody positivity with cancer (RR 1.16, 95% CI 0.73–1.87)[9]. However, the Expert Group deemed the available evidence sufficient to categorise anti-NXP2 antibody positivity as a 'high risk' factor.

Older age at time of IIM onset is associated with increased cancer risk. Selection of a specific age threshold is challenging owing to the probable incremental risk that older age of IIM-onset confers; a threshold of 40 years was chosen due to the clear age cut-off for cancer development identified in studies of anti-TIF1γ antibody positive adults[25,26]. It is important to note that no clear age cut-off has been established in the context of other autoantibody profiles and an incremental risk with increasing age is likely; however, the 40-year threshold was selected for clarity across all patients regardless of clinical features and autoantibody status. The accuracy of this age threshold will be assessed in future research into the utility of the guideline.

Features of persistent high disease activity despite immunosuppressive therapy were deemed by the Expert Group to be associated with a high risk of cancer. Evidence exists to support the relationship between persistent high disease activity, including myositis and skin involvement[27–29], and increased cancer risk, especially when associated with anti-TIF1γ antibody positivity; overall, however, the body of evidence is limited. Dysphagia, especially when treatment-refractory, has been associated with cancer, hence being deemed a 'high risk' factor by the Expert Group. The mechanism between dysphagia and increased IIM-associated cancer risk is not clear; however, dysphagia could represent a manifestation of persistent high disease activity. Finally, cutaneous necrosis and/or ulceration, which has been associated with increased risk of cancer, potentially owing to its association with severe refractory dermatomyositis, was deemed a 'high risk' factor by the Expert Group.

[H3] Factors associated with intermediate risk for IIM-related cancer.

Eight intermediate risk factors (three subtypes, four autoantibodies and one clinical feature) were identified by the Expert Group. The subtypes CADM, polymyositis and IMNM were assigned as being associated with intermediate cancer risk; evidence suggests that the risk of cancer in these IIM subtypes is lower than that in dermatomyositis, but higher than that in ASSD and 'overlap IIM'. The definition of polymyositis is challenging, with studies in the past 5 years indicating that some patients might be more appropriately classified as having other IIM subtypes such as IBM, IMNM or ASSD[30,31]. Polymyositis is still a commonly diagnosed condition, however; therefore, the Expert Group agreed to its inclusion as an 'intermediate' cancer risk factor. CADM is less commonly associated with cancer, compared to dermatomyositis, however the evidence base is limited. Overall, IMNM was classified as an intermediate cancer risk factor by the Expert Group. Recognising the results of a study by Allenbach et al[32], the Expert Group deemed it appropriate to distinguish cancer risk for patients with IMNM according to MSA positivity, with anti-HMGCR antibody positivity assigned as an 'intermediate' risk factor and anti-SRP antibody positivity a 'low' risk factor. The study by Allenbach et al[32], however, identified different cancer risks for anti-SRP, anti-HMGCR and autoantibody negative IMNM cohorts using the general population, not an IIM cohort, as a comparator group. Male sex and anti-MDA5, anti-Mi2 and anti-SAE1 antibody positivity were assigned as 'intermediate' risk factors by the Expert Group in light of the results of our meta-analysis[9]. In particular, anti-MDA5, anti-Mi2 and anti-SAE1 antibody

positivity were assigned as intermediate risk factors due to their non-significant association with cancer in the meta-analysis[9]. Defining MSA negativity is challenging due to variations of testing techniques and ability to test for more recently identified MSAs across countries and health systems; therefore MSA negativity was not included within risk stratification.

[H3] Factors associated with low risk for IIM-related cancer.

Nine 'low risk' factors (two subtypes, four autoantibodies, three clinical feature) were identified by the Expert Group. Our meta-analysis[9] and other evidence indicates a low risk of cancer for patients with ASSD, ASSD-associated clinical features (such as ILD, inflammatory arthropathy and Raynaud phenomenon) and MSAs (such as anti-Jo1 antibodies), and for patients with overlap IIM or connective tissue disease-associated IIM.

[H3] Stratification of cancer risk.

Three recommendations address estimation of the risk of IIM-associated cancer according to combinations of IIM subtype, clinical features and MSAs: patients with two 'high risk' factors are deemed to have high risk, patients with one 'high risk' factor or two 'intermediate risk' factors are deemed to have moderate risk, and the remainder are deemed to have have standard risk. It is important to note that these combinations are based on expert opinion and available observational evidence, rather than empirical evidence quantifying cancer risk according to each combination. The examples of IIM-associated cancer risk stratification in individual patients in Box 1 illustrate the implementation of these recommendations.

[H2] Recommendation 9. 'Basic cancer screening' should include the following investigations (in addition to country- or region-specific age- and sex-appropriate cancer screening programmes for the general population): comprehensive history; comprehensive physical examination; complete blood count; serum liver function tests; serum erythrocyte sedimentation rate and/or plasma viscosity; serum C-reactive protein; serum protein electrophoresis and measurement of free light chains; urinalysis; and plain chest X-ray radiograph.

- Strong recommendation.
- Evidence level: C.
- Voting: 50 votes, median vote rating 7 (IQR 6–8).

[H2] Recommendation 10. 'Enhanced cancer screening' should include the following investigations: CT scan of the neck, thorax, abdomen and pelvis; cervical screening; mammography; prostate-specific antigen blood test; CA-125 blood test; pelvic or transvaginal ultrasonography for ovarian cancer; faecal occult blood test.

- Strong recommendation.
- Evidence level: C.
- Voting: 50 votes, median vote rating 7 (IQR 6–8).

Cervical screening, mammography, prostate-specific antigen (PSA) blood test, pelvic or trans-vaginal ultrasonography for ovarian cancer and faecal occult blood test should be included in 'enhanced cancer screening' if not already part of country- or region-specific age and sex-appropriate screening programmes for the general population.

[H2] Recommendation 11. Patients with adult-onset IIM at 'standard risk of IIM-related cancer' should undergo 'basic cancer screening' at the time of IIM diagnosis. This screening is in addition to country- or region-specific age- and sex-appropriate screening programmes for the general population.

- Strong recommendation.
- No corresponding evidence base; recommendation formed via expert consensus only.
- Voting: 67 votes, median vote rating 8 (IQR 7–9).

[H2] Recommendation 12. Patients with adult-onset IIM at 'moderate risk of IIM-related cancer' should undergo 'basic cancer screening' and 'enhanced cancer screening' at the time of IIM diagnosis.

- Strong recommendation.
- No corresponding evidence base; recommendation formed via expert consensus only.
- Voting: 66 votes, median vote rating 8 (IQR 7–9).

[H2] Recommendation 13. Patients with adult-onset IIM at 'high risk of IIM-related cancer' should undergo 'enhanced cancer screening' and 'basic cancer creening' at the time of diagnosis and 'basic cancer screening' annually for 3 years.

- Strong recommendation.
- No corresponding evidence base; recommendation formed via expert consensus only.
- Voting: 67 votes, median vote rating 8 (IQR 7–9).

The Expert Group deemed it appropriate to form two panels of screening approaches —basic and enhanced — beyond age- and sex-based general population screening. The 'basic' screening panel aims to facilitate clinicians' ability to identify clinical features potentially consistent with IIM-associated cancer, such as iron deficiency anaemia indicating colon cancer, monoclonal gammopathy indicating multiple myeloma and chest X-ray radiograph-visible lung cancer.

The 'enhanced' screening panel was formulated to facilitate the identification of the most common IIM-associated cancers, such as breast, lung and ovarian cancer. Patients might have undergone a number tests as part of country- or region-specific age- and sex-appropriate screening programmes, such as mammography or prostate-specific antigen (PSA) level measurement; clinicians should balance the benefits of repeating such investigations against the risks on an individual patient basis in the context of cancer risk. Clinicians should also consider the potential increased cancer risk due to investigations that involve radiation exposure, such as CT-based investigations.

The Expert Group formed recommendations relating to the timing and frequency of carrying out 'basic' and 'enhanced' screening according to IIM-associated cancer risk category (see Figure 1 for a flowchart detailing risk stratification). Screening should be carried out for patients diagnosed within 3 years of IIM symptom onset; the recommendations therefore do not apply to those diagnosed after this time period. These recommendations are based on expert opinion only; no study has empirically investigated the utility of the timing and frequency of these specific panels of basic and enhanced cancer screening, hence the inability to ascribe an evidence quality grade.

[H2] Recommendation 14. Clinicians should consider carrying out an ^{18}F-FDG PET–CT scan for patients with adult-onset IIM at 'high risk of IIM-related cancer' where underlying cancer has not been detected by investigations at the time of IIM diagnosis.

- Conditional recommendation.
- Evidence level: C.
- Voting: 67 votes, median vote rating 8 (IQR 7–9).

[H2] Recommendation 15. Clinicians should consider carrying out an ^{18}F-FDG PET–CT scan as a single screening investigation for patients with anti-TIF1γ antibody positive dermatomyositis with disease onset at age >40 years and with ≥1 additional 'high risk' clinical feature.

- Conditional recommendation.
- Evidence level: C.
- Voting: 67 votes, median vote rating 8 (IQR 7–9).

A growing body of evidence demonstrates the utility of ^{18}F-FDG PET–CT as a screening modality for IIM-associated cancer[33–37]. The Expert Group deemed it appropriate to form a conditional recommendation relating to the use of ^{18}F-FDG PET–CT scanning as a screening method only in those with 'high' risk of cancer when 'basic' and 'enhanced' screening panels have not identified a cancer, especially if lymphoma is suspected. Evidence has also shown that ^{18}F-FDG PET–CT can identify cancers at a comparable rate to a large number of conventional screening investigations, including complete physical examination, laboratory tests (complete blood count and serum chemistry panel), thoraco-abdominal CT scan, tumour markers (CA125, CA19-9, CEA and PSA), gynaecological examination, ovarian ultrasonography and mammography[34]. The Expert Group therefore agreed that ^{18}F-FDG PET–CT could be considered as a single screening method in patients with dermatomyositis with onset at age >40 years with anti-TIF1γ antibody positivity and ≥1 additional 'high risk' clinical feature, thus potentially facilitating an earlier diagnosis and the need for fewer investigations. Clinicians should, however, balance the increased cancer risk attributed to ^{18}F-FDG PET–CT-related radiation exposure against the benefit of potential cancer detection. The Expert Group also acknowledged that ^{18}F-FDG PET–CT might not be available in all healthcare systems.

[H2] Recommendation 16. Clinicians should consider carrying out upper and lower gastrointestinal endoscopy for patients with adult-onset IIM at 'high risk of IIM-related cancer' where underlying cancer has not been detected by investigations at the time of IIM diagnosis.
- Conditional recommendation.
- Evidence level: D.
- Voting: 67 votes, median vote rating 8 (IQR 7–9).

The gastrointestinal tract is a common site of cancer in people with IIM-associated cancer [5]. Evidence relating to the utility of upper and lower gastrointestinal endoscopy as a cancer screening modality in patients with IIM is limited and this procedure confers potential risks (for example, bowel perforation) [33,38,39]; therefore the Expert Group formed a conditional recommendation. Upper and lower gastrointestinal endoscopy should be considered after other cancer screening investigations, including 'basic' and 'enhanced' screening panels, have been carried out in patients with adult-onset IIM at high risk of IIM-related cancer. The Expert Group recognised that upper and/or lower gastrointestinal endoscopy could be carried out as part of country- or region-specific age- and sex-appropriate cancer screening programmes.

[H2] Recommendation 17. Clinicians should consider carrying out nasoendoscopy at the time of diagnosis in patients with adult-onset IIM in geographical regions where the risk of nasopharyngeal carcinoma is increased.
- Conditional recommendation.
- Evidence level: D.
- Voting: 67 votes, median vote rating 8 (IQR 7–9).

The nasopharynx is a leading site of IIM-associated cancer in certain populations, especially those of East Asian and South-East Asian heritage; a 2021 meta-analysis estimated a prevalence of nasopharyngeal cancer in adults with dermatomyositis of 37% in Hong Kong, 28% in Malaysia and 12% in Singapore[40]. Consideration of nasoendoscopy is therefore advocated as a cancer screening modality for patients at high risk of nasopharyngeal cancer.

[H2] Recommendation 18. Clinicians should consider cancer screening in all patients with IIM with the following 'red-flag' symptoms or clinical features, regardless of risk category: unintentional weight loss, family history of cancer, smoking, unexplained fever or night sweats.
- Conditional recommendation.
- Evidence level: D.
- Voting: 66 votes, median vote rating 9 (IQR 7–9).

The Expert Group recognized that identification of certain 'red flag' symptoms or clinical features can aid clinicians in identifying patients with underlying IIM-associated cancer.

Clinicians should identify organ-specific features of cancer during the comprehensive history and examination (recommendation 9), such as haemoptysis (potentially a symptom of lung cancer) and dysphagia (potentially a symptom of oesophageal cancer).

[H1] Discussion

The International Guideline for IIM-Associated Cancer Screening provides, for the first time, evidence-supported and consensus-based recommendations addressing IIM-associated cancer risk stratification for the individual patient, cancer screening modalities and screening frequency.

The recommendations provide practical guidance for clinicians serving IIM populations across varying countries and health systems. Implementation of the recommendations aims to facilitate early detection of IIM-associated cancer, especially in those at high risk, thus potentially improving outcomes, including survival. The recommendations can help standardize cancer screening practices for use in patients with IIM across the globe, especially benefitting those without access to specialist services. Recommendations can foster open and clear clinician–patient discussions regarding individualized cancer risk and facilitate shared decision-making.

This guideline has a number of strengths. Firstly, the recommendations were developed via a process that assimilated current evidence, the results of a meta-analysis, and experts' experience and expertise, thus maximizing the applicability of the recommendations to clinical care. Secondly, the recommendations were formed by a large (n = 75) Expert Group with academic expertise in IIM management (in rheumatology, neurology, respiratory medicine and dermatology) and cancer screening. Members of the Expert Group were located in a wide variety of countries with varying health systems and populations, thus ensuring international applicability of the recommendations. Thirdly, formation of the recommendations via an online questionnaire using the Delphi process conferred a number of benefits: assurance of anonymity, thus reducing peer influence; equal weighting of each response; and practicality of response collation, thus facilitating involvement of international Expert Group members without the need for a face-to-face meeting. Finally, input from three patient partners allowed for assessment of the guidelines from a practical perspective with the added benefit of improving engagement and integration into clinical systems.

This guideline nonetheless has a number of limitations. Firstly, the evidence base pertaining to the utility of IIM-associated cancer screening approaches is markedly limited, thus reducing the strength of the recommendations. Indeed, no recommendation had a 'high (A)' quality body of supporting evidence, thus highlighting the pressing need for high-quality studies that can strengthen the evidence base and inform future iterations of this guideline. Secondly, although the Expert Group comprised members from 22 countries, geographic diversity was limited with representation from a limited number of countries or regions (27 members were from the USA, 30 were from Europe). Specifically, no Expert Group member practiced in any country from Africa, only one member was from China, one was from South America and no members were from Indonesia or Pakistan, which have the fourth and fifth largest

populations in the world. This disparity illustrates the international distribution of IIM specialists and future iterations of this guideline should ensure wider inclusion, where possible. Indeed, implementation of recommendations might not be possible in all countries and health systems, especially in resource-challenged areas; future iterations of the guideline should aim to address identified disparities. Finally, the definition of cancer risk groups was based on available evidence, not empirical research. Future research focusing upon the ability of the risk stratification groups to accurately differentiate and predict cancer development is warranted and will influence subsequent iterations of this guideline.

The guideline development process has highlighted a number of unmet needs, thus facilitating the formation of a research agenda. Firstly, the utility of the cancer screening recommendations have not been empirically investigated; research addressing this topic could guide future iterations and improve clinicians' ability to detect cancer. Secondly, no study investigated the utility of repeated screening or determined optimal screening frequency; research specifically addressing the optimal frequency and/or interval of screening, especially CT scanning of the thorax, abdomen and pelvis, could greatly enhance cancer detection. Thirdly, future research investigating complications or harm resulting from this guideline's recommendations is vital; for example, identification of the number of false-positive cancer diagnoses and any resulting harm via recommended screening will be key in the formation of future iterations of the guideline.

It is anticipated that revision of this guideline after a 5-year period will be appropriate, thus allowing for the inclusion of emerging research and findings into the evidence base upon which recommendations can be revised and created.

An audit tool, developed by the Steering Committee, is included (see Supplementary Table 10) to enable clinicians and clinical teams to measure their concordance with recommendations, thus aiding service quality improvement.

[H1] Conclusions

In conclusion, this International Guideline for IIM-Associated Cancer Screening provides guidance to clinicians and patients regarding individual-patient risk stratification, cancer screening modalities and screening frequency. The guideline standardizes patient care and provides a foundation upon which future IIM-cancer screening research can build.

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Author contributions

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Supplementary information

International Myositis Assessment and Clinical Studies Group Cancer Screening Expert Group

Anthony A. Amato [22], Helena Andersson [23], Lilia Andrade-Ortega [24, 25], Dana Ascherman [21], Olivier Benveniste [26, 27], Lorenzo Cavagna [28, 29], Christina Charles-Shoeman [30], Benjamin F. Chong [31], Lisa Christopher-Stine [32], Jennie T. Clarke [33], Emma J. Crosbie [1, 34, 35], Philip A. J. Crosbie [1, 36], Sonye Danoff [37], Maryam Dastmalchi [38], Marianne De Visser [39], Paul Dellaripa [40], Louise Pyndt Diederichsen [41, 42], Mazen M. Dimachkie [43], Erik Ensrud [44], Floranne Ernste [45], D. Gareth R. Evans [1, 46], Manabu Fujimoto [47], Ignacio Garcia-De La Torre [48], Abraham Garcia-Kutzbach [49], Zoltan Griger [50], Latika Gupta [3, 51, 52], Marie Hudson [53], Florenzo Iannone [54], David Isenberg [10, 12, 55], Joseph Jorizzo [56], Helen Kurtz [57], Masataka Kuwana [58], Vidya Limaye [59, 60], Ingrid E. Lundberg [38], Andrew L. Mammen [32, 61], Herman Mann [62, 63], Frank Mastaglia [64], Lorna McWilliams [1, 65], Christopher A. Mecoli [32], Federica Meloni [28, 66], Frederick W. Miller [67], Siamak Moghadam-Kia [21], Sergey Moiseev [68], Yoshinao Muro [69], Melinda Nagy-Vincze [70], Clive Nayler [71], Merrilee Needham [72, 73, 74], Ichizo Nishino [75, 76], Chester V. Oddis [22], Julie J. Paik [33], Joost Raaphorst [40], Lisa G. Rider [68], Jorge Rojas-Serrano [77, 78], Lesley Ann Saketkoo [79, 80, 81, 82], Adam Schiffenbauer [68], Samuel Katsuyuki Shinjo [83], Vineeta Shobha [84], Yeong-Wook Song [85], Tania Tillett [86], Yves Troyanov [87, 88], Anneke J. van der Kooi [40], Mónica Vázquez-Del Mercado [89, 90], Jiri Vencovsky [63, 64], Qian Wang [91], Steven Ytterberg [46]

22. Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
23. Department of Rheumatology, Oslo University Hospital, Oslo, Norway.
24. Department of Rheumatology, Centro Médico Nacional 20 de Noviembre, ISSSTE, Mexico City, México.
25. Universidad Nacional Autónoma de México, Mexico City, México.

26. Department of Internal Medicine and Clinical Immunlogy, Assistance Public Hôpitaux de Paris, Paris, France.

27. Sorbonne Université, Pitié-Salpêtrière University Hospital, Paris, France.

28. Department of Internal Medicine and Therapeutics, Università di Pavia, Pavia, Italy.

29. Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

30. Department of Medicine, Division of Rheumatology, University of California, Los Angeles, CA, USA.

31. Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, USA.

32. Department of Medicine, Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

33. Department of Dermatology, University of Utah School of Medicine, Salt Lake City, UT, USA.

34. Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

35. Department of Obstetrics and Gynaecology, St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.

36. Division of Infection, Immunity, and Respiratory Medicine, University of Manchester, Manchester, UK.

37. Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

38. Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, and Karolinska University Hospital, Stockholm, Sweden.

39. Department of Neurology, Amsterdam University Medical Centres, locatie AMC, University of Amsterdam, Neuroscience institute, Amsterdam, Netherlands.

40. Division of Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

41. Centre for Rheumatology and Spine Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.

42. Department of Rheumatology, Odense University Hospital, Odense, Denmark.

43. Department of Neurology, The University of Kansas Medical Center, Kansas City, KS, USA.

44. Department of Neurology, Department of Physical Medicine and Rehabilitation, University of Missouri School of Medicine, Columbia, MO, USA.

45. Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA.

46. Manchester Centre for Genomic Medicine, Manchester Academic Health Science Centre, Division of Evolution and Genomic Medicine, University of Manchester, St Mary's Hospital, Manchester Universities NHS Foundation Trust, Manchester, UK.

47. Department of Dermatology, Osaka University Graduate School of Medicine, Osaka, Japan.

48. Department of Immunology and Rheumatology, Hospital General de Occidente and Universidad de Guadalajara, Guadalajara, Mexico.

49. Internal Medicine Rheumatology Secion, Francisco Marroquín University, Guatemala City, Guatemala.

50. Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary.

51. Department of Rheumatology, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK.
52. Department of Rheumatology, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK.
53. Division of Rheumatology and Department of Medicine, Jewish General Hospital and McGill University, Montreal, QC, Canada.
54. Rheumatology Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy.
55. Department of Rheumatology, University College London Hospitals NHS Foundation Trust, London, UK.
56. Wake Forest University School of Medicine, Winston Salem, North Carolina, USA.
57. Patient Partner, Norwich, Norfolk, UK.
58. Department of Allergy and Rheumatology, Nippon Medical School, Tokyo, Japan.
59. Rheumatology Department, Royal Adelaide Hospital, Adelaide, SA, Australia.
60. Discipline of Medicine, University of Adelaide, Adelaide, SA, Australia
61. Muscle Disease Unit, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA.
62. Institute of Rheumatology, Prague, Czech Republic.
63. Department of Rheumatology, 1st Medical Faculty, Charles University, Prague, Czech Republic.
64. Perron Institute for Neurological and Translational Science, Perth, WA, Australia.
65. Manchester Centre for Health Psychology, Division of Psychology and Mental Health, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK.
66. Respiratory Disease Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.
67. Environmental Autoimmunity Group, Clinical Research Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, MD, USA.
68. Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia.
69. Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan.
70. Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary.
71. Patient Partner, Malvern, Worcester, UK.
72. Department of Neurology, Fiona Stanley Hospital, Perth, WA, Australia.
73. Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Murdoch, WA, Australia.
74. School of Medicine, University of Notre Dame, Fremantle, Perth, WA, Australia
75. Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan.
76. Department of Genome Medicine Development, Medical Genome Center, National Center of Neurology and Psychiatry, Tokyo, Japan.
77. Clínica de Reumatología, Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico.
78. Programa de Maestría y Doctorado en Ciencias Médicas, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City, Mexico.

79. Scleroderma and Sarcoidosis Patient Care and Research Center, Department of Medicine, Section of Rheumatology, LSU Health Sciences Center, New Orleans, LA, USA.

80. Comprehensive Pulmonary Hypertension Center, University Medical Center, New Orleans, LA, USA.

81. Tulane University School of Medicine, New Orleans, LA, USA.

82. Louisiana State University School of Medicine, New Orleans, LA, USA.

83. Division of Rheumatology, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil.

84. Department of Clinical Immunology and Rheumatology, St John's Medical College Hospital, St John's National Academy of Medical Sciences, Bangalore, India.

85. Department of Internal Medicine, College of Medicine, Medical Research Center, Institute of Human-Environment Interface Biology, Seoul National University, Seoul, South Korea.

86. Department of Oncology, Royal United Hospitals NHS Foundation Trust Bath, Bath, UK.

87. Department of Medicine, University of Montreal, Montreal, QC, Canada.

88. Division of Rheumatology, Hôpital du Sacré-Coeur, Montreal, QC, Canada.

89. Servicio de Reumatología, Hospital Civil Dr. Juan I. Menchaca, Guadalajara, Mexico.

90. Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Mexico.

91. Department of Rheumatology and Clinical Immunology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

Table 1. Summary of all recommendations from the International Guideline for IIM-Associated Cancer Screening.

Recommendation	Strength	Level of evidence[a]	Consensus	
			Number of votes	Median score (IQR)
1. Screening for IIM-associated cancer is not routinely required in patients with juvenile-onset IIM.	Strong	Moderate	62	8 (8–9)
2. Screening for IIM-associated cancer is not routinely required in patients with verified inclusion body myositis.	Strong	Moderate	62	8 (7–9)
3. All patients with IIM, irrespective of cancer risk, should continue to participate in country- or region-specific age- and sex-appropriate cancer screening programmes.	Strong	Moderate	64	9 (9–9)
4. All adult patients with new-onset IIM should be tested for myositis-specific autoantibodies and myositis-associated autoantibodies to assist stratification of cancer risk.	Strong	Moderate	64	9 (8–9)
5. Underlying cancer risk of patients with adult-onset IIM should be stratified according to IIM subtype, autoantibody status and clinical features in the following manner: High risk:- • Dermatomyositis • Anti-TIF1γ antibody positivity • Anti-NXP2 antibody positivity • Age >40 years at the time of IIM onset • Features of persistent high disease activity despite immunosuppressive therapy (including relapse of previously controlled disease) • Dysphagia (moderate to severe) • Cutaneous necrosis or ulceration Intermediate risk:	Strong	Moderate	52	8 (7–9)

• CADM • Polymyositis • IMNM • Anti-SAE1 antibody positivity • Anti-HMGCR antibody positivity • Anti-Mi2 antibody positivity • Anti-MDA5 antibody positivity • Male sex Low risk: • ASSD • Overlap IIM–CTD -associated myositis • Anti-SRP antibody positivity • Anti-Jo1 antibody positivity • Non-Jo1 ASSD antibody positivity • Myositis-associated antibody positivity (anti-PM-Scl, anti-Ku, anti-RNP, anti-SSA/Ro, anti-SSB/La antibodies) • Raynaud phenomenon • Inflammatory arthropathy • Interstitial lung disease				
6. Patients with adult-onset IIM who have two or more 'high risk' factors (subtype, autoantibody or clinical feature) should be considered to have 'high risk for IIM-related cancer'.[b]	Strong	Moderate	67	8 (8–9)
7. Patients with adult-onset IIM who have two or more 'intermediate risk' factors (subtype, autoantibody or clinical feature) or only one 'high risk' factor (subtype, autoantibody or clinical feature) should be considered to have 'moderate risk for IIM-related cancer'. [b]	Strong	Moderate	67	7 (7–9)
8. Patients with adult-onset IIM who do not fulfil the 'high' or 'moderate' risk definitions as outlined in recommendations 6 and 7 should be considered to have 'standard risk for IIM-related cancer'. [b]	Strong	Moderate	67	8 (7–9)
9. 'Basic cancer screening' should include the following investigations (in addition to country- or region-specific age- and sex-appropriate cancer screening programmes for the general population): • Comprehensive history • Comprehensive physical examination • Complete blood count • Serum liver function tests • Serum erythrocyte sedimentation rate and/or plasma viscosity • Serum C-reactive protein • Serum protein electrophoresis and measurement of free light chains • Urinalysis • Plain chest X-ray radiograph	Strong	Low	50	7 (6–8)
10. 'Enhanced cancer screening' should include the following investigations: • CT scan of the neck, thorax, abdomen and pelvis • Cervical screening[c] • Mammography[c] • Prostate-specific antigen blood test[c] • CA-125 blood test • Pelvic or transvaginal ultrasonography for ovarian cancer • Faecal occult blood[c]	Strong	Low	51	8 (7–8)
11. Patients with adult-onset IIM at 'standard risk of IIM-related cancer' should undergo 'basic cancer screening' at the time of IIM diagnosis. This screening is in addition to country- or region-specific age- and sex-appropriate screening programmes for the general population.	Strong	NA[d]	67	8 (7–9)
12. Patients with adult-onset IIM at 'moderate risk of IIM-related cancer' should undergo 'basic cancer screening' and 'enhanced cancer screening' at the time of IIM diagnosis.	Strong	NA[d]	66	8 (7–9)
13. Patients with adult-onset IIM at 'high risk of IIM-related cancer' should undergo 'enhanced cancer screening' and 'basic cancer screening' at the time of diagnosis and 'basic cancer screening' annually for 3 years.	Strong	NA[d]	67	8 (7–9)
14. Clinicians should consider carrying out an ^{18}F-FDG PET–CT scan for patients with adult-onset IIM at 'high risk of IIM-related cancer' where underlying cancer has not been detected by investigations at the time of IIM diagnosis.	Conditional	Low	67	8 (7–9)
15. Clinicians should consider carrying out an ^{18}F-FDG PET–CT scan as a single screening investigation for patients with anti-TIF1γ antibody positive dermatomyositis with disease onset at age >40 years and with ≥1 additional 'high risk' clinical feature.	Conditional	Low	67	8 (7–9)

16. Clinicians should consider carrying out upper and lower gastrointestinal endoscopy for patients with adult-onset IIM at 'high risk of IIM-related cancer' where underlying cancer has not been detected by investigations at the time of IIM diagnosis.	Conditional	Very low	67	8 (7–9)
17. Clinicians should consider carrying out nasoendoscopy at the time of diagnosis in patients with adult-onset IIM in geographical regions where risk of nasopharyngeal carcinoma is increased.	Conditional	Very low	67	8 (7–9)
18. Clinicians should consider cancer screening in all patients with IIM with the following 'red flag' symptoms or clinical features, regardless of risk category: • Unintentional weight loss • Family history of cancer • Smoking • Unexplained fever • Night sweats	Conditional	Very low	66	9 (7–9)

^{18}F-FDG PET–CT, [18F]fluoro-deoxy-glucose PET–CT; ASSD, anti-synthetase syndrome; CADM, clinically amyopathic dermatomyositis; HMGCR, 3-hydroxy 3-methylutaryl coenzyme A reductase; IIM, idiopathic inflammatory myopathy; IMNM, immune-mediated necrotising myopathy; IQR, interquartile range; MDA5, melanoma differentiation-associated gene 5; NA, not applicable; NXP2, nuclear matrix protein 2; RNP, ribonucleoprotein; SAE1, small ubiquitin-like modifier-1 activating enzyme; SRP, signal recognition particle; TIF1γ, transcription intermediary factor 1γ.

[†a]According to Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology, with evidence quality graded as high (A), moderate (B), low (C) or very low (D).

[b]Risk categories are in comparison to the IIM population, not the general population.

[c]If not already part of country- or region-specific age- and sex-appropriate screening programmes.

[d] These recommendations had no corresponding evidence base and were formed via expert consensus only.

Figure Legend

Figure 1. Risk stratification and frequency of screening for IIM-related cancer.

The recommendations apply only to adult patients diagnosed with idiopathic inflammatory myopathy (IIM) within the 3-year period after IIM symptom onset. Individual patients with adult-onset IIM can be risk-stratified according to IIM subtype, myositis specific antibody (MSA) and myositis-associated autoantibody (MAA) profile and clinical features, resulting in assignment to categories of 'high', 'intermediate' or 'standard' risk of IIM-associated cancer. Screening modalities and frequency are recommended according to the assigned risk category. 'Basic' and 'enhanced' screening panels are outlined in the figure. Additional screening with ^{18F}-fluoro-deoxy-glucose PET–CT (^{18}F-FDG PET–CT) should be considered for patients with adult-onset IIM who are considered at 'high risk of IIM-related cancer' where underlying cancer has not been detected by investigations at the time of IIM diagnosis or as a single screening investigation for patients with anti-TIF1γ antibody positive dermatomyositis with disease onset at age >40 years and with ≥1 additional 'high risk' clinical feature. Clinicians should consider carrying out upper and lower gastrointestinal endoscopy for patients with adult-onset IIM at 'high risk of IIM-related cancer' where underlying cancer has not been detected by investigations at the time of IIM diagnosis, and nasoendoscopy at the time of diagnosis of adult-onset IIM in geographical regions where the risk of nasopharyngeal carcinoma is increased. Screening for IIM-associated cancer is not routinely required for patients with juvenile-onset IIM or verified inclusion body myositis. ASSD, anti-synthetase syndrome; CADM, clinically amyopathic dermatomyositis; HMGCR, 3-hydroxy 3-methylutaryl coenzyme A reductase; IMNM, immune-mediated necrotizing myopathy; MDA5, melanoma differentiation-associated gene 5; NXP2, nuclear matrix protein 2; RNP, ribonucleoprotein; SAE1, small ubiquitin-like modifier-1 activating enzyme; SRP, signal recognition particle; TIF1γ, transcription intermediary factor 1γ.
[a]Anti-PM-Scl, anti-Ku, anti-RNP, anti-SSA/Ro, anti-SSB/La antibodies.
[b]If not already part of country/region-specific age- and sex-appropriate cancer screening programmes.
Adapted with permission from Oldroyd, A. et al. Cancer Screening Recommendations for Patients with Idiopathic Inflammatory Myopathy [abstract]. *Arthritis Rheumatol.* **74** (suppl 9) (2022). https://acrabstracts.org/abstract/cancer-screening-recommendations-for-patients-with-idiopathic-inflammatory-myopathy/

Box 1: Examples of IIM-associated cancer risk stratification
[bH1] Example 1:
A 70 year old woman with anti-NXP2 antibody positive dermatomyositis who initially developed symptoms 6 months previously would be classified as having 'high' risk, due to fulfilment of three individual 'high risk' factors: dermatomyositis, anti-NXP2 antibody positivity and age >40 years at the time of IIM onset.
[bH1] Example 2:

A 52-year-old woman with anti-HMGCR antibody positive immune-mediated necrotizing myopathy who developed symptoms 3 months previously would be classified as having 'moderate' risk, due to fulfilment of two individual intermediate risk factors: immune-mediated necrotizing myopathy and anti-HMGCR antibody positivity).

[bH1] Example 3:

A 26-year-old man with anti-Jo1 positive anti-synthetase syndrome who developed symptoms 2 months previously would be classified as having 'standard' risk, due to non-fulfilment of 'moderate' or 'high risk' criteria.

HMGCR, 3-hydroxy 3-methylutaryl coA reductase; IIM, idiopathic inflammatory myopathy; NXP2, nuclear matrix protein 2.

Editor's Summary

In this Evidence-Based Guideline article, an international, multidisciplinary group of experts presents evidence-based consensus recommendations on screening for cancer in patients with adult-onset idiopathic inflammatory myopathy, addressing cancer risk stratification, screening modalities and screening frequency.