European Association of Nuclear Medicine (EANM) Focus 4 consensus recommendations

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European Association of Nuclear Medicine (EANM) Focus 4 consensus recommendations: molecular imaging and therapy in haematological tumours

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Given the paucity of high-certainty evidence, and differences in opinion on the use of nuclear medicine for hematological malignancies, we embarked on a consensus process involving key experts in this area. We aimed to assess consensus within a panel of experts on issues related to patient eligibility, imaging techniques, staging and response assessment, follow-up, and treatment decision-making, and to provide interim guidance by our expert consensus. We used a three-stage consensus process. First, we systematically reviewed and appraised the quality of existing evidence. Second, we generated a list of 153 statements based on the literature review to be agreed or disagreed with, with an additional statement added after the first round. Third, the 154 statements were scored by a panel of 26 experts purposively sampled from authors of published research on haematological tumours on a 1 (strongly disagree) to 9 (strongly agree) Likert scale in a two-round electronic Delphi review. The RAND and University of California Los Angeles appropriateness method was used for analysis. Between one and 14 systematic reviews were identified on each topic. All were rated as low to moderate quality. After two rounds of voting, there was consensus on 139 (90%) of 154 of the statements. There was consensus on most statements concerning the use of PET in non-Hodgkin and Hodgkin lymphoma. In multiple myeloma, more studies are required to define the optimal sequence for treatment assessment. Furthermore, nuclear medicine physicians and haematologists are awaiting consistent literature to introduce volumetric parameters, artificial intelligence, machine learning, and radiomics into routine practice.

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Introduction

The use of nuclear medicine techniques has changed the standard of care in many clinical situations relating to molecular imaging and therapy in haematological malignancies.[1,2] Haematological malignancies represent one of the first entities in which nuclear medicine has had a major impact by advancing fundamental changes in both diagnostic and therapeutic practices within the past 2–3 decades.[3]

To consolidate what constitutes best clinical practice, and to harmonise the guidance on currently uncertain topics, the European Association of Nuclear Medicine (EANM) initiated the Focus 4 meeting dedicated to haematological malignancies. The Focus meetings are an annual event organised by EANM to provide guidance on nuclear medicine topics in which evidence is weak or absent, with three previous successful iterations tackling molecular imaging and theranostics in prostate cancer,[4] dementia,[5] and neuroendocrine tumours.[6] Within Focus 4, all medical disciplines responsible for the care of patients with haematological malignancy were brought together to interpret the current evidence and to provide practical guidance. Given that there might be differences of opinion on how to interpret the current evidence in haematological malignancies and apply it in clinical practice, our aim in this project was to assess consensus robustly and transparently within a panel of experts on issues related to patient eligibility, imaging techniques, staging, treatment decision making, response assessment, and follow-up, and to provide interim guidance by our expert consensus.

Within our overarching aim, our objectives were to describe the extent of consensus on the use of [^{18}F] fluorodeoxyglucose ([^{18}F]FDG)-PET in non-Hodgkin lymphoma, Hodgkin lymphoma, and multiple myeloma among a panel of experts and to identify which situations require further evidence and information to enable decision making. A further objective was to illuminate both the role of nuclear medical methods within haemato-oncological malignancies and progressive technical developments such as artificial intelligence and machine learning.

Methods

To meet the project's aims, a three-stage consensus process was used. First, relevant medical and scientific literature was systematically searched for and the quality of the evidence summarised (appendix pp 1–38). Second, on the basis of this literature review, the Focus 4 co-chairs (CN and CK) and Focus 4 Scientific Committee members (KH and JK) drafted a list of 153 positively framed statements that could be agreed or disagreed with and could not be currently answered by the available evidence. Finally, in a two-round, modified online Delphi (e-Delphi) process, the expert panel was invited to score the statements by indicating agreement, disagreement, uncertainty, or unable to score. An additional consensus statement was added after round 1 to bring the total to 154. A face-to-face consensus conference was planned to take place after the second e-Delphi round to ratify the results and discuss and rescore statements for which

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there was still no consensus reached. However, the meeting was postponed and later cancelled due to the COVID-19 pandemic. A further pragmatic consideration in cancelling the in-person meeting was that consensus thresholds had been met for 139 (90%) of 154 of the statements after the two online rounds. Hence, an additional scoring round appeared to be of little value.

The panellists in the e-Delphi process included experts in all aspects of the management of haematological tumours, including, but not limited to, molecular imaging and radionuclide therapy. Experts were identified via authorship of published research on haematological tumours. 30 experts were invited to participate of which 28 initially completed round 1, but two experts withdrew due to not having the required expertise, not due to disagreeing with the group, and asked for their data to be deleted; therefore, their scores were not included in the round 1 analysis. The remaining 26 experts completed both rounds (appendix pp 2–38).

Search strategy and selection criteria

The PubMed database was searched until Dec 11, 2021, for literature published in English regarding molecular imaging and therapy of haematological malignancies. We searched for literature published after Jan 1, 2010, to ensure we analysed publications that are up-to-date on the use of PET in haematology. Within these topics, separate searches were made regarding areas that were envisioned to be covered by statements developed by the Scientific Committee for the panellists to score. The terms used in the search and a summary of the results appear in the appendix (pp 3–38). To increase the sensitivity of the search, PubMed filters were omitted.

Systematic reviews, meta-analyses, evidence-based guidelines, and evidence-based review articles related to the respective potential statement topics were included. If no systematic reviews were found, a search of primary studies published since Jan 1, 2010, was performed. When possible, the European Society for Medical Oncology (ESMO) clinical practice guidelines on haematological malignancies were retrieved and their bibliographies were checked against the search results to ensure that influential studies were not missed.

We assessed the quality of the retrieved systematic reviews using AMSTAR2 criteria (appendix pp 2–38).[7] The papers retrieved in the literature search were made available to the expert panellists with tables summarising the quality assessment of the systematic reviews 4 weeks before scoring the statements.

Modified Delphi process

In round 1 of the modified e-Delphi, panellists were emailed a link to an online survey containing 153 statements organised into five thematic tracks with subthemes. Each statement was phrased so that panellists could indicate their strength of agreement on a Likert scale ranging from 1 (strongly disagree) to 9 (strongly agree), with 5 meaning neither agree nor disagree. Panellists were urged to only choose a score in the 4–6 range if they felt that they had sufficient information and expertise to opine on the statement and truly neither agree nor disagree; otherwise, they were asked to choose the unable to score option. Panellists were permitted to comment on any statement in round 1 and to submit statements for consideration by the scientific committee that they believed should be added for scoring in round 2. Three statements were suggested, one of which was added and numbered as 999 to maintain sequencing across rounds.

In round 2 of the modified e-Delphi, panellists were reminded of their own round 1 score and shown the distribution the scores of other panellists for each statement. They were asked to rescore the 153 original items and to score the statement that was added after round 1. DelphiManager software (Core Outcome Measures for Effectiveness Trials [COMET] Initiative) was used to create the e-Delphi survey.

e-Delphi data analysis

We analysed the e-Delphi data following the RAND and University of California Los Angeles appropriateness method, which has been shown to provide robust results regardless of panel size.[8] For each statement, we calculated the median score and 30th to 70th inter-percentile range (IPR). We calculated the IPR adjusted for symmetry (IPRAS) using the formula: IPRAS=2·35+(asymmetry index×1·5). The asymmetry index is defined as the absolute difference between the central point of the IPR and 5 (ie, central point on the 1–9 scoring scale). We interpreted as no extreme dispersion of scores if IPR was less than IPRAS (ie, the median score is considered to represent consensus). We categorised the median scores in the range of 1–3 as disagree, 4–6 as uncertain, and 7–9 as agree. We used Stata 11 (StataCorp LP; College Station, TX, USA) for analysis.

Results

Systematic literature review

The complete results of the systematic literature review are reported in the appendix (pp 2–38). Each track focused on a different thematic topic and had subthemes, hence the inclusion and exclusion criteria were different for each topic. Between one and 14 systematic reviews were included for each subtheme. The panellists rated the systematic reviews as moderate quality to low quality on AMSTAR2 assessment, with none meeting the criteria for high quality.

Modified Delphi

There was consensus (ie, to agree, to disagree, or uncertain) on 133 (87%) and no consensus on 20 (13%) of 153 statements after round 1. There was consensus

	Statement	Median score	30th centile	70th centile	Consensus (yes or no)	Interpretation	Number of panellists unable to score
Track 1.1: patient eligibility for staging with [^{18}F]FDG-PET-CT							
1	All patients with DLBCL and possibly other FDG-avid aggressive non-Hodgkin lymphoma should undergo staging with [^{18}F]FDG-PET-CT.	9·0	9·0	9·0	Yes	Consensus to agree	1
2	All patients with follicular lymphoma (grade 1–3a) and possibly other FDG-avid indolent non-Hodgkin lymphoma should undergo staging with [^{18}F]FDG-PET-CT.	9·0	9·0	9·0	Yes	Consensus to agree	3
3	Patients with follicular lymphoma (grade 1–3a), possibly other FDG-avid indolent non-Hodgkin lymphoma, and questionable early stage should undergo staging with [^{18}F]FDG-PET-CT.	9·0	9·0	9·0	Yes	Consensus to agree	3
4	Patients with indolent lymphoma with clinical suspicion of high grade transformation should undergo [^{18}F]FDG-PET-CT.	9·0	9·0	9·0	Yes	Consensus to agree	3
5	PET-CT can guide biopsy in indolent lymphoma if there is a suspicion of transformation.	9·0	9·0	9·0	Yes	Consensus to agree	3
6	Staging DLBCL or other FDG-avid aggressive non-Hodgkin lymphoma with [^{18}F]FDG-PET-CT can be used to show bone marrow involvement and replace bone marrow biopsy in most patients.	9·0	9·0	9·0	Yes	Consensus to agree	4
7	Use of [^{18}F]FDG-PET-CT for staging patients with non-Hodgkin lymphoma should be restricted to clinical trials.	1·0	1·0	1·0	Yes	Consensus to disagree	1
999*	The size of lymphoma residual masses should be reported even if there is no FDG uptake.	8·5	7·0	9·0	Yes	Consensus to agree	4
Track 1.2: use of non-imaging biomarkers, including circulating tumour DNA, protein biomarkers, and tissue genotyping							
8	To improve individualised treatment, non-imaging, blood-based biomarkers should be further investigated.	9·0	8·0	9·0	Yes	Consensus to agree	2
Track 1.3: [^{18}F]FDG-PET-CT response assessment							
9	In patients with DLBCL and possibly other FDG-avid aggressive non-Hodgkin lymphoma, [^{18}F]FDG-PET-CT should be performed for response assessment at interim staging.	9·0	8·0	9·0	Yes	Consensus to agree	3
10	In patients with follicular lymphoma (grade 1–3a) and possibly other FDG-avid indolent non-Hodgkin lymphoma, [^{18}F]FDG-PET-CT should be performed for response assessment at interim staging.	7·0	3·6	9·0	No	No consensus	3
11	In patients with DLBCL and possibly other FDG-avid aggressive non-Hodgkin lymphoma, [^{18}F]FDG-PET-CT should be performed for response assessment after chemotherapy.	9·0	9·0	9·0	Yes	Consensus to agree	2
12	In patients with follicular lymphoma (grade 1–3a) and possibly other FDG-avid indolent non-Hodgkin lymphoma, [^{18}F]FDG-PET-CT should be performed for response assessment after chemotherapy.	9·0	9·0	9·0	Yes	Consensus to agree	2
13	CECT is obligatory for response assessment in patients with DLBCL or other FDG-avid aggressive non-Hodgkin lymphoma even if [^{18}F]FDG-PET-CT using low-dose CT is performed.	7·0	1·0	9·0	No	No consensus	2
14	In both aggressive and indolent non-Hodgkin lymphoma, [^{18}F]FDG-PET-CT is not necessary for response assessment.	1·0	1·0	1·0	Yes	Consensus to disagree	2

(Table 1 continues on next page)

on 139 (90%) and no consensus on 15 (10%) of 154 statements after round 2. The median number of panellists choosing unable to score was 6 (range 1–13) and although, on some statements, some panellists scored differently in the second round, the median and range were the same in round 2. The results of the e-Delphi after the second round are shown in tables 1–5, including the median, IPR, direction of agreement, and consensus status.

Section 1: non-Hodgkin lymphoma (statements 1–28)

Staging and response assessment with [^{18}F]FDG-PET-CT

There was strong agreement that some subgroups of patients with non-Hodgkin lymphoma should undergo staging with [^{18}F]FDG-PET-CT in routine clinical practice: all patients with diffuse large B-cell lymphoma (DLBCL) and possibly other [^{18}F]FDG-avid aggressive non-Hodgkin lymphoma; all patients with follicular lymphoma (grade 1–3a) and possibly other [^{18}F]FDG-avid indolent non-Hodgkin lymphoma, including those with early stage; and patients with indolent lymphoma with clinical suspicion of high-grade transformation and questionable early stage (table 1). The panel also agreed that [^{18}F]FDG-PET-CT should be performed and can guide biopsy in indolent lymphoma if there is a suspicion of transformation, and that staging DLBCL or other [^{18}F]FDG-avid aggressive non-Hodgkin lymphoma with [^{18}F]FDG-PET-CT can be used to show bone marrow involvement and replace bone marrow biopsy in most patients.

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	Statement	Median score	30th centile	70th centile	Consensus (yes or no)	Interpretation	Number of panellists unable to score
(Continued from previous page)							
Track 1.4: [^{18}F]FDG-PET-CT in decision making for the use of radiotherapy							
15	End-of-chemotherapy [^{18}F]FDG-PET-CT provides information necessary for making the decision to use or not to use radiotherapy in DLBCL and possibly other FDG-avid aggressive non-Hodgkin lymphoma.	9·0	8·0	9·0	Yes	Consensus to agree	2
16	End-of-chemotherapy [^{18}F]FDG-PET-CT provides information necessary for making the decision to use or not to use radiotherapy in patients with follicular lymphoma (grade 1–3a) and possibly other FDG-avid indolent non-Hodgkin lymphoma.	6·0	4·3	8·0	Yes	Consensus uncertain	4
Track 1.5: Ann Arbor classification in staging non-Hodgkin lymphoma							
17	Ann Arbor and IPI classifications are an adequate prognostic factor for staging patients with non-Hodgkin lymphoma.	7·0	3·0	7·0	No	No consensus	3
18	Ann Arbor and IPI classifications could be improved by new PET features, such as metabolic tumour volume, to better characterise lymphoma lesions.	9·0	9·0	9·0	Yes	Consensus to agree	2
Track 1.6: follow-up examinations after treatment for aggressive non-Hodgkin lymphoma							
19	During follow-up of aggressive non-Hodgkin lymphoma, clinical examination should be performed.	9·0	9·0	9·0	Yes	Consensus to agree	2
20	During follow-up of aggressive non-Hodgkin lymphoma, CECT or MRI should be performed routinely for up to 24 months.	1·0	1·0	3·0	Yes	Consensus to disagree	5
21	During follow-up of aggressive non-Hodgkin lymphoma, [^{18}F]FDG-PET-CT should be performed routinely for up to 24 months.	1·0	1·0	1·0	Yes	Consensus to disagree	5
Track 1.7: follow-up examinations after treatment for indolent non-Hodgkin lymphoma							
22	During follow-up of indolent non-Hodgkin lymphoma, clinical examination should be performed.	9·0	9·0	9·0	Yes	Consensus to agree	3
23	During follow-up of indolent non-Hodgkin lymphoma, CECT or MRI should be performed routinely for up to 24 months.	1·0	1·0	1·0	Yes	Consensus to disagree	5
24	During follow-up of indolent non-Hodgkin lymphoma, [^{18}F]FDG-PET-CT should be performed routinely for up to 24 months.	1·0	1·0	1·0	Yes	Consensus to disagree	5
Track 1.8: follow-up examinations in suspected non-Hodgkin lymphoma relapse							
25	CECT or MRI should be performed in patients with suspected non-Hodgkin lymphoma relapse.	9·0	7·0	9·0	Yes	Consensus to agree	3
26	[^{18}F]FDG-PET-CT should be performed in patients with suspected relapse of FDG-avid non-Hodgkin lymphoma.	9·0	9·0	9·0	Yes	Consensus to agree	3
27	Patients with low grade lymphoma with clinical suspicion of high grade transformation should undergo [^{18}F]FDG-PET-CT.	9·0	9·0	9·0	Yes	Consensus to agree	3
28	PET-CT can guide biopsy in indolent lymphoma if there is a suspicion of transformation.	9·0	9·0	9·0	Yes	Consensus to agree	3

CECT=contrast-enhanced CT. DLBCL=diffuse large B-cell lymphoma. e-Delphi=online Delphi. FDG=fluorodeoxyglucose. IPI=International Prognostic Index. *Additional statement suggested by panellists in round 1 and scored by all panellists in round 2.

Table 1: **Results after the second round of the e-Delphi on section 1: non-Hodgkin lymphoma**

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In consideration of response assessment in non-Hodgkin lymphoma, the panel agreed that in patients with DLBCL and possibly other [^{18}F]FDG-avid aggressive non-Hodgkin lymphoma, [^{18}F]FDG-PET-CT should be performed for response assessment at interim staging; but there was no consensus regarding interim staging in patients with follicular lymphoma (grade 1–3a) and possibly other [^{18}F]FDG-avid indolent non-Hodgkin lymphoma. After chemotherapy, the panel strongly agreed that [^{18}F]FDG-PET-CT should be performed in both patients with DLBCL and possibly other [^{18}F]FDG-avid aggressive non-Hodgkin lymphoma and in patients with follicular lymphoma (grade 1-3a) and possibly other [^{18}F]FDG-avid indolent non-Hodgkin lymphoma.

Considering that [^{18}F]FDG-PET-CT includes low-dose CT for attenuation correction, no consensus was reached to recommend contrast-enhanced CT (CECT) for response assessment in patients with DLBCL or other [^{18}F]FDG-avid aggressive non-Hodgkin lymphoma. Concerning the statement 999 (which was added during round 1), the panel agreed that the size of lymphoma residual masses should be reported even if there is no [^{18}F]FDG uptake. On the topic of [^{18}F]FDG-PET-CT in decision making for radiotherapy, there was agreement that at the end of chemotherapy, [^{18}F]FDG-PET-CT provides information necessary to decide for or against radiotherapy in DLBCL and possibly other [^{18}F]FDG-avid aggressive non-Hodgkin lymphoma; however,

	Statement	Median score	30th centile	70th centile	Consensus (yes or no)	Interpretation	Number of panellists unable to score
Track 2.1: patient eligibility for staging with [^{18}F]FDG-PET-CT							
29	All patients with Hodgkin lymphoma should undergo staging using [^{18}F]FDG-PET-CT.	9·0	9·0	9·0	Yes	Consensus to agree	2
30	To exclude advanced stages, [^{18}F]FDG-PET-CT can be restricted to presentations of early-stage Hodgkin lymphoma.	1·0	1·0	1·0	Yes	Consensus to disagree	3
31	[^{18}F]FDG-PET-CT should be used in patients with Hodgkin lymphoma to exclude bone marrow involvement instead of bone marrow biopsy.	9·0	9·0	9·0	Yes	Consensus to agree	4
32	Only patients with Hodgkin lymphoma in clinical trials should undergo staging using [^{18}F]FDG-PET-CT.	1·0	1·0	1·0	Yes	Consensus to disagree	2
Track 2.2: use of non-imaging biomarkers, including circulating tumour DNA, protein biomarkers, and tissue genotyping							
33	[^{18}F]FDG-PET-CT should be performed only in centres with EARL-accredited PET-CT scanners.	5·0	1·0	6·4	No	No consensus	3
Track 2.3: the role of [^{18}F]FDG-PET-CT for Hodgkin lymphoma response assessment							
34	A combination of non-imaging blood-based biomarkers and [^{18}F]FDG-PET-CT in Hodgkin lymphoma is promising to further improve response prediction.	8·0	7·0	8·0	Yes	Consensus to agree	4
35	[^{18}F]FDG-PET-CT is necessary for response assessment at interim staging in advanced-stage Hodgkin lymphoma after two rounds of ABVD chemotherapy.	9·0	9·0	9·0	Yes	Consensus to agree	4
36	[^{18}F]FDG-PET-CT is necessary for response assessment at interim staging in advanced stage Hodgkin lymphoma after two rounds of BEACOPP chemotherapy.	9·0	9·0	9·0	Yes	Consensus to agree	4
37	The use of [^{18}F]FDG-PET-CT in Hodgkin lymphoma should be tailored depending on the therapy protocol.	9·0	9·0	9·0	Yes	Consensus to agree	4

(Table 2 continues on next page)

in patients with follicular lymphoma (grade 1–3a) and possibly other [^{18}F]FDG-avid indolent non-Hodgkin lymphoma, the panel was uncertain whether to base the decision for or against radiotherapy on [^{18}F]FDG-PET-CT.

Follow-up

There was agreement within the panel that during follow-up of aggressive non-Hodgkin lymphoma, clinical examination should be performed. However, the panel disagreed that [^{18}F]FDG-PET-CT, CECT, and MRI should be performed routinely for up to 24 months. In the follow-up of indolent non-Hodgkin lymphoma, clinical examination should be performed; the panel also voted against the routine use of CECT, MRI, or [^{18}F]FDG-PET-CT for up to 24 months. Contrastingly, CECT, MRI, and [^{18}F]FDG-PET-CT should be performed in patients with suspected relapse and in patients with [^{18}F]FDG-avid non-Hodgkin lymphoma.

Potential for innovation

Despite the International Prognostic Index (IPI) being the most robust clinical risk factor, there was no consensus on whether Ann Arbor and IPI classifications should be further improved or not, even though PET-assessed metabolic tumour volume (MTV)-supplemented IPI (International Metabolic Prognostic Index [IMPI]) has been described and outperformed the IPI.[9] However, the panel strongly agreed the current staging system might be improved by new PET features, such as dissemination features and MTV. Furthermore, they agreed that non-imaging blood-based markers are worth further investigation to better guide treatment decisions in lymphoma.

Section 2: Hodgkin lymphoma (statements 29–56)

Staging and response assessment with [^{18}F]FDG-PET-CT

The panel strongly agreed that all patients should undergo staging with [^{18}F]FDG-PET-CT without any restriction before the start of treatment, and that [^{18}F]FDG-PET-CT should be used in patients with Hodgkin lymphoma to exclude bone marrow involvement instead of bone marrow biopsy (table 2). Furthermore, the panel strongly agreed that [^{18}F]FDG-PET-CT is necessary for response assessment at interim staging in advanced-stage Hodgkin lymphoma after two cycles of chemotherapy and that the use of [^{18}F]FDG-PET-CT in Hodgkin lymphoma should be tailored depending on the therapy protocol. For all patients with Hodgkin lymphoma, not only in advanced stages, [^{18}F]FDG-PET-CT is seen as the central guiding tool to decide whether or not to treat patients with radiotherapy.

Follow-up

Agreement was achieved that follow-up should be restricted to clinical examination and laboratory blood testing in the routine setting, and CECT, MRI, ultrasound, and [^{18}F]FDG-PET-CT should not be performed routinely. Contrastingly, in patients with suspected relapse, [^{18}F]FDG-PET-CT and CECT should be performed in addition to clinical examination and routine laboratory testing,

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See **Online** for appendix

	Statement	Median score	30th centile	70th centile	Consensus (yes or no)	Interpretation	Number of panellists unable to score
(Continued from previous page)							
Track 2.4: the role of [^{18}F]FDG-PET-CT for decision making in radiotherapy							
38	For all patients with Hodgkin lymphoma, [^{18}F]FDG-PET-CT is necessary when deciding whether to perform radiotherapy.	9·0	7·3	9·0	Yes	Consensus to agree	4
39	[^{18}F]FDG-PET-CT for advanced Hodgkin lymphoma response assessment at the end of BEACOPP chemotherapy can be used to decide for or against radiotherapy.	9·0	9·0	9·0	Yes	Consensus to agree	4
40	[^{18}F]FDG-PET-CT for advanced Hodgkin lymphoma response assessment at the end of ABVD chemotherapy can be used to decide for or against radiotherapy.	9·0	9·0	9·0	Yes	Consensus to agree	4
41	[^{18}F]FDG-PET-CT provides information necessary for making the decision to use or not to use radiotherapy in patients with favourable early-stage Hodgkin lymphoma characteristics.	9·0	4·9	9·0	Yes	Consensus to agree	4
42	[^{18}F]FDG-PET-CT provides information necessary for deciding whether or not to use radiotherapy in patients with unfavourable early-stage Hodgkin lymphoma characteristics.	9·0	9·0	9·0	Yes	Consensus to agree	4
43	[^{18}F]FDG-PET-CT provides information necessary for deciding whether or not to use radiotherapy in patients with advanced-stage Hodgkin lymphoma.	9·0	9·0	9·0	Yes	Consensus to agree	4
44	[^{18}F]FDG-PET-CT is not necessary for the decision for or against radiotherapy in Hodgkin lymphoma.	1·0	1·0	1·0	Yes	Consensus to disagree	3
Track 2.5: the role of Ann Arbor classification for staging							
45	Ann Arbor classification and International Prognostic Score area are an adequate prognostic factor in all patients with Hodgkin lymphoma.	4·0	3·0	6·4	No	No consensus	3
46	Ann Arbor classification alone is inadequate for staging because it does not reflect current diagnostic opportunities.	9·0	8·0	9·0	Yes	Consensus to agree	4
Track 2.6: follow-up examinations							
47	During follow-up of Hodgkin lymphoma, clinical examination should be performed.	7·5	6·0	8·0	Yes	Consensus to agree	0
48	During follow-up of Hodgkin lymphoma, laboratory blood testing should be routinely performed.	8·0	6·5	9·0	Yes	Consensus to agree	0
49	During follow-up of Hodgkin lymphoma, CECT or MRI should be performed routinely for up to 3 years.	1·0	1·0	1·0	Yes	Consensus to disagree	3
50	During follow-up of Hodgkin lymphoma, ultrasound should be performed routinely.	1·0	1·0	1·8	Yes	Consensus to disagree	3
51	During follow-up of Hodgkin lymphoma, [^{18}F]FDG-PET-CT should be performed routinely for up to 3 years.	1·0	1·0	1·0	Yes	Consensus to disagree	3
Track 2.7: follow-up methods in patients with suspected Hodgkin lymphoma relapse							
52	In all patients with suspected Hodgkin lymphoma relapse, clinical examination should be performed.	9·0	9·0	9·0	Yes	Consensus to agree	3
53	In all patients with suspected Hodgkin lymphoma relapse, laboratory testing is mandatory.	9·0	9·0	9·0	Yes	Consensus to agree	3
54	CECT or MRI should be performed in all patients with suspected Hodgkin lymphoma relapse.	9·0	5·0	9·0	Yes	Consensus to agree	3
55	Ultrasound should be performed in all patients with suspected Hodgkin lymphoma relapse.	1·0	1·0	1·0	Yes	Consensus to disagree	3
56	[^{18}F]FDG-PET-CT should be performed in all patients with suspected Hodgkin lymphoma relapse.	9·0	9·0	9·0	Yes	Consensus to agree	3

ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine. BEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. CECT=contrast-enhanced CT. EARL=European Association of Nuclear Medicine Research Limited. e-Delphi=online Delphi. FDG=fluorodeoxyglucose.

***Table 2*: Results of section 2 of the e-Delphi after the second round**

although routine ultrasound does not appear recommended for all patients.

Potential for innovation

The panel strongly agreed that Ann Arbor classification does not reflect current diagnostic opportunities and that the Ann Arbor classification alone is inadequate for staging and risk assessment. However, there was no consensus within the panel on whether Ann Arbor and IPI classifications should be further improved or not.

The aim for standardised imaging was not sufficient for consensus recommendation for European

	Statement	Median score	30th centile	70th centile	Consensus (yes or no)	Interpretation	Number of panellists unable to score
Track 3.1: patient eligibility for staging with [^{18}F]FDG-PET-CT in suspected active multiple myeloma							
57	Patients with suspected active multiple myeloma should undergo staging with [^{18}F]FDG-PET-CT to create a baseline for response assessment.	9·0	7·0	9·0	Yes	Consensus to agree	5
58	Patients with non-secretory multiple myeloma should undergo staging with [^{18}F]FDG-PET-CT to assess the disease burden.	9·0	9·0	9·0	Yes	Consensus to agree	6
59	Patients with suspected active multiple myeloma with lytic lesions at LDCT should undergo staging using [^{18}F]FDG-PET-CT.	9·0	7·0	9·0	Yes	Consensus to agree	6
60	Patients with suspected active multiple myeloma and a positive or equivocal standard or whole-body MRI should undergo staging with [^{18}F]FDG-PET-CT.	9·0	8·0	9·0	Yes	Consensus to agree	6
61	Patients with suspected active multiple myeloma in clinical trials (eg, frontline treatment) should undergo staging with [^{18}F]FDG-PET-CT.	9·0	7·7	9·0	Yes	Consensus to agree	6
62	Patients with multiple myeloma and a strong suspicion of extramedullary disease should undergo staging with [^{18}F]FDG-PET-CT.	9·0	9·0	9·0	Yes	Consensus to agree	6
Track 3.2: eligibility of patients with suspected smouldering multiple myeloma for [^{18}F]FDG-PET-CT							
63	To stratify the risk of progression of smouldering multiple myeloma to active multiple myeloma, patients with smouldering multiple myeloma with negative whole-body LDCT and negative whole-body MRI should undergo [^{18}F]FDG-PET-CT.	5·0	5·0	7·0	Yes	Consensus uncertain	7
64	Patients with smouldering multiple myeloma should not undergo [^{18}F]FDG-PET-CT.	5·0	3·0	5·0	Yes	Consensus uncertain	8
65	Patients with smouldering multiple myeloma should undergo [^{18}F]FDG-PET-CT instead of whole-body LDCT because it provides both morphologic and functional features.	9·0	3·0	9·0	No	No consensus	9
66	Patients with smouldering multiple myeloma should undergo [^{18}F]FDG-PET-CT instead of whole-body MRI.	3·0	3·0	3·0	Yes	Consensus to disagree	9
67	Patients with smouldering multiple myeloma with only a single focal lesion in whole-body MRI, a lesion <5 mm in LDCT, or equivocal lesions in whole-body MRI or LDCT should undergo [^{18}F]FDG-PET-CT.	7·0	7·0	8·8	Yes	Consensus to agree	8
Track 3.3: patients with MGUS with eligibility for [^{18}F]FDG-PET-CT							
68	Patients with MGUS should not undergo [^{18}F]FDG-PET-CT.	8·0	8·0	9·0	Yes	Consensus to agree	6
69	Patients with MGUS of low risk should undergo [^{18}F]FDG-PET-CT.	1·0	1·0	1·0	Yes	Consensus to disagree	6
70	Patients with MGUS of high risk should undergo [^{18}F]FDG-PET-CT.	1·0	1·0	1·0	Yes	Consensus to disagree	6
71	All patients with MGUS should undergo [^{18}F]FDG-PET-CT.	1·0	1·0	1·0	Yes	Consensus to disagree	6

(Table 3 continues on next page)

Association of Nuclear Medicine Research Limited (EARL) accreditation of all PET-CT scanners, but it was acknowledged that the combination of non-imaging blood-based biomarkers and [^{18}F]FDG-PET-CT in Hodgkin lymphoma is promising to further improve response prediction.

Section 3: multiple myeloma (statements 57–123)

Of the 15 statements that did not reach consensus, 7 (46%) pertained to the section on multiple myeloma (table 3). The most controversial statement was on the sequence of PET-CT in active multiple myeloma. Regarding the staging of suspected active multiple myeloma, panellists agreed on the use of [^{18}F]FDG-PET-CT in all patients (ie, with both secretory and non-secretory disease) regardless of the result of other imaging procedures, such as low-dose CT (LDCT) and MRI. On the contrary, the panel's opinion on smouldering myeloma or monoclonal gammopathy of undetermined significance (MGUS) was that no [^{18}F]FDG-PET-CT should be performed, except for those patients with one small lesion or equivocal findings at LDCT or MRI. No definitive agreement was reached on the timepoints of [^{18}F]FDG-PET-CT scan during active disease history.

Strong agreement was found on the need for a standardised report at staging that outlines the number and size of lytic lesions on LDCT, fractures on LDCT, the exact number of [^{18}F]FDG-PET-CT positive focal lesions (grouped 0, 1–3, or >3), the maximum standardised uptake value (SUV_{max}) of the hottest focal lesion, increased diffuse uptake in the bone marrow,

	Statement	Median score	30th centile	70th centile	Consensus (yes or no)	Interpretation	Number of panellists unable to score
(Continued from previous page)							
Track 3.4: sequence of [^{18}F]FDG-PET-CT scans in patients with active multiple myeloma							
72	The optimal sequence is: staging PET, interim PET (after induction), end-of-therapy PET (pre-maintenance), yearly during maintenance.	3·0	3·0	3·0	Yes	Consensus to disagree	9
73	The optimal sequence at suspected relapse is: staging PET then end-of-therapy PET (pre-maintenance).	7·0	3·0	8·0	No	No consensus	9
74	The optimal sequence is: staging PET then end-of-therapy PET (pre-maintenance), yearly during maintenance.	3·0	3·0	3·0	Yes	Consensus to disagree	9
75	The optimal sequence is: staging PET then end-of-therapy PET (pre-maintenance) if staging PET was positive, yearly during maintenance if end-of-therapy PET was positive.	9·0	3·0	9·0	No	No consensus	9
76	The optimal sequence is: staging PET then end-of-therapy PET (pre-maintenance; if staging PET was positive) when relapse is suspected if end of therapy PET was negative.	9·0	3·0	9·0	No	No consensus	9
77	The optimal sequence is: staging PET then end-of-therapy PET (pre-maintenance), yearly during maintenance if end-of-therapy PET was positive.	3·0	3·0	3·4	Yes	Consensus to disagree	9
78	The optimal sequence is: staging PET then end-of-therapy PET (pre-maintenance) when relapse is suspected if end-of-therapy PET was negative.	7·0	3·0	9·0	No	No consensus	9
Track 3.5: reporting of staging outcomes for patients with active multiple myeloma							
79	In patients with active multiple myeloma, the number and size of lytic lesions on LDCT should be reported.	9·0	8·0	9·0	Yes	Consensus to agree	4
80	In patients with active multiple myeloma, fractures on LDCT should be reported.	9·0	9·0	9·0	Yes	Consensus to agree	4
81	In patients with active multiple myeloma, the exact number of [^{18}F]FDG-PET-CT positive focal lesions (grouped 0, 1–3, or >3) should be reported.	9·0	9·0	9·0	Yes	Consensus to agree	4
82	In patients with active multiple myeloma, the SUV_{max} of the hottest focal lesion should be reported.	9·0	8·0	9·0	Yes	Consensus to agree	5
83	In patients with active multiple myeloma, increased diffuse uptake in the bone marrow should be reported.	9·0	8·0	9·0	Yes	Consensus to agree	5
84	In patients with active multiple myeloma, locations with substantially increased risk of fracture on LDCT should be reported.	9·0	9·0	9·0	Yes	Consensus to agree	4
Track 3.6: reporting of outcomes during or after therapy							
85	During or after therapy of multiple myeloma, the number and size of lytic lesions on LDCT independent of [^{18}F]FDG uptake should be reported only if increased as compared with baseline measurements.	9·0	8·0	9·0	Yes	Consensus to agree	8
86	During or after therapy of multiple myeloma, fractures on LDCT should be reported.	9·0	9·0	9·0	Yes	Consensus to agree	5
87	During or after therapy of multiple myeloma, the exact number of [^{18}F]FDG-PET-CT positive focal lesions (grouped 0, 1–3, or >3) should be reported and compared with baseline measurements.	9·0	9·0	9·0	Yes	Consensus to agree	7
88	During or after therapy of multiple myeloma, the SUV_{max} of the hottest focal lesion should be reported.	9·0	8·4	9·0	Yes	Consensus to agree	7
89	During or after therapy of multiple myeloma, increased diffuse uptake in the bone marrow should be reported.	9·0	9·0	9·0	Yes	Consensus to agree	8
90	During or after therapy of multiple myeloma, decreases in the number and size of [^{18}F]FDG-PET-CT positive focal lesions (ie, bony, paramedullary, or extramedullary), along with the Deauville score of the hottest focal lesion, should be reported.	9·0	8·4	9·0	Yes	Consensus to agree	7
91	During or after therapy of multiple myeloma, the change of SUV_{max} and Deauville score of the hottest focal lesion and a decrease of diffuse uptake in the bone marrow should be reported.	9·0	8·1	9·0	Yes	Consensus to agree	8

(Table 3 continues on next page)

and locations with substantially increased risk of fracture on LDCT. The panel also agreed that a standardised report is required during and after therapy to document the number and size of lytic lesions on LDCT independent of [^{18}F]FDG uptake, only if increased as compared with the baseline; fractures on LDCT; the exact number of [^{18}F]FDG-PET-CT positive focal lesions (grouped 0, 1–3, or >3) and compared with the baseline;

	Statement	Median score	30th centile	70th centile	Consensus (yes or no)	Interpretation	Number of panellists unable to score
(Continued from previous page)							
Track 3.7: eligibility criteria of patients with suspected solitary plasmacytoma to undergo [^{18}F]FDG-PET-CT							
92	All patients with suspected solitary plasmacytoma of the bone should undergo [^{18}F]FDG-PET-CT.	9·0	9·0	9·0	Yes	Consensus to agree	7
93	All patients with extramedullary solitary plasmacytoma should undergo [^{18}F]FDG-PET-CT.	9·0	9·0	9·0	Yes	Consensus to agree	7
94	Only when contraindications for whole-body MRI are present should patients undergo [^{18}F]FDG-PET-CT.	1·0	1·0	1·0	Yes	Consensus to disagree	7
95	All patients with only one lesion detected by whole-body MRI should undergo [^{18}F]FDG-PET-CT.	9·0	8·1	9·0	Yes	Consensus to agree	8
96	The use of [^{18}F]FDG-PET-CT might not be dependent on availability.	5·0	3·0	8·0	No	No consensus	7
97	The use of [^{18}F]FDG-PET-CT should be dependent on approval or label.	2·0	2·0	4·2	Yes	Consensus to disagree	7
Track 3.8: eligibility criteria of patients with active multiple myeloma for PET imaging with [^{18}F]fluorochlorine and [^{11}C]choline or [^{11}C]methionine for staging							
98	All patients, regardless of the result of [^{18}F]FDG-PET-CT, should undergo PET imaging with [^{18}F]fluorochlorine and [^{11}C]choline or [^{11}C]methionine to improve the lesion detection rate.	1·0	1·0	1·0	Yes	Consensus to disagree	11
99	All patients with negative [^{18}F]FDG-PET-CT, but with lytic lesions detected by LDCT, should undergo imaging with [^{18}F]fluorochlorine and [^{11}C]choline or [^{11}C]methionine.	2·0	1·0	3·0	Yes	Consensus to disagree	11
100	All patients with negative [^{18}F]FDG-PET-CT should undergo imaging with [^{18}F]fluorochlorine and [^{11}C]choline or [^{11}C]methionine.	2·0	1·0	3·0	Yes	Consensus to disagree	11
101	All patients with diabetes, regardless of the result of [^{18}F]FDG-PET-CT, should undergo imaging with [^{18}F]fluorochlorine and [^{11}C]choline or [^{11}C]methionine to improve the lesion detection rate.	1·0	1·0	1·8	Yes	Consensus to disagree	11
102	There is no clinical need for performing imaging with [^{18}F]fluorochlorine and [^{11}C]choline or [^{11}C]methionine.	8·0	5·2	8·8	Yes	Consensus to agree	11
Track 3.9: the PET field of view in the context of multiple myeloma affecting the skeleton and extramedullary sites							
103	The PET field of view in multiple myeloma should cover from the top of the head to the feet with arms down.	9·0	9·0	9·0	Yes	Consensus to agree	6
104	The PET field of view in multiple myeloma should cover from the top of the head to the proximal metaphysis of the tibia with arms down.	1·0	1·0	1·0	Yes	Consensus to disagree	7
105	The PET field of view in multiple myeloma should cover from the orbitae to the feet with arms down. The typical brain uptake reduces the detection rate for skull lesions substantially.	1·0	1·0	1·0	Yes	Consensus to disagree	8
106	The PET field of view in multiple myeloma should cover from the orbitae to the mid femurs with arms down. The typical brain uptake reduces the detection rate for skull lesions.	1·0	1·0	1·0	Yes	Consensus to disagree	8
107	The PET field of view in multiple myeloma should be as standard (from the orbitae to the groin with arms up).	1·0	1·0	1·0	Yes	Consensus to disagree	8
108	The PET field of view in multiple myeloma can be variable depending on the patient characteristics (ie, soma and compliance because of bone pain).	3·0	3·0	7·0	No	No consensus	8
Track 3.10: pathology reporting of diffuse bone marrow uptake							
109	Bone marrow uptake should be reported as pathological in multiple myeloma when it is visually higher than the mediastinal blood pool.	3·0	2·8	5·2	Yes	Consensus to disagree	9
110	Bone marrow uptake should be reported as pathological in multiple myeloma when it is visually higher than the normal liver uptake.	9·0	7·8	9·0	Yes	Consensus to agree	9
111	Bone marrow uptake should be reported as pathological in multiple myeloma if SUV_{max} in L3 measured outside focal lesions is ≥2·5.	3·0	3·0	3·0	Yes	Consensus to disagree	11
112	Bone marrow uptake should be reported as pathological in multiple myeloma if SUV_{mean} in L3 measured outside focal lesions is ≥2·5.	3·0	2·9	3·0	Yes	Consensus to disagree	12
113	Bone marrow uptake should be reported as pathological in multiple myeloma when there is an increased diffuse uptake in the bone marrow of limbs associated to that of the axial skeleton.	5·0	1·0	5·0	Yes	Consensus uncertain	12
114	Bone marrow uptake should not be reported as pathological because it is not specific.	1·0	1·0	1·0	Yes	Consensus to disagree	9

(Table 3 continues on next page)

	Statement	Median score	30th centile	70th centile	Consensus (yes or no)	Interpretation	Number of panellists unable to score
(Continued from previous page)							
Track 3.11: measurement of MTV and TLG with [^{18}F]FDG-PET-CT							
115	MTV and TLG in patients with multiple myeloma are potentially informative variables, but there is little standardisation. There is no application in clinical practice at present.	9·0	9·0	9·0	Yes	Consensus to agree	7
116	MTV and TLG in multiple myeloma should only be reported for staging PET.	3·0	3·0	5·2	Yes	Consensus to disagree	9
117	MTV and TLG in multiple myeloma should always be reported. Regardless of how they are measured, the trend during and after therapy is a risk stratification factor.	1·0	1·0	2·6	Yes	Consensus to disagree	7
118	Measurement of MTV and TLG is time-consuming so their role is confined to clinical trials.	7·0	7·0	7·0	Yes	Consensus to agree	7
Track 3.12: definitions of complete normalisation of [^{18}F]FDG-PET-CT in multiple myeloma at the end of therapy							
119	A complete normalisation of [^{18}F]FDG-PET-CT in multiple myeloma at the end of therapy can be seen if there is no measurable uptake in previous hot focal lesions, no measurable diffuse uptake in the bone marrow, and no new lytic lesions in LDCT images.	9·0	8·0	9·0	Yes	Consensus to agree	11
120	A complete normalisation of [^{18}F]FDG-PET-CT in multiple myeloma at the end of therapy can be seen if uptake in previous hot focal lesions and diffuse uptake in the bone marrow are visually below the liver uptake.	9·0	9·0	9·0	Yes	Consensus to agree	11
121	A complete normalisation of [^{18}F]FDG-PET-CT in multiple myeloma at the end of therapy can be seen if uptake in previous hot focal lesions and diffuse uptake in the bone marrow are visually below the mediastinal blood pool uptake.	3·0	3·0	6·0	Yes	Consensus to disagree	11
122	A complete normalisation of [^{18}F]FDG-PET-CT in multiple myeloma at the end of therapy can be seen if the SUV_{max} uptake in previous hot focal lesions and diffuse uptake in the bone marrow decrease to less than 2·5.	3·0	3·0	4·5	Yes	Consensus to disagree	10
123	A complete normalisation of [^{18}F]FDG-PET-CT in multiple myeloma at the end of therapy can be seen if the uptake in previous hot focal lesions and diffuse uptake in the bone marrow are visually below the liver uptake and the bone is completely normal at LDCT.	3·0	1·0	3·0	Yes	Consensus to disagree	11

e-Delphi=online Delphi. FDG=fluorodeoxyglucose. LDCT=low-dose CT. MGUS=monoclonal gammopathy of undetermined significance. MTV=metabolic tumour volume. TLG=total lesion glycolysis. SUVmax=maximum standardised uptake value.

***Table 3*: Results after the second round of the e-Delphi on section 3: multiple myeloma**

the SUV_{max} of the hottest focal lesion; increased diffuse uptake in the bone marrow; decreases in number and size of [^{18}F]FDG-PET-CT positive focal lesions (ie, bony, paramedullary, and extramedullary) along with the Deauville score of the hottest focal lesion; the change of SUV_{max} and Deauville score of the hottest focal lesion; and the decrease of diffuse uptake in the bone marrow.

The panel agreed that all patients with solitary plasmacytoma located in the bone or in extramedullary areas should undergo [^{18}F]FDG-PET-CT, including those with only one lesion detected by whole-body MRI. However, there was no consensus among the panellists on the opportunity to include [^{18}F]FDG-PET-CT in the testing of the patient depending on its availability, but they agreed that the use of [^{18}F]FDG-PET-CT should not be dependent on approval or label. The panel agreed that there is currently not enough evidence supporting the need to perform any other tracer than [^{18}F]FDG (statements 98–102) in routine clinical practice because of a current absence of data.

The panel agreed that the [^{18}F]FDG-PET-CT field of view should cover from top of the head to feet with arms down. Regarding the reporting system at staging, the panel agreed that diffuse bone marrow uptake should be reported when it is visually higher than the normal liver uptake, but the utility of increased diffuse uptake in the bone marrow of limbs associated to that of the axial skeleton remains uncertain.

The measurement of MTV and total lesion glycolysis (TLG) was considered to be currently confined to clinical trials and should not be routinely reported. At the end of therapy, a complete normalisation of [^{18}F]FDG-PET-CT in multiple myeloma can be seen if the uptake in previous hot focal lesions and bone marrow are not measurable or are visually lower than the liver and no new lytic lesions in LDCT images are present.

For the evaluation of minimal residual disease, [^{18}F]FDG-PET-CT should be performed even in patients with negative multiparametric flow cytometry or genomic tests on bone marrow aspiration. There was no consensus on whether [^{18}F]FDG-PET-CT is fundamental if multiparametric-flow cytometry genomic tests are positive on bone marrow aspiration. [^{18}F]FDG-PET-CT and multiparametric-flow cytometry genomic tests on bone marrow

	Statement	Median score	30th centile	70th centile	Consensus (yes or no)	Interpretation	Number of panellists unable to score
Track 4.1: [^{68}Ga]CXCR4 imaging in active multiple myeloma							
124	All multiple myeloma patients, regardless of the result of [^{18}F]FDG-PET-CT, will benefit from [^{68}Ga]CXCR4 imaging because it will improve the lesion detection rate.	1·0	1·0	3·0	Yes	Consensus to disagree	8
125	[^{18}F]FDG-PET-CT is fundamental after therapy even if multiparametric flow cytometry, next generation flow, or next generation sequencing are negative on bone marrow aspiration.	8·0	6·6	9·0	Yes	Consensus to agree	9
126	[^{18}F]FDG-PET-CT is fundamental after therapy even if multiparametric flow cytometry, next generation flow, or next generation sequencing are positive on bone marrow aspiration.	6·0	2·0	9·0	No	No consensus	10
127	[^{18}F]FDG-PET-CT and multiparametric flow cytometry, next generation flow, or next generation sequencing after therapy provides a stronger patient stratification as compared with each technique taken alone.	8·5	7·5	9·0	Yes	Consensus to agree	10
128	All patients with multiple myeloma, regardless of the result of [^{18}F]FDG-PET-CT, will benefit from [^{68}Ga]CXCR4 imaging because it will improve the lesion detection rate.	1·0	1·0	1·0	Yes	Consensus to disagree	13
129	All patients with multiple myeloma with negative [^{18}F]FDG-PET-CT but lytic lesions at LDCT will benefit from [^{68}Ga]CXCR4 imaging.	1·0	1·0	1·0	Yes	Consensus to disagree	13
130	No patients with multiple myeloma will benefit from [^{68}Ga]CXCR4 imaging.	2·0	1·0	3·8	Yes	Consensus to disagree	13
131	[^{68}Ga]CXCR4 is clinically relevant only in the light of a subsequent radiometabolic therapy.	6·0	5·0	8·0	Yes	Consensus uncertain	13
Track 4.2: the role of [^{90}Y]ibritumomab tiuxetan and [^{177}Lu]lilotomab satetraxetan in non-Hodgkin lymphoma							
132	[^{90}Y]ibritumomab tiuxetan should only be used in clinical trials.	3·0	2·0	3·0	Yes	Consensus to disagree	7
133	[^{90}Y]ibritumomab tiuxetan is a standard treatment for patients with relapsed or refractory follicular lymphoma [^{177}Lu].	7·0	5·0	7·0	Yes	Consensus to agree	7
134	[^{177}Lu]lilotomab satetraxetan can be expected to be the standard in the treatment of non-Hodgkin lymphoma.	3·0	3·0	4·6	Yes	Consensus to disagree	7
135	PD-1 PET-CT imaging is urgently needed to further improve response prediction in lymphoma.	7·0	4·3	7·0	Yes	Consensus to agree	4
136	Immunotherapies substantially influence [^{18}F]FDG-PET-CT imaging in first-line treatment of lymphoma.	7·0	7·0	7·0	Yes	Consensus to agree	4
Track 4.3: evaluation of patients with Hodgkin lymphoma under checkpoint-inhibiting immunotherapy with [^{18}F]FDG-PET-CT							
137	Patients with Hodgkin lymphoma who are scheduled for immunotherapy should undergo [^{18}F]FDG-PET-CT before starting treatment.	9·0	9·0	9·0	Yes	Consensus to agree	3
138	Patients with Hodgkin lymphoma who undergo immunotherapy should undergo restaging with [^{18}F]FDG-PET-CT after 4 months.	8·0	8·0	9·0	Yes	Consensus to agree	4
139	Patients with Hodgkin lymphoma who undergo immunotherapy should undergo restaging with [^{18}F]FDG-PET-CT after 8 months.	8·0	8·0	8·0	Yes	Consensus to agree	5

e-Delphi=online Delphi. FDG=fluorodeoxyglucose. LDCT=low-dose CT.

Table 4: **Results after the second round of the e-Delphi on section 4: nuclear medicine and therapy in haematological malignancies**

provide a stronger patient stratification as compared with each technique taken alone.

Section 4: nuclear medicine and therapy in haematological malignancies (statements 124–139)

When considering the role of nuclear medical therapies, agreement was made that therapy with [^{90}Y] ibritumomab tiuxetan (ie, ZEVALIN [Bayer; Newbury, UK]) has not become a standard for most patients with non-Hodgkin lymphoma, but can be used as an option for patients with relapsed or refractory follicular lymphoma (table 4). Contrastingly, the role of [^{68}Ga] CXCR4-ligand remained somewhat unclear, even in patients with multiple myeloma in whom CXCR4-expression might be clinically relevant considering a subsequent radiotheranostic approach. Here it appears that the [^{68}Ga]CXCR4-specific radioligand treatment for multiple myeloma has not yet become an international standard and more clinical data and scientific research are needed.

	Statement	Median score	30th centile	70th centile	Consensus (yes or no)	Interpretation	Number of panellists unable to score
Track 5.1: new targets for therapy and diagnosis							
140	AI can be routinely used to guide therapeutic decisions.	1·0	1·0	2·8	Yes	Consensus to disagree	1
141	Radiomics can provide further prognostic parameters that might be included in nomograms to refine risk stratification.	7·0	7·0	7·0	Yes	Consensus to agree	2
142	Radiomics should be included in standard PET reporting.	3·0	1·2	3·0	Yes	Consensus to disagree	1
143	The use of radiomics requires the standardisation of PET images or of PET features.	9·0	8·2	9·0	Yes	Consensus to agree	1
144	AI models have the advantage of being fully explainable.	1·0	1·0	3·0	Yes	Consensus to disagree	3
145	The standardisation of MTV and TLG measurement is essential for providing reproducible new prognostic biomarkers.	9·0	8·0	9·0	Yes	Consensus to agree	2
146	The standardisation of PET imaging is essential to provide robust implementation of the diagnostic testing.	9·0	8·0	9·0	Yes	Consensus to agree	1
147	Staging of patients with Hodgkin lymphoma and non-Hodgkin lymphoma with [^{18}F]FDG-PET-CT should only be done in centres with EARL-accredited PET-CT scanners.	7·0	1·0	7·0	No	No consensus	5
Track 5.2: The possible role of [^{68}Ga]FAPI-PET-CT once more evidence becomes available							
148	[^{68}Ga]FAPI-PET-CT will be used for staging of patients with Hodgkin lymphoma and high-grade non-Hodgkin lymphoma instead of [^{18}F]FDG-PET-CT.	1·0	1·0	2·9	Yes	Consensus to disagree	8
149	[^{68}Ga]FAPI-PET-CT will be used for staging low-grade non-Hodgkin lymphoma instead of [^{18}F]FDG-PET-CT.	2·0	1·0	4·8	Yes	Consensus to disagree	8
150	[^{68}Ga]FAPI-PET-CT will be used for driving FAPI-based therapy in refractory patients without any other therapeutic options.	3·0	2·0	5·0	Yes	Consensus to disagree	9
Track 5.3: the possible role of [^{18}F]fluciclovine-PET-CT once more evidence becomes available							
151	[^{18}F]fluciclovine-PET-CT should be used for staging of patients with Hodgkin lymphoma and non-Hodgkin lymphoma when renal localisation is suspected.	2·5	1·0	3·0	Yes	Consensus to disagree	10
152	[^{18}F]fluciclovine-PET-CT will be used for staging and restaging low-grade lymphomas.	3·0	2·0	4·0	Yes	Consensus to disagree	10
153	[^{18}F]fluciclovine-PET-CT could be an option for the evaluation of brain lymphomas.	5·0	3·4	7·6	No	No consensus	11

EARL=European Association of Nuclear Medicine Research Limited. e-Delphi=online Delphi. FAPI=fibroblast activation protein inhibitor. FDG=fluorodeoxyglucose. MTV=metabolic tumour volume. TLG=total lesion glycolysis.

***Table 5*: Results after the second round of the e-Delphi on section 5: radiomics, AI (including machine learning), and standardisation**

So far, the relatively new tracers [^{68}Ga]fibroblast activation protein inhibitor (FAPI) and [^{18}F]fluciclovine are not seen as potential candidates for staging in patients with lymphoma, even if they might support a specific theranostic treatment.

The panel agreed that new treatment opportunities, such as immune checkpoint inhibition, might have an influence on [^{18}F]FDG-PET-CT imaging and they were interested concerning the clinical introduction of a [^{68}Ga] PD-1-specific PET radiotracer. However, in the meantime, [^{18}F]FDG-PET-CT remains the standard for staging before treatments start and under ongoing treatment (eg, after 4 and 8 months).

Section 5: radiomics, artificial intelligence (AI; including machine learning) and standardisation (statements 140–153)

The panel did not identify a radiomic signature that should be included in standard PET reporting (table 5). The panel acknowledged that prognostic information obtained by AI and machine learning is not always fully explainable. There was agreement that the use of radiomics requires standardisation of PET images or of PET features, including MTV and TLG measurement, to provide a robust implementation of the diagnostic tests. There was no consensus on the point of whether staging Hodgkin lymphoma and non-Hodgkin lymphoma with [^{18}F]FDG-PET-CT should only be done in centres with EARL-accredited PET-CT scanners, which would ensure the comparability and harmonisation of image quality.

Discussion

After two modified Delphi rounds and an email discussion within the expert panel in preparation of the manuscript, the main findings emerging from our study are discussed. Importantly, the Delphi results could not be overturned in the discussion process so as not to introduce bias. The email discussion was to

ensure clarity and interpretation, not to supersede the Delphi results.

Non-Hodgkin lymphoma

Staging and response assessment with [18F]FDG-PET-CT has become a consensual standard in non-Hodgkin lymphoma.[1,10–17] However, there remains room for discussion concerning interim staging in patients with follicular lymphoma (grade 1–3a) and possibly other [18F]FDG-avid indolent non-Hodgkin lymphoma and whether to use or not use additional CECT for staging and response assessment.[18]

Although the decision for or against radiotherapy might be based on the end-of-chemotherapy in DLBCL and possibly other [18F]FDG-avid aggressive non-Hodgkin lymphoma,[19] further research appears to be needed in patients with follicular lymphoma (grade 1–3a) and possibly other [18F]FDG-avid indolent non-Hodgkin lymphoma. At the same time, it became clear during repetitive discussions that follow-up examinations, including [18F]FDG-PET-CT, CECT, and MRI, should be restricted to patients with suspected relapse.[20]

The greatest potential for innovation was concordantly seen in the MTV measurement,[9,21,22] and further investigation to better guide treatment decisions with PET and non-PET biomarkers are awaited.

Hodgkin lymphoma

Staging and response assessment with [18F]FDG-PET-CT is the standard of care in patients with Hodgkin lymphoma and might allow for treatment escalation, de-escalation, and the decision for or against radiotherapy.[23–33] Concerning patient follow-up, the view of the panel was to restrict use of PET to patients with suspected relapse.[34–37] Risk assessment might be further improved by the use of non-imaging blood-based biomarkers and [18F]FDG-PET-CT in Hodgkin lymphoma, even though additional data are required.[38,39]

Multiple myeloma

[18F]FDG-PET-CT is recognised as standard of care in patients with active multiple myeloma at staging due to its great prognostic value and accurate morphological evaluation of the skeleton (ie, LDCT). After therapy, [18F]FDG-PET-CT should be performed to provide a deep therapy assessment regardless the result of multiparametric-flow cytometry or genomic tests on bone marrow aspiration. However, the subsequent timepoints of PET imaging during follow-up remains controversial. This controversy is certainly because of the high number of experts who declared to be unable to score, meaning each expert's opinion had a heavier weighting in the analysis of consensus. The high number of panellists who were unable to score was somewhat predictable because there is no literature available suggesting a diagnostic FDG-PET-CT flowchart on the basis of clinical results during the whole history of the disease; there is only expert recommendation from the International Myeloma Working Group with a negligible amount of evidence.[40] Although FDG-PET-CT has shown its added value at staging and pre-maintenance, there are very few papers taking into consideration its detection rate after the first-line treatment, its clinical effect, and its prognostic relevance. Therefore, from one perspective, the use of FDG-PET-CT after the first line relies on PET performance extrapolated from the testing phase, and from the other side, on the reimbursement and accessibility at disease relapse that is certainly different in different countries.

One important point in favour of [18F]FDG-PET-CT in multiple myeloma is the high degree of standardisation in terms of both technical variables (eg, field of view, SUV harmonisation, and timing of image acquisition) and image reading and interpretation (ie, which finding should be reported and how), making this accurate test reproducible despite some complexity of image reading.

There are some open issues on the use of non-FDG tracers for multiple myeloma, which provides a higher rate of detection at staging compared with [18F]FDG, but of which the clinical effect remains unclear. In parallel, the report of metabolic volumes is not considered mandatory due to an absence of standardisation of measurement.

Beside multiple myeloma, [18F]FDG-PET-CT is considered effective in patients with solitary plasmacytoma of the bone or of extramedullary sites to rule out other lesions, although no consensus was reached on the opportunity to include it in the patient's assessment. So far, there is no role for [18F]FDG-PET-CT in patients with monoclonal gammopathy of undetermined significance or smoldering multiple myeloma.

Nuclear medicine and therapy in haematological malignancies

Other than [90Y]ibritumomab tiuxetan for the treatment of lymphoma, the use of nuclear medical methods in haematological malignancies remains restricted despite [68Ga]CXCR4-specific radioligand treatment for multiple myeloma showing promising data.[41,42] Although there is potential for new targets and new tracers, none are currently fit for use as an alternative to standard FDG-PET imaging.

Radiomics, AI (including machine learning), and standardisation

Although AI including machine learning are promising techniques to assist image analysis, their use is not yet recommended to guide therapeutic decisions. The translation of AI into clinical routine is limited because prognostic information obtained by AI and machine learning is not always fully explainable.

Limitations

Although expert consensus is low-certainty evidence, we have controlled for group processes and dominant voices through anonymised voting and controlled feedback in the

e-Delphi process. Furthermore, for some statements, a relatively large proportion of the panellists chose the unable to score option. This option can be explained by the wide-ranging scope of the consensus statements and that no individual panellist was likely to be an expert in every topic. Even though face-to-face communication between panellists was restricted, the wide variety of experts in the field nominated by EANM provides a high breadth and depth of expertise, and communication via email was encouraged during the discussion process and the preparing of the manuscript. We feel that, on balance, the wide scope of the consensus statements and their implications for improving interim guidance is warranted despite some panellists not feeling well enough informed to answer some questions.

This study was conducted on behalf of EANM and most invited experts were from Europe; therefore, the results are most applicable to Europe. However, our intent has been to include high-level experts both in the field of lymphoma and myeloma, so expertise independent of country or continent of practice was also sought. Nonetheless, the applicability of the results to areas other than Europe should be interpreted by clinical practitioners in those areas.

Conclusion

There was consensus within the expert panel on 90% of the 154 statements. Consensus was especially clear for the use of FDG-PET in non-Hodgkin and Hodgkin lymphoma. Regarding multiple myeloma, there were some statements with less consensus among the expert panel, indicating that further research is needed before a standard-of-care imaging protocol can be proposed. MTV is a biomarker obtained by FDG-PET imaging, which provides additional prognostic information that is desired by both diagnostic and treating physicians in all haematological malignancies.

Contributors

KH and JK conceptualised the project. CN, CK, and SM did the project administration. KH, JK, CN, CK, and SM supervised the project. SM did the investigation, methodology, formal analysis, and visualisation of the Delphi process. GT did the investigation of the systematic review. CN, CK, SM, and GT wrote the original draft of the manuscript, and SM, GT, KH, JK, BB, CB, RB, PB, AB, IB, BC, BDC, RC, A-SC, UD, LE, MH, WJ, FK-B, EL, SL, NGM, MN, PR-O, NW, EZ, PLZ, and JMZ were involved in the review and edit of the manuscript. All authors except GT and SM were on the experts panel and were research participants.

Declaration of interests

IB has received research grants from Dosisoft, GE Healthcare, and Siemens Healthineers, and is a member of the Society of Nuclear Medicine and Molecular Imaging Artificial Intelligence Task Force. BC has received research support from GWT and Technical University of Dresden, and won a 2021 Gilead Oncology Award to support his research; has received consulting fees from and is on the data safety monitoring board for Roche, BMS, Regeneron, and ADC; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Roche, BMS, and Astra Zeneca; has received support for travel from Gilead; has submitted patents for molecular subclassification of DLBCL; and declares that he is a speaker of the Aggressive Lymphoma working group and is a steering board member of the German Lymphoma Alliance. UD has received institutional funding from Celgene and has served as a member of the Data Safety Monitoring Board for Amgen and Avencell Europe. EL has received grants from AIRC and the Italian Ministry of Health, royalties from Springer, and honoraria for lectures at the European Society of Molecular Imaging, Therapy and Molecular Imaging, and Therapy congresses. MN has received a research grant from Takeda. PR-O has received honoraria from Amgen, Bristol-Myers Squibb, Glaxo SmithKline, Janssen, Regeneron, and Sanofi, and has served as a member of the data safety monitoring board for Bristol-Myers Squibb, Glaxo SmithKline, Janssen, Oncopeptides, Pfizer, Sanofi, and Takeda. EZ has received honoraria from Amgen, Bristol Myers Squibb, Janssen, and Takeda. PLZ has received honoraria from and has participated on advisory boards or data safety monitoring boards for AstraZeneca, Beigene, Bristol Myers Squibb, Eusapharma, Gilead, Incyte, Janssen, Kyowa Kirin, Merck, Mundipharma, Novartis, Roche, Sanofi, and Takeda. KH reports personal fees from Adacap, Ktis Oncology, Amgen, Bayer, Curium, Endocyte, Ipsen, GE Healthcare, Novartis, Pharma15, Siemens Healthineers, SIRTEX, Theragnostics, and ymabs; personal fees and other from Sofie Biosciences; grants and personal fees from BTG; and non-financial support from ABX outside the submitted work. JK has received consulting fees from Telix and has served as a member of the data safety monitoring board for Novartis. All other authors declare no competing interests.

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