GID-HTG10153 MMprofiler for estimating risk in newly diagnosed multiple myeloma

Final Protocol

Produced by: **Newcastle External Assessment Group (EAG)**

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1. Decision problem

Table 1 summarises the decision problem to be addressed in this assessment. Further detail on each element can be found in the published scope for the assessment.

Table 1. Summary table of the decision problem

Item	Description	EAG comments
Population(s)	People with newly diagnosed multiple myeloma who are being considered for an autologous stem cell transplant pathway.	Technology indications for use include patients with relapsed multiple myeloma, and unsuitable for stem cell transplant; therefore, evidence in this population will need considering and excluding based on clinical feedback. The EAG would interpret eligibility for stem cell transplant as being eligible for the stem cell transplant pathway determined at the point of diagnosis. The EAG note that eligibility for the stem cell transplant pathway may change over time. The EAG also note that allogenic transplant is used rarely in the NHS.
Intervention(s)	MMprofiler in addition to standard care prognostic testing.	MMprofiler (SkylineDx BV) is an RNA-based gene expression profiling test. Older names of the technologies will be sought from the company and incorporated in the literature search strategy and inclusion/exclusion criteria.
Comparators	Standard care for prognostic testing which may include: • assessing a combination of serum biomarkers (beta-microglobulin, albumin and lactate dehydrogenase) • identifying adverse risk abnormalities using FISH or other validated DNA-based tests	Thresholds of serum β-2 microglobulin and albumin markers are stated in the International Staging System (ISS) for multiple myeloma. Thresholds of serum β-2 microglobulin, albumin, cancer gene abnormalities (cytogenetic abnormalities) and lactate dehydrogenase levels (LDH) are stated in the Revised International Staging System (R-ISS) for multiple myeloma. The International Myeloma Society International Myeloma Working Group Consensus Genomic Staging of high risk multiple myeloma is

		stated in Avet-Louiseau et al. 2025; which also includes genetic factors.
Setting	Genomic laboratory hubs (GLHs)	The EAG note that there are 7 regional NHS GLHs (NHS England, Genomic Laboratory Hubs) in England as part of the Genomic Medicines Service.
Outcomes eligible for inclusion	Intermediate outcomes: • Prognostic accuracy • Change in risk category • Impact on treatment decisions about care (including treatment escalation, treatment de-escalation or planned treatment breaks) • Treatment-free days • Time to results • Test failure rate • Ease of use of test • Impact of test implementation and use on healthcare resources Clinical outcomes: • Progression-free survival • Time to relapse • Overall survival • Presence of minimal residual disease Patient-reported outcomes: • Health-related quality of life (including impact on mental and social wellbeing) • Symptom-free days Costs and resource use: • Cost of test (including device costs, additional upfront equipment costs, consumable costs, quality assurance costs, costs related to informatics and data storage). • Treatment costs (including costs of medicines, administration and appointment costs and the cost of treatment adverse events) • Costs for healthcare professional time (including time for staff to do testing and interpret results, time taken to	The EAG searched the Core Outcome Measures in Effectiveness Trials (COMET) database (21/04/2026; "multiple myeloma") and identified the study by Blade et al. (2018) which reported outcomes measures for management in newly diagnosed multiple myeloma. This included: - Treatment and adverse events (completed treatment with or without dosage reduction; maintenance treatments) - Disease control (including minimal residual disease, response criteria) - Adherence - Patient reported outcome measures collected through European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core questionnaire 30 (C30), three items from EORTC-QLQ-Multiple Myeloma (MY20) and EORTC-QLQ-Breast Cancer (BR23), pain Visual Analogue Scale and Morisky-Green questionnaire - Patient reported experiences (including preferences and satisfaction) - Performance status The EAG also considered that transportation costs, treatment breaks, maintenance doses, tandem stem cell transplantation may be applicable. The EAG would consider these as subheadings within the broad outcomes outlined in the Final Scope where data are available.

	discuss with people about implications of testing, additional training needed to do testing).	

1.1 Objectives

The purpose of this evidence assessment is to summarise the existing evidence for the health technology included in the Final Scope. The aim is to evaluate the potential for clinical-effectiveness and cost-effectiveness, identify evidence gaps, and highlight any risks associated with the potential use of the technology in the NHS while further evidence is generated. Based on the Final Scope developed by NICE, the following specific primary objectives are proposed:

- To identify, review and summarise evidence of the clinical effects and safety of the included technology that estimate risk in patients with newly diagnosed multiple myeloma in those deemed eligible for the stem cell transplant pathway.
- To identify, review and summarise the economic evidence for the technology, when compared with standard care.
- To develop a conceptual economic model to identify key model parameters and the relationship between them. An initial assessment of the potential cost-effectiveness of the technology when compared with standard care will only be provided if feasible.
- To summarise information on the impact of implementing the technology on capacity and capabilities in the NHS.
- To identify important evidence gaps and outline what data could be collected to address them.

2. Evidence review methods

The EAG will review the standard request for information forms and instructions for use (IFU) submitted to NICE for each technology within scope to develop a technology summary. Any missing or incomplete information may be supplemented from information found in the public domain, for example from company websites, as appropriate. Indications and contraindications listed in each technology's IFU will be considered and any evidence identified which has been undertaken exclusively in a contraindicated population will be excluded by the EAG. The EAG will summarise key features of the technology. Technology summary tables may be sent to the company to ensure accuracy of content. NICE will be responsible for providing a summary of the relevant regulatory and Digital Technology Assessment Criteria (DTAC) status of the technology.

The EAG may ask clinical experts if any additional national guidance or data collection is relevant to this topic. Relevant sources will be summarised in the clinical context section.

The EAG will review the standard request for evidence forms submitted to NICE for each technology within scope. This will be supplemented by an independent pragmatic literature search undertaken by the EAG in line with the NICE HealthTech programme manual.

2.1 Search methods

An independent literature search will be conducted for clinical effectiveness (which would include prognostic evidence) and full economic evaluations and cost analyses. A pragmatic search strategy will be developed based on the literature search strategy shared by the NICE Evidence and Knowledge team during scoping, edited to focus on the intervention (or prognostic type of intervention) included in the Final Scope (draft example in Appendix A). The EAG will optimise the search to align with the decision problem (for example, including company and technology names listed in the Final Scope, and appropriate older device names as advised by the companies in their completed request for information), searching for new clinical evidence published since the date of last search (on 8 April 2021) for the published medtech innovation briefing (MIB). For economic evaluations no date restriction will

be applied as the existing MIB did not search for economic evaluations. Searches will supplement information provided by the companies. The search strategy for clinical evidence will be initially constructed using technology and manufacturer names only. If any of the names retrieve too many irrelevant records, then they will be combined with terms for multiple myeloma to improve precision. The search strategy for full economic evaluations and cost-analyses will take the same approach as the clinical strategy, however, where there is limited evidence specific to the technology in scope, the EAG may supplement this with a broader economic search to identify published full economic evaluations and cost-analyses of newly diagnosed multiple myeloma risk classification.

The search strategies will be designed in Embase (Ovid) and translated to the following sources:

- MEDLINE (Ovid), Embase (OVID), Cochrane CENTRAL (Wiley), International HTA database (INAHTA) for clinical evidence
- MEDLINE (OVID), Embase (OVID), International HTA database (INAHTA, IDEAS (RePEc), PEDE (Paediatric Economic Database Evaluation), CEA Registry (produced by Tufts) for economic evidence
- ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) for ongoing studies

The search strategy will be developed by one of the EAG's information specialists and peer reviewed by a second information specialist using the PRESS checklist (MacGowan et al. 2016).

Conference abstracts are included in both Embase and CENTRAL and will not be excluded from the clinical evidence searches, however, additional specific searches for other potentially relevant conference abstracts will not be undertaken. Conference abstracts will be excluded from the search for full economic evaluations and cost-analyses.

The EAG will search MHRA Field Safety Notices for adverse events using the technology and company name.

Filters may be applied, as appropriate, to identify clinical evaluations and full economic evaluations and cost-analyses which may be sifted in parallel for time efficiencies. The EAG will apply a date limit to capture the latest clinical evidence associated with the technology that has been published since the search for MIB270 (08 April 2021). The EAG will also apply additional limits (for example human studies, published in English language). No date limits will be applied for the search for economic evaluations and cost analyses. Studies may be identified from searching relevant references of included papers.

Evidence provided by Companies and other stakeholders will also be considered and included if relevant to the decision problem and meets the inclusion criteria listed in Section 2.1. Where evidence is unable to be identified from the information provided, further clarification will be requested via NICE to enable source retrieval. Evidence submitted by 03 June 2026 (2 weeks prior to the submission of the draft External Assessment Report (EAR) to NICE) will be considered by the EAG. Information arriving after this date may not be considered.

The PRISMA-S checklist will be used to guide reporting of the search methods (Rethlefsen et al. 2021).

2.2 Study selection

Titles and abstracts (within clinical and economic searches) will be screened by a single reviewer with at least a 20% sample checked by a second reviewer for relevance to the scope applying the inclusion and exclusion criteria outlined in

Table 2. For those deemed potentially relevant to the scope, full papers will be retrieved and reviewed by two reviewers for relevance to the scope. Studies included in the previous MIB for MMProfiler (MIB270, 2021) will also be reviewed for relevance to the scope applying the inclusion and exclusion criteria outlined in

Table 2. Any disagreements will be considered by a third reviewer for arbitration. Any exclusions of full papers will have the reason for exclusion tabulated and checked by a second reviewer.

Table 2: Inclusion and exclusion criteria

	Inclusion Criteria	Exclusion Criteria
Population	People with newly diagnosed multiple myeloma who are being considered for an autologous stem cell transplant pathway. Populations who are being considered for each technology in line with their intended use outlined in their Instructions for Use.	People with relapsed or refractory multiple myeloma, or unsuitable for autologous stem cell transplant.
Intervention	Technology listed in scope in addition to standard care: • MMprofiler (SkylineDx BV; previous distributor named as Everything Genetic Ltd) – also referred to as SKY92 or EMC92	All other gene expression profiling technologies which are not commercially available in the NHS.
Comparators	Standard care for prognostic testing which may include: • assessing a combination of serum biomarkers (beta-microglobulin, albumin and lactate dehydrogenase) • identifying adverse risk abnormalities using FISH or other validated DNA-based tests	If any alternate comparators are identified in the published literature, the EAG will liaise with Clinical Experts to determine the generalisability of that evidence to the NHS.
Outcomes	Intermediate outcomes: • Prognostic accuracy • Change in risk category • Impact on treatment decisions about care (including treatment escalation, treatment de-escalation or planned treatment breaks) • Treatment-free days • Time to results • Test failure rate • Ease of use of test • Impact of test implementation and use on healthcare resources Clinical outcomes: • Progression-free survival • Time to relapse • Overall survival	Outcomes not listed in the Final scope.

	Inclusion Criteria	Exclusion Criteria
	• Presence of minimal residual disease Patient-reported outcomes: • Health-related quality of life (including impact on mental and social wellbeing) • Symptom-free days Costs and resource use: • Cost of test (including device costs, additional upfront equipment costs, consumable costs, quality assurance costs, costs related to informatics and data storage). • Treatment costs (including cost of medicines, administration and appointment costs and the cost of treating adverse events) • Costs for healthcare professional time (including time for staff to do testing and interpret results, time taken to discuss with people about implications of testing, additional training needed to do testing).	
Study design	Any study design	-

If a large amount of relevant evidence is identified, the EAG will prioritise evidence that it considers most relevant to the decision problem; this may be based on study location or setting, study design (such as comparative evidence prioritised over single arm studies for some outcomes), and sample size (Carroll et al. 2025). The EAG will prioritise published over unpublished studies, and full publications over abstracts.

2.3 Data extraction strategy

Data will be extracted from included studies into bespoke tables to enable descriptive statistics. Independent, second review of data extraction may be done subject to time and resource availability. Data points to be extracted include

information about the study reference, setting, design, population characteristics (including subgroup where reported), intervention characteristics and results of relevant outcomes as listed in the Decision Problem (see Table 1).

2.4 Quality assessment strategy

Formal risk of bias assessment will not be completed for the early use assessment. Discussion will be included in the External Assessment Report on potential biases in included studies and how the risk of bias could affect key outcomes. The report will explicitly detail the potential sources of bias such as the main confounding factors and will comment on the generalisability of the results to clinical practice in the NHS.

2.5 Methods of synthesis and analysis

Results from clinical evidence will be extracted and tabulated. These will be narratively synthesised by outcome (where evidence exists) included in the Final Scope.

Methods and findings from included published economic evidence will be summarised in a tabular format and synthesised in a narrative review by technology. Economic evidence from the perspective of the UK NHS and Personal Social Services will be presented in greater detail.

3. Economic analysis methods

The primary aim of the economic analysis is to work out whether it is plausible that gene expression profiling tests for estimating risk in newly diagnosed multiple myeloma (in those being considered for the stem cell transplant pathway at the time of diagnosis) is cost-effective in the NHS. An economic evaluation model that could be used to assess cost-effectiveness will be conceptualised. It is unlikely that there will be a published economic evaluation that fully meets the scope of this assessment, so it is likely that a de novo conceptual model will be developed. Model conceptualisation will include defining parameters and functional relationships needed to populate the model. Clinical experts will be asked to comment on the validity of the model structure, its inputs, and assumptions, to make sure they are appropriate, especially where evidence is lacking.

3.1 Model development

A conceptual model will be informed by published economic evaluations or other publications describing the diagnostic (including prognostic) pathway. The conceptual model will use features of available economic models of treatments that represent current standard of care or treatments that may represent standard of care in the future (like that described by the ongoing Technology Appraisal for daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable, GID-TA11254) if appropriate. It will consider the value propositions outlined in the final scope (improved knowledge for the patient leading to better mental and social wellbeing, intensification of treatment in high-risk patients leading to longer progression-free and overall survival, avoidance of excess treatments in standard risk leading to better quality of life) and may include additional learnings from published economic studies. The EAG will describe the appropriate characteristics of the model (for example structure, setting, input parameters, sources of data, assumptions). The EAG will also identify, if appropriate, sensitivity analysis that could be undertaken to explore uncertainty. These may include deterministic and probabilistic sensitivity analysis, scenario analyses and subgroup analyses focused on what are believed to be the key characteristics and population subgroups identified in the scope. Costs will be considered from an NHS and Personal Social Services perspective, with cost-effectiveness evaluated against a range of cost-effectiveness thresholds consistent with the NICE reference case framework (NICE, PMG48, 2025); £20,000 to £30,000/QALY as of 28th April 2026.

The EAG plans to construct a single conceptual economic model built in R Programming Language. The EAG will then go on to consider the availability of data with which the model could be populated. This will identify key evidence gaps that could be filled with further evidence generation, and targeted searches for economic model inputs may be considered where appropriate. Should there be sufficient data to populate the conceptual model the EAG will consider formally estimating cost-effectiveness. This will also seek to identify key model drivers and so further clarify key evidence gaps. If possible, the EAG will explore the impact of different cost

options supplied by companies on the economic model, and carry out further sensitivity analysis, as appropriate.

Cost of reversing a decision

Where possible, the EAG can consider the costs associated with implementing each technology within the NHS, including consideration of whether any of these costs are irrecoverable or not, for example, any fixed or up-front costs related to the purchase of equipment, training costs or changes to organisation of care pathways. These will also be considered in sensitivity analysis, if appropriate.

4. Evidence gap analysis

Evidence gaps identified pertaining to the intermediate and final outcomes from the scope and those pertaining to the conceptual economic modelling will be summarised in tabular and narrative form. Key areas for evidence generation will be summarised in tabular form. Narrative text will also address missing evidence for other parts of the scope, such as population, intervention, comparators, outcomes and setting. The EAG will outline potential study designs to address specific research questions to address identified evidence gaps, incorporating feedback from the clinical experts on the feasibility of proposed studies.

5. Handling information from the companies and other stakeholders

All data submitted by the companies in evidence and information requests by NICE, or data submitted by other stakeholders will be considered by the EAG if received by (03 June 2026). Information arriving after this date may not be considered. If the data included in the information provided meets the inclusion criteria for the review, it will be extracted and quality assessed following the procedures outlined in this protocol. The EAG may seek clarification or additional information from companies and other stakeholders where necessary. All correspondence between the EAG and companies will happen through NICE.

Any ‘commercial in confidence’ data provided by a company and specified as such will be highlighted in blue and underlined in the assessment report. Any ‘academic in

confidence' data provided by a company, and specified as such, will be highlighted in yellow and underlined in the assessment report. If confidential information is included in the economic model, the EAG will provide a copy of the model with 'dummy variable values' for the confidential values (using non-confidential values).

6. Additional information sources

The EAG will consult with experts to address queries about the clinical pathways and context of this assessment in addition to commenting on the validity and appropriateness of the conceptual economic model structure, its inputs and assumptions. The EAG note that NICE will recruit experts for this assessment. Experts are recruited in accordance with NICE's policy on declaring and managing interests for NICE advisory committees. The EAG may also consult with local clinical experts based within the Newcastle upon Tyne Hospitals NHS Foundation Trust who are subject to the same confidentiality agreements as the EAG.

7. Competing interests of authors

None

8. References

Avet-Loiseau H, Davies FE, Samur MK, Corre J, D'Agostino M, Kaiser MF, Raab MS, Weinhold N, Gutierrez NC, Paiva B, Neri P, Weisel K, Maura F, Walker BA, Bustoros M, Stewart AK, Usmani SZ, Hillengass J, Chng WJ, Keats JJ, Martinez-Lopez J, Sperling AS, Touzeau C, Zhan F, Raje NS, Cavo M, Bolli N, Ghobrial IM, Dhodapkar MV, Jagannath S, Spencer A, Parekh S, Bahlis NJ, Lonial S, Sonneveld P, Bergsagel L, Orlowski RZ, Morgan G, Mateos MV, Rajkumar SV, San Miguel JF, Anderson KC, Moreau P, Kumar S, Prósper F, Munshi NC. International Myeloma Society/International Myeloma Working Group Consensus Recommendations on the Definition of High-Risk Multiple Myeloma. J Clin Oncol. 2025 Aug 20;43(24):2739-2751. doi: 10.1200/JCO-24-01893. Epub 2025 Jun 9. Erratum in: J Clin Oncol. 2025 Aug;43(22):2553. doi: 10.1200/JCO-25-01367. PMID: 40489728.

Blade J, Calleja MÁ, Lahuerta JJ, Poveda JL, de Paz HD, Lizán L. Defining a set of standardised outcome measures for newly diagnosed patients with multiple myeloma using the Delphi consensus method: the IMPORTA project. BMJ Open. 2018 Feb

22;8(2):e018850. doi: 10.1136/bmjopen-2017-018850. PMID: 29472263; PMCID: PMC5855445.

McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016 Jul;75:40-6. doi: 10.1016/j.jclinepi.2016.01.021. Epub 2016 Mar 19. PMID: 27005575.

Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB; PRISMA-S Group. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev. 2021 Jan 26;10(1):39. doi: 10.1186/s13643-020-01542-z. PMID: 33499930; PMCID: PMC7839230.

Appendix: Draft literature search strategy

Clinical

Embase <1974 to 2026 April 28>

Date of search: 30 April 2026

1	myeloma/ or multiple myeloma/ or myeloma*.mp.	157631
2	(mmprofiler* or mm-profiler* or emc-92 or emc92 or sky92 or sky-92 or erasmus-medical-center-92 or erasmus-medical-center92 or erasmus-medical-centre-92 or erasmus-medical-centre92).ti,ab,kf,dv,dm,dq.	147
3	2 and 1	146
4	(skyline-DX or skylineDX).ti,ab,kf,dv,dm,dq,in. not 2	292
5	limit 4 to conference abstract status	240
6	4 not 5	52
7	exp gene expression profiling/	308583
8	differential gene expression/ or gene expression/ or genetic marker/ or marker gene/ or genetic susceptibility/ or genetic risk/ or gene expression assay/ or genetic analyzer/ or high throughput sequencer/	1822176
9	((gene or genes or genetic) adj2 (signature* or expression* or profil* or assess* or marker* or biomarker*)).ti,ab.	968762
10	(predict* or prognos*).ti,ab. or risk factor/ or risk assessment/ or (risk adj2 (factor* or stratif* or assess* or model* or algorithm* or score* or scoring* or screen* or strateg* or index* or classif*)).ti,ab.	6735431
11	6 and 1 and (7 or 8 or 9 or 10)	5
12	3 or 11	151
13	limit 12 to "remove clinical trial (clinicaltrials.gov) records" [potential named results, no date limits]	148

14	limit 13 to yr="2021 -Current"	69

Economic

Embase <1974 to 2026 April 28>

Date of search: 30 April 2026

1	(economic* or cost* or ((direct or indirect) adj3 utilit*)).ti.	304998
2	((economic* or cost*) adj3 (analy* or evaluat* or model* or effective* or benefit* or utilit* or direct or indirect or illness)).ab. /freq=2 or ((direct or indirect) adj3 utilit*).ab. /freq=2	146647
3	*health economics/ or *device economics/ or exp *economic evaluation/ or *economic aspect/ or exp economic model/ or *healthcare cost/ or *"numbers needed to treat"/	181920
4	(*Economics/ or *Cost/ or *Budget/ or *disease burden/ or health economics/ or device economics/ or exp economic evaluation/) and (economic* or cost*).ab. /freq=2	196788
5	or/1-4	466673
6	myeloma*.ti. or *multiple myeloma/	86829
7	(multiple myeloma/ or myeloma*.kf.) and (myeloma or mm or ndmm).ab. /freq=2	68511
8	(((haematol* or hematol* or blood) adj3 (cancer* or malign*)).ti. or *myeloma/ or *hematologic malignancy/ or *myeloproliferative disorder/) and myeloma*.ab.	10196
9	myeloma*.ab. and (myeloma or mm or ndmm).ab. /freq=4	48970
10	or/6-9	100194
11	((*diagnosis/ or *clinical decision making/ or *diagnostic accuracy/ or *diagnostic test/ or *diagnostic test accuracy study/ or *differential diagnosis/ or *early diagnosis/) and diagnos.ab.) or diagnosis.ti. or diagnosis.ab. /freq=4 or di.fs.	4279450
12	exp gene expression profiling/ or differential gene expression/ or gene expression/ or genetic marker/ or marker gene/ or genetic susceptibility/ or genetic risk/ or gene expression assay/ or genetic analyzer/ or high throughput sequencer/ or ((gene or genes or genetic) adj2 (signature* or expression* or profil* or assess* or marker* or biomarker*)).ti,ab.	2312978
13	(prognost* or stratif* or risk).ti. or ((risk or prognost*) adj4 (predict* or stratif* or marker* or biomarker*)).ab. or risk management/ or cancer prognosis/ or survival prediction/ or cancer risk/ or genetic risk/ or high risk patient/ or low risk patient/ or patient risk/ or risk assessment/ or health risk assessment/	2632495
14	(prognos* or diagnosis).ab. and (prognos* or diagnos*).ab. /freq=5	454136
15	((gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or	173031

	welsh*).ti. or (nhs*.ti. and exp United Kingdom/)) not ((exp "arctic and antarctic"/ or exp oceanic regions/ or exp western hemisphere/ or exp africa/ or exp asia/ or exp "australia and new zealand"/) not (exp united kingdom/ or europe/))	
16	or/11-15	8777315
17	10 and 16 and 5	186
18	limit 17 to (english language and "remove clinical trial (clinicaltrials.gov) records")	183
19	limit 18 to conference abstract status	96
20	18 not 19	87