NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HealthTech Programme

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

Final scope

1. Introduction

The technology included in this NICE HealthTech evaluation is MMprofiler for estimating risk in newly diagnosed multiple myeloma.

The technology will be assessed for early use. Early-use assessment considers HealthTech products that could address a national NHS unmet need. It rapidly assesses products early in the lifecycle (but that have appropriate regulatory approval for use in the UK) or that have limited use in the NHS and need further evidence to support wider use. Technologies considered for early use can be conditionally recommended for use while further evidence is generated during the evidence generation period. This enables early access to promising new technologies for patients. Conditional recommendations are for a fixed period of time and the technologies will be reassessed for routine use using the evidence generated.

A glossary of terms is in appendix A. The methods and process for the assessment follow the NICE HealthTech programme manual.

2. The condition

Multiple myeloma is a form of cancer that comes from abnormal plasma cells (a type of white blood cell) in the bone marrow. Myeloma cells suppress the development of normal blood cells that are responsible for fighting infection (white blood cells), carrying oxygen around the body (red blood cells) and blood clotting (platelets). The term multiple myeloma refers to the presence of

more than one site of affected bone marrow at the time of diagnosis. Multiple myeloma is the third most common blood cancer in the UK with over 6,200 new cases reported each year. It is a relapsing and remitting cancer, where people have a period of symptoms or complications followed by a period of remission where it does not cause symptoms. It is currently incurable, but treatment aims to help people live longer and maintain a good quality of life by controlling the disease and relieving symptoms.

3. Current practice

In the NHS, diagnosis and management of newly diagnosed myeloma follows the:

- The British Society of Haematology and UK Myeloma Forum guidelines on the diagnosis, investigation and initial treatment of myeloma (2021)
- NICE guideline for the diagnosis and management of myeloma (2018)

Other guidance related to high-risk multiple myeloma includes:

- The International Myeloma Society and International Myeloma Working Group consensus recommendations (2025)
- British Society for Haematology/UK Myeloma Society good practice paper on diagnosis and initial treatment of transplant-eligible high-risk myeloma patients (2024)

3.1 Diagnosis

People with suspected multiple myeloma are referred to secondary care to see a haematologist for further tests. These include both imaging and laboratory investigations.

Whole-body MRI should be considered as first line imaging. Whole-body low-dose CT should be used if MRI is unsuitable, and a skeletal survey may be done if both CT and MRI are unsuitable. A bone marrow aspirate and trephine biopsy are taken for laboratory-based diagnostic testing. Serum protein electrophoresis and serum-free light chain assay are used to confirm the

presence of a paraprotein indicating possible myeloma. If serum protein electrophoresis is abnormal, serum immunofixation may be used. Morphology and flow cytometry are used to determine the amount and type of plasma cells present.

3.2 Prognostic testing

Prognostic tests use the same bone marrow samples as diagnostic tests, so people usually need only 1 bone marrow aspirate and trephine biopsy. Typically, identifying high-risk myeloma is based on the revised international staging system (R-ISS), which categorises a person's disease using a combination of serum biomarkers (beta-microglobulin, albumin and lactate dehydrogenase) and DNA-based tests to look for high-risk abnormalities and copy number changes. These tests may include:

- fluorescent in-situ hybridisation (FISH)
- multiplex ligation-dependent probe amplification (MLPA)
- next-generation sequencing (NGS) panels
- single-nucleotide polymorphism (SNP) array.

Genetic testing is done by 7 regional NHS genomic laboratory hubs (GLHs) which are part of the NHS Genomic Medicine Service. Tests are listed on NHS England's National Genomic Test Directory, which specifies which genomic tests are commissioned by the NHS in England, and the people who will be eligible to access to a test. The type of test used and high-risk abnormalities that are assessed can vary between GLHs depending on local pathways. But, the genetic testing typically includes using FISH to test for t(4;14), t(14;16), t(14;20), 1q gain, del(1p) and del(17p). Clinical experts stated that, in some centres, genetic tests may not be used due to limited capacity, education or lack of risk-based treatment options. Additional detail related to recommendations for genetic tests from specific organisations is in appendix B.

3.3 Treatment

Clinical experts stated that first-line treatment decisions are typically based on a person's eligibility for an autologous stem-cell transplant rather than risk-stratification. NICE's guideline for the diagnosis and management of myeloma recommends considering using frailty and performance status measures that include comorbidities to assess the suitability of first autologous stem cell transplant.

Treatment for newly diagnosed multiple myeloma where an autologous stem cell transplant pathway is suitable typically includes:

- using 3 to 4 medicines to rapidly reduce the amount of myeloma (induction).
- high-dose chemotherapy and autologous stem cell transplant.
- a short course of additional treatment (often the same medicines as induction) to try and remove minimal residual disease (consolidation). This may not always be done as part of standard care.
- long-term lower-intensity treatment aiming to delay relapse (maintenance).

NICE has a suite of technology appraisal guidance for newly diagnosed multiple myeloma either published or in development. A full list of related NICE guidance is in appendix C.

Bortezomib is recommended as an option in combination with dexamethasone, or with dexamethasone and thalidomide, or with dexamethasone, thalidomide and daratumumab for the induction treatment of adults with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with autologous stem cell transplantation. The same combination of 4 medicines is also recommended as an option for consolidation treatment. These medicines are currently the only quadruplet therapy regime recommended for use in the NHS for people with newly diagnosed multiple myeloma where autologous stem cell transplant is suitable. The treatment regimens used do not differ between standard-risk and high-risk disease. Clinical experts stated that, when an autologous stem

cell transplant pathway is being considered, most people will be offered this quadruplet therapy regimen as a first line treatment.

A technology appraisal evaluating daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable is currently ongoing.

Lenalidomide is currently the only medicine recommended as maintenance treatment after autologous stem cell transplant in the NHS for the same population.

4. Unmet need

Currently over 33,000 people in the UK are living with multiple myeloma (Myeloma UK, 2025). While there are several treatment options for newly diagnosed multiple myeloma, it follows a relapsing and remitting cycle and is currently incurable. DNA-based prognostic tests are currently used to identify people with standard- or high-risk disease. Standard-risk disease is characterised by a slow progression rate and low resistance to treatments, whereas high-risk disease has a greater risk of early relapse and is more likely to be resistant to treatment. The Myeloma XI trial reported that median overall survival for people relapsing within 12 months after stem cell transplant was only 26 months, compared to 91 months in the non-early relapse group. Clinical experts stated that some people with features of high-risk disease, such as early relapse, are not currently identified with DNA-based prognostic tests.

The national cancer plan for England (2026) aims to expand and evolve the use and type of genomic testing and states that more comprehensive genomic testing will deliver more personalised and impactful treatments. Using genomic testing for personalised cancer care is also a key component of the NHS 10-year plan for England (2025).

Using an RNA-based gene expression profiling test alongside current prognostic tests for people with newly diagnosed multiple myeloma may more accurately estimate a person's disease risk. Providing more personalised risk

estimates could improve people's knowledge and understanding of the prognosis of their cancer, guide treatment decisions and potentially lead to improved outcomes for people with both standard-risk and high-risk disease. Clinical experts stated that people who are less frail and eligible for more intense treatments, such as an autologous stem cell transplantation pathway, would benefit the most from a gene expression profiling test. This is because they may be able to withstand stronger treatments if they have high-risk disease. But, they noted that the test could be used to provide more accurate prognostic information for everyone with newly diagnosed multiple myeloma.

5. The technology

This section describes the properties of the technologies based on information provided to NICE by manufacturers and experts, and publicly available information. NICE has not carried out an independent evaluation of these descriptions.

People with suspected multiple myeloma have bone marrow biopsies taken for diagnostic and prognostic testing. Genetic tests are done to identify adverse risk abnormalities that indicate a person has high-risk disease and may have a poorer response to treatment and overall prognosis. Gene expression profiling tests measure the activity levels of selected genes to help identify whether a person has standard-risk or high-risk disease. The tests use the same bone marrow samples as current diagnostic and prognostic tests. They could give more accurate prognostic information to people and their healthcare professionals when interpreted alongside current tests.

MMprofiler is not currently included in NHS England's national genomic test directory. But, a British Society for Haematology/UK Myeloma Society good practice paper (2024) recommends equitable access to gene expression profiling tests for people with newly diagnosed multiple myeloma where an autologous stem cell transplant is suitable.

Section 5.1 describes the included technology. The technology was available to the NHS at the time of writing this scope. Gene expression profiling tests for relapsed or refractory multiple myeloma are out of scope for this assessment.

5.1 MMprofiler (SkylineDx BV)

MMprofiler (SkylineDx BV) is an RNA-based genomic test designed to provide prognostic information about progression-free and overall survival. It is UKCA marked as a general in-vitro diagnostic (IVD) medical device. MMprofiler is indicated for use for people:

- with newly diagnosed multiple myeloma
- with relapsed multiple myeloma
- when autologous stem cell transplant is suitable
- when autologous stem cell transplant is unsuitable.

It is intended for use by clinical scientists working in molecular diagnostic laboratories. Users are required to complete the MMprofiler training and proficiency programme before using the test. The company states that haematologists and other relevant healthcare professionals may also benefit from educational sessions on interpretation of the results alongside current standard care. The test uses RNA extracted from CD138-selected bone marrow plasma cells that come from the same bone marrow biopsy samples taken for standard diagnostic and prognostic testing. MMprofiler uses a microarray to measure the expression of 92 genes that make up the SKY92 gene signature. It consists of:

- a plastic microarray cartridge containing SKY92 probes
- assay software that uses an algorithm that runs on a ThermoFisher GeneChip microarray system.

The GeneChip system scans the cartridge and sends the data to the external SkylineDx data analysis server, where it is processed using the MMprofiler algorithm. A report is produced which gives a binary output of the presence or absence of the SKY92 gene signature, indicating whether a person has high-risk disease. The result could be reviewed alongside standard care markers to

inform healthcare professionals and people with multiple myeloma about the risk profile of the disease. Test results can be available from 4 days after a bone marrow sample is received by a laboratory. MMprofiler is not currently used in the NHS.

5.2 The place of the technology in the care pathway

This assessment will consider MMprofiler used alongside standard prognostic tests for people with newly diagnosed multiple myeloma when an autologous stem cell transplant pathway is suitable.

5.3 Innovative aspects

MMprofiler is designed to identify people with high-risk disease.

The main aims of the technology include:

- improving the accuracy of identifying people with standard-risk or high-risk multiple myeloma
- giving people more personalised information about their disease, improving their knowledge and understanding of the prognosis of their cancer
- improving progression free survival and overall survival by informing treatment decisions for people with high-risk disease
- reducing side-effects and long-term toxicity by informing treatment decisions for people with standard-risk disease, including potential de-escalation, treatment breaks and reduced monitoring.

6. Comparator

The comparator for this assessment is standard care for prognostic testing for people with newly diagnosed myeloma. Standard care may vary between regional genomic laboratory hubs. But, it typically includes assessing a combination of serum biomarkers (beta-microglobulin, albumin and lactate dehydrogenase) and identifying adverse risk abnormalities using FISH or other validated DNA-based tests.

7. Patient issues and preferences

Multiple myeloma is a highly individualistic and complex cancer that has significant and varied symptoms and progression. Living with multiple myeloma is likely to be extremely stressful due to the incurable nature of the disease and dealing with the constant possibility of relapse. This, alongside managing the significant physical symptoms and frequent hospital appointments, can severely impact a person's quality of life. People who are eligible for an autologous stem cell transplant pathway tend to be younger, more likely to be working and often have caring responsibilities, so multiple myeloma can also have a large impact on their families and carers.

People with multiple myeloma often face difficult treatment decisions. They have to weigh up the potential benefits of prolonging their time in remission and length of life with the potential side-effects of potent medicines and the burden of different treatments on their everyday life. A study by Fifer et al. (2020) highlighted the importance of quality of life when making treatment decisions. It also highlighted that there is variation between people in what they value the most from their treatment.

Clinical and patient experts explained that understanding a person's disease risk is extremely important and should be communicated appropriately. A gene expression profiling test that can more accurately estimate risk may help to inform these conversations and could give people a better understanding and more certainty around how their disease may progress. Patient experts highlighted the importance of treatment breaks and the positive impact time without treatment side-effects can have on quality of life. Tests that can allow more personalised care could increase confidence for people with myeloma and their healthcare professionals when making treatment decisions.

8. Potential equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with protected characteristics (Equality Act 2010) and others.

Cancer is considered a disability under the Equality Act 2010 from the point of diagnosis. Multiple myeloma is more common in people 65 years and over and in men. Cancer Research UK's statistics for myeloma reports that multiple myeloma incidence rates are lower in the Asian ethnic group, higher in the Black ethnic group, and similar in people of mixed or multiple ethnicity, compared with the White ethnic group in England.

Age, disability, race and sex are protected characteristics under the Equality Act 2010.

Multiple myeloma is a relapsing and remitting cancer, and people often have to travel to hospital for repeated treatments over multiple different treatment cycles in their lifetime. People living in more rural areas or further away from treatment centres may have more difficulty attending regular hospital appointments, which may influence their treatment decisions.

9. Guidance type

MMprofiler will be assessed for early use. This approach to guidance development was chosen because:

- the assessed technology has limited or no current use in the NHS
- the technology has the potential to address a high unmet need in the NHS.

Initial scoping searches suggest that the evidence base for MMprofiler includes:

- a prospective screening study combined with a phase 2 single arm trial
- secondary analyses of randomised controlled trials
- validation studies.

10. Decision problem

The key decision questions for this assessment are:

- Does offering gene expression profiling tests for estimating risk in newly diagnosed multiple myeloma have the potential to be a clinically and cost-effective use of NHS resources?
- Are there gaps in the evidence base and what are the key gaps?

Table 1: Decision problem

Proposed type of assessment	Early use
Population	People with newly diagnosed multiple myeloma who are being considered for an autologous stem cell transplant pathway
Interventions	MMprofiler in addition to standard care
Comparator	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
Setting	Genomic laboratory hubs (GLHs)
Outcomes and costs (may include but are not limited to)	Intermediate outcomes: • Prognostic accuracy • Change of risk category • Impact of test results on 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 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)
Economic analysis	A health economic model will be developed comprising a cost utility or cost-comparison analysis. Costs will be considered from an NHS and Personal Social Services perspective. Sensitivity and scenario analysis should be undertaken to address the relative effect of parameter or structural uncertainty on results. The time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared.

11. Other issues for consideration

11.1 Potential implementation issues

Clinical experts stated that genomic laboratory hubs are not currently set up to use MMprofiler, as additional equipment and specialist training would be needed to perform the test and interpret the results. Experts also noted that RNA is less stable than DNA, which may increase the risk of test failure. Some experts highlighted that the test uses CD138-selected bone marrow plasma cells that are prepared in the same way and come from the same samples as current prognostic tests. They also noted that the skills needed for sample processing and doing the test are similar to other tests already used for some solid tumours. Clinical experts agreed that further consideration would be needed on how the test could be implemented into current pathways. For example, if testing was limited to a smaller number of genomic medicine services, local sample preprocessing pathways would need to be in place alongside shipping procedures for processed material to centralised services.

Clinical experts stated that incorporating the test would not change interactions with people with multiple myeloma and their families or carers, as

results from current prognostic testing are already communicated as part of the care pathway.

The company state that data analysis for MMprofiler is done on a secure and validated remote server. Data security is essential for the implementation of a gene expression profiling test where patient data is analysed and stored on external servers. There may be challenges around confidentiality, integrity, and governance. Issues relating to data ownership and custodianship, risks of re-identification of depersonalised data, unauthorised access and system vulnerabilities, and consent and data sharing should be considered. The location of data analysis and storage (for example, on-site or cloud-based), and the security measures employed are key to these concerns.

11.2 Risk-based treatment pathway

Treatment is typically based on whether an autologous stem cell transplant pathway is being considered, rather than the risk status of their disease. In some cases, clinicians may suggest a slightly different treatment approach or offer a more intensive treatment for people with high-risk disease. But, there is variation in practice across the NHS and currently only 1 quadruplet treatment option is currently available. A British Society for Haematology/UK Myeloma Society good practice paper (2024) recommends enrolling people with high-risk disease into clinical trials when appropriate and clinical experts stated that tandem stem cell transplant may also be offered. Clinical experts also noted that, for some people, they may submit an individual funding request for treatments that they consider may be beneficial that are not routinely commissioned in the NHS.

The OPTIMUM/MUK 9 clinical trial used MMprofiler in addition to DNA-based tests to identify people with ultra-high risk multiple myeloma. The trial induction treatment included 5 medicines (daratumumab, cyclophosphamide, bortezomib, lenalidomide and dexamethasone), followed by high-dose chemotherapy and stem cell transplantation. This treatment combination is currently not available in the NHS.

A mixed-method study from Myeloma UK found that personalised treatment pathways are only available to people in clinical trials, because they are not routinely commissioned by NHS England. It also reported that successful commissioning of prognostic risk stratification tests is dependent on factors such as how it impacts treatment for people with multiple myeloma. Clinical experts agreed that risk-stratified treatment pathways are needed to see the full benefits from more accurate prognostic testing.

Clinical experts explained that the treatment landscape for multiple myeloma is rapidly changing and highlighted the need for more treatment options for people with high-risk disease in the NHS. They stated that minimal residual disease detection could also be used alongside more accurate prognostic testing to further personalise treatment pathways. But, this is not currently a part of standard care in the NHS. Treatment pathways may change in the near future (see appendix C), so the external assessment group may need to consider these changes in their assessment. Older evidence may not reflect the current standard of care.

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Appendix A: Glossary of terms

Autologous stem cell transplant

A procedure that replaces damaged bone marrow with healthy bone marrow stem cells from a person's own body.

Bone marrow aspirate

A procedure where a small amount of liquid bone marrow is taken from inside the bone using a syringe with a small hollow needle.

CD138-selected bone marrow plasma cells

Mature antibody-producing white blood cells that are separated from other cells in the bone marrow and used for genetic prognostic tests.

Copy number changes

When a piece of DNA has more copies (duplication) or fewer copies (deletion) than usual.

Fluorescent in-situ hybridisation

A laboratory technique that uses fluorescently labelled pieces of DNA (probes) to detect specific DNA sequences on chromosomes.

Flow cytometry

A laboratory technique that is used to analyse the physical and chemical characteristics of particles of a fluid as it passes through a laser.

Microarray

A laboratory technique that identifies copy number changes across the genome.

Minimal residual disease

Residual myeloma cells present after treatment at levels that are only detectible using sensitive molecular techniques.

Morphology

Microscopic assessment of the size, shape, structure and appearance of bone marrow plasma cells.

Multiplex ligation-dependent probe amplification

A laboratory technique that uses pairs of DNA probes to detect specific copy number changes in the genome.

Next-generation sequencing panel

A collection of genes that have been grouped together for testing allowing detection of multiple abnormalities linked with a disease or condition.

Paraprotein

An abnormal antibody made in large amounts by myeloma plasma cells.

Serum-free light chain assay

A blood test that detects free kappa and lambda light chains (small pieces of antibodies made by plasma cells) in a person's blood.

Serum immunofixation

A blood test used to identify which type of abnormal antibody (paraprotein) a person has.

Serum protein electrophoresis

A blood test used to measure the amount paraprotein in the blood by separating it from other proteins.

Single-nucleotide polymorphism array

A type of DNA microarray used to detect single changes to DNA sequences across the genome.

Tandem stem cell transplant

When 2 autologous stem cell transplants are performed within 6 months of each other.

Trephine biopsy

A procedure in which a small core or piece of the bone marrow is removed using a small hollow needle.

t(4;14), t(14;16), t(14;20), 1q gain, del(1p) and del(17p)

A list of chromosomal abnormalities found in multiple myeloma, including:

- translocations (swap of genetic material) between chromosomes 4 and 14, 14 and 16 and 14 and 20
- extra copies of the long arm (q arm) of chromosome 1
- deletion of the short arm (p arm) of chromosomes 1 and 17.

Appendix B: Recommendations for prognostic tests in multiple myeloma

NICE's guideline for the diagnosis and management of myeloma recommends using FISH on CD138-selected bone marrow plasma cells to identify the adverse risk abnormalities t(4;14), t(14;16), 1q gain, del(1p) and del(17p)(TP53 deletion). It states that these abnormalities, combined with International Staging System (ISS) scores can be used to identify people with high-risk myeloma. It also recommends considering performing:

- FISH on CD138-selected bone marrow plasma cells to identify the adverse risk abnormality t(14;20), and the standard risk abnormalities t(11;14) and hyperdiploidy.
- Immunophenotyping of bone marrow to identify plasma cell phenotype, and to inform subsequent monitoring.
- Immunohistochemistry (including Ki-67 staining and p53 expression) on the trephine biopsy to identify plasma cell phenotype and give an indication of cell proliferation, to provide further prognostic information.

The International Myeloma Society and International Myeloma Working Group consensus recommendations (2025) propose the consensus genomic staging of high-risk myeloma as the presence of at least 1 of the following abnormalities:

- del(17p) with a cutoff of over 20% clonal fraction, or TP53 mutation
- an immunoglobulin heavy chain translocation including t(4;14), t(14;16), or t(14;20) along with 1q gain or del(1p32)
- monoallelic del(1p32) along with 1q gain or biallelic del(1p32)
- beta-2 microglobulin of at least 5.5 mg/L with normal creatinine.

The European Haematology Association and European Myeloma Network evidence-based guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma (2025) recommends using:

- FISH for detection of del17p, t(4;14), t(14;16), t (14;20), 1q gain or amplification, del1p32 and t(11;14)
- and next-generation sequencing for TP53 mutations.

A British Society for Haematology/UK Myeloma Society good practice paper (2024) recommends that all people with newly diagnosed multiple myeloma should be offered extended tumour genetic profiling suitable for detecting 2 or more high-risk cytogenetic abnormalities by testing for t(4;14), t(14;16), t(14;20), del(1p), gain(1q) and del(17p) by FISH or equivalent validated molecular methods.

Appendix C: Related NICE guidance

Published

- Myeloma: diagnosis and management (2016 updated 2018) NICE guideline NG35
- Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable (2022) NICE technology appraisal guidance 763
- Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (2014) NICE technology appraisal guidance 311
- Bortezomib and thalidomide for the first-line treatment of multiple myeloma (2011) NICE technology appraisal guidance 228
- Lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma (2021) NICE technology appraisal guidance 680
- MMprofiler for prognostic risk classification in multiple myeloma (2021) NICE medtech innovation briefing 270

Awaiting or in development

- Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable. NICE technology appraisal guidance [ID6249].
- Isatuximab in combination for maintenance treatment of newly diagnosed multiple myeloma after an autologous stem cell transplant [ID6639]. Expected publication date to be confirmed