

Using QIP-MS to Guide the Timing of MRD Testing in Patients With Multiple Myeloma: A Budget Impact Analysis From the French Payer Perspective

Christian Siegfried¹, Miyuru Amarapala¹, Xavier Leleu², Lauren Fufeld¹

¹Veranex, Boston, MA, USA; ²Department of Hematology, CHU, Poitiers, Poitiers, France

Correspondence: Christian Siegfried, CRO and Consulting Services, Veranex, 100 Federal St Suite 3302A, Boston, MA, 02110, USA, Email christian.siegfried@Veranex.com

Purpose: Serum or urine protein electrophoresis (SPEP or UPEP) and immunofixation electrophoresis (SIFE or UIFE) are routinely used to detect M-proteins in MM patients. However, SPEP and SIFE are not sensitive enough to measure M-protein levels that are low but still clinically significant. This study aimed to evaluate the potential cost savings associated with using the EXENT GAM Assay, a serum-based quantitative-immunoprecipitation mass spectrometry (QIP-MS) diagnostic test instead of SIFE to guide the timing of minimal residual disease (MRD) testing for patients with multiple myeloma (MM).

Patients and Methods: A simple 2-year budget impact model was created in Excel using data from MM clinical trials and fee schedules. Patients are tested with either QIP-MS or SIFE at predetermined timepoints. If patients test negative, they will receive MRD testing. The result of the MRD test will determine if the preceding serum-based test was a true negative result (MRD test is negative) or a false negative result (MRD test is positive). Patients receiving autologous stem cell transplant (henceforth referred to as transplant) and those not receiving transplant are both eligible for one MRD test per year. MRD testing for transplant-eligible patients occurs prior to transplant and one year following transplant.

Results: Across a hypothetical population of 5154 mm patients receiving 1st-line treatment in France, using QIP-MS instead of SIFE prior to MRD testing leads to 1973 fewer false negative results and 744 more false positive results (due, in part, to the detection of residual IgG). Net savings per QIP-MS test would be €260 or total savings of €2,481,832.

Conclusion: This study suggests that the use of QIP-MS prior to MRD testing may be cost-saving for testing French patients with MM.

Keywords: mass spectrometry, minimal residual disease, immunofixation electrophoresis, plasma cell disorder

Introduction

Multiple myeloma (MM) is a malignancy of the blood caused by the proliferation of abnormal clonal plasma cells within the bone marrow. Monoclonal proteins (M-proteins), which are immunoglobulins produced by the abnormal plasma cells, are a marker of disease activity and can be used to diagnose MM; in France, 5425 new cases are diagnosed each year.¹ M-proteins can also be used for disease monitoring following treatment of MM patients.

In current practice in France, several tests are routinely used to detect M-proteins in MM patients: serum or urine protein electrophoresis (SPEP or UPEP) and immunofixation electrophoresis (SIFE or UIFE).² However, these tests are not sensitive enough to measure M-protein levels that are low but still clinically significant.³ Patients receiving new therapies, such as the combination of daratumumab, bortezomib, thalidomide, and dexamethasone (D-VTd) or daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VRd), can generate responses deeper than SIFE can detect.⁴⁻⁶ Without the use of supplementary assays, therapeutic antibodies can also interfere with the results of SIFE testing, leading to false positive results.⁷ Consequently, patients testing negative with SIFE may be required to undergo

more sensitive tests such as minimal residual disease (MRD) testing with next-generation flow cytometry (NGF) or next-generation sequencing (NGS) at sensitivities of 10^{-5} or 10^{-6} to determine the presence or absence of malignant cells.⁸ In newly diagnosed multiple myeloma (NDMM) patients who have achieved CR, up to 31% can still be positive via MRD testing.⁹

Studies demonstrate an association between improved progression-free survival (PFS) or overall survival (OS) and MRD negativity where CR is less prognostic.^{6,9} The use of MRD in MM recently gained unanimous support from the FDA's Oncologic Drugs Advisory Committee (ODAC) as a surrogate primary endpoint in MM clinical trials to enable accelerated approvals of new therapies.¹⁰ The FDA's position on MRD has sparked discussions with the European Medicines Agency (EMA), which announced it would use both cost and clinical data to make a determination on the use of MRD as a surrogate endpoint by July 1, 2024. As MRD testing transitions from clinical trials to routine clinical practice in France, more sensitive tests will be needed to detect M-proteins in the blood and reduce the additional costs and invasive bone marrow (BM) aspiration procedures associated with NGF/NGS.^{11–13}

Noting the improved accuracy of mass spectrometry (MS) over conventional serum- or urine-based methods and MS' ability to distinguish endogenous M-proteins from therapeutic antibodies, the International Myeloma Working Group (IMWG) has endorsed the use of MS-based tests for the monitoring of patients with MM and other plasma cell disorders.^{3,14} The EXENT GAM Assay (Thermo Fisher, Waltham, Massachusetts, United States), a quantitative immunoprecipitation mass spectrometry (QIP-MS) system, is a serum-based test that can detect and quantify M-proteins at much lower levels than serum immunofixation electrophoresis (SIFE) and SPEP.^{3,15,16} QIP-MS measures immunoglobulins G, A, and M, as well as total kappa and lambda. The lower limit of measuring interval (LLMI) for QIP-MS is 0.015 g/L, roughly ten times as sensitive as SIFE.¹⁷ By identifying proteins based on their unique isotype and mass-to-charge ratio of their light chains, QIP-MS can also distinguish between endogenous M-proteins and therapeutic antibodies.^{16,18}

In anticipation of the potential increase in MRD testing in MM in clinical practice, this study uses a simple budget impact model to compare QIP-MS versus SIFE as a precursor to testing MRD with NGF or NGS in France.

Materials and Methods

Study Design

A two-year budget impact analysis was developed in Excel to compare the hypothetical use of SIFE or QIP-MS as a precursor to MRD testing from the French payer perspective. The French healthcare system, *l'Assurance Maladie*, is a mandatory-enrollment, single-payer national healthcare system which covers nearly all residents of France.¹⁹

Patients receive MRD testing only after a negative M-protein test via SIFE or QIP-MS. MRD testing is considered definitive in this model; a positive MRD assessment means the preceding M-protein test with either SIFE or QIP-MS was a false negative.

The frequency of MRD testing in the model is based on a practicing French hematologist's clinical trial experience regarding the times MRD has been most informative in the management of patients (XL). Patients receiving autologous stem cell transplant (henceforth referred to as transplant) and those not receiving transplant are both eligible for one MRD test per year. Transplant patients are eligible for MRD testing prior to transplant and one year following transplant. [Figure 1](#) provides an overview of the diagnostic pathway that occurs at each testing time point.

Model Development

The model framework and input values were selected via a focused review of literature on PubMed, published fee schedules, and primary research with a practicing French hematologist (XL). The model includes direct costs associated with M-protein and MRD tests, extraction of blood and bone marrow aspirate, and associated physician visits. In accordance with budget impact modeling best practices, the model does not include cost discounting.²⁰

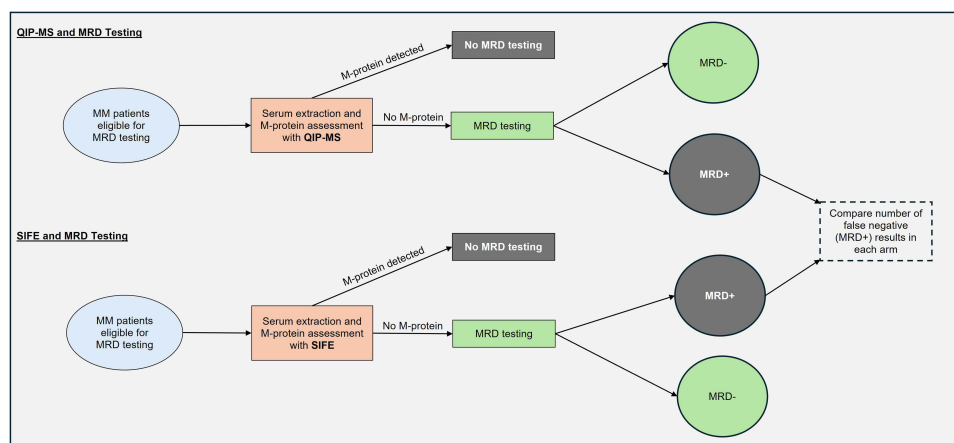


Figure 1 Budget Impact Model Framework.

Abbreviations: QIP-MS, quantitative immunoprecipitation mass spectrometry; SIFE, serum immunofixation electrophoresis; MRD, minimal residual disease.

Clinical Inputs

The number of patients entering the model is determined by the total insured population, the number of insured patients who are newly diagnosed with MM, and, finally, the percentage of those insured NDMM patients who would benefit from treatment. The true presence of disease in the model is determined by the positivity of MRD tests. These values are provided by the GEM2012MENOS65 trial, which tested NDMM patients with NGF.²¹ Given the short timeframe of the model and the population (newly diagnosed patients), the one-year survival rate is assumed to be the same for patients receiving transplant and those not receiving transplant. This assumption is supported by the DETERMINATION trial, which did not show a significant difference in survival between these two groups over a one-year period.²² The number of patients entering the second year of the model is multiplied by this survival rate. The clinical values are provided in Table 1.

Table 2 provides the sensitivity and specificity of the M-protein testing methods. These values were calculated using each test's concordance with NGS MRD results in NDMM patients.

Cost Inputs

Costs are from published literature as well as the Common Classification of Medical Procedures (CCAM) and National Biology Coding Table (NABM) when possible and were reviewed by a hematologist (XL). The cost of QIP-MS, provided by the manufacturer, is €90. All costs are in 2023 Euros. Additional costs can be found in Table 3

Table 1 Clinical Inputs

Parameter	Value
Insured Population in France	68,521,974 ²³
Incidence of MM	0.0079% ¹
Percentage of Patients Receiving 1st-Line Therapy	95% (XL)
Percentage of Patients Receiving Transplant	40% (XL)
True Proportion of Underlying Disease, Prior to Transplant	69% ²¹
True Proportion of Underlying Disease, Year 2	29% ²¹
1-Year Survival Rate of NDMM Patients	85% ^{22,24,25}

Abbreviations: MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; XL, Dr. Xavier Leleu.

Table 2 Test Specifications

Parameter	QIP-MS	SIFE
Sensitivity	95.5%	54.5%
Specificity	76.3%	92.1%

Notes: Sensitivity and specificity values for QIP-MS and SIFE were calculated using values from Derman 2021.¹⁸

Abbreviations: QIP-MS, quantitative immunoprecipitation mass spectrometry; SIFE, serum immunofixation electrophoresis.

Table 3 Costs

Parameter	Code	Cost
SIFE	NABM I57I	€41.60 ²⁶
QIP-MS	NA	€90 (TF)
MRD Testing (NGS)	NA	€1032.00 (XL)
MRD Testing (NGF)	RIHN G065	€270.00 ²⁷
Venipuncture	FEHB00I	€9.60 ²⁸
Bone Marrow Aspiration	FDHB004	€67.50 ²⁸
Physician Visit	NA	€60.00 ²⁷

Abbreviations: SIFE, serum immunofixation electrophoresis; QIP-MS, quantitative immunoprecipitation mass spectrometry; MRD, minimal residual disease; TF, Thermo Fisher (test manufacturer); NGS, next generation sequencing; XL, Dr. Xavier Leleu; NGF, next-generation flow cytometry.

The cost of MRD testing per patient is a weighted average of the costs of testing with NGS and NGF, based on the hematologist's experience with the proportion of testing performed with either method and his expectations for future MRD testing in clinical practice (XL). The average cost of MRD testing includes the cost of the bone marrow aspiration and specialist visit. The proportions of testing with NGS/ NGF and the average cost of MRD testing are provided in Table 4.

Sensitivity Analysis

A one-way sensitivity analysis examined the effect of varying each input by $\pm 10\%$ of its base case value.

Results

Across a hypothetical population of 5154 mm patients receiving 1st-line treatment in France, using QIP-MS instead of SIFE prior to MRD testing leads to a reduction in premature MRD tests of 1973 and total savings of €2,481,832.

Table 4 Average Cost of MRD Testing

Parameter	Value
Percentage of Testing with NGS	90% (XL)
Percentage of Testing with NGF	10%
Average Cost of MRD Testing	€1083.30

Abbreviations: MRD, minimal residual disease; NGS, next-generation sequencing; XL, Dr. Xavier Leleu; NGF, next-generation flow cytometry.

Table 5 Test Volume

	QIP-MS Arm	SIFE Arm	Difference
M-Protein Tests	9535	9535	0
True Positives	4606	2633	1973
True Negatives	3594	4338	-744
False Positives	1115	371	744
False Negatives	220	2193	-1973
MRD Tests	3814	6531	-2717

Note: bold formatting indicates that this row is the sum of the indented rows beneath it.

Abbreviations: QIP-MS, quantitative immunoprecipitation mass spectrometry; SIFE, serum immunofixation electrophoresis; MRD, minimal residual disease.

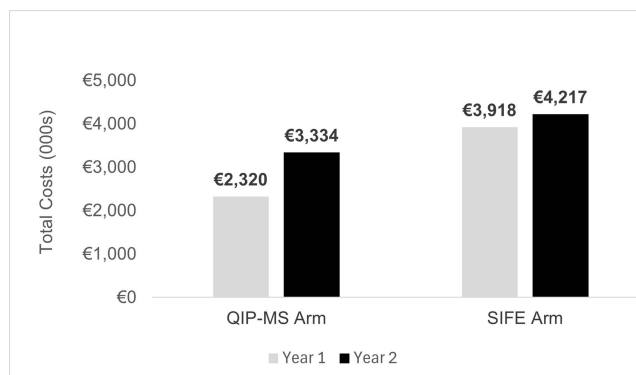
Table 6 Total Costs

	QIP-MS Arm	SIFE Arm	Savings
M-Protein Tests	€1,521,786	€1,060,292	-€461,494
MRD Tests	€4,131,706	€7,075,032	€2,943,326
MRD-	€3,893,380	€4,699,355	€805,975
MRD+	€238,326	€2,375,677	€2,137,351
Total	€5,653,492	€8,135,324	€2,481,832

Note: bold formatting indicates that this row is the sum of the indented rows beneath it.

Abbreviations: QIP-MS, quantitative immunoprecipitation mass spectrometry; SIFE, serum immunofixation electrophoresis; MRD, minimal residual disease.

Compared with SIFE, QIP-MS would produce 744 additional false positive results and 1973 fewer false negative results. Net savings per QIP-MS test would be €260. For the 2062 transplant and 3029 non-transplant patients, QIP-MS would save €993,478 and €1,488,354, respectively. [Table 5](#) provides a breakdown of the distribution of test results, with associated costs in [Table 6](#). Total costs by year are provided in [Figure 2](#), with higher costs in year two when rates of underlying disease are lower.

**Figure 2** Total Yearly Costs for the QIP-MS and SIFE Arms.

Abbreviations: QIP-MS, quantitative immunoprecipitation mass spectrometry; SIFE, serum immunofixation electrophoresis.

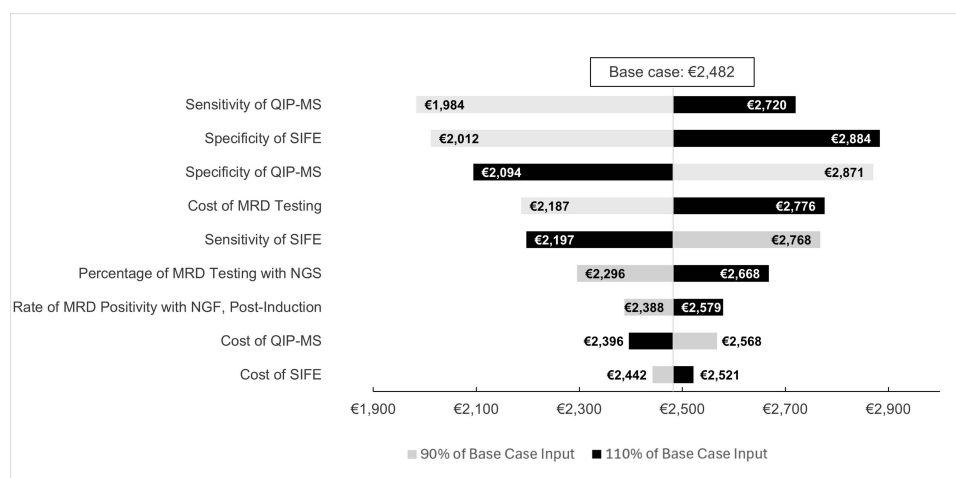


Figure 3 One-Way Sensitivity Analysis (Total Savings in 000s).

Note: All input percentages must be within 0% and 100% in the model. Consequently, the one-way sensitivity analysis uses 100% as the upper limit for the sensitivity of QIP-MS and the specificity of SIFE rather than 110% times the base case value.

Abbreviations: QIP-MS, quantitative immunoprecipitation mass spectrometry; SIFE, serum immunofixation electrophoresis; MRD, minimal residual disease.

The most influential input parameters in the one-way sensitivity analysis are the sensitivity of QIP-MS, the specificity of SIFE, the cost of MRD testing, and the specificity of QIP-MS, presented in Figure 3.

Discussion

Using MRD tests to inform clinical decision-making has been established in many hematological malignancies, and clinicians are already beginning to incorporate MRD testing in MM clinical practice in several countries. For example, some clinicians in Spain review MRD results at specific times in the MM patient journey, such as prior to and following transplant, following consolidation therapy in those patients that receive it, and a year following transplant.^{21,29} While MRD testing is not currently a part of routine clinical practice in France, its use in MM clinical trials has been growing, and MRD testing could become part of the standard of care in the future.⁴

For countries using MRD testing, clinicians may be able to optimize patient assessment by first employing a blood-based test that is more sensitive than SIFE to accurately identify patients who would be eligible for MRD testing with NGS/NGF. Utilizing a sensitive test as a precursor to MRD could improve the number of accurately diagnosed MRD-negative patients and postpone invasive bone aspirations in patients who would otherwise have been subjected to premature MRD testing.

This study is the first to demonstrate the economic feasibility of using QIP-MS rather than SIFE as a precursor to MRD testing in France.

Limitations

Intended as a preliminary evaluation, this model has several limitations, including a short two-year time horizon. Clinicians confirmed, however, that this timeframe would capture most MRD testing in a patient's journey. Any additional uses of QIP-MS for monitoring MM patients, aside from serving as a precursor to MRD testing, have been excluded from the model but could be added once data on these applications have been published. Without regular monitoring, MM patients, such as those with IgG myeloma, may have false positive test results with QIP-MS due to residual M-proteins continuing to circulate in their blood for as long as six months.^{15,30,31} When used regularly, QIP-MS can quantify low concentrations of M-proteins and could allow physicians to determine when IgG levels are decreasing even while the MS test result remains positive.^{15,30,31} Studies suggest MS can also detect disease in patients who test MRD-negative with NGF, which is likely to occur for two reasons: patients have MM proliferating outside of the bone marrow, (known as extramedullary disease) or, due to limitations on where the bone marrow aspiration can be extracted, the sample is not extracted from a region with cancerous cells.^{32–35} Conversely, in the roughly 1% to 3% of myeloma

patients with non-secretory myeloma, QIP-MS will be unable to monitor the disease due to the absence of M-proteins in the blood. While conventional blood-based methods are also unable to detect M-proteins in patients with oligosecretory MM, which comprises roughly 2% to 3% of all MM patients, QIP-MS has demonstrated the ability to detect and monitor disease in small studies of these patients.^{36,37} QIP-MS's ability to detect M-proteins in these patients is due to its LLMI of 0.0015 g/dl, which is well below the 1 g/dl threshold of serum M-protein that defines patients as oligosecretory.^{17,38} The model also does not incorporate treatment and patient outcomes. When patient outcomes following MS testing become available, an expanded economic model including treatments and patient outcomes would be useful to consider. Lastly, hematologists, acknowledging the potential complications and patient discomfort associated with the extraction of bone marrow, indicate that minimizing premature bone marrow aspirations would be of value to patients, but data limitations prevent the model from accounting for these improvements in quality of life.³⁹ Patient-related outcome measures, such as quality of life, should be evaluated in future studies.

Conclusions

As evidence supporting the use of MRD in MM grows, it will be important to understand how best to incorporate MRD testing in clinical practice. This study suggests that the use of QIP-MS prior to MRD testing may be cost-saving for testing French patients with MM.

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Disclosure

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