

Archives of Hematology and Blood Transfusion

Review Article

Role of Minimal Residual Disease Monitoring in Guiding Maintenance Therapy for Multiple Myeloma

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Received: 4 July 2025; Accepted: 3 October 2025; Published: 7 January 2026.

Citation of this article: Olejnik X, Turcan L, Valach N (2026) Role of Minimal Residual Disease Monitoring in Guiding Maintenance Therapy for Multiple Myeloma. Arch Hematol Blood Transfus, 8(1): 01-06. DOI: [10.5281/zenodo.22818820](https://doi.org/10.5281/zenodo.22818820)

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Abstract

Background: Complete response by conventional serologic and morphologic criteria no longer separates multiple myeloma patients with durable remission from those destined to relapse, and measurable residual disease (MRD) testing has emerged to recover that lost prognostic resolution.

Objective: To synthesize published evidence on MRD detection methods, the prognostic and surrogate value of MRD negativity, and the use of serial MRD results to guide the duration and intensity of post-induction maintenance therapy.

Methods: Narrative synthesis of peer-reviewed literature on next-generation flow cytometry, next-generation sequencing, MRD meta-analyses and surrogacy analyses, and prospective MRD-adapted maintenance trials in newly diagnosed multiple myeloma.

Findings: EuroFlow next-generation flow and immunoglobulin-sequencing assays now detect residual clones below 10^{-6} and predict progression-free and overall survival more sharply than complete response; trial-level surrogacy analyses link MRD-negativity gains to progression-free survival gains (R^2 approximately 0.70); and MRD-adapted trials including MASTER, AURIGA, FORTE and ATLAS show that stopping therapy in sustained MRD-negative patients and intensifying it in persistently MRD-positive patients each changes outcomes.

Conclusions: MRD status is prognostically validated and increasingly surrogate-validated; the remaining barriers to MRD-guided maintenance are trial maturation, serial-testing infrastructure and reimbursement rather than unresolved biology.

Keywords: minimal residual disease; multiple myeloma; maintenance therapy; next-generation flow cytometry; next-generation sequencing

1. Introduction

Multiple myeloma has moved, within a single professional generation, from a disease staged by serum protein electrophoresis and skeletal survey to one staged by clonal plasma cells counted one in a million. The shift happened because complete response stopped discriminating: a large fraction of patients meeting International Myeloma Working Group criteria for complete response still relapse, and the prognostic information that used to separate them has migrated below the sensitivity floor of immunofixation and bone marrow morphology [1]. Measurable residual disease, still called minimal residual disease (MRD) in most of the literature, was built to recover that lost signal by asking a narrower question: after treatment, can a malignant plasma cell still be found among a million or ten million normal ones.

Two technologies now answer that question with enough sensitivity and reproducibility to serve as trial endpoints. Next-generation flow cytometry (NGF), standardized by the EuroFlow consortium, resolves clonal plasma cells to a limit of detection below 2×10^{-6} using an eight-color, two-tube panel that superseded four-to-six-color multiparameter flow [2]. Next-generation sequencing (NGS) of the immunoglobulin heavy-chain locus, first validated by Martinez-Lopez and colleagues [3] and later commercialized as the clonoSEQ assay, reaches a comparable or deeper limit of detection without requiring a fresh, same-day sample. Both replaced allele-specific oligonucleotide RQ-PCR, which was accurate but too labor-intensive and primer-dependent to scale [4]. MRD negativity, however measured, is now one of the strongest single predictors of progression-free and overall survival reported in myeloma, and is under active study as a tool for shortening or intensifying maintenance therapy rather than merely reporting a number at one time point.

This review synthesizes the evidence on how MRD assessment works, what MRD negativity predicts, and how trials have begun using serial MRD results to guide

the duration and intensity of maintenance therapy after induction and transplant, and addresses the practical friction that keeps MRD-adapted maintenance a research strategy in most centers.

2. Methods for detecting minimal residual disease

Flow cytometry MRD testing has a longer pedigree than sequencing. Paiva and colleagues formalized immunophenotypic criteria for complete response nearly two decades ago, using four- and six-color panels that separated clonal from normal plasma cells at sensitivities around 10^{-4} to 10^{-5} [5]. That approach was validated at scale in the UK Medical Research Council Myeloma IX trial, where flow-defined MRD negativity after intensive therapy was independently associated with better progression-free and overall survival regardless of the depth of serologic response [6]. EuroFlow's next-generation flow protocol extended this logic with a bulk-lysis, two-tube, eight-color design that pushed the limit of detection below 2×10^{-6} and standardized antibody clones, instrument settings and analysis software across laboratories [2]. In that founding study, NGF identified MRD in 47% of samples that conventional eight-color flow called negative, and NGF-negative patients in conventional complete response had progression-free survival not reached at analysis versus a median of 7 months for NGF-positive patients.

Sequencing-based MRD reads the rearranged immunoglobulin heavy-chain sequence unique to a patient's clone, identified from a diagnostic sample, and searches follow-up samples for that same sequence among millions of receptors. Martinez-Lopez and colleagues first validated a deep-sequencing method against flow cytometry and allele-specific PCR, showing it added independent prognostic value [3]. The approach matured into the FDA-authorized clonoSEQ assay, applied prospectively within the IFM/DFCI 2009 trial, where MRD status by NGS was highly predictive of progression-free survival independent of cytogenetic risk

[7]. Sequencing does not require same-day processing and can be run centrally from a shipped aspirate, but depends on identifying a trackable clone from a diagnostic sample, which fails in a meaningful minority of patients.

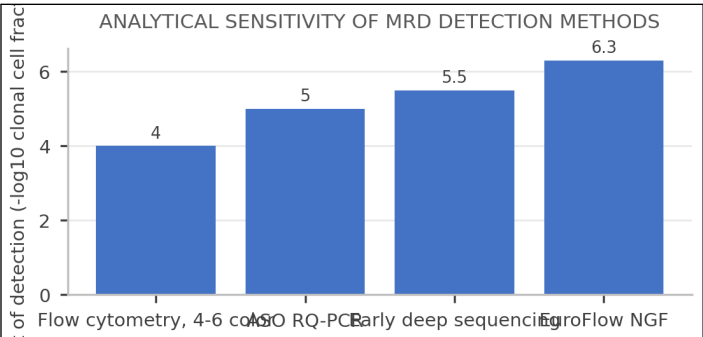


Figure 1: Analytical sensitivity (limit of detection, expressed as clonal cells detectable per total cells evaluated) achieved by successive MRD detection methods in multiple myeloma, from first-generation four- to six-color flow cytometry at approximately 10^{-4} [5], through allele-specific oligonucleotide RQ-PCR at approximately 10^{-5} [4] and early deep sequencing at approximately 10^{-5} to 10^{-6} [3], to EuroFlow next-generation flow cytometry with a limit of detection below 2×10^{-6} [2]; methods are not from a single comparative study and the bars illustrate the field's trajectory rather than a head-to-head trial.

A bone marrow sample can be genuinely MRD-negative while disease persists in a focal lesion an iliac crest aspirate cannot sample. The IMAJEM sub-study of IFM/DFCI 2009 paired whole-body MRI and FDG-PET/CT with marrow assessment before maintenance and found that a substantial minority of patients in complete response still had PET-avid lesions predicting inferior progression-free survival [8], which is why the IMWG's 2016 criteria defined "imaging-negative MRD negativity" as a category distinct from marrow-based negativity alone [1].

Head-to-head comparisons of NGF and NGS generally find concordance in the 80-90% range, and a PETHEMA/GEM cooperative-group comparison found the two techniques similarly predictive of progression-free survival, supporting their use as interchangeable standards [9]. Both now feature in the IMWG's 2016 consensus criteria, which specified sustained, imaging-negative, and flow- or sequencing-based MRD negativity as distinct categories of response deeper than

complete response [1]. A subsequent harmonization effort formalized reporting standards - assessment timing, minimum cells or reads evaluated, handling of low-quality aspirates - so that MRD data generated across cooperative groups and sponsors could be pooled [10], which is what made the aggregate meta-analyses below possible.

3. MRD negativity as a prognostic and surrogate endpoint

The strength of MRD as a prognostic marker is no longer contested; the open question is whether it qualifies as a valid surrogate endpoint for regulatory purposes. Munshi and colleagues' 2017 meta-analysis pooled individual patient data from 14 studies and more than 1,200 patients and found MRD-negative status associated with a hazard ratio for progression-free survival of roughly 0.41 and for overall survival of roughly 0.57, holding regardless of assay or transplant status [11]. Landgren and colleagues' contemporaneous meta-analysis of newly diagnosed patients found roughly three-fold better progression-free survival for MRD-negative patients irrespective of cytogenetic risk [12]. Perrot and colleagues then showed, using NGS in the IFM 2009 population, that MRD negativity at 10^{-6} sensitivity separated outcomes even among patients already in conventional complete response, demonstrating that MRD adds information on top of, not merely in place of, standard response criteria [13].

Table 1: Meta-analyses and trial-level surrogacy analyses linking MRD negativity to progression-free and overall survival in multiple myeloma [11,12,13,17,19].			
Analysis	Scope	Key statistic	Endpoint
[11]	14 studies, >1,200 patients	HR approx 0.41 (PFS), 0.57 (OS)	PFS and OS
[12]	Newly diagnosed, pooled cohorts	~3-fold better PFS if MRD-negative	PFS
[13]	IFM 2009, NGS at 10^{-6}	MRD separates outcomes within CR	PFS
[17]	POLLUX, CASTOR, ALCYONE, MAIA	MRD-benefit tracks PFS-benefit across trials	PFS
[19]	15 randomized trials, 3 disease settings	Trial-level R 0.70 (range 0.62-0.83)	PFS

Surrogacy is a harder bar: a treatment's effect on MRD-negative rate must predict its effect on a hard endpoint across trials, not merely within one. Combined analysis of four randomized daratumumab trials - POLLUX [14], CASTOR [15], ALCYONE and MAIA [16] - found that the magnitude of the MRD-negativity benefit tracked the magnitude of the progression-free survival benefit across all four [17]. A focused analysis restricted to MAIA and ALCYONE showed it was specifically sustained, rather than transient, MRD negativity that carried the daratumumab survival advantage [18]. Paiva and colleagues pooled 15 randomized trials across transplant-eligible, transplant-ineligible and relapsed/refractory populations and reported a weighted trial-level R of 0.70 between a treatment's effect on MRD-negative rate and on progression-free survival, strongest in relapsed/refractory and transplant-ineligible settings (R 0.83) and weaker among transplant-eligible patients (R 0.74) [19]. Trials with a progression-free survival hazard ratio below 0.60 showed a median 21 percentage-point difference in MRD-negative rate between arms versus 2.5 points for trials at or above 0.60, and a roughly 10-point improvement in MRD-negative rate corresponded to a 5.5-to-17-month difference in median progression-free survival depending on setting. That imperfect but substantial trial-level correlation is the evidentiary basis on which regulators have begun treating MRD negativity as an early efficacy signal, though it has not replaced progression-free or overall survival as the endpoint required for full approval.

4. MRD-adapted duration of maintenance therapy

Prognostic value is necessary but not sufficient for using MRD to make treatment decisions; a marker also has to move in response to therapy in a way that changes outcomes when acted upon, which requires randomizing on the marker itself. The MASTER trial supplied the first large prospective test of this logic in newly diagnosed, transplant-eligible myeloma. Patients received

daratumumab-carfilzomib-lenalidomide-dexamethasone induction and transplant, then had treatment duration directed by serial NGS MRD testing: two consecutive MRD-negative results at 10^{-5} sensitivity allowed maintenance to stop entirely, with resumption only if MRD resurfaced [20]. In the final report, 78% of patients achieved MRD negativity by the end of consolidation and two-year progression-free survival exceeded 90% among standard- and one-hit high-risk patients but was closer to 58% among patients with two or more high-risk cytogenetic abnormalities, who tended not to sustain MRD negativity long enough to qualify for cessation [21]. MASTER thus demonstrated both the feasibility of stopping therapy in molecularly defined deep responders and the persistence of a high-risk subgroup for whom de-escalation is not yet appropriate.

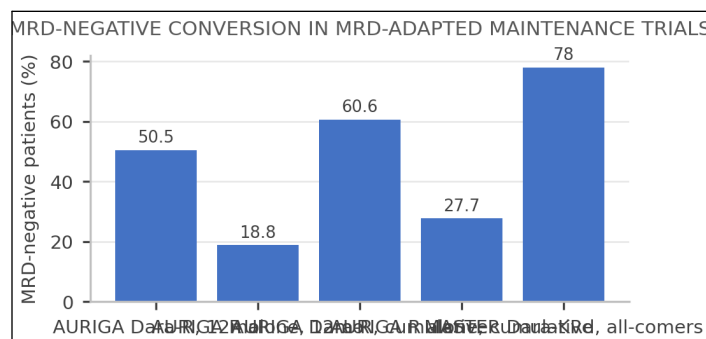


Figure 2: MRD-negative conversion rates at the 10^{-5} threshold reported in trials of MRD-adapted or MRD-intensified maintenance therapy after transplant: AURIGA at 12 months, daratumumab-lenalidomide versus lenalidomide alone in patients MRD-positive after transplant (50.5% vs 18.8%) [22]; AURIGA cumulative conversion by longer follow-up (60.6% vs 27.7%) [22]; and MASTER, where 78% of all-comers reached MRD negativity by the end of consolidation under daratumumab-carfilzomib-lenalidomide-dexamethasone [21]; trial populations, thresholds and follow-up durations differ and the figure is not a direct comparison of regimens.

The phase 3 AURIGA trial enrolled patients who remained MRD-positive after transplant and induction - the population least likely to benefit from a fixed lenalidomide-only strategy - and randomized them to daratumumab plus lenalidomide or lenalidomide alone as maintenance. At 12 months, MRD-negative conversion at 10^{-5} occurred in 50.5% of patients on

daratumumab-lenalidomide versus 18.8% on lenalidomide alone, and at 10^{-6} in 23.2% versus 5.0%; by longer follow-up, cumulative conversion at 10^{-5} reached 60.6% versus 27.7% [22]. That improvement translated into a clinical benefit, with 30-month progression-free survival of 82.7% versus 66.4% (hazard ratio 0.53). AURIGA thus shows that intensifying maintenance in patients who have not cleared MRD after transplant recovers much of the outcome gap separating them from spontaneous converters.

The GRIFFIN trial, which added daratumumab to lenalidomide-bortezomib-dexamethasone induction and consolidation before randomizing daratumumab-lenalidomide versus lenalidomide maintenance, showed the same pattern earlier in treatment: daratumumab raised MRD-negative rates by end of consolidation, and that depth carried forward into lower loss of response during maintenance [23]. FORTE randomized patients to carfilzomib-lenalidomide or lenalidomide-alone maintenance after carfilzomib-based induction and consolidation, with or without transplantation, and found carfilzomib-intensified maintenance produced deeper, more durable MRD negativity, particularly benefiting patients entering maintenance MRD-positive or high-risk [24]. ATLAS took a more explicitly MRD-driven design, randomizing post-transplant patients to carfilzomib-lenalidomide-dexamethasone versus lenalidomide alone with duration informed by sustained MRD status, and its interim analysis reported a significant progression-free survival advantage for the carfilzomib-containing arm [25]. Together with MASTER and AURIGA, these trials describe a coherent strategy: use MRD status after induction or transplant to identify patients needing intensified maintenance, and use sustained MRD negativity to identify patients in whom maintenance can plausibly be shortened, rather than treating everyone to the same fixed duration.

5. Sustained versus point-in-time MRD negativity

A single MRD-negative bone marrow sample is a photograph, not a trend, and the literature increasingly treats the two differently. Persistence of MRD negativity across multiple consecutive time points, usually two assessments a year or more apart, predicts outcome more strongly than a single negative result, which is why MASTER permitted treatment cessation only after two consecutive negatives [21]. Registry and single-center analyses of patients who lost MRD negativity after achieving it have found that a meaningful minority of deep responders - often estimated at one in five to one in four across cohorts - re-emerge as MRD-positive on subsequent testing, and that this loss precedes clinical relapse by months, making it a plausible trigger for reintroducing therapy rather than waiting for biochemical progression. AURIGA and MASTER reinforce the point from the treatment side: AURIGA enrolled patients still MRD-positive after standard induction and transplant and showed that risk modifiable with intensified maintenance [22], while MASTER's high-risk cytogenetic subgroup could reach a single MRD-negative result but often failed to sustain it, with two-year outcomes remaining inferior despite reaching the same depth of response at some point [21].

MRD-adapted algorithms therefore cannot rest on a single test result the way cytogenetic risk stratification rests on a single baseline karyotype. They require serial testing on a defined schedule, a threshold for "sustained," and a plan for a previously negative patient who converts back - decisions current trials have made differently, which is part of why MRD-adapted maintenance has not converged on one accepted algorithm outside a clinical trial.

Table 2: MRD-adapted and MRD-intensified maintenance trials in newly diagnosed multiple myeloma, with headline efficacy findings [20,21,22,24,25].

Trial	Design	Headline finding
MASTER [20,21]	Dara-KRd, MRD-stop after 2 negatives	78% MRD-negative by end of consolidation; 2-yr PFS >90% in standard/1-hit risk
AURIGA [22]	Dara-R vs R maintenance, MRD-positive enrollees	30-mo PFS 82.7% vs 66.4%, HR 0.53
FORTE [24]	KRd vs R maintenance after carfilzomib induction	Deeper, more durable MRD negativity with KRd
ATLAS [25]	KRd vs R maintenance, MRD-informed duration	Significant PFS advantage for KRd, interim analysis

6. Barriers to routine MRD-guided practice

Despite the strength of the prognostic and surrogacy data, MRD testing has not become a routine driver of maintenance decisions in most centers, for reasons more logistical than scientific. NGF requires a same-day, adequately cellular, non-hemodiluted aspirate processed by an operator trained to the EuroFlow protocol, difficult to guarantee outside specialized centers [2]. NGS avoids same-day processing but depends on identifying a trackable clonal sequence from a diagnostic sample not always available retrospectively, and the assay is not uniformly reimbursed, limiting how often it can be repeated [10]. The IMWG's harmonization effort addressed technical standardization but could not by itself resolve reimbursement and infrastructure gaps determining whether a community practice can order serial MRD testing at all [10,1].

There is also a gap between "MRD predicts outcome" and "acting on MRD improves outcome," a higher bar that only a handful of MRD-directed trials - MASTER, AURIGA, ATLAS and the ongoing DRAMMATIC (SWOG S1803) study - have been designed to clear, none yet with mature overall-survival data. DRAMMATIC was designed specifically to test, randomized, whether MRD-directed discontinuation of maintenance is non-inferior to continuous therapy, and its results are likely to be the most influential dataset in this area because they address duration rather than intensification. Until then, guideline

bodies recommend MRD testing as informative but not yet the sole basis for stopping or escalating maintenance outside a research protocol, and center-to-center variability in access to standardized testing means even willing clinicians often cannot practice MRD-adapted care uniformly.

7. Conclusion

Minimal residual disease testing in multiple myeloma has traveled from a research correlate to a load-bearing endpoint in a remarkably short span, propelled by two convergent, standardized, high-sensitivity technologies that push detection past the point where conventional serologic and morphologic criteria can see [2,3]. The prognostic case is settled: across meta-analyses spanning thousands of patients, MRD negativity predicts progression-free and overall survival more sharply than complete response, across disease settings and detection methods [11,12,13]. The surrogacy case is strong but not definitive, resting on trial-level correlations between a regimen's effect on MRD-negative rate and its effect on progression-free survival that explain a large but not complete share of the variance across trials [17,19]. The interventional case is the newest and thinnest layer of evidence, but MASTER, AURIGA, FORTE and ATLAS have each supplied a piece of it, showing that MRD-guided cessation is feasible in favorable-risk disease and that MRD-guided intensification recovers a meaningful fraction of the survival deficit carried by patients remaining MRD-positive after standard therapy [20,21,22,24,25]. What remains is largely trial maturation, technical standardization and health-system access rather than biological uncertainty: the marker works, and the question DRAMMATIC and its successors are built to answer is not whether MRD status should guide maintenance therapy, but exactly how, and for how long.

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