UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

REVIEW OPEN ACCESS

Rising Biomarkers in the Diagnosis of Multiple Myeloma: A Narrative Review

Anaïs Miners, BA Student [1]*, Lyndon C. Walsh, BA Student [2]

[1] Department of Psychology, McGill University, Montreal, Quebec, Canada H2W 2C5
[2] Department of Biology, McGill University, Montreal, Quebec, Canada H3A 1B1

*Corresponding Author: anais.miners@mcgill.mail.ca

Abstract

Introduction: Multiple Myeloma, a rare and historically deemed incurable blood cancer, continues to pose a significant health challenge. While the standard of care for multiple myeloma involves managing symptoms long term, there is a growing interest in new modalities of diagnosing and characterizing the disease. Biomarkers, a broad classification of objective medical signs which can be measured with accuracy and consistency, play a dual role, not only in monitoring the disease but also in the diagnostic process, offering valuable insight into the nature of the cancer.

Methods: This narrative review evaluated studies published to large academic databases through the utilization of filtering Medical Subjects Headings (MESH) terms pertaining to the topic of multiple myeloma biomarkers. Specific biomarkers and their significance to the development of an understanding of multiple myeloma will be identified and categorized by feasibility of use, taking into account current data and available detection techniques.

Results: Both traditionally utilized and novel biomarkers for multiple myeloma were included in this study. Literature pertaining to six biomarkers of interest was reviewed: M Protein, immunoglobulin free light chain (FLC), Lactate Dehydrogenase (LDH), circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), and the utilization of bone lesion imaging. M-Protein still remains the gold standard for diagnosing multiple myeloma, but other liquid biopsy measurements (FLC, LDH, ctDNA, cfDNA) and imaging evaluations have become crucial in diagnosing, treating, and understanding the heterogeneity of the disease.

Discussion: These biomarkers have been shown to improve the diagnostic and prognostic process of cancer treatment by identifying and measuring patient attributes. As ongoing research endeavors continue to unveil the mechanisms and prevalence of various biomarkers in multiple myeloma, there is an opportunity for refinement and standardization of international guidelines for managing MM patients. Biomarker implementation into the standards of care gives rise to the opportunity of reducing variability between studies and optimizing personalized patient care.

Conclusion: Biomarkers in multiple myeloma is a rapidly advancing field of translational science which is influencing daily clinical decision making. Further studies are needed to limit variability in biomarker standards and to broaden our understanding of the correlations between biomarkers and disease progression.

Keywords: multiple myeloma; biomarkers; M protein; free light chains; lactate dehydrogenase; ctDNA; cfDNA; bone lesion imaging

Introduction

Multiple Myeloma (MM), a rare and historically incurable cancer affecting plasma cells (i.e. white blood cells found in bone marrow), in which the overgrowth and proliferation of these cancerous plasma cells blocks healthy blood cells, continues to present significant health challenges globally, with an estimated 588, 000 cases reported worldwide each year [1]. In the year 2022 alone, Canada experienced 4,000 newly diagnosed cases. Despite progress in research, relapses manifest repeatedly in a single patient over the course of the disease and the 5-year survival rate for MM patients remains at 48.5% [2, 3]. These rates underscore the persisting challenges in managing MM.

The progression of MM from pre-malignancy to full malignancy can be divided into three different diagnoses, namely monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM) and Multiple Myeloma itself. Both MGUS and SMM are considered premalignant stages. MGUS is associated with a low likelihood of progression to full malignancy (i.e., estimated at 1% per year) [4]. The subsequent stage, SMM, carries a higher risk, with a 10% per year chance of

progressing to full malignancy. MM is classified as a full malignancy characterized by end organ damage, necessitating chemotherapy [5]. Critical distinctions between these disorders are identified through bone marrow biopsies. In MGUS, patients exhibit a plasma cell population of less than 10%, while in SMM, the population exceeds 10%, yet both don't express end organ damage. Conversely, MM patients have 10% or more abnormal plasma cell populations along with evident end organ damage, which encompasses anemia, hypercalcemia, renal dysfunction, bone damage, or any combination of these four manifestations [5]. Patient outcomes exhibit variability, with certain individuals experiencing rapid progression from MGUS/SMM to MM, while others maintain an indolent disease course characterized by minimal progression over their lifetimes [3].

The intricacies of MM lie in its cytogenetic and genomic aberrations, such as the translocation of the immunoglobulin heavy chain (IGC) locus, containing the gene responsible for encoding the heavy chain of antibodies [6]. Recognizing such molecular complications is pivotal for advancing targeted therapeutic interventions, and improving outcomes for individuals grappling with MM. Currently, the commonly used treatment paradigm is the RVD regimen, utilizing lenalidomide, bortezomib, and dexamethasone [7, 8]. Patients who have sufficiently robust health may be eligible for an autologous stem cell transplant. This is followed by maintenance therapy, consisting of a lower and less frequent dose of one of the three agents of the RVD regimen, usually being lenalidomide or bortezomib [9]. A more recent and promising second-line clinical treatment involves the use of daratumumab, a human IgGκ monoclonal antibody specifically targeting CD38 [10]. The decision to explore daratumumab for multiple myeloma treatment was prompted by the exceptionally high expression of CD38 on myeloma cells [11]. Demonstrating both safety and efficacy as a standalone therapy in extensively treated multiple myeloma patients, daratumumab has also exhibited positive outcomes when combined with bortezomib in newly diagnosed multiple myeloma patients, alongside other anti-myeloma agents [10, 12].

Biomarkers, a broad classification of objective medical signs which can be measured with accuracy and consistency [13], have played a crucial role in the diagnosis and treatment of MM. They serve a dual purpose of not only monitoring the disease but also contributing to the diagnostic process, offering valuable insight into the nature of the cancer. Precisely, biomarker testing focuses on discerning genes, proteins, and other molecular components to extract relevant information specific to MM [14]. Moreover, biomarkers can serve distinct purposes, encompassing diagnostic, prognostic, or predictive functions, with their applicability often contingent upon the severity of a patient's diagnosis. The disparity between these biomarkers is described as follows: predictive biomarkers assess the risk of developing cancer; diagnostic biomarkers are employed to screen individuals for the detection of cancer; and prognostic biomarkers are utilized for estimating the likely disease course, response to treatment, and determining the most appropriate management strategy [3, 15].

By utilizing these biomarkers, severity classification systems have been developed. The more recent International Staging System (ISS) introduced in 2005, utilizes serum β2 microglobulin, serum albumin, platelet count, serum creatinine, and age as predictors of survival [16]. A combined assessment of Sβ2M and serum albumin yields a three-stage classification, providing a convenient and highly accurate method to assess prognosis in MM [3].

Furthermore, biomarkers are categorized based on the invasiveness of their measurement. Non-invasive biomarkers are typically identified in bodily fluids, such as urine, blood, or saliva. Notably, the first biomarker discovered in MM was the Bence Jones protein, denoting immunoglobulin light chains found at abnormally elevated levels in the urine of individuals diagnosed with MM [15]. Moving along the spectrum, minimally invasive biomarkers are primarily detected in fluids like blood, necessitating a blood draw for assessment. Finally, invasive biomarkers are typically discerned in tissue biopsies, frequently obtained from bone marrow and tumor tissues [3].

In the pursuit of presenting an up-to-date profile of biomarkers in the diagnosis and treatment of Multiple Myeloma, this narrative review systematically compares the reliability and utility of novel biomarkers with traditional counterparts. By synthesizing current knowledge and spotlighting breakthroughs, this review actively contributes to the ongoing efforts aimed at refining the precision and efficacy of biomarker-based approaches in the management of MM. Notably, the integration of innovative biomarkers is particularly crucial in addressing the genetic clonal heterogeneity inherent in multiple myeloma.

Methods

Articles published in the English language between the period of 1977 and 2024 were read for this review. An emphasis was put on modern articles published in the last 15 years, while articles prior to that were used to contextualize the history of biomarkers. The articles were retrieved from the electronic databases PubMed, GoogleScholar, and Scopus. Databases were filtered by use of key terms and Medical Subjects Headings (MESH) terms: multiple myeloma, biomarkers, and each individual biomarker name, including M Protein, free light chains, lactate dehydrogenase, circulating tumor DNA, and cell-free DNA as of interest (Table 1).

Table 1. Overview of Biomarkers and Biomarker Uses

Biomarker	Use (Diagnostic/Prognostic)	Description
M-Protein	Diagnostic	The presence of immunologic and electrophoretic homogeneous monoclonal proteins (M-Protein) is measured using serum and urine analysis. Serum M protein is also an important prognostic biomarker, as it assumes a critical role in evaluating the severity and in monitoring the progression of MM, particularly when its concentration exceeds 10 g/L.
Free light chains	Diagnostic + Follow-Up	When there's no measurable M-protein in serum and urine, it is possible to use free light chains instead to gage response by looking at the percentage decrease in the difference between involved and non-involved FLC levels. The International Myeloma Working Group (IMWG) recommendation, an involved-to-non-involved FLC ratio ≥ 100, with involved FLC concentration ≥ 100 mg/l, is sufficient to differentiate between SMM and MM
Lactate Dehydrogenase (LDH)	Prognostic	Lactate dehydrogenase (LDH) is an enzyme involved in glycolysis that actively converts pyruvate to lactate within a reversible reaction of reducing NAD+. Some studies consider any LDH value over 240 U/L to be high. LDH can provide insights to the clotting feature of multiple myeloma.
Circulating Tumor DNA (ctDNA)	Prognostic	Circulating Tumor DNA (ctDNA) can be extracted from peripheral blood and used to assess the spread of disease or genetic profile of the tumor. It is becoming more popular as a liquid biopsy technique to assess present mutations in the disease.
Cell-free DNA (cfDNA)	Prognostic	Cell-free DNA (cfDNA) is fragmented DNA that is found within the bloodstream, not necessarily from tumor origin, and is used as a biomarker in liquid biopsies for Multiple Myeloma. cfDNA provides a non-invasive alternative to bone marrow aspirates, as taking an aspirate from a single location fails to elucidate the spatial heterogeneity.
Bone Lesions	Prognostic	Identifying bone lytic lesions helps medical providers to assess the advancement and destructiveness of the patient's multiple myeloma. Imaging of bone lesions via 18F-FDG and MRI assists in the staging of patients and accounts for the spatial heterogeneity of the disease.

Before conducting the searches, the authors identified specific biomarkers of interest by searching review articles. These biomarkers were selected based on their established or potential significance in multiple myeloma diagnosis, prognosis, or treatment monitoring. Additionally, the review will explore the emerging role of imaging in detecting biomarkers associated with multiple myeloma.

Results

M Protein

The presence of immunologic and electrophoretic homogeneous monoclonal proteins, commonly referred to as M Proteins, serves as a distinctive and significant biomarker for MM, playing a pivotal role as an independent risk factor for disease progression. Typically, monoclonal proteins, like

M protein, comprises two identical heavy (H) polypeptide chains and two identical light (L) polypeptide chains of the same class and subclass. The heavy chains belong to immunoglobulin classes IgG, IgA, IgM, IgD, and IgE, while the light chains exist in kappa (κ) and lambda (λ) types [17]. Under normal circumstances, plasma cells produce immunoglobulins to combat infections. However, in the case of MM, the abnormal proliferation of plasma cells results in the production of an M protein, which can be an abnormal form of IgG, IgM, or IgA, and less frequently IgE or IgD [18]. This unrestrained proliferation of plasma cells in the bone marrow and subsequent infiltration into nearby bones lead to complications such as hyperviscosity and invasive bone lesions, culminating in bone pain and pathological fractures [17].

Detection of M-proteins involves both serum and urine analyses. In cases where MM is suspected, serum protein electrophoresis is employed, revealing an M-protein as a concentrated peak or band on the densitometer tracing [17]. Subsequent immunofixation is often performed to detect smaller M-proteins that might be concealed within the normal β or γ regions, preventing oversight.

Urine analysis is integral to assessing M protein, with approximately 75% of patients showing its presence. When combined with serum tests, these analyses collectively demonstrate high efficacy in M-protein detection. Importantly, at the time of diagnosis, 97% of patients with multiple myeloma exhibit the presence of M-protein in either the serum or urine [17].

M protein remains an important and reliable diagnosis biomarker, as 80% of patients at the time of diagnosis exhibit a serum M spike or peak [17], emphasizing the consistent prominence of abnormal M protein levels in MM diagnosis. The inclusion of these abnormal M protein levels in the diagnostic criteria further highlights their relevance in identifying and confirming MM [18]. Serum M protein is also an important prognostic biomarker, as it assumes a critical role in evaluating the severity and in monitoring the progression of MM, particularly when its concentration exceeds 10 g/L. Additionally, the identification of M Proteins has significantly improved the ability to detect relapses [19, 20].

Free Light Chains

Free light chains (FLC) ratio was first introduced in 2001 as a potential biomarker for MM and can be used both during the initial diagnostic assessment and follow-up monitoring [21]. Indeed, when there's no measurable M-protein in serum and urine, it is possible to use free light chains instead to gage response by looking at the percentage decrease in the difference between involved and non-involved FLC levels. The International Myeloma Working Group (IMWG) recommendation, an involved-to-non-involved FLC ratio ≥ 100, with involved FLC concentration ≥ 100 mg/l, is sufficient to differentiate between SMM and MM needing treatment [21].

Traditionally, MM diagnosis involves detecting monoclonal plasma cells at ≥ 10% in bone marrow, alongside negative serum and urine electrophoresis and immunofixation test results [22]. However, testing with serum immunoglobulin-free light chains (sFLC) appear to be a more efficient way to measure levels of circulating free κ and λ immunoglobulin light chains unbound to heavy chains [23]. Indeed, it has been proven to be invaluable in diagnosing MM as it can detect the less frequent subtype light-chain multiple myeloma, which has a more aggressive course and poorer prognosis of MM, often overlooked due to its minimum urine excretion of free-light-chains [24, 25]. Similarly, the imbalance of sFLC can be detected at diagnosis in 70% of patients having non-secretory MM, and in nearly all patients with light chain only MM [26, 27]. One study suggests that, owing to the heightened sensitivity and accuracy of sFLC, urinalysis may seldom be necessary for diagnosing and monitoring such patients [25].

The utilization of sFLC has also demonstrated prognostic significance in evaluating response and monitoring disease progression, despite the absence of recommendations for serum free light chain monitoring during therapy. Recent research highlights that achieving sFLC normalization during treatment serves as a crucial and straightforward method for assessing prognostic factors in MM [28]. Additionally, incorporating a normal sFLC ratio into the definition of complete response, alongside conventional criteria, is proposed [23]. Furthermore, an increase of at least 25% from the lowest difference between involved and uninvolved sFLC levels—where the absolute increase is a minimum of 100 mg/L—is suggested as an indicator of disease progression [23, 28].

Lactate Dehydrogenase (LDH)

Lactate dehydrogenase (LDH) is an enzyme involved in glycolysis that actively converts pyruvate to lactate within a reversible reaction of reducing NAD+. There exist five isomers of LDH in tetrameric form but can be classified into two subunits of muscle and heart [29]. Since the 1950's, it has been known that an increase in glycolytic processes is an important characteristic of cancer [30]. In 1991, it was argued that LDH levels could be used as a predictor of poor prognosis and help select MM patients for more intensive therapy [31].

LDH is notably not a diagnostic biomarker for multiple myeloma. There is evidence of its correlation with ß2-microglobulin, creatinine, and thymidine kinase levels within blood serum, but at the onset of MM, LDH levels tend to be low [32]. Nonetheless, LDH levels have prognostic importance and have been integrated into the International Staging System (ISS). One study of just under a thousand patients found that patients with a high LDH (11% of the population) concentration have an overall survival of 22 months vs. 76 months in the normal LDH groups [33].

Another caveat to the disease is that patients with MM run the risk of developing extramedullary plasmacytomas,

the occurrence of myeloma tumors in organs such as the throat and lungs. These patients have been found to have an increase in LDH up to 7556 U/L, far over the normal range of 140-280 U/L [29, 34]. That said, what is considered to be a normal value does vary with some studies, such as the aforementioned overall survival study considering any LDH value over 240 U/L to be high [33]. Mechanistically it is understood that LDH levels increase in serum as a result of clotting, a feature commonly found in instances of extramedullary plasmacytomas [29].

Quantifying LDH serum levels carries many benefits. It is inexpensive and does not put an undue burden on the patient when they are already undergoing other blood tests as part of the standard of care [35]. The test costs less than $100 USD and can easily be implemented as another step within a routine test. Thus, there are few limitations in quantifying LDH serum levels, and would rather like to emphasize that LDH is a prognostic biomarker used to provide possible insights about a patient's MM rather than diagnose them with MM.

Circulating Tumor DNA

Circulating tumor DNA (ctDNA) is gaining recognition as a valuable non-invasive prognostic biomarker for longitudinal assessment of solid tumors [36]. Compared to other serological markers, ctDNA provides a more accurate assessment of tumor burden [36]. This is especially intriguing given the limitations of interventional biopsies for assessing molecular residual disease (MRD), such as variability in sample quality and dilution in bone marrow samples. Moreover, the procedures of collecting tumor DNA acquired via BM may be difficult, painful, and associated with rare but significant complications, such as infections [37].

ctDNA, which can be extracted from peripheral blood (PB), offers a promising alternative for MRD assessment [38]. Indeed, the findings of one study, analyzing the protein-coding exons of genes KRAS, NRAS, BRAF, EGFR, and PIK3CA in 64 ctDNA samples in MM patients, revealed that this approach accurately predicted 96% of mutations detected in corresponding bone marrow-derived tumor DNA samples, with a specificity of over 98% [37]. However, in terms of test sensitivity, the present evidence showed no superiority of ctDNA over biopsy. Additionally, in another study, ctDNA targeted next-generation sequencing analysis unveiled a broader genomic landscape in comparison to bone marrow aspirates among individuals newly diagnosed with multiple myeloma [39]. The researchers discovered that ctDNA, when contrasted with bone marrow samples, displayed a greater diversity of driver mutations within shared driver genes, elevated counts of uniquely mutated genes and subclonal clusters, increased incidence of translocation-associated mutations, and higher frequencies of mutated genes enriched in the transcriptional regulation pathway. These findings, which provide extensive insights into genomic instability, underscore the significance of ctDNA as a biomarker for risk assessment in newly diagnosed multiple myeloma cases compared to bone marrow analysis.

As we continue to define more accurate circulating gene targets, particularly those indicative of the most frequently mutated genes in tumor tissue, there is optimism for enhancing the sensitivity of ctDNA testing [40]. In addition, although there may currently be no significant differences in sensitivity, ctDNA still may be the better therapeutic option since it is less invasive.

Research has demonstrated that analyzing ctDNA may enable the early identification of MM patients at risk of relapse before conventional clinical parameters can detect it [37]. Moreover, given the non-invasive nature and short half-life of ctDNA, it can offer real-time insights into tumor dynamics during therapy, potentially signaling early responses or resistance to treatment [40].

Cell-free DNA

Cell-free DNA (cfDNA) is fragmented DNA that is found within the bloodstream, not necessarily from tumor origin, and is used as a biomarker in liquid biopsies for MM. The presence of higher levels of cfDNA in cancer patients has been known since 1977, but with the advancement of technologies such as polymerase chain reaction and next generation sequencing, has increased the utilization of cfDNA over the past three decades [41]. While these modalities exist, they are extremely expensive with next generation sequencing for patients costing approximately $3,600 for one run per patient [42]. For patients with MM, cfDNA provides a non-invasive alternative to bone marrow aspirates, as taking an aspirate from a single location fails to elucidate the spatial heterogeneity of MM and fails to provide a complete genetic profile of tumors. Like other biomarkers, cfDNA can be used as a prognostic measurement.

Specifically, cfDNA can be used as an efficient way to predict response to treatment in MM. Mithraprabhu et al. (2019) demonstrated that a decrease in cfDNA levels 5 days after treatment was a strong predictor of increased progression free survival [43]. Although one study found that bone marrow cfDNA samples have a higher DNA yield per sample compared to peripheral blood cfDNA (2462 ng vs. 1408 ng), the easy access to peripheral blood draws makes blood biopsy cfDNA a better longitudinal lab test to evaluate the progression of MM [44].

Mutational profiling is also a continuously developing keystone feature of using cfDNA quantification. It is well characterized that N and K-RAS mutations occur in approximately 50% of multiple myeloma cases and that BRAF gene mutations occur in approximately 4% of cases [45, 46]. Being able to detect these mutations via cfDNA, however, has been a challenge with some studies only being able to detect mutations in a small number of patients [44, 47]. This caveat might suggest that mutational profiling is possible in cfDNA, but ctDNA is a more viable modality of

detecting mutations. While cfDNA from blood biopsies is a promising advancement to the field of MM biomarkers, further investigations are necessary to address its limitations as compared to other biomarkers such as ctDNA and cfDNA from bone marrow aspirates.

Bone Lesion Imaging

Imaging for MM has been used as a modality to assess disease burden and identify bone lytic lesions, locations where bone has been destroyed by the disease. Approximately 80% of patients with MM will develop myeloma bone disease suffering destructive lesions [48]. Importantly, other markers used for staging MM fail to account for the spatial heterogeneity of the disease, highlighting a gap that imaging techniques help address [49].

Full body skeletal surveys with conventional radiography tended to be the standard imaging practice to assess MM, but modern high performance imaging techniques have taken over [50]. The utilization of (18)fluorine-fluorodeoxyglucose ((18)F-FDG) positron emission tomography/computed tomography (PET/CT) has become the gold standard of MM imaging; this technique has demonstrated superiority over planar radiographs in 46% of patients [51]. When coupled with a magnetic resonance imaging (MRI) regimen this approach was able to successfully detect sites of active MM in 92% of cases both medullary and extramedullary [51]. A shortcoming of (18)F-FDG PET/CT is that it has a poor sensitivity to bone marrow infiltration, but makes up for this by being able to anticipate future fractures and can easily discriminate old from newly developing pathological fractures [52]. This makes 18(F)-FDG an ideal assessor of disease progression and disease response to treatment modalities (radiotherapy or chemotherapy).

There are situations when MRI is a favored imaging technique. Specifically, dynamic contrast-enhanced MRI which uses an intravenous Gadolinium-containing contrast agent paired with pharmacokinetic models can be used to quantify variables such as blood volume, capillary surface exchange, vessel permeability, and local perfusion by assessing contrast agent signal intensity [53]. These variables are harder to derive from (18F)-FDG PET/CT and provide practitioners with a deeper understanding of the status of bodily processes within the patient. There should also be a preference to use MRI when vertebral bodies involvement is suspected [52].

Both (18)F-FDG and MRI play specific roles within the diagnosis, prognosis, and follow-up of MM. (18)F-FDG carries a prognostic value for patients even after receiving chemotherapy or receiving autologous stem cell transplantation, making it the ideal imaging biomarker for assessing progression free survival and overall survival [54]. These techniques have also been added to the Durie-Salmon staging system in the mid-2000's [55]. Combining the Revised International Staging System with (18)F-FDG PET/CT has similarly shown that this imaging carries a strong prognostic power by correlating focal lesions to patients staging and overall survival [56]. Imaging as a biomarker can help physicians determine the burden of MM and assess how best to treat the patient. These approaches will no doubt become more accurate and comprehensive in characterizing the nature of MM.

Discussion

Biomarkers are undoubtedly transforming the standard of care of multiple myeloma for the betterment of all patients. M-Protein remains the gold standard for diagnosing multiple myeloma, but other liquid biopsy measurements (FLC, LDH, ctDNA, cfDNA) and imaging evaluations have become crucial in diagnosing, treating, and understanding the heterogeneity of the disease. The utilization of circulating blood liquid biopsies is a particularly promising approach to measure biomarkers in these patients as it eliminates the invasiveness of traditional bone marrow aspirates and provides medical oncologists with accurate data. In the era of personalized targeted therapy, understanding the importance of these biomarkers will ultimately drive clinical decision making.

Trials such as the MyDrug (NCT03732703) for MM are actively implementing biomarker measurements within their inclusion criteria to help understand specific patient populations and their response to commonly used therapeutic drugs (venetoclax, cobimetinib, dexamethasone, etc.) [57]. These trials have further advanced the understanding in the field that these biomarkers cannot be analyzed alone. Rather, multiple biomarkers must be used to assess the full landscape of the patient's disease. As more studies elucidate the mechanisms and presence of different biomarkers in MM, the ISS for MM patients will become more precise, hopefully leading to less variability between studies.

The patient needs to remain the priority as more biomarkers are found. There arise multiple ethical considerations in the use of biomarkers. Informed consent and patient education must be the first step before testing for biomarkers, especially within large scale clinical trials. Having access to measure biomarkers does not mean every patient needs to be put through blood biopsies daily or bone marrow aspirations constantly to measure these markers. Many of these trials are funded by third-parties and as such patient privacy needs to be maintained; biomarker data are protected by health privacy laws and patients need to understand how their data is being used at all times [58]. These ethical concerns are intensified in situations dealing with patients who are unable to give informed consent themselves such as children under the age of 18 [59]. Biomarkers are a keystone in modern MM treatment, but the ability to measure a biological specimen carries great responsibility for both basic scientists and clinicians.

We acknowledge that this review is not completely comprehensive due to the scope and nature of a literature review. While this article does not evaluate every biomarker used in the field of multiple myeloma research, we believe it

highlights some of the most important and commonly used biomarkers in the field today. Furthermore, the reviewed biomarkers provide a combination of both traditional and rising biomarkers for the field. We also recognize that we were limited in our search to articles published and indexed within article databases. Most modern academic journals have indexing with databases such as PubMed and Google Scholar, but it is possible some articles were inaccessible or unsearchable as a result of lack of indexing or due to articles being published outside our chosen range as indicated in the methods section.

Conclusions

Biomarkers in multiple myeloma is a rapidly advancing field of translational science which is influencing daily clinical decision making. Further studies need to be done to limit variability in biomarker standards as well as to broaden our understanding of the correlations between biomarkers and disease progression.

List of Abbreviations Used

(18)F-FDG: (18)fluorine-fluorodeoxyglucose
cfDNA: cell-free DNA
CT: computed tomography
ctDNA: circulating tumor DNA
DNA: deoxyribonucleic acid
FLC: free light chains
IGC: immunoglobulin heavy chain
ISS: International Staging System
LDH: lactate dehydrogenase
M protein: myeloma protein
MGUS: monoclonal gammopathy of undetermined significance
MM: multiple myeloma
MRD: molecular residual disease
MRI: magnetic resonance imaging
PET: positron emission tomography
sFLCL serum immunoglobulin-free light chains
SMM: smoldering multiple myeloma

Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval and/or Participant Consent

Ethics approval was not required because this review only sought to examine previously published research.

Authors' Contributions

AM: Contributed to the design and planning of the study, collected and analyzed data, drafted the manuscript, and gave final approval of the version to be published.
LCW: Contributed to study design and planning, assisted with the collection and analysis of data, drafted the manuscript, and gave final approval of the version to be published.

Acknowledgements

The authors would like to acknowledge our mentor Liliane Kreuder, and express our deep appreciation for her valuable feedback, guidance, and support throughout the entire process of producing this paper.

Funding

This study was not funded.

References

[1] International Agency for the Research on Cancer. Global Cancer Observatory: Multiple Myeloma. In: World Health Organization, editor. 2022.
[2] Waldschmidt JM, Vijaykumar T, Knoechel B, Lohr JG. Tracking myeloma tumor DNA in peripheral blood. Best Pract Res Clin Haematol. 2020;33(1):101146. https://doi.org/10.1016/j.beha.2020.101146
[3] Bustoros M, Mouhieddine TH, Detappe A, Ghobrial IM. Established and Novel Prognostic Biomarkers in Multiple Myeloma. Am Soc Clin Oncol Educ Book. 2017;37:548-60. https://doi.org/10.1200/EDBK_175175
[4] Abeykoon JP, Tawfiq RK, Kumar S, Ansell SM. Monoclonal gammopathy of undetermined significance: evaluation, risk assessment, management, and beyond. Fac Rev. 2022;11:34. https://doi.org/10.12703/r/11-34
[5] Abduh MS. An overview of multiple myeloma: A monoclonal plasma cell malignancy's diagnosis, management, and treatment modalities. Saudi J Biol Sci. 2024;31(2):103920. https://doi.org/10.1016/j.sjbs.2023.103920
[6] Dyer MJS, Akasaka T, Capasso M, Dusanjh P, Lee YF, Karran EL, et al. Immunoglobulin heavy chain locus chromosomal translocations in B-cell precursor acute lymphoblastic leukemia: rare clinical curios or potent genetic drivers? Blood. 2010;115(8):1490-9. https://doi.org/10.1182/blood-2009-09-235986
[7] Punke AP, Waddell JA, Solimando DA, Jr. Lenalidomide, Bortezomib, and Dexamethasone (RVD) Regimen for Multiple Myeloma. Hosp Pharm. 2017;52(1):27-32. https://doi.org/10.1310%2Fhpj5201-27
[8] Rosiñol L, Beksac M, Zamagni E, Van de Donk NWCJ, Anderson KC, Badros A, et al. Expert review on soft-tissue plasmacytomas in multiple myeloma: definition, disease assessment and treatment considerations. British Journal of Haematology. 2021; 194(3):496-507. https://doi.org/10.1111/bjh.17338
[9] Muchtar E, Dingli D, Kumar S, Buadi FK, Dispenzieri A, Hayman SR, et al. Autologous stem cell transplant for multiple myeloma patients 70 years or older. Bone Marrow Transplantation. 2016;51(11):1449-55. https://doi.org/10.1038/bmt.2016.174

[10] Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. New England Journal of Medicine. 2016;375(8):754-66. https://doi.org/10.1056/NEJMoa1606038

[11] Plesner T, Krejcik J. Daratumumab for the Treatment of Multiple Myeloma. Frontiers in Immunology. 2018;9. https://doi.org/10.3389/fimmu.2018.01228

[12] Nooka AK, Kaufman JL, Hofmeister CC, Joseph NS, Heffner TL, Gupta VA, et al. Daratumumab in multiple myeloma. Cancer. 2019;125(14):2364-82. https://doi.org/10.1002/cncr.32065

[13] Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS. 2010;5(6):463-6. https://doi.org/10.1097/COH.0b013e32833ed177

[14] National Cancer Institute. Biomarker Testing for Cancer Treatment [Internet]. c2021 [updated 2021 Dec 14, cited 2024 Apr 15]. Available from: https://www.cancer.gov/about-cancer/treatment/types/biomarker-testing-cancer-treatment#:~:text=Biomarker%20testing%20is%20a%20way,how%20certain%20cancer%20treatments%20work

[15] Chang JYH, Ladame S. Chapter 1.1 - Diagnostic, prognostic, and predictive biomarkers for cancer. In: Ladame S, Chang JYH, editors. Bioengineering Innovative Solutions for Cancer; https://doi.org/10.1016/B978-0-12-813886-1.00001-2: Academic Press; 2020. p. 3-21

[16] Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-20. https://doi.org/10.1200/JCO.2005.04.242

[17] The International Myeloma Working G. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. British Journal of Haematology. 2003;121(5):749-57. https://doi.org/10.1046/j.1365-2141.2003.04355.x

[18] Nau KC, Lewis WD. Multiple myeloma: diagnosis and treatment. Am Fam Physician. 2008;78(7):853-9. https://www.ncbi.nlm.nih.gov/pubmed/18841734

[19] Evliyaoglu O, van Helden J, Jaruschewski S, Imöhl M, Weiskirchen R. Reference change values of M-protein, free light chain and immunoglobulins in monoclonal gammopathy. Clinical Biochemistry. 2019;74:42-6. https://doi.org/10.1016/j.clinbiochem.2019.09.004

[20] Atrash S, Robinson M, Slaughter D, Aneralla A, Brown T, Robinson J, et al. Evolving changes in M-protein and hemoglobin as predictors for progression of smoldering multiple myeloma. Blood Cancer Journal. 2018;8(11):107. https://doi.org/10.1038/s41408-018-0144-x

[21] Schieferdecker A, Hörber S, Ums M, Besemer B, Bokemeyer C, Peter A, et al. Comparison of three different serum-free light-chain assays—implications on diagnostic and therapeutic monitoring of multiple myeloma. Blood Cancer Journal. 2020;10(1):2. https://doi.org/10.1038/s41408-019-0267-8

[22] Corso A, Mangiacavalli S. Non-Secretory Myeloma: Ready for a new Definition? Mediterr J Hematol Infect Dis. 2017;9(1):e2017053. https://doi.org/10.4084/MJHID.2017.053

[23] Tacchetti P, Rocchi S, Zamagni E, Barbato S, Rizzello I, De Cicco G, et al. Role of serum-free light chain assay for defining response and progression in immunoglobulin secretory multiple myeloma. American Journal of Hematology. 2022;97(12):1607-15. https://doi.org/10.1002/ajh.26747

[24] Silva C, Costa A, Paiva D, Freitas S, Alves G, Cotter J. Light-Chain Multiple Myeloma: A Diagnostic Challenge. Cureus. 2021;13(10):e19131. https://doi.org/10.7759/cureus.19131

[25] Bradwell AR, Carr-Smith HD, Mead GP, Harvey TC, Drayson MT. Serum test for assessment of patients with Bence Jones myeloma. The Lancet. 2003;361(9356):489-91. https://doi.org/10.1016/S0140-6736(03)12457-9

[26] Drayson M, Tang LX, Drew R, Mead GP, Carr-Smith H, Bradwell AR. Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. Blood. 2001;97(9):2900-2. https://doi.org/10.1182/blood.V97.9.2900

[27] Mead GP, Carr-Smith HD, Drayson MT, Morgan GJ, Child JA, Bradwell AR. Serum free light chains for monitoring multiple myeloma. British Journal of Haematology. 2004;126(3):348-54. https://doi.org/10.1111/j.1365-2141.2004.05045.x

[28] Klein E-M, Tichy D, Salwender HJ, Mai EK, Duerig J, Weisel KC, et al. Prognostic Impact of Serum Free Light Chain Ratio Normalization in Patients with Multiple Myeloma Treated within the GMMG-MM5 Trial. Cancers. 2021;13(19):4856. https://doi.org/10.3390/cancers13194856

[29] Farhana A, Lappin SL. Biochemistry, Lactate Dehydrogenase: National Center for Biotechnology Information (NCBI); 2023 https://www.ncbi.nlm.nih.gov/books/NBK557536/
[30] Warburg O. On the Origin of Cancer Cells. Science. 1956;123(3191):309-14. https://doi.org/10.1126/science.123.3191.309
[31] Dimopoulos MA, Barlogie B, Smith TL, Alexanian R. High serum lactate dehydrogenase level as a marker for drug resistance and short survival in multiple myeloma. Ann Intern Med. 1991;115(12):931-5. https://doi.org/10.7326/0003-4819-115-12-931
[32] Simonsson B, Brenning G, Kallander C, Ahre A. Prognostic value of serum lactic dehydrogenase (S-LDH) in multiple myeloma. Eur J Clin Invest. 1987;17(4):336-9. https://doi.org/10.1111/j.1365-2362.1987.tb02197.x
[33] Lee H, Jimenez-Zepeda Victor H. The Prognostic Role of Lactate Dehydrogenase at First Relapse of Multiple Myeloma. Acta Haematologica. 2020;143(6):516-7. https://doi.org/10.1159/000506174
[34] Teke HU, Basak M, Teke D, Kanbay M. Serum Level of Lactate Dehydrogenase is a Useful Clinical Marker to Monitor Progressive Multiple Myeloma Diseases: A Case Report. Turk J Haematol. 2014;31(1):84-7. https://doi.org/10.4274/Tjh.2013.0044
[35] Dimopoulos MA, Kastritis E, Roussou M, Gkotzamanidou M, Migkou M, Gavriatopoulou M, et al. Elevated Serum Lactate Dehydrogenase (LDH) Should Be Included Among the Variables Which Define High Risk Multiple myeloma. Blood. 2010;116 (21):2969. https://doi.org/10.1182/blood.V116.21.2969.2969
[36] Cescon DW, Bratman SV, Chan SM, Siu LL. Circulating tumor DNA and liquid biopsy in oncology. Nature Cancer. 2020;1(3):276-90. https://doi.org/10.1038/s43018-020-0043-5
[37] Kis O, Kaedbey R, Chow S, Danesh A, Dowar M, Li T, et al. Circulating tumour DNA sequence analysis as an alternative to multiple myeloma bone marrow aspirates. Nature Communications. 2017;8(1):15086. https://doi.org/10.1038/ncomms15086
[38] Dhakal B, Sharma S, Balcioglu M, Shchegrova S, Malhotra M, Zimmermann B, et al. Assessment of Molecular Residual Disease Using Circulating Tumor DNA to Identify Multiple Myeloma Patients at High Risk of Relapse. Front Oncol. 2022;12:786451. https://doi.org/10.3389/fonc.2022.786451
[39] Liu Y, Guo J, Yi Y, Gao X, Wen L, Duan W, et al. Circulating Tumor DNA: Less Invasive, More Representative Method to Unveil the Genomic Landscape of Newly Diagnosed Multiple Myeloma Than Bone Marrow Aspirates. Cancers. 2022; 14(19):4914. https://doi.org/10.3390/cancers14194914
[40] Tan X, Yan H, Chen L, Zhang Y, Sun C. Clinical Value of ctDNA in Hematological Malignancies (Lymphomas, Multiple Myeloma, Myelodysplastic Syndrome, and Leukemia): A Meta-Analysis. Front Oncol. 2021;11:632910. https://doi.org/10.3389/fonc.2021.632910
[41] Leon SA, Shapiro B, Sklaroff DM, Yaros MJ. Free DNA in the serum of cancer patients and the effect of therapy. Cancer Res. 1977;37(3):646-50. https://www.ncbi.nlm.nih.gov/pubmed/837366
[42] Carlson JJ, Eckert B, Zimmerman M. Cost-effectiveness of next-generation sequencing minimal residual disease testing during maintenance treatment for multiple myeloma. Journal of Clinical Oncology. 2019;37(15_suppl):e19529-e. https://doi.org/10.1200/JCO.2019.37.15_suppl.e19529
[43] Mithraprabhu S, Hocking J, Ramachandran M, Choi K, Klarica D, Khong T, et al. DNA-Repair Gene Mutations Are Highly Prevalent in Circulating Tumour DNA from Multiple Myeloma Patients. Cancers (Basel). 2019;11(7). https://doi.org/10.3390/cancers11070917
[44] Abelman DD, Eagles J, Pedersen S, Danesh A, Croucher D, Bruce JP, et al. Cell-Free DNA from Blood or Bone Marrow as Alternatives to Bone Marrow Cells for Molecular Diagnostics and Monitoring of Multiple Myeloma. Blood. 2023;142: 4693. https://doi.org/10.1182/blood-2023-173685
[45] Bezieau S, Devilder MC, Avet-Loiseau H, Mellerin MP, Puthier D, Pennarun E, et al. High incidence of N and K-Ras activating mutations in multiple myeloma and primary plasma cell leukemia at diagnosis. Hum Mutat. 2001;18(3):212-24. https://doi.org/10.1002/humu.1177
[46] O'Donnell E, Raje NS. Targeting BRAF in multiple myeloma. Cancer Discov. 2013;3(8):840-2. https://doi.org/10.1158/2159-8290.CD-13-0297
[47] Ye X, Li W, Zhang L, Yu J. Clinical Significance of Circulating Cell-Free DNA Detection in Multiple Myeloma: A Meta-Analysis. Front Oncol. 2022;12: 852573. https://doi.org/10.3389/fonc.2022.852573
[48] Hameed A, Brady JJ, Dowling P, Clynes M, O'Gorman P. Bone disease in multiple myeloma: pathophysiology and management. Cancer Growth Metastasis. 2014;7:33-42. https://doi.org/10.4137/CGM.S16817
[49] Wallington-Beddoe CT, Mynott RL. Prognostic and predictive biomarker developments in multiple myeloma. J Hematol Oncol. 2021;14(1):151. https://doi.org/10.1186/s13045-021-01162-7

[50] Spinnato P, Filonzi G, Conficoni A, Facchini G, Ponti F, Sambri A, et al. Skeletal Survey in Multiple Myeloma: Role of Imaging. Curr Med Imaging. 2021; 17(8):956-65. https://doi.org/10.2174/1573405617666210126155129
[51] Zamagni E, Nanni C, Patriarca F, Englaro E, Castellucci P, Geatti O, et al. A prospective comparison of 18F-fluorodeoxyglucose positron emission tomography-computed tomography, magnetic resonance imaging and whole-body planar radiographs in the assessment of bone disease in newly diagnosed multiple myeloma. Haematologica. 2007;92(1):50-5. https://doi.org/10.3324/haematol.10554
[52] Dammacco F, Rubini G, Ferrari C, Vacca A, Racanelli V. (1)(8)F-FDG PET/CT: a review of diagnostic and prognostic features in multiple myeloma and related disorders. Clin Exp Med. 2015;15(1):1-18. https://doi.org/10.1007/s10238-014-0308-3
[53] Delorme S, Baur-Melnyk A. Imaging in multiple myeloma. Recent Results Cancer Res. 2011;183:133-47. https://doi.org/10.1007/978-3-540-85772-3_7
[54] Mesguich C, Hulin C, Latrabe V, Lascaux A, Bordenave L, Hindié E. 18F-FDG PET/CT and MRI in the Management of Multiple Myeloma: A Comparative Review. Frontiers in Nuclear Medicine. 2022;1. https://doi.org/10.3389/fnume.2021.808627
[55] Durie BG. The role of anatomic and functional staging in myeloma: description of Durie/Salmon plus staging system. Eur J Cancer. 2006;42(11):1539-43. https://doi.org/10.1016/j.ejca.2005.11.037
[56] Cho HJ, Jung S-H, Jo J-C, Lee YJ, Yoon SE, Park S-S, et al. Development of a new risk stratification system for patients with newly diagnosed multiple myeloma using R-ISS and 18F-FDG PET/CT. Blood Cancer Journal. 2021;11(12):190. https://doi.org/10.1038/s41408-021-00577-2
[57] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2018 Oct 29 - .Identifier NCT03732703, Myeloma-Developing Regimens Using Genomics (MyDRUG) (Genomics Guided Multi-arm Trial of Targeted Agents Alone or in Combination With a Backbone Regimen); 2021 Sept. [cited 2024 Apr 15]. Available from: https://clinicaltrials.gov/study/NCT03732703?id=NCT03732703&rank=1&tab=table
[58] Schulte PA, Hunter D, Rothman N. Ethical and social issues in the use of biomarkers in epidemiological research. IARC Sci Publ. 1997(142):313-8. https://www.ncbi.nlm.nih.gov/pubmed/9354930
[59] Sly PD, Eskenazi B, Pronczuk J, Sram R, Diaz-Barriga F, Machin DG, et al. Ethical issues in measuring biomarkers in children's environmental health. Environ Health Perspect. 2009;117(8):1185-90. https://doi.org/10.1289/ehp.0800480

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Liliane Kreuder, Alita Gideon
Article Dates: Received Apr 15 24; Accepted Jun 06 24; Published Aug 20 24

Citation
Please cite this article as follows:
Miners A, Walsh LC. Rising biomarkers in the diagnosis of multiple myeloma: A narrative review. URNCST Journal. 2024 Aug 20: 8(8). https://urncst.com/index.php/urncst/article/view/599
DOI Link: https://doi.org/10.26685/urncst.599