Knowledge of genetic mutations and how these affect patient outcomes is rapidly expanding in the care of individuals diagnosed with multiple myeloma (MM). Genetic analysis of bone marrow biopsies now provides information about diagnosis, response to treatment, and prognosis. Oncology nurses need to understand the science and meaning of bone marrow biopsy reports, including the implications of genetic alterations and minimal residual disease. This will allow them to provide care, support, and education related to MM and its treatment to patients and their families.

**AT A GLANCE**
- Cytogenetics should be considered an integral part of treatment management in patients with MM.
- Minimal residual disease testing should be performed in patients who have a complete response to treatment.
- Oncology nurses should educate themselves on gene mutations that identify a patient as having high-risk disease.

**Multiple Myeloma**
Detecting genetic changes through bone marrow biopsy and the influence on care

Donna Catamero, ANP-BC, OCN®, CCRC

Multiple myeloma, or MM, is a cancer of the plasma cells, which are found in the bone marrow and are important in immune system function. Plasma cells are responsible for producing antibodies; they respond to infection. Bone marrow analysis is a significant element in establishing the diagnosis of MM and provides necessary information on the genetic makeup of the plasma cells (Dimopoulos et al., 2011). The cause of MM remains unclear; genetic mutations are not inherited but occur during a person’s lifetime. Some of these mutations play a critical role in regulating cell division, resulting in the excessive proliferation of plasma cells that distinguish MM from other diseases (Morgan, Walker, & Davies, 2012). In addition, advances in technology and the mapping of the human genome have led to discoveries that abnormalities in the expression or number of some specific genes are associated with the risk for early relapse of MM (Rajan & Rajkumar, 2015). Identifying genetic abnormalities helps providers predict the outcome of treatment for patients (see Figure 1).

**Diagnosis and Response Assessment**
To diagnose MM, a bone marrow biopsy must be performed (Dimopoulos et al., 2011). Biopsies are performed at specific time points throughout the disease course. This is to (a) confirm the initial diagnosis; (b) differentiate among monoclonal gamopathy of undetermined significance (MGUS), smoldering myeloma (patients are more likely to progress to MM), and MM; (c) assess the disease at 90–100 days post-stem cell transplantation; (d) confirm remission at any time point; and (e) evaluate burden of disease and further genetic changes at each disease progression (Rajkumar et al., 2011). Despite advances in patient outcomes, more genetic markers need to be identified to improve risk prediction and to expand targeted therapy choices.

Cytogenetics, which is a technique of analyzing cells for chromosome abnormalities in MM, can be assessed by karyotype and fluorescence in situ hybridization (FISH). A karyotype is a picture of a patient’s chromosomes. It can assess the appearance of the chromosomes and evaluate for deletions, additions, and translocations. FISH studies are important to help classify patients with MM into standard-, intermediate-, and high-risk groups. Patients with standard risk have the presence of chromosomal abnormalities t(11;14), t(6;14), or hyperdiploidy, whereas those with intermediate risk have the presence of t(4;14), del 13, or hypodiploidy, and those with high risk have the presence of del 17p, t(14;16), or t(14;20) (Mikhail et al., 2013). Cytogenetic abnormalities in MM influence every aspect of the disease, including progression from MGUS, a benign condition, to MM, as well as a patient’s risk of relapse and his or her clinical presentation (Bergsagel, Mateos, Gutierrez, Rajkumar, & San Miguel, 2013).

Flow cytometry is a method used to examine cell surface markers, as well as the number and genetic characteristics of cells taken from bone marrow. Flow cytometry
also confirms the differential diagnosis between MM and other plasma cell-related disorders, such as Gaucher disease, Kaposi sarcoma, myasthenia gravis, and pernicious anemia (Paiva et al., 2010). Flow cytometry can be used to identify high-risk MGUS and smoldering myeloma. It has become a valuable method to monitor minimal residual disease (MRD) and evaluate the depth of response (Kumar et al., 2018). MRD testing is performed in patients who have undergone therapy and have a complete response. Patients with MM who achieve a complete response have no evidence of disease in the serum or in the bone marrow. Those who have a complete response to treatment and are found to be MRD negative in their bone marrow biopsy by flow cytometry have better survival than those who are MRD positive (Liu et al., 2012).

**FIGURE 1.**
TESTS ON BONE MARROW ASPIRATE AND BIOPSY SPECIMENS

**CYTOGENETIC ANALYSIS**
Detects chromosomal changes in MM

**FLOW CYTOMETRY**
Analyzes B-cell surface markers in MM; determines lineage and stage of differentiation

**FLUORESCENCE IN SITU HYBRIDIZATION**
Establishes clonality of a cell population, determines cell lineage, rearranges B-cell and T-cell receptor genes, and detects minimal residual disease in MM

**GENE EXPRESSION PROFILING**
Quantifies the expression of 70 genes commonly altered in MM; primarily used as a prognostic tool; assesses risk of disease relapse and survival outcomes

**NEXT-GENERATION SEQUENCING**
Allows for a deeper and more detailed evaluation of MM genetics; identifies diagnostic, prognostic, predictive, and therapeutic biomarkers for MM

**Note.** Based on information from American Cancer Society, 2018; Faiman, 2007; Mitsiades et al., 2011.

With the growing use of MRD assessment, the International Myeloma Working Group updated its response criteria in 2011 to incorporate new designations of complete remission definitions that reflect emerging technologies for disease assessment (Kumar et al., 2016). However, these endpoints have not been proven to be clinically relevant. Clinical investigations are ongoing to determine how to best use this information. Questions under investigation include the following:

- When is it beneficial to escalate therapy for patients who are MRD positive?
- What is the impact of de-escalating therapy to achieve MRD negativity?
- What is the effect of delaying autologous transplantation to achieve MRD negativity following induction therapy?
- Should lenalidomide maintenance therapy be discontinued with sustained MRD negativity (Mailankody et al., 2015)?

**Treatment**
Advances in therapies (including autologous bone marrow transplantation and novel therapies, such as daratumumab, carfilzomib, ixazomib, and elotuzumab) have significantly improved patient outcomes; however, the majority of patients with MM will relapse after initial treatment (Kumar et al., 2018). Next-generation sequencing technology has allowed for a more detailed assessment of the genetic makeup of MM. The main indication for performing next-generation sequencing on the bone marrow sample is for patients with treatment-resistant myeloma (Mitsiades et al., 2011). Next-generation sequencing allows for further risk classification by identifying additional genetic mutations in genes of key cancer pathways, which affect patient outcomes and are targetable by new drugs (Lionetti & Neri, 2017). For example, mutations in the gene that encodes the KRAS protein are frequent in numerous cancers. Trametinib is a treatment approved by the U.S. Food and Drug Administration (FDA) that targets this gene in melanoma (Novartis Pharmaceuticals, 2018). Likewise, mutations in the BRAF gene act as an accelerator for cell growth (Andrulis et al., 2013). Dabrafenib is another FDA-approved agent for melanoma that targets this gene (Novartis Pharmaceuticals, 2017). These agents are not approved in MM and are being investigated in a clinical trial (NCT03091257) for patients who have mutations in the KRAS and BRAF genes.

**Relapse Risk**
Gene expression profiling measures the expression levels of 70 risk-related genes in MM. A risk score is generated and predicts whether a patient is at high or low risk for relapse. Risk scores can be useful in determining which patients may benefit from more aggressive treatment. Gene expression profiling can differentiate myeloma into seven different molecular subgroups, each of which behaves in a clinically different way (Kuiper et al., 2013). For example, some subgroups are more sensitive to proteasome inhibitors (e.g., bortezomib, carfilzomib, ixazomib), whereas others are indolent and pose a low risk for disease progression. Patients in high-risk subgroups are often resistant to drugs (e.g., lenalidomide, bortezomib), and their treatment remains challenging. Identifying patients in these subgroups is important, particularly as more therapeutic options become available. An International Myeloma Working Group updated its response criteria in 2011 to incorporate new designations of complete remission definitions that reflect emerging technologies for disease assessment (Kumar et al., 2016). However, these endpoints have not been proven to be clinically relevant. Clinical investigations are ongoing to determine how to best use this information. Questions under investigation include the following:

- When is it beneficial to escalate therapy for patients who are MRD positive?
- What is the impact of de-escalating therapy to achieve MRD negativity?
- What is the effect of delaying autologous transplantation to achieve MRD negativity following induction therapy?
- Should lenalidomide maintenance therapy be discontinued with sustained MRD negativity (Mailankody et al., 2015)?

"More genetic markers need to be identified to improve risk prediction and expand targeted therapy choices."
Group consensus statement has identified patients with high-risk gene expression profiling as having a poor median overall survival of two years. High-risk patients should be considered for clinical trials (Sonneveld et al., 2016).

**Implications for Nursing and Conclusion**

Bone marrow examination is essential for the diagnosis of and risk classification in MM. In addition, bone marrow biopsies are used for disease assessment and for targeted therapy based on mutations. Clinicians can gain insight into how a patient’s myeloma will behave and determine the best treatment options for each patient. MRD testing in MM may help to determine the intensity of a treatment regimen and how long patients will remain on therapy (Bergsagel et al., 2013). Nurses must understand a patient’s risk stratification. Patients with high-risk disease are most likely to relapse quickly and should be closely monitored for signs of relapse. These patients need clear education and support regarding the importance of close monitoring.

Because staging is significant in MM, the genetic makeup of a patient’s MM is revolutionizing how agents are selected for treatment. Treatment is becoming more individualized, based on mutations found with bone marrow biopsy (Bergsagel et al., 2013). Oncology nurses will need to reinforce information about why a specific agent is being selected for treatment and the management of side effects associated with that agent. Nurses must be informed of evolving technology for disease and risk assessment and the clinical applications of these technologies. MM is a difficult disease for many to comprehend. The emerging genetic evaluation of MM makes understanding the disease process even more complicated (Kurtin & Fairman, 2013). Nurses are challenged to provide continuous patient education and reinforcement of information related to the meaning of bone marrow biopsy results. Patients and families will need support and time, in many cases, to absorb the meaning of these results. The diagnostic and follow-up periods can be stressful, and nurses can provide support and encouragement to assist patients and families in coping with a diagnosis of MM.

**Donna Catamero, ANP-BC, OCN®, CCRC, is a nurse practitioner at Mount Sinai Hospital in New York, NY. Catamero can be reached at donna.catamero@mountsinai.org, with copy to CJONEditor@ons.org.**

The author takes full responsibility for this content. Catamero has previously consulted for Celgene Corporation and has received additional support for participation on speakers bureaus for medical and pharmaceutical companies, including Amgen, Celgene Corporation, Janssen Pharmaceuticals, and Takeda.

**REFERENCES**