Myeloma Prognostic Risk Signature (MyPRS)

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What is MyPRS

Definition

The Myeloma Prognostic Risk Signature (MyPRS®) (Signal Genetics™) has been developed to estimate the underlying activity of disease progression, in patients diagnosed with active MM. The test may be used as a potentially useful risk stratification tool to predict treatment response to chemotherapy, predict risk of survival and relapse, and tailor therapy selection. Specifically, MyPRS may identify a high-risk patient group for disease progression based on the expression levels of 70 selected genes measured at baseline. It may be helpful to stratify patients into high-, high risk-borderline, low-risk borderline, and low-risk categories to optimize individual treatment.

- Multiple myeloma (MM) is a malignant and often incurable hematological cancer, characterized by the abnormal and uncontrolled proliferation of plasma cells in bone marrow, leading to impaired hematopoiesis and production of monoclonal immunoglobulin (Ig).1,2 The disease is responsible for about 1% of all cancers worldwide and 10 to 15% of all hematological cancers. MM usually affects older adults (median age of onset is 71 and 74 years for men and women, respectively). For the period between 2009 and 2010, the relative world-wide 5-year survival rate was approximately 45%.

- Clinical features of MM include anemia (73%), bone pain (58%), fatigue (32%), and unusual weight loss (25%).3 Diagnostic laboratory and clinical assessments include hypercalcemia, kidney dysfunction, anemia, and bone lesions.4 In general, patients are treated with autologous stem-cell transplantation (ASCT), along with supportive measures, such as pain therapy, administration of bisphosphonates, and irradiation of skeletal/extramedullary lesions.3

- A growing body of research suggests specific genetic lesions play an important role in the tumor biology of MM. Furthermore, the high number of chromosomal
aberrations and multiple changes in gene expression of these lesions has demonstrated that the underlying genetic features of MM tumor cells are responsible for the significant degree of clinical heterogeneity typically observed in this disease. Several molecular subtypes, each with a unique path of pathogenesis and clinical presentation, have also been identified. The inherent molecular heterogeneity of the disease is believed to translate into highly variable treatment responses and survival times (ranging from a few months to 15 years or more). Given the considerable heterogeneity of associated outcomes, various prognostic risk factors specific to MM have been identified to predict the course of disease, define individualized treatment strategies, predict survival, and enhance overall therapeutic decision making.

- Conventional cytogenetic methods, such as karyotyping and fluorescence in situ hybridization (FISH), are used in clinical practice to assess disease prognosis and stratify MM patients based on recurrent chromosomal changes. Risk stratification is intended to ensure patients receive proper treatment, depending on disease severity. One available risk stratification strategy is the evidence-based algorithm, the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART), used to inform treatment decisions for patients with newly diagnosed disease. However, given the heterogeneity of MM, conventional prognostic methods may not accurately estimate risk.

**Test information**

- According to Signal Genetics, the MyPRS test uses the Affymetrix GeneChip® 3000Dx v.2 System, a whole-genome microarray platform, and requires at least 20,000 CD138+ plasma cells in order to obtain sufficient genetic material for gene expression analysis.

- The MyPRS gene expression profiling model consists of a continuous gene score that is a linear combination of the 70 genes along with a cutoff, such that patients with a score greater than the cutoff are categorized as high risk and otherwise low risk for disease progression.

- The MyPRS prognostic score has the ability to predict a patient’s likely event-free survival (EFS) and overall survival (OS) at the time of diagnosis or after relapse. The algorithm used to develop this prognostic score was based on mathematical models using microarray technology and multivariate analysis of independent patient cohorts over 8 years of follow-up. Results of the model indicate that on a risk score of 0 (lowest likelihood of risk; good prognosis) to 100 (highest likelihood of risk; poor prognosis), a cut-off point of 45.2 discriminates between low and high risk patients.

- The test also provides results of a molecular subtype (7-class molecular subtype taxonomy), each associated with unique genetic lesions, altered genes, and outcome variation.
• Patients are provided results of virtual karyotyping to predict cytogenic abnormalities associated with MM, which is based on an 816-gene algorithm using gene expression data, and validated against multiple traditional cytogenic techniques.\textsuperscript{8}

• In November 2016, Quest Diagnostics purchased MyPRS assets from Signal Genetics.\textsuperscript{10}

Guidelines and evidence

• The National Comprehensive Cancer Network (NCCN, 2017) Clinical Practice Guidelines stated the following regarding gene expression profiling (GEP):
  
  o “GEP is a powerful and fast tool with the potential to provide additional prognostic value to further refine risk stratification, help therapeutic decisions, and inform novel drug design and development.” \textsuperscript{11}

  o “The NCCN Panel unanimously agreed that although GEP is not currently routinely used in clinical practice during diagnostic workup, GEP is a useful tool and may be helpful in selected patients to estimate the aggressiveness of the disease and individualize treatment.”

  o The NCCN Panel does not make any explicit recommendations for its use in its diagnostic and treatment pathways for cases of MM.

• There is insufficient evidence in the peer-reviewed literature to draw definitive conclusions regarding the analytical validity, clinical validity, and clinical utility of the MyPRS test to accurately provide prognostic risk stratification among patients who are newly diagnosed with MM or who have relapsed following treatment.\textsuperscript{12-15}

  o The evidence base mostly consists of retrospective studies evaluating small numbers of patients that evaluated the strength of the association between the MyPRS score with various survival measures, including post relapse survival, overall survival, and progression-free survival. Although the available studies reported significant associations between MyPRS and survival measures (patients with high MyPRS scores may be at increased risk of relapse and death), with study authors concluding that MyPRS has value as a risk stratification tool, the quality of the overall evidence is low given the retrospective study designs across the evidence base, and the lack of reported accuracy measures, including sensitivity, specificity, PPV, NPV, and clinical utility values. Furthermore, there is little to no evidence regarding the comparative accuracy of MyPRS with FISH testing or MyPRS with karyotyping. It is unknown if MyPRS can be an adequate substitute for FISH testing in patients with MM as part of the routine workup of the disease.

  o Future prospective studies, allocating patients to therapies determined to be most effective based on MyPRS score, with adequate sample sizes, using gold standard diagnostic and/or prognostic measures, are necessary to elucidate its
role as an adjunct to existing risk stratification measures or as a stand-alone test. Well-designed clinical utility studies are also needed to assess whether the MyPRS test leads to improved therapeutic clinical decision-making and improved patient outcomes.

Criteria

- This test is considered investigational and/or experimental.
  - Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.
  - In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

References


Therapy (mSMART) consensus guidelines 2013. Mayo Clinic proceedings. 2013 Apr;88(4):360-76.


