

## **Medical Policy Manual**

**Topic:** Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification

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### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

Microarray-based gene expression profile analysis has been proposed as a means to risk-stratify patients with multiple myeloma to guide treatment decisions.

### **Multiple myeloma**

Multiple myeloma is a genetically complex, neoplasm of plasma cells. Cytogenetic and other laboratory tests identify markers to classify newly diagnosed multiple myeloma patients into high, intermediate and standard clinical risk categories. The level of risk reflects the aggressiveness of the disease, and thus dictates the intensity of initial treatment. Thus, a risk-adapted approach is considered to provide optimal therapy to patients, ensuring intense treatment for those with aggressive disease and minimizing toxic effects delivers sufficient but less-intense therapy for lower-risk disease. However, clinical outcomes may vary substantially, using standard methods, among patients with the same estimated risk who undergo a similar intensity of treatment.

### Pathogenesis and Genetic Architecture of Multiple Myeloma

Multiple myeloma is a complex disease that presents in distinct clinical phases and risk levels. These include monoclonal gammopathy of undetermined significance (MGUS), and smoldering multiple

myeloma, also known as asymptomatic myeloma.<sup>[1]</sup> MGUS is a generally benign condition, with a transformation rate to symptomatic plasma cell disorders of about 1% to 2% annually.<sup>[2]</sup> Smoldering multiple myeloma represents a progression from MGUS to frank multiple myeloma; it has an annual risk for transformation to multiple myeloma of about 10% for the first 5 years.<sup>[2]</sup> Although both of these entities lack many clinical features of multiple myeloma, they may ultimately share characteristics that necessitate therapy. By contrast, symptomatic multiple myeloma is defined by specific clinical symptoms, accumulation of monoclonal immunoglobulin proteins in the blood or urine, and associated organ dysfunction including nephropathy and neuropathy. The acronym, CRAB, is used to reflect the hallmark features of multiple myeloma: calcium elevation; renal insufficiency; anemia; and, bone disease.<sup>[3]</sup> Pre-myeloma plasma cells initially require interaction with the bone marrow microenvironment, but during disease progression, develop the ability to proliferate outside the bone marrow, manifesting as extramedullary myeloma and plasma cell leukemia. These “bone marrow independent” cells represent the end stages in a multistep transformation process from normal to multiple myeloma.

Complex genetic abnormalities commonly identified in multiple myeloma plasma cells are considered to play major roles in disease initiation, progression and pathogenesis, and are used in conjunction with laboratory and radiographic studies to stratify patients for therapeutic decisions.<sup>[4-6]</sup>

### Prognosis and Risk Stratification

Two validated clinical systems have been in widespread use to assess prognosis in newly diagnosed multiple myeloma patients: the Durie-Salmon Staging System (DSS) and the International Staging System (ISS).<sup>[3,7]</sup> The more than 30-years old DSS provides a method to measure multiple myeloma tumor burden, according to multiple myeloma cell numbers and clinical, laboratory and imaging studies, but is recognized to have significant shortcomings due to the use of observer-dependent studies (e.g., radiographic evaluation of bone lesions) primarily focused on tumor mass, not behavior. The ISS, incorporating serum albumin and  $\beta$ 2-microglobulin measures, is considered valuable to permit comparison of outcomes across clinical trials and is more reproducible than the DSS. However, the ISS is useful only if a diagnosis of multiple myeloma has already been made; it has no role in MGUS, smoldering multiple myeloma or other related plasma cell dyscrasias.<sup>[3]</sup> It also does not provide a good estimate of tumor burden; is not generally useful for therapeutic risk stratification; and, may not retain prognostic significance in the era of novel drug therapies.<sup>[5]</sup>

Although multiple myeloma cells may appear morphologically similar across risk levels, the disease exhibits substantial genetic heterogeneity that may change with progression or at relapse.<sup>[4,6]</sup> Investigators have used conventional cytogenetic methods (karyotyping) and fluorescence in situ hybridization (FISH) to prognostically stratify multiple myeloma patients according to a host of recurrent chromosomal changes (immunoglobulin heavy chain translocations, chromosome deletions, or amplifications). This stratification forms the basis of the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART), an evidence-based algorithm to make treatment decisions for patients with newly diagnosed multiple myeloma.<sup>[8]</sup> (Table 1).

**Table 1. Mayo Clinic Stratification of Multiple Myeloma and Risk-Adapted Therapy (mSMART)<sup>[8]</sup>**

High Risk	Intermediate Risk	Standard Risk
Any of the following:	t(4;14) by FISH	All others including:

Del 17p	Cytogenetic del 13	t(11;14) by FISH
t(14;16) by FISH	Hypodiploidy	t(6;14) by FISH
t(14;20) by FISH	Plasma cell labeling index >3.0	Incidence: 60%
GEP high-risk signature*	Incidence: 20%	Median OS (yrs): 8-10
Incidence: 20%	Median OS (yrs): 4-5	
Median overall survival (OS) (yrs): 3		

In addition to the cytogenetic characteristics noted in Table 1, other findings are typically considered in this model (Table 2). Although GEP analysis is included in Tables 1 and 2, the Mayo Clinic does not currently recommend nor routinely performs GEP analysis in a nonresearch setting. However, the investigators suggest GEP analysis will likely play a greater role in management of multiple myeloma as evidence develops.<sup>[8]</sup>

The risk stratification model outlined in Table 1 is meant for prognostication and to determine the treatment approach; it is not utilized to decide whether to initiate therapy, but to guide the type of therapy (see Therapy Synopsis below).<sup>[5]</sup> Furthermore, therapeutic outcomes among individuals in these categories may vary significantly, to the effect that additional means of subdividing patients into response groups are under investigation, in particular molecular profiling using microarray-based methods.

Criteria for the diagnosis, staging, and response assessment of multiple myeloma have been reported by the International Myeloma Working Group and are in widespread use.<sup>[3,5,7]</sup> The decision to treat is based on criteria set forth in the diagnosis of multiple myeloma, which includes serum hypercalcemia, renal dysfunction, anemia and bone lesions (i.e., CRAB). Patients with MGUS or smoldering myeloma do not require therapy, irrespective of any associated risk factors, except on specifically targeted protocols.

According to the Mayo Clinic recommendations, a large number of prognostic factors have been validated and categorized into three main groups: tumor biology, tumor burden, and patient-related factors. These must be considered to individualize the choice of therapy in multiple myeloma patients.(Table 2).<sup>[8]</sup>

**Table 2. Prognostic factors in multiple myeloma<sup>[8]</sup>**

Tumor biology	Tumor burden	Patient-related
Ploidy	Durie-Salmon stage	Eastern Cooperative Oncology Group performance status
17p- (p53 deletion)	International Staging System stage	Age
t(14;16)	Extramedullary disease	Renal function
t(14;20)		
t(4;14)		
Deletion 13 on conventional cytogenetics		

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Alterations in chromosome 1

t(11;14)

t(6;14)

Lactate dehydrogenase levels

Plasma cell proliferative rate

Presentation as plasma cell leukemia

High-risk GEP signature\*

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\*The Mayo Clinic does not currently recommend nor routinely performs GEP analysis in a nonresearch setting. However, the authors suggest GEP analysis will likely play a greater role in management of multiple myeloma as evidence develops.

### Therapy Synopsis

Asymptomatic (smoldering) multiple myeloma and MGUS currently require only ongoing clinical observation, as early treatment with conventional chemotherapy has shown no benefit. However, for symptomatic patients diagnosed with multiple myeloma, prompt induction therapy is indicated. For patients younger than age 65 years who have adequate heart, liver and lung function, this will comprise combinations that may include melphalan, dexamethasone, cyclophosphamide or doxorubicin with thalidomide, lenalidomide, or bortezomib, followed by autologous hematopoietic stem-cell transplantation (HSCT).<sup>[9,10]</sup> Older patients or those with underlying liver, lung, or cardiovascular dysfunction may be candidates for induction followed by reduced-intensity conditioning allogeneic HSCT.<sup>[9]</sup>

A program referred to as Total Therapy, developed primarily at the University of Arkansas for Medical Science and Mayo Clinic, utilizes all available agents as induction, followed by 2 cycles of high-dose melphalan and autologous HSCT support, with a 4-years event-free survival as high as 78%.<sup>[9,11]</sup> Despite achievement of complete remission and apparent eradication of disease, the clinical response is transitory in all cases, and multiple myeloma is considered incurable with current approaches.

### **Microarray-based gene expression profile (GEP) analysis**

GEP analysis estimates the underlying activity of cellular biological pathways that control, for example, cell division or proliferation, apoptosis, metabolism, or other signaling pathways. Relative over- or under-expression of these pathways is considered to mirror disease aggressiveness independent of cytogenetics and other laboratory measures. GEP analysis has been proposed as a means to more finely stratify multiple myeloma patients into risk categories to personalize therapy selection according to tumor biology, with the goal of avoiding over- or under-treating patients. It could be used as a supplement to existing stratification methods or as a stand-alone test, but further study is necessary to establish its role.

The term, “gene expression” refers to the process by which the coded information of genes (DNA) is transcribed into messenger RNA (mRNA) and translated into proteins. A gene expression profile (GEP) assay examines the patterns of many genes in a tissue sample at the same time to assess those that are actively producing mRNA or not, ultimately producing proteins or not. By simultaneously measuring

the cellular levels of mRNA of thousands of genes, a GEP test creates a picture of the rate at which those genes are expressed in a tissue sample.

GEP tests are not “genetic” tests. Genetic tests measure an individual DNA signature to identify genetic changes or mutations that remain constant in the genome. Gene expression tests measure the activity of mRNA in a tissue or bodily fluid at a single point, reflecting an individual’s current disease state or the likelihood of developing a disease. However, because mRNA levels are dynamic and change as a result of disease processes or environmental signals, dynamic changes in these processes can be studied over time. This information thus reflects the pathogenic process and in theory can be used to assess the effects of therapeutic interventions or select therapy based on specifically expressed gene targets.

### GEP Test

The MyPRS™/MyPRS Plus™ GEP70 test analyzes all of the “nearly 25,000 genes” in the human genome to determine the level of aggressiveness of diagnosed multiple myeloma based on 70 of the most relevant genes involved in cellular signaling and proliferation.

### **Regulatory Status**

The MyPRS™/MyPRS Plus™ GEP70 test (Signal Genetics LLC, Little Rock, AR) is being offered as a laboratory-developed test. The laboratory performing this test is accredited by the Centers for Medicare and Medicaid (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The test will be performed by Signal Genetics and offered commercially through certain specialty commercial labs (e.g., Caris Life Sciences, Phoenix, AZ)

### **MEDICAL POLICY CRITERIA**

Microarray-based gene expression profile testing for multiple myeloma is considered **investigational** for all indications.

### **SCIENTIFIC EVIDENCE**

Validation of the clinical use of any genetic test focuses on 3 main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

### **Literature Appraisal**

Multiple myeloma is an invariably fatal disease.<sup>[12]</sup> A host of well-characterized factors related to tumor biology, tumor burden and patient-centered characteristics are used to stratify patients into high,

intermediate and standard risk categories for purposes of prognostication and to determine treatment intensity.<sup>[5,8]</sup> However, clinical outcomes have been variable among patients in the same risk category who received similar therapy. Thus, more specific methods have been sought to more finely classify multiple myeloma, including microarray-based GEP analysis that shows the underlying activity of cellular biological pathways that control, for example, cell division or proliferation, apoptosis, metabolism, or other signaling pathways.<sup>[13,14]</sup>

The MyPRS™/MyPRS Plus™ test under evaluation was developed primarily by investigators at the University of Arkansas for Medical Science (UAMS) using microarray-based technology.<sup>[14]</sup> Two key publications reported the application of this method to construct molecular profiles of multiple myeloma in newly diagnosed patients and retrospectively associate treatment outcomes with specific gene expression profiles.<sup>[15,16]</sup>

- In a widely cited validation paper by Shaughnessy and colleagues from UAMS, GEP data were reported for 523 newly diagnosed patients (training group n=351, validation group n=181) who underwent similar treatments for multiple myeloma on National Institutes of Health-sponsored clinical trials (UARK 98-026 and UARK 03-033, respectively).<sup>[15]</sup> Both protocols used induction regimens followed by melphalan-based tandem autologous hematopoietic stem-cell transplantation (HSCT), consolidation chemotherapy and maintenance treatment. Plasma cells were purified from bone marrow aspirates using a fully automated ROBOSEP cell separation system that uses immunomagnetic technology to positively select for CD-138+ cells from which messenger RNA (mRNA) was isolated. These preparations were hybridized to total human genome DNA using Affymetrix U133Plus2.0 microarrays, and ultimately processed to identify 19 underexpressed and 51 overexpressed prognostic genes (GEP70 test) that mapped primarily to chromosome 1 and were linked to short survival among the multiple myeloma patients. A high-risk GEP score, defined by the mean expression levels of up-regulated to down-regulated genes, was observed in 13% of patients who had significantly shorter durations of overall survival (OS) at 5-years compared to those with a low risk score (28% versus 78%, p<0.001; hazard ratio [HR]: 5.16). Absence of a high-risk score identified a favorable subset of patients with a 5-years continuous complete remission of 60%, as opposed to a 3-year rate of only 20% in those with a high-risk GEP70 score. Multivariate analyses suggested significant correlations between OS and event-free survival (EFS), the presence of a high-risk GEP70 score, and laboratory parameters associated with a poor prognosis, including lactate dehydrogenase (LDH), albumin, and β<sub>2</sub>-microglobulin as used in the International Staging System (ISS) (see Background). This evidence suggests a potential connection between a GEP70 test result indicative of high-risk multiple myeloma, and survival of patients treated on the same intensity protocol for this disease. However, this validation study was performed retrospectively on multiple myeloma plasma cells obtained prior to therapy, and associated with those clinical outcomes in a small number of patients treated at one center in the U.S., primarily in the context of autologous HSCT.
- A paper published by Kumar and colleagues in 2011 examined the utility of the GEP70 risk-stratification test among patients undergoing initial therapy with lenalidomide in the context of a Phase III trial.<sup>[16]</sup> Patients with previously untreated multiple myeloma enrolled in the E4A03 trial were randomly allocated to lenalidomide and either standard-dose dexamethasone (40 mg days 1-4, 9-12, and 17-21) or low-dose dexamethasone (40 mg weekly). After the first 4 cycles of therapy, patients could discontinue therapy to pursue HSCT or continue on protocol until progression. Overall, 445 patients were randomized: 222 to the low-dose arm and 2,223 to the high-dose arm. As in the GEP70 UAMS validation study, CD-138+ plasma cells were isolated from bone marrow aspirates of consenting patients. Total mRNA was isolated from those cells and analyzed by high-

density oligonucleotide microarrays containing probes for 50,000 transcripts and variants including 14,500 known human genes (Affymetrix U133Plus2.0 array). The GEP70 signature was determined as described by Shaughnessy in the 2007 report and compared to OS data and other variables. Overall, 7 of 45 patients with adequate mRNA samples (15.6%) were considered high risk by the GEP70 test, similar to the proportion described previously.<sup>[15]</sup> Among patients who had fluorescence in situ hybridization (FISH) cytogenetic data available, 10 of 44 (22.7%) were considered high risk by the presence of t(4;14), t(14;16), t(14;20) or del17p. Six of the FISH high-risk patients and 2 of the standard-risk patients were reclassified into the low- and high-risk categories by GEP70, respectively. The median overall survival (OS) was 19 months for the 7 GEP70 high-risk patients and did not reach the median for the standard-risk group; for 10 high-risk FISH patients, the median OS was 39 months and did not reach median for the standard risk group. The predictive ability of the GEP70 test, estimated using the C-statistic for the GEP70 score dichotomously, was 0.74 (95% confidence interval [CI]: 0.61, 0.88), a value conventionally considered as reflecting a prediction model with good discriminatory ability. The C-statistic for FISH-based risk stratification was 0.70 (95% CI: 0.55, 0.84), very similar to the GEP70 finding. These results suggest the GEP70 test high-risk results are inversely associated with OS among patients treated outside the context of HSCT, in a cohort of patients treated primarily with novel agents. The small number of patients and the retrospective nature of the association between GEP70 scores and survival rates preclude conclusions on the clinical utility of the test in risk stratification and therapeutic decisions, as well as assessment of the incremental value of GEP70 compared to FISH.

#### Analytical Performance of MyPRS™/ MyPRS Plus™

Published data on analytical performance characteristics of the MyPRS™ test was not found. Information available online from the manufacturer of the microarray chip used in this test (Human Genome U133Plus 2.0, Affymetrix, Santa Clara, CA) shows a detection call sensitivity of 1.5 pM, a concentration of messenger RNA (mRNA) that corresponds to approximately 1 transcript in 100,000, or 3.5 copies per cell. The false-positive rate of making a present call for an expressed gene was reported as about 10%, noted by 90% of clone sequences being called absent when not spiked into the test sample (0 pM concentration).

#### **Clinical Practice Guidelines**

##### National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) practice guidelines (V.2.2014) for multiple myeloma state that GEP is emerging as a tool to further decipher the molecular nature of multiple myeloma, including potential use in risk stratification and disease prognostication.<sup>[17]</sup> It eventually may be used to assist in clinical decision making, particularly in therapeutic choice, and to inform novel drug design and development. However, the NCCN cautions that standardized testing for GEP is not yet widely available and clinical evidence is insufficient to determine how the information from available tests can improve health outcomes by directing care management. The NCCN offers no specific recommendation for the use of the MyPRS™ GEP70 test.

#### **Summary**

There is insufficient data on how microarray-based gene expression testing alters clinical practice and clinical health outcomes (clinical utility) in patients with multiple myeloma. Additionally, there are no evidence-based clinical practice guidelines which recommend the use of these tests to prospectively

allocate patients to risk-based therapies for multiple myeloma. Therefore, microarray-based gene expression testing, including the MyPRS™/MyPRS Plus™ GEP70 tests, is considered investigational for all indications, including the classification of multiple myeloma. A trial in which patients with multiple myeloma are randomized to receive treatment based on the results of these tests or on existing risk-stratification methods is needed to determine whether gene-expression testing results in improved treatment decisions and health outcomes.

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## CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
	86849	Unlisted immunology procedure
HCPCS	None	