MEDICAL POLICY – 12.04.97
Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification

BCBSA Ref. Policy: 2.04.97
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Last Revised: Nov. 9, 2017
Replaces: N/A

RELATED MEDICAL POLICIES:
8.01.17  Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
12.04.54  Gene Expression-Based Assays for Cancers of Unknown Primary

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Introduction

Multiple myeloma is a cancer that forms in a type of white blood cell called a plasma cell. Doctors aren’t sure what causes multiple myeloma. Abnormal changes (mutations) in genes have been found in the plasma cells of people who have multiple myeloma. Not everyone with multiple myeloma has the same genetic changes in their plasma cells, and some genetic changes seem to make the cancer more deadly than others. It has been suggested that a type of testing called “microarray-based gene expression profiling” can be used to try to determine the prognosis of an individual’s multiple myeloma. Not enough good quality medical studies have been done to show that this type of testing is reliable and helpful in taking care of multiple myeloma patients. For this reason, microarray-based gene expression profiling is still considered to be unproven (investigational).

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
**Policy Coverage Criteria**

<table>
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<th>Testing</th>
<th>Investigational</th>
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<tbody>
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<td>Microarray-based gene expression profile testing</td>
<td>Microarray-based gene expression profile testing for multiple myeloma is considered investigational for all indications.</td>
</tr>
<tr>
<td></td>
<td><strong>Note:</strong> Commercially available tests include MyPRS™/MyPRS Plus™ GEP70 test.</td>
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See **Related Information** for a key to acronyms used in this policy.

**Coding**

<table>
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<th>Description</th>
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<td>Unlisted multianalyte assay with algorithmic analysis (MAAA)</td>
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<td>86849</td>
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**Related Information**

**Acronym Key**

**CRAB:** This stands for the four clinical features of multiple myeloma: calcium elevation; renal insufficiency; anemia; and, bone disease.
**DSS:** This stands for Durie-Salmon Staging System. One of the two validated clinical system used to assess prognosis in newly diagnosed multiple myeloma patients. The DSS estimates the clinical stage (stage range is 1-3) of disease by assessing multiple myeloma cell numbers, clinical, laboratory and imaging studies. The DSS is primarily focused on tumor mass, rather than tumor behavior. (See **ISS** system)

**GEP:** This stands for gene expression profile. GEP testing measures the activity of messenger RNA (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. GEP tests are not “genetic” tests.

**ISS:** This stands for the International Staging System. One of the two validated clinical systems used to assess prognosis in patients newly diagnosed with multiple myeloma. The ISS divides myeloma into 3 stages based on levels of serum albumin and β2-microglobulin in the blood. The ISS is considered valuable to permit comparison of outcomes across clinical trials, but can only be useful if diagnosis has already been made. (See **DSS** system).

**MGUS:** This stands for monoclonal gammopathy of undetermined significance. MGUS is a generally benign condition, with a transformation rate to symptomatic plasma cell disorders (like multiple myeloma) of about 1% to 2% annually.

### Evidence Review

### Description

Multiple myeloma is a genetically complex, and invariably fatal, disease\(^1\). 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 prognostic purposes, as well as determining treatment intensity. However, clinical outcomes have varied among patients in the same risk category who received similar therapy. Thus, more specific methods have been sought to classify multiple myeloma. One such method being proposed is the utilization of a microarray-based gene expression profile (GEP) analysis, which serves to reveal the underlying activity of cellular biologic pathways. This method lends itself to a variety of benefits including the ability to risk-stratify patients with multiple myeloma, as well as guide treatment decisions.
**Disease Description**

Multiple myeloma is a malignant plasma cell disorder characterized by clonal proliferation of plasma cells derived from B cells in the bone marrow. It accounts for about 1 in every 100 cancers and 13% of hematologic cancers. The American Cancer Society had estimated 21,700 new cases of multiple myeloma would occur in the United States in 2012, and some 10,200 deaths would occur due to the disease. The annual age-adjusted incidence is about 6 cases per 100,000 persons, with a median age-at-diagnosis of about 70 years. Before the advent of current treatment protocols, most patients with multiple myeloma succumbed to their disease within 5 to 10 years; in the pre-chemotherapy era, median survival was less than 1 year. Among patients who present at an age younger than 60 years, 10-year overall survival with current treatment protocols may now exceed 30%.

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. The decision to treat is based on these criteria, which include calcium elevation; renal insufficiency; anemia; and bone disease (CRAB). Patients with monoclonal gammopathy of undetermined significance (MGUS) or smoldering myeloma do not require therapy, irrespective of any associated risk factors, except on specifically targeted protocols.

**Pathogenesis and Genetic Architecture of Multiple Myeloma**

Multiple myeloma is a complex disease that presents itself in distinct clinical phases and risk levels. They include MGUS and smoldering multiple myeloma (also known as asymptomatic myeloma). MGUS is a generally benign condition, with a transformation rate to symptomatic plasma cell disorders of about 1% to 2% annually. Smoldering multiple myeloma represents a progression from MGUS to frank multiple myeloma, and the risk of this happening is about 10% for the first 5 years. 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. Premyeloma plasma cells initially require interaction with the bone marrow microenvironment. However, during disease progression, the cells 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.
As outlined below in this evidence review, complex genetic abnormalities that are commonly identified in multiple myeloma plasma cells are considered to play major roles in disease initiation, progression, and pathogenesis. Further, these abnormalities are used in conjunction with laboratory and radiographic studies to stratify patients for therapeutic decisions.\textsuperscript{5,10,11}

\section*{Diagnosis}

Cytogenetic and other laboratory tests identify markers to classify newly diagnosed multiple myeloma patients into high, intermediate, and standard risk categories. The level of risk reflects the aggressiveness of the disease, and ultimately dictates the intensity of initial treatment.\textsuperscript{5,12-14} Thus, a risk-adapted approach provides optimal therapy to patients, ensuring intense treatment for those with aggressive disease. Further, this approach minimizes the toxic effects of treatment, thereby delivering sufficient, but less-intense, therapy for those with lower risk of disease. However, it should be noted that clinical outcomes can vary substantially among patients with the same estimated risk who undergo a similar intensity of treatment.

Microarray-based gene expression profile (GEP) analysis estimates the underlying activity of cellular biological pathways, and these pathways control a host of mechanisms including cell division, cell 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 for two purposes: (1) to personalize therapy selection according to tumor biology,\textsuperscript{13,14} and (2) to avoid over- or under-treating patients. Moreover, GEP analysis could be used as a supplement to existing stratification methods, or as a stand-alone test. However, further study is needed to confirm that the analysis would be helpful in this way.

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 GEP assay simultaneously examines the patterns of multiple genes in a single tissue sample. It does this to identify those genes that are actively producing mRNA and proteins. By concurrently 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 variants 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.

**Gene Expression Profile (GEP) Analysis of Cancer using Microarray Technology**

GEP analysis using microarray technology is based on the Watson-Crick pairing of complementary nucleic acid molecules. A collection of DNA sequences, referred to as “probes,” are “arrayed” on a miniaturized solid support (the “microarray”). These are used to determine the concentration of the corresponding complementary mRNA sequences, called “targets,” isolated from a tissue sample. Laboratory advancements in attaching nucleic acid sequences to solid supports, combined with robotic technology, have allowed investigators to miniaturize the scale of the reactions. As a result of these advances, it is possible to assess the expression of thousands of different genes in a single reaction.

A basic microarray GEP analysis uses mRNA targets harvested from a patient’s tissue sample and labeled with a fluorescent dye. These are hybridized to the DNA probe sequences attached to the microarray medium, then incubated in the presence of mRNA from a different sample labeled with a different fluorescent dye. In a two-color experimental design, samples can be directly compared to one another or to a common reference mRNA, and their relative expression levels can be quantified. After hybridization, gray-scale images corresponding to fluorescent signals are obtained by scanning the microarray with dedicated instruments, and the fluorescence intensity corresponding to each gene is quantified by specific software. After normalization, the intensity of the hybridization signals can be compared to detect differential expression by using sophisticated computational and statistical techniques.

Technical variability is a major concern in the use of microarray technologies for clinical management. For example; the source of mRNA is one technical variable that can affect test results. A typical biopsy sample from a solid tumor contains a mixture of malignant and normal (stromal) cells that in turn will yield total RNA that reflects all the cells contained in the specimen. To address this, tissue samples may be macro- or micro-dissected (prior to RNA extraction) to ensure that the specimens contain a sufficiently representative percentage of cancer cells to reflect the disease. For analysis of hematologic cancers including multiple myeloma, immunomagnetic cell separation technology is used to isolate and enrich cancerous cells from bone marrow aspirates that contain a mixture of cell types.
The instability of mRNA compared to DNA complicates GEP analysis studies, especially when comparing the method against genomic analyses. Two factors that affect RNA quality include pre-analysis storage time and the reagents used to prepare mRNA. Moreover, pH changes in the storage media can trigger mRNA degradation, as can ribonucleases that are present in cells and can remain active in the RNA preparation if not stringently controlled.

As noted above, Watson-Crick hybridization of complementary nucleic acid moieties in the sequences of mRNA and DNA is the basis of any microarray-based GEP test. For this reason, sequence selection and gene annotation are among the most important factors that can contribute to analytical variability, and hence validity, in results. Different technological platforms, protocols, and reagents can affect the analytical variability of the results, and therefore affect reproducibility within and across laboratories. Gene expression measures are virtually never used as raw output but undergo sequential steps of mathematical transformation; thus, data pre-processing and analysis may increase variability in results. Moreover, different levels of gene expression can be further processed and combined according to complex algorithms to obtain composite summary measurements that are associated with the phenotype(s) under investigation. A statistical analytic technique known as “unsupervised clustering analysis” is applied to the data to produce a visual display, known as a “dendrogram” that shows a hierarchy of similar genes, differentially expressed as mRNA.

International standards have been developed to address the quality of microarray-based GEP analysis. Additional topics of interest include interplatform and interlaboratory reproducibility. Quality control efforts emphasize the importance of minimizing the sources of variability in gene expression analysis, thus ensuring that the information derived from such analyses is specific and does not represent accidental associations.

**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). The DSS provides a method to measure multiple myeloma tumor burden, according to multiple myeloma cell numbers and clinical, laboratory and imaging studies. However, the system has 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 β2-microglobulin measures, is considered valuable because it permits comparison of outcomes across clinical trials, and is even 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. Further, it also does not provide a good estimate of tumor burden, nor is it generally useful for therapeutic risk stratification. In fact, it may not retain prognostic significance in the era of novel drug therapies.

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. 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.

The Mayo Clinic does not currently recommend or routinely perform GEP analysis in a non-research setting. Their risk stratification model is meant to prognosticate and to determine the treatment approach; it is not utilized to decide whether to initiate therapy (see Therapy Synopsis subsection below). Furthermore, therapeutic outcomes among individuals in their risk categories may vary significantly. As a result, additional means of subdividing patients into response groups are under investigation, in particular, by doing molecular profiling using microarray-based methods.

**Therapy Synopsis**

Asymptomatic (smoldering) multiple myeloma and MGUS currently require only ongoing clinical observation (this is because 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. Next, the therapy includes autologous hematopoietic cell transplantation (HCT). Older patients (or those with underlying liver, lung, or cardiovascular dysfunction) may be candidates for induction followed by reduced-intensity conditioning allogeneic HCT.

A program referred to as Total Therapy was developed primarily at the University of Arkansas for Medical Science and the Mayo Clinic. It uses all available agents as induction, followed by 2 cycles of high-dose melphalan and autologous HCT support, with a 4-year event-free survival as high as 78%. Despite the 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.

**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.

**Summary of Evidence**

For individuals who have multiple myeloma who received risk stratification using a gene expression profiling, the evidence includes retrospective series that correlate risk scores with survival. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and other test performance measures. The microarray-based GEP70 test (MyPRS™/MyPRS Plus™) has been reported to risk-stratify multiple myeloma patients. Patients with a high GEP70 risk score have a substantially increased risk of mortality than patients without a high score. However, there is no evidence (from available studies) that this test would add incremental value to existing risk-stratification methods, nor have any studies prospectively allocated patients to risk-based therapies according to the GEP70 score. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this medical policy are listed in Table 1.

**Table 1. Summary of Key Trials**

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<tr>
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<td>Randomized Phase III Trial of Bortezomib, Lenalidomide and Dexamethasone (VRd) Versus Carfilzomib, Lenalidomide, Dexamethasone (CRd) Followed by Limited or Indefinite Lenalidomide Maintenance in Patients With Newly Diagnosed Symptomatic Multiple Myeloma</td>
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<td>NCT01169337</td>
<td>Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients With Asymptomatic High-Risk Smoldering Multiple Myeloma</td>
<td>380</td>
<td>Jul 2026</td>
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NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (NCCN) practice guidelines (v.2.2018) 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. Further, GEP may eventually 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.

**Mayo Clinic Stratification of Multiple Myeloma and Risk-Adapted Therapy**

The Mayo Clinic does not currently recommend or routinely perform GEP analysis of multiple myeloma in a non-research setting. However, Mikhael et al (2013) have suggested GEP analysis will likely play a greater role in management of multiple myeloma as evidence develops.
Medicare National Coverage

Medicare does not have a national coverage determination for this testing.

In 2012, Novitas Solutions, the Medicare contractor over Jurisdiction H (which includes Arkansas), issued a Medicare local coverage decision for the MyPRS™ test. Because all MyPRS tests are processed through Signal Genetics CLIA-certified laboratory in Little Rock, Arkansas, the LCD applies to all Medicare patients in the United States.

This test is used only after the initial diagnosis of multiple myeloma is made and will be available to help stratify therapeutic interventions. The coverage is set to include only two clinical settings (https://www.novitas-solutions.com/policy/jh/l32636-r1.html):

1. Once after initial diagnosis is made. In the event MyPRS was not tested at diagnosis of myeloma and there is ongoing initial therapy with persistent disease, MyPRS can be done still as an initial test.

2. If relapse has occurred and a change in the therapeutic modalities is contemplated.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

The MyPRS™/MyPRS Plus™ GEP70 was acquired by Quest Diagnostics in December 2016. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration does not require any regulatory review of this test.

References


**History**

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<td>12/23/13</td>
<td>Coding Update. Add CPT 81504 effective 01/01/14.</td>
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<td>01/20/14</td>
<td>Update Related Policies. Add 12.04.54.</td>
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<tr>
<td>09/08/14</td>
<td>Annual Review. Policy revised with literature review through May 19, 2014. New references 24-27 added; reference 28 updated. No change to the policy statement.</td>
</tr>
<tr>
<td>10/06/17</td>
<td>Policy moved to new format. No changes to policy statements.</td>
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