Name of Policy:
Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification

Policy #: 551       Latest Review Date: October 2015
Category: Laboratory       Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
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 is a genetically complex, invariably fatal, 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.

Microarray-based gene expression profile (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.
Policy:
Microarray-based gene expression profile testing for multiple myeloma does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational for all indications.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
Gene Expression Analysis of Cancer Using Microarray Technology
This section comprises a generalized description of microarray-based technology. It also addresses laboratory issues that potentially affect the technical variability, hence reliability and interpretation, of GEP tests in cancer, including MyPRS™.

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 microdissected 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 relative instability of mRNA compared to DNA complicates GEP analysis studies compared to genomic analyses. Factors that affect RNA quality include pre-analysis storage time and the reagents used to prepare mRNA, including particular lots or batches of reagents. 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, hence validity, in results. Different technological platforms, protocols, and reagents can affect the analytical variability of the results, and thus 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. These focus on documentation of experimental design, details, and results. Inter-platform and inter-laboratory reproducibility also are topics of interest. 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.

**Multiple Myeloma**

**Disease Description**

Multiple myeloma is a malignant plasma-cell dyscrasia characterized by clonal proliferation of plasma cells derived from B cells in the bone marrow. It accounts for about one in every 100 cancers, and 13% of hematologic cancers. The American Cancer Society has estimated 21,700 new cases of multiple myeloma will occur in the U.S. in 2012, and some 10,200 deaths due to the disease. The annual age-adjusted incidence is about six cases per 100,000 persons, with 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 five to 10 years; in the pre-chemotherapy era, median survival was less than one year. Among patients who present at age younger than 60 years, 10-year overall survival with current treatment protocols now may reach more than 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 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.

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. 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; it has an annual risk for transformation to multiple myeloma of about 10% for the first five 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: calcium elevation; renal insufficiency; anemia; and, bone disease. Premyeloma 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.

As outlined below in this Policy, 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.

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 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 β2-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. 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.
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 (Table 1).

Table 1: Mayo Clinic Stratification of Multiple Myeloma and Risk-Adapted Therapy (mSMART)

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Standard Risk</th>
</tr>
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<tbody>
<tr>
<td>Any of the following:</td>
<td>t(4;14) by FISH</td>
<td>All others including:</td>
</tr>
<tr>
<td>• Del 17p</td>
<td>Cytogenetic del 13</td>
<td>• t(11;14) by FISH</td>
</tr>
<tr>
<td>• t(14;16) by FISH</td>
<td>Hypodiploidy</td>
<td>• t(6;14) by FISH</td>
</tr>
<tr>
<td>• t(14;20) by FISH</td>
<td>Plasma cell labeling index &gt;3.0</td>
<td>• Incidence: 60%</td>
</tr>
<tr>
<td>• GEP high-risk signature*</td>
<td>Incidence: 20%</td>
<td>• Median OS (yrs): 8-10</td>
</tr>
<tr>
<td>• Median overall survival (OS) (yrs): 3</td>
<td>Median OS (yrs): 4-5</td>
<td></td>
</tr>
</tbody>
</table>
*The Mayo Clinic does not currently recommend nor routinely performs GEP analysis in a non-research setting.

In addition to the cytogenetic characteristics noted in Table 1, other findings are typically considered in this model. 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).

Table 2: Prognostic factors in multiple myeloma

<table>
<thead>
<tr>
<th>Tumor biology</th>
<th>Tumor burden</th>
<th>Patient-related</th>
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<tbody>
<tr>
<td>Ploidy</td>
<td>Durie-Salmon stage</td>
<td>Eastern Cooperative Oncology Group performance status</td>
</tr>
<tr>
<td>17p- (p53 deletion)</td>
<td>International Staging System stage</td>
<td>Age</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>Extramedullary disease</td>
<td>Renal function</td>
</tr>
<tr>
<td>t(14;20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(4;14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deletion 13 on conventional cytogenetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alterations in chromosome 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(11;14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(6;14)</td>
<td></td>
<td></td>
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<tr>
<td>Lactate dehydrogenase levels</td>
<td></td>
<td></td>
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<tr>
<td>Plasma cell proliferative rate</td>
<td></td>
<td></td>
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<tr>
<td>Presentation as plasma cell leukemia</td>
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<td></td>
</tr>
<tr>
<td>High-risk GEP signature*</td>
<td></td>
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</tbody>
</table>
*The Mayo Clinic does not currently recommend nor routinely performs GEP analysis in a non-research setting.

Although GEP analysis is included in Tables 1 and 2, the Mayo Clinic does not currently recommend nor routinely performs GEP analysis in a non-research setting. However, the
investigators suggest GEP analysis will likely play a greater role in management of multiple myeloma as evidence develops.

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). 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 (Rationale).

**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). Older patients or those with underlying liver, lung, or cardiovascular dysfunction may be candidates for induction followed by reduced-intensity conditioning allogeneic HSCT.

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 two cycles of high-dose melphalan and autologous HSCT support, with a four-year’s event-free survival as high as 78%. 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.

**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.

**Literature Review**

This evidence review was last updated with a literature review covering the period through October 5, 2015.

Multiple myeloma is a genetically complex, invariably fatal, disease. 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. 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.
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 described in the Background of this Policy. Two key publications report 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.

**Analytical Validity**
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 one 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 Validity**
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). 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 five-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 five-years continuous complete remission of 60%, as opposed to a three-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 β2-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. 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 four 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 2,233 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, seven of 45 patients with adequate mRNA samples (15.6%) were considered high risk by the GEP70 test, similar to the proportion described previously. 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 two 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 seven 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.

Papanikolaou et al published an analysis of predictive factors for survival in patients with multiple myeloma. Clinical and demographic factors were combined with cytoplasmic immunoglobulin and the GEP70 model. Cytoplasmic immunoglobulin is a new prognostic factor that was being tested in conjunction with other known predictors of survival. The outcome variables used were overall survival and progression-free survival. Both cytoplasmic immunoglobulin and GEP70 score were independent predictors of survival. The multivariate predictive model derived included the GEP70 score, the cytoplasmic immunoglobulin index, and the albumin level.

Review Articles
In the literature search update for this Policy in 2014, we did not identify any systematic reviews or meta-analyses that addressed clinical data on GEP70 for risk analysis of MM. Several review articles on risk stratification of MM reported on the use of GEP70 but the
authors uniformly stated this technology has not yet been proven to have clinical utility for this purpose.

Summary
Multiple myeloma is a genetically complex, invariably fatal, disease. 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. 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 gene expression profile (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.

The evidence for the use of gene expression profiling for risk stratification in multiple myeloma 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 compared to patients without a high score. No evidence is available from studies that report the incremental value that this test would add 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.

Practice Guidelines and Position Statements
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. 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.

Mayo Clinic Stratification of Multiple Myeloma and Risk-Adapted Therapy
The Mayo Clinic does not currently recommend nor routinely performs GEP analysis of multiple myeloma in a non-research setting. However, the authors suggest GEP analysis will likely play a greater role in management of multiple myeloma as evidence develops.

U.S. Preventive Services Task Force Recommendations
Not applicable.
Key Words:
Gene expression profiling, myeloma, myPRS

Approved by Governing Bodies:
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)

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
AT&T contracts: No special consideration.
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:
CPT Codes:
81479 Unlisted molecular pathology procedure
81599 Unlisted multianalyte assay with algorithmic analysis
86849 Unlisted immunology procedure

References:

**Policy History:**
Medical Policy Panel, July 2014,
Medical Policy Group, July 2014 (1) New Policy, previously only listed on Investigational Listing; remains investigational
Medical Policy Administration Committee, August 2014
Available for comment August 21 through October 4, 2014
Medical Policy Panel, October 2015
Medical Policy Group, October 2015 (3): 2015 Updates to Key Points & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.