Medical Policy

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

Section 2.0 Medicine
Effective Date September 30, 2014

Subsection 2.04 Pathology/Laboratory
Original Policy Date September 30, 2014
Next Review Date September 2015

Description

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

Related Policies

• Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome

Policy

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

Policy Guidelines

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.(12,14,16) 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 monoclonal gammopathy of undetermined significance (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 (see Table 1).(17)

Table 1. Prognostic Factors in Multiple Myeloma(17)

<table>
<thead>
<tr>
<th>Tumor Biology</th>
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<tbody>
<tr>
<td>• Ploidy</td>
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<tr>
<td>• 17p- (p53 deletion)</td>
</tr>
<tr>
<td>• t(14;16)</td>
</tr>
<tr>
<td>• t(14;20)</td>
</tr>
<tr>
<td>• t(4;14)</td>
</tr>
<tr>
<td>• Deletion 13 on conventional cytogenetics</td>
</tr>
<tr>
<td>• Alterations in chromosome 1</td>
</tr>
<tr>
<td>• t(11;14)</td>
</tr>
<tr>
<td>• t(6;14)</td>
</tr>
<tr>
<td>• Lactate dehydrogenase levels</td>
</tr>
<tr>
<td>• Plasma cell proliferative rate</td>
</tr>
</tbody>
</table>
### Tumor Burden
- Durie-Salmon stage
- International Staging System stage
- Extramedullary disease

### Patient-Related
- ECOG Performance Status
- Age
- Renal function

ECOG: Eastern Cooperative Oncology Group; GEP: gene expression profile.

The Mayo Clinic does not currently recommend nor routinely performs GEP analysis 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.

### Coding
There is no specific CPT code for this test. It would be reported with an unlisted code.

The Novitas Medicare Local Coverage Determination (LCD) policy lists the following CPT code:
- **86849**: Unlisted immunology procedure

The test may also be reported using the following CPT codes:
- **81479**: Unlisted molecular pathology procedure
- **81599**: Unlisted multianalyte assay with algorithmic analysis (MAAA)

### Benefit Application
Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

### Rationale
**Background**

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 undertreating 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.

**Gene Expression Analysis of Cancer Using Microarray Technology**

This section of the Background 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.(1) 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.(2) 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 2-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 a 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. Interplatform and interlaboratory 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 1 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 6 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 5 to 10 years; in the prechemotherapy era, median survival was less than 1 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%.

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 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: calcium elevation; renal insufficiency; anemia; and, bone disease. 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.

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 (see Table 2).
Table 2. Mayo Clinic Stratification of Multiple Myeloma and Risk-Adapted Therapy (mSMART)(17)

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Any of the following:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>• Del 17p</td>
</tr>
<tr>
<td></td>
<td>• t(14;16) by FISH</td>
</tr>
<tr>
<td></td>
<td>• t(14;20) by FISH</td>
</tr>
<tr>
<td></td>
<td>• GEP high-risk signature*</td>
</tr>
<tr>
<td></td>
<td>• Incidence: 20%</td>
</tr>
<tr>
<td></td>
<td>• Median OS, y: 3</td>
</tr>
</tbody>
</table>

| Intermediate Risk | • t(4;14) by FISH |
|                  | • Cytogenetic del 13 |
|                  | • Hypodiploidy      |
|                  | • Plasma cell labeling index >3.0 |
|                  | • Incidence: 20%    |
|                  | • Median OS, y: 4-5 |

<table>
<thead>
<tr>
<th>Standard Risk</th>
<th>All others including:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• t(11;14) by FISH</td>
</tr>
<tr>
<td></td>
<td>• t(6;14) by FISH</td>
</tr>
<tr>
<td></td>
<td>• Incidence: 60%</td>
</tr>
<tr>
<td></td>
<td>• Median OS, y: 8-10</td>
</tr>
</tbody>
</table>

FISH: fluorescence in situ hybridization; GEP: gene expression profile; OS: overall survival.

In addition to the cytogenetic characteristics noted in Table 2, other findings are typically considered in this model (see Table 1, Policy Guidelines section). 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.(17)

The risk stratification model outlined in Table 2 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 subsection below).(14) 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.

**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). (7,18) Older patients or those with underlying liver, lung, or cardiovascular dysfunction may be candidates for induction followed by reduced-intensity conditioning allogeneic HSCT.(7)

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%.(7,19) 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.

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).

Literature Review

Multiple myeloma is a genetically complex, invariably fatal, disease.(20) 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.(14,17)
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.(3,21)

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.(21) 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 GEPs.(22,23)

Clinical or Validation Studies

In a widely cited validation paper by Shaughnessy et al. 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).(22) 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 with those with a low risk score (28% vs 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 β2-microglobulin as used in the International Staging System (ISS). 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 1 center in the U.S., primarily in the context of autologous HSCT.

A paper published by Kumar et al. in 2011 examined the utility of the GEP70 risk-stratification test among patients undergoing initial therapy with lenalidomide in the context of a phase 3 trial.(23) Patients with previously untreated multiple myeloma enrolled in the E4A03 trial were randomly allocated to lenalidomide and either standard-dose dexamethasone (40 mg on 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 2232 to the high-dose arm. As in the GEP70 UAMS validation study, CD138+ 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.(22) 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 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 to 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 to 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.

Review Articles

In the literature search update for this Policy in 2014, no systematic reviews or meta-analyses that addressed clinical data on GEP70 for risk analysis of MM were identified. 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. (24-27)
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 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).

Summary

Multiple myeloma is a genetically complex, invariably fatal, disease.(20) 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.(14,17) 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.(3,21)

The microarray-based GEP70 test considered in this Policy (MyPRS™ /MyPRS Plus™) has been evaluated in retrospective studies that associated survival outcomes with risk scores based on messenger RNA expression patterns in plasma cells obtained from newly diagnosed multiple myeloma patients. No evidence is available from studies that use this test to prospectively allocate patients to risk-based therapies, nor is it known what incremental value this test would add to existing risk-stratification methods. Therefore, microarray-based gene expression profile testing for multiple myeloma is considered investigational for all indications.

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.(28) 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(17)

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

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

A search of the NCI Clinical Trial Database on May 27, 2014 identified the following phase 3 trials that will use the GEP70 test to stratify patients for therapy (available at: (http://www.cancer.gov/clinicaltrials/search/printresults?cid=230950&protocolsearchid=11815226):
• **Bortezomib or Carfilzomib With Lenalidomide and Dexamethasone in Treating Patients With Newly Diagnosed Multiple Myeloma**
  - Phase: Phase 3
  - Type: Biomarker/Laboratory analysis, Supportive care, Treatment
  - Status: Active
  - Age: 18 and over
  - Sponsor: NCI, Other
  - Protocol IDs: E1A11, NCI-2012-02608, U10CA021115, NCT01863550

• **Lenalidomide or Observation in Treating Patients With Asymptomatic High-Risk Smoldering Multiple Myeloma**
  - Phase: Phase 3, Phase 2
  - Type: Biomarker/Laboratory analysis, Treatment
  - Status: Active
  - Age: 18 and over
  - Sponsor: NCI
  - Protocol IDs: NCI-2011-02057, ECOG-E3A06, CDR0000682012, E3A06, U10CA021115, NCT01169337

• **UARK 2008-01, Total Therapy 4 - A Phase III Trial for Low Risk Myeloma**
  - Phase: Phase 3
  - Type: Treatment
  - Status: Active
  - Age: 18 to 75
  - Sponsor: Other
  - Protocol IDs: UARK 2008-01, NCT00734877

**Medicare National Coverage**

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

In 2012, Novitas Solutions Inc., the Medicare contractor over Jurisdiction H (which includes Arkansas), issued a Medicare local coverage decision (LCD) for the MyPRS™ test. Since 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 has been made and will be available to be used in the stratification of therapeutic interventions. The coverage is set to include only two clinical settings (https://www.novitas-solutions.com/policy/jh/32636-r1.html):

1. Once after initial diagnosis is made (ICD-9-CM 203.00). 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 (ICD-9-CM 203.02).

**References**


**Documentation Required for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

IE

The following services are considered investigational and therefore not covered for any indication.

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<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<td>Unlisted molecular pathology procedure</td>
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<td>81599</td>
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<td>86849</td>
<td>Unlisted immunology procedure</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>9/30/2014</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine medical necessity.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.
The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.