Policy Statement

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

Policy Guidelines

According to Mayo Clinic recommendations, a large number of prognostic factors have been validated and categorized into 3 main groups: tumor biology, tumor burden, and patient-related factors. These factors must be considered to individualize the choice of therapy in multiple myeloma patients (see Table PG1).

**Table PG1. Prognostic Factors in Multiple Myeloma**

<table>
<thead>
<tr>
<th>Tumor Biology</th>
<th>Tumor Burden</th>
<th>Patient-Related</th>
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<tr>
<td>• Ploidy</td>
<td>• Durie-Salmon stage</td>
<td>• ECOG 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>
</tr>
<tr>
<td>• Lactate dehydrogenase levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Plasma cell proliferative rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Presentation as plasma cell leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-risk GEP signature&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Mikhael et al (2013).
ECOG: Eastern Cooperative Oncology Group; GEP: gene expression profile.
<sup>a</sup> The Mayo Clinic does not currently recommend or routinely perform GEP analysis in a nonresearch setting. However, Mikhael et al (2013) have suggested GEP analysis will likely play a greater role in the 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 might also be reported using the following CPT codes:

- **81479**: Unlisted molecular pathology procedure
- **81599**: Unlisted multianalyte assay with algorithmic analysis

Description

Multiple myeloma is a genetically complex—and 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 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.

**Related Policies**

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

**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]) prohibits 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.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The MyPRS™ / MyPRS Plus™ GEP70 test was acquired by Quest Diagnostics in December 2016. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**Rationale**

**Background**

**Multiple Myeloma**

Multiple myeloma is a genetically complex—and invariably fatal—neoplasm of plasma cells.¹

**Literature Review**

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.
MyPRS/MyPRSPlus
Multiple myeloma is a 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 clinical risk categories for prognostication purposes, as well as to determine 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.

The MyPRS/MyPRS Plus test was developed primarily using the microarray-based technology described in the Background section. Two key publications have reported the application of this method can do two things: (1) construct molecular profiles of multiple myeloma in newly diagnosed patients; and (2) retrospectively associate treatment outcomes with specific GEPs.

Clinical Context and Therapy Purpose
The purpose of a microarray-based GEP test (e.g., MyPRS/MyPRS Plus) in patients who have multiple myeloma is to provide risk stratification information that can be used to guide treatment decisions.

The question addressed in this evidence review is: Does the use of a microarray-based GEP test improve the net health outcome in patients with multiple myeloma?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are patients with multiple myeloma.

Interventions
The therapy being considered is a microarray-based GEP test (e.g., MyPRS/MyPRS Plus), which provides risk stratification information. The level of risk reflects the aggressiveness of the disease, and ultimately dictates the intensity of initial treatment. The MyPRS/MyPRS Plus GEP70 test analyzes 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.

Clinical laboratories licensed by the Clinical Laboratory Improvement Amendment for high-complexity testing perform this test.

Comparators
Tests such as the following may be used to perform standard clinical risk evaluation for multiple myeloma. Some of these tests may also be part of the diagnostic evaluation.

- complete blood count and differential examination of peripheral blood smear
- chemistry screen plus serum calcium, albumin, lactate dehydrogenase, and β2-microglobulin
- serum creatinine and glomerular filtration rate estimate
- serum free light chain assay
- serum protein electrophoresis, routine urinalysis, and 24-hour urine collection
- bone marrow aspiration and biopsy with immunophenotyping and fluorescence in situ hybridization
- cross-sectional imaging (e.g., computed tomography, positron emission tomography with computed tomography, or magnetic resonance imaging).

Outcomes
Longer-term outcomes involve overall survival (OS) as well as disease-specific morbidity and mortality.
Measurement of long-term outcomes requires follow-up over years; multiple myeloma has a 5-year OS rate of 50%.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Randomized Controlled Trials**
A phase 3 trial by Kumar et al (2011) examined the utility of the GEP70 risk stratification test among patients undergoing initial therapy with lenalidomide. Patients with previously untreated multiple myeloma who enrolled in the E4A03 trial were randomized to lenalidomide plus either standard-dose dexamethasone (40 mg on days 1-4, 9-12, and 17-21) or low-dose dexamethasone (40 mg/wk). After the first four cycles of therapy, patients could discontinue therapy to pursue hematopoietic cell transplantation (HCT) or continue on protocol until progression. Overall, 445 patients were randomized: 222 to the low-dose arm and 223 to the high-dose arm. As in the GEP70 validation study, CD138-positive plasma cells were isolated using bone marrow aspirates of consenting patients. Total messenger RNA was isolated from those cells and analyzed by high-density oligonucleotide microarrays containing probes for 50000 transcripts and variants including 14500 known human genes (Affymetrix U133Plus2.0 array). The GEP70 signature was determined as described by Shaughnessy et al (2007) and compared with OS data and other variables. Overall, 7 (15.6%) of 45 patients with adequate messenger RNA samples 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 (22.7%) of 44 were considered high-risk by the presence of the following translocations and deletions: t(4;14), t(14;16), t(14;20), and del(17p). Six of the FISH high-risk patients 2 of the standard-risk patients were reclassified into the low- and high-risk categories by GEP70, respectively. Median OS was 19 months for the 7 GEP70 high-risk patients; OS did not reach the median for the standard-risk group. For 10 high-risk FISH patients, the median OS was 39 months; OS did not reach the median for the standard-risk group. The predictive ability of the GEP70 test, which was estimated using the C-statistic for the GEP70 score dichotomously, was 0.74 (95% confidence interval, 0.61 to 0.88), a value conventionally considered to reflect a prediction model with good discriminatory ability. The C-statistic for FISH-based risk stratification was 0.70 (95% confidence interval, 0.55 to 0.84), very similar to the GEP70 finding. These results would suggest the GEP70 high-risk results are inversely associated with OS among patients treated outside the context of HCT, 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 precluded conclusions on the clinical utility of the test in risk stratification and therapeutic decisions, as well as an assessment of the incremental value of GEP70 compared with FISH.

**Cohort Studies**
Papanikolaou et al (2015) analyzed 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 being tested in conjunction with other known predictors of survival. The outcome variables used were OS 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. In a widely cited validation paper by Shaughnessy et al (2007), GEP data were reported for 523 newly diagnosed patients (training group n=351, validation group n=181) who underwent similar treatments for
multiple myeloma in 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 HCT, 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 CD138-positive cells from which messenger RNA was isolated. These preparations were hybridized to total human genome DNA using Affymetrix U133Plus2.0 microarrays; they were then 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 OS at 5 years (28%) than those with a low-risk score (78% p < 0.001; hazard ratio, 5.16). The absence of a high-risk score identified a favorable subset of patients with a 5-year 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, the presence of a high-risk GEP70 score, and laboratory parameters associated with a poor prognosis, including lactate dehydrogenase, albumin, and β2-microglobulin as used in the International Staging System (see Background section). This evidence would suggest a potential connection between a GEP70 test result indicative of high-risk multiple myeloma; moreover, the evidence would suggest that survival is higher when patients are treated on the same intensity protocol. However, this validation study was performed retrospectively on multiple myeloma plasma cells obtained prior to therapy; further, the study was associated with the clinical outcomes from a small number of patients treated at a single-center in the U. S., primarily in the context of autologous HCT.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

In the 2018 literature search update of this evidence review, BCBSA did not identify any systematic reviews or meta-analyses that addressed clinical data on GEP70 for risk analysis of multiple myeloma. Several review articles on risk stratification of multiple myeloma reported on the use of GEP70; however, reviewers uniformly stated this technology has not yet been proven to have clinical utility for this purpose.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of this test for multiple myeloma has not been established, a chain of evidence cannot be constructed to support the test's clinical utility.

**Summary of Evidence**

For individuals who have multiple myeloma who received risk stratification using a GEP test, the evidence includes a retrospective series that correlate risk scores with survival. The relevant outcomes are OS, disease-specific survival, test 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 with 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 demonstrated the need to prospectively allocate patients to risk-based therapies based on the GEP70 score. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

National Comprehensive Cancer Network
The National Comprehensive Cancer Network practice guidelines (v.3.2019) on multiple myeloma state that “although GEP [gene expression profiling] is not currently routinely used in clinical practice during diagnostic workup, GEP is a useful tool and may be helpful in selected patients to estimate the aggressiveness of the disease and individualize treatment.”29, The Network offered no specific recommendation for the use of the MyPRS GEP70 test.

Mayo Clinic Stratification of Multiple Myeloma and Risk-Adapted Therapy
Guidelines from the Mayo Clinic (2017) have stated that “if indicated, gene expression profiling may be performed to further understand the behavior of the disease and guide therapy.”30.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
Medicare does not have a national coverage determination for this testing. Novitas Solutions retired its local coverage decision on the MyPRS test (L32636) in 2014.31.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCTNo.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT00734877a</td>
<td>UARK 2008-01, Total Therapy 4 - A Phase III Trial for Low-Risk Myeloma: A Randomized Trial Comparing Standard Total Therapy 3 (S-TT3) With TT3-LITE (L-TT3)</td>
<td>400</td>
<td>Sep 2019</td>
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<td>NCT03409692</td>
<td>Validation of a Personalized Medicine Tool for Multiple Myeloma that Predicts Treatment Effectiveness in Patients</td>
<td>200</td>
<td>Dec 2019</td>
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<tr>
<td>NCT01169337</td>
<td>Randomized Phase III Trial of Lenalidomide Versus Observation Alone in Patients With Asymptomatic High-Risk Smoldering Multiple Myeloma</td>
<td>180</td>
<td>Mar 2020</td>
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<tr>
<td>NCT01863550</td>
<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>
<td>1080</td>
<td>Nov 2023</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References


31. Novitas Solutions. Medical Policy Update History for Jurisdiction H. 2018; https://www.novitas-solutions.com/webcenter/portal/MedicareJL/pagebyid;jsessionid=BpHN6XycFavHcd_h7c0Vzhyj46jXrKu1tDjsqFb9UcLQxT2jMnfI1528408334!-2108564542?contentId=00006151&_afrLoop=42675766086142#%40%40%3F_afrLoop%3D42675766086142%26centerWidth%3D100%25%26leftWidth%3D0%2526rightWidth%3D0%2526showFooter%3Dfalse%26showHeader%3Dfalse%26adf.ctrl-state%3DZ281w4k0y_4 Accessed October 8, 2018.


**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

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<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<td>CPT®</td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
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<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</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.

<table>
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<td>09/30/2014</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
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<td>06/01/2016</td>
<td>Policy revision without position change</td>
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<td>12/16/2019</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
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</table>

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 (as applicable to your plan)

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 be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.