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

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome is addressed separately in medical policy 00060.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers microarray-based gene expression profile (GEP) testing for multiple myeloma (e.g., myPRS™/MyPRS *Plus*™ GEP70 test)‡ for all indications to be **investigational.***

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 individuals with multiple myeloma (Table PG1).

Table PG1. Prognostic Factors in Multiple Myeloma

Tumor Biology	Tumor Burden	Patient-Related
• Ploidy • 17p (p53 deletion) • t(14;16) • t(14;20) • t(4;14)	• Durie-Salmon stage • International Staging System stage • Extramedullary disease	• ECOG Performance Status • Age • Renal function

• Deletion 13 on conventional cytogenetics • Alterations in chromosome 1 • t(11;14) • t(6;14) • Lactate dehydrogenase levels • Plasma cell proliferative rate • Presentation as plasma cell leukemia • High-risk GEP signature[a]		

Adapted from Mikhael et al (2013).
ECOG: Eastern Cooperative Oncology Group; GEP: gene expression profile.
[a] The Mayo Clinic does not currently recommend or routinely perform GEP analysis in a non-research 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.

Background/Overview

Multiple Myeloma

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

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 35,730 new cases of multiple myeloma will occur in the U.S. in 2023, and some 12,590 deaths will occur due to the disease. The annual age-adjusted incidence is about 7 cases per 100,000 persons, with a median age-at-diagnosis of about 70 years. Before the advent of current treatment protocols, most patients with multiple myeloma succumbed to their disease within 5 to 10 years; in the prechemotherapy era, median survival was less than 1 year. Among patients who present at an age younger than 60 years, 10-year overall survival with current treatment protocols may now exceed 30%. Black individuals have double the risk of multiple myeloma compared with White individuals and tend to be diagnosed with multiple myeloma at a younger age. Furthermore, Hispanic individuals have a slightly higher

incidence rate than White individuals (6.7 per 100,000 vs. 6.2 per 100,100). Recent US Surveillance, Epidemiology, and End Results Program data estimates that the 5-year age-adjusted mortality rate of Black individuals due to multiple myeloma is 6.2 per 100,000, compared with 3.1 per 100,000 White individuals. However, the 5-year relative survival appears to comparable at 53.9% and 51.3% for Black and White individuals in the US, respectively. When treatment is standardized, there is some evidence that Black individuals have superior survival after multiple myeloma diagnosis compared to White individuals, suggesting that Black individuals have a more indolent disease subtype. However, significant disparities in treatment use, access, and referral patterns persist that may impair clinical outcomes.

Criteria for the diagnosis, staging, and response assessment of multiple myeloma developed by the International Myeloma Working Group are in widespread use. The decision to treat is based on criteria set forth in the diagnosis of multiple myeloma, which includes calcium elevation; renal insufficiency; anemia; and bone disease (CRAB). Patients with monoclonal gammopathy of undetermined significance (MGUS) or smoldering myeloma do not require therapy, irrespective of any associated risk factors-except on specifically targeted protocols.

Pathogenesis and Genetic Architecture of Multiple Myeloma
Multiple myeloma is a complex disease that presents itself in distinct clinical phases and risk levels. They include MGUS and smoldering multiple myeloma (also known as asymptomatic myeloma). Monoclonal gammopathy of undetermined significance 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; the risk of the disease transforming to multiple myeloma is about 10% for the first 5 years. Although both of these conditions 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 reflects the hallmark features of multiple myeloma. Premyeloma plasma cells initially require interaction with the bone marrow microenvironment; however, during disease progression, the cells develop the ability to proliferate outside the bone marrow, manifesting as extramedullary myeloma and plasma cell leukemia. These “bone marrow independent” cells represent the end stages in a multistep transformation process from normal to multiple myeloma.

As outlined below, complex genetic abnormalities, commonly identified in multiple myeloma plasma cells, are considered to play major roles in disease initiation, progression, and pathogenesis. Further, these abnormalities are used in conjunction with laboratory and radiographic studies to stratify patients for therapeutic decisions.

Diagnosis

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 ultimately dictates the intensity of initial treatment. Thus, a risk-adapted approach provides optimal therapy to patients, ensuring intense treatment for those with the aggressive disease. Further, this approach minimizes toxic effects, thereby delivering sufficient-but less-intense-therapy for those with a lower risk of disease. However, it should be noted that clinical outcomes can vary substantially, using even the most standard of methods, among patients with the same estimated risk who undergo a similar intensity of treatment.

Microarray-based gene expression profile (GEP) analysis can be used to estimate the underlying activity of cellular biological pathways, and these pathways control a host of mechanisms such as cell division, cell proliferation, apoptosis, metabolism, and other signaling pathways. Relative over- or underexpression of these pathways is considered to mirror disease aggressiveness, independent of cytogenetics and other laboratory measures. Gene expression profile analysis has been proposed as a means to more finely stratify multiple myeloma patients into risk categories for 2 purposes: (1) to personalize therapy selection according to tumor biology and (2) to avoid over- or undertreating patients. Moreover, GEP analysis could be used as a supplement to existing stratification methods, or as a stand-alone test; however, further study is needed to confirm that the analysis has the capability to perform those roles.

The term *gene expression* refers to the process by which the coded information of genes (DNA) is transcribed into messenger RNA (mRNA) and translated into proteins. A GEP assay simultaneously examines the patterns of multiple genes in a single tissue sample; it does this to identify those that are actively producing mRNA or not, ultimately producing proteins or not. By concurrently measuring the cellular levels of mRNA of thousands of genes, a GEP test creates a picture of the rate at which those genes are expressed in a tissue sample.

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

Gene Expression Analysis of Cancer Using Microarray Technology

Gene expression profile 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 miniaturized solid support (the "microarray"). They 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 that have been both harvested from a patient's tissue sample and labeled with a fluorescent dye. These samples 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 with one another or with a common reference mRNA, and their relative expression levels can be quantified. After hybridization, grayscale images corresponding to fluorescent signals are obtained by scanning the microarray with dedicated instruments; the fluorescence intensity corresponding to each gene is then 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 with microarray technologies for clinical management; eg, 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 instability of mRNA relative to DNA complicates GEP analysis studies, especially when comparing the method with genomic analyses. Two factors that affect RNA quality include preanalysis storage time and the reagents used to prepare mRNA. Moreover, pH changes in the storage media can trigger mRNA degradation, as can ribonucleases present in cells, which can remain active in the RNA preparation if not stringently controlled.

As noted, Watson-Crick hybridization of complementary nucleic acid moieties in the sequences of mRNA and DNA is the basis of any microarray-based GEP test. This means that sequence selection and gene annotation are among the most important factors that can contribute to analytic variability, hence validity, in results. Different technologic platforms, protocols, and reagents can affect the analytic variability of the results, and therefore affect reproducibility within and across laboratories. Gene expression measures are virtually never used as raw output but undergo sequential steps of mathematical transformation; thus, data preprocessing 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 standards focus on documentation of experimental design, details, and results. Additional topics of interest include interplatform and interlaboratory reproducibility. Quality control efforts emphasize the importance of minimizing the sources of variability in gene expression analysis, thus ensuring that the information derived from such analyses is specific and does not represent accidental associations.

Prognosis and Risk Stratification

Two validated clinical systems are in widespread use to assess prognosis in newly diagnosed multiple myeloma patients: the Durie-Salmon Staging System and the International Staging System. The Durie-Salmon Staging System provides a method to measure multiple myeloma tumor burden, based on multiple myeloma cell numbers and clinical, laboratory and imaging studies; however, the system has significant shortcomings due to its use of observer-dependent studies (eg, radiographic evaluation of bone lesions), primarily focused on tumor mass-not behavior. The International Staging System, incorporating serum albumin and β_2-microglobulin measures, is considered valuable because it permits comparison of outcomes across clinical trials; and it is even more reproducible than the Durie-Salmon Staging System. However, the International Staging System is useful only if a diagnosis of multiple myeloma has already been made; it has no role in MGUS, smoldering multiple myeloma, or related plasma cell dyscrasias. Further, the International Staging System does not provide a good estimate of tumor burden, nor is it generally useful for therapeutic risk stratification. In fact, it may not retain prognostic significance in the era of novel drug therapies.

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

Table 1. Mayo Clinic Stratification of Multiple Myeloma and Risk-Adapted Therapy

Variables	High Risk	Intermediate Risk	Standard Risk
Variants	Any of the following: • Del 17p • t(14;16) by FISH • t(14;20) by FISH	• t(4;14) by FISH • Cytogenetic del 13 • Hypodiploidy • Plasma cell labeling index >3.0	All others including: • t(11;14) by FISH • t(6;14) by FISH

	• GEP high-risk signature		
Incidence	2%	20%	60%
Median overall survival	3 y	4 to 5 y	8 to 10 y

Adapted from Mikhael et al (2013).
FISH: fluorescence in situ hybridization; GEP: gene expression profile.

In addition to the cytogenetic characteristics noted in Table 1, other findings are typically considered in this model. Although GEP analysis is included in Table 1, the Mayo Clinic does not currently recommend or routinely perform GEP analysis in a nonresearch setting.

The risk stratification model outlined in Table 1 is meant to prognosticate and to determine the treatment approach; it is not used to decide whether to initiate therapy (see Therapy Synopsis subsection). Furthermore, therapeutic outcomes among individuals in these categories may vary significantly, to the extent 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 (this is because early treatment with conventional chemotherapy has shown no benefit). However, for symptomatic patients diagnosed with multiple myeloma, prompt induction therapy is indicated. Induction therapy generally consists of an immunomodulatory drug (most often lenalidomide), a proteasome inhibitor (eg, bortezomib), and dexamethasone, and may include daratumumab. Eligible patients will then undergo autologous hematopoietic cell transplantation; following transplantation, or induction in transplant-ineligible patients, treatment will typically continue with low-dose maintenance therapy (eg, with lenalidomide).

Gene Expression Profile Test
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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 (CLIA). 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 CLIA 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/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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.

Summary of Evidence

For individuals who have multiple myeloma who received risk stratification using a GEP test, the evidence includes retrospective series that correlate risk scores with survival. Relevant outcomes are progression-free survival, overall survival, 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. Some predictive models in the body of evidence combine

risk status as determined by the GEP70 test with additional clinical or genetic variables. 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 that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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."

National Comprehensive Cancer Network
The National Comprehensive Cancer Network practice guidelines (2.2024) on multiple myeloma do not provide recommendations regarding use of gene expression profiling.

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

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00734877[a]	UARK 2013-13 , Total Therapy 4B - Formerly 2008-01 - A Phase III Trial for Low-Risk Myeloma Ages 65 and Under: A Trial Enrolling Subjects to Standard Total Therapy 3 (S-TT3)	382	Sep 2024
NCT03409692	Validation of a Personalized Medicine Tool for Multiple Myeloma that Predicts Treatment Effectiveness in Patients	278	July 2022
NCT01863550	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 (ENDURANCE)	1087	Feb 2034
NCT04764942	Phase 1/2 Trial of Selinexor in Combination With Pomalidomide and Dexamethasone ± Carfilzomib for Patients With Proteasome-Inhibitor and Immunomodulatory Drug Refractory Multiple Myeloma (SCOPE)	81	Mar 2026
NCT05665140	Phase II Trial for Newly Diagnosed Low-risk Multiple Myeloma Patients Comparing 6 Cycles of Isatuximab With Lenalidomide/Bortezomib/Dexamethasone (I-VRD) Compared to 3 Cycles of I-VRD followed by One Cycle of High-dose Therapy and Both Arms Followed by Maintenance Therapy With I-R	100	Oct 2028

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

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01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. New policy.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review

01/18/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/04/2018	Medical Policy Committee review
01/17/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/29/2018	Coding update
01/10/2019	Medical Policy Committee review
01/23/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2022	Medical Policy Committee review
11/09/2022	Medical Policy Implementation Committee approval. Added myPRS™/MyPRS *Plus*™ GEP70 test as examples to the investigational statement for microarray-based gene expression profile (GEP) testing for multiple myeloma. Coverage eligibility unchanged.
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/01/2024	Medical Policy Committee review
02/14/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2025

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Coding

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HCPCS	No codes
ICD-10 Diagnosis	C90.00-C90.02

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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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