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

Effective: March 1, 2024

Next Review: January 2025
Last Review: January 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

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

MEDICAL POLICY CRITERIA

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

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Investigational Gene Expression, Biomarker, and Multianalyte Testing, Laboratory, Policy No. 77
2. Hematopoietic Cell Transplantation for Multiple Myeloma and POEMS Syndrome, Transplant, Policy No. 45 22

BACKGROUND

MULTIPLE MYELOMA

Multiple myeloma is a genetically complex, 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.

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.[1] MGUS is a generally benign condition, with a transformation rate to symptomatic plasma cell disorders of about 1% to 2% annually.[2] 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.[2] 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.[3] 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.

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.[4-6]

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).[3, 7] 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.[3] 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.[5]

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.[4, 6] 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.[8] (Table 1).

Table 1. Mayo Clinic Stratification of Multiple Myeloma and Risk-Adapted Therapy (mSMART)[8]

High Risk	Intermediate Risk	Standard Risk
Any of the following: • Del 17p • t(14;16) by FISH • t(14;20) by FISH • GEP high-risk signature* • Incidence: 20% • Median overall survival (OS) (yrs): 3	• t(4;14) by FISH • Cytogenetic del 13 • Hypodipolidy • Plasma cell labeling index >3.0 • Incidence: 20% • Median OS (yrs): 4-5	All others including: • t(11;14) by FISH • t(6;14) by FISH • Incidence: 60% • Median OS (yrs): 8-10

GEP=gene expression profiling

In addition to the cytogenetic characteristics noted in Table 1, other findings are typically considered in this model (Table 2). 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.[8]

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).[5] 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.

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.[3, 5, 7] 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.

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).[8]

Table 2. Prognostic Factors in Multiple Myeloma[8]

Tumor biology	Tumor burden	Patient-related
• Ploidy • 17p- (p53 deletion)	• Durie-Salmon stage • International Staging System stage	• Eastern Cooperative Oncology Group performance status

Tumor biology	Tumor burden	Patient-related
• t(14;16) • t(14;20) • t(4;14) • 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*	• Extramedullary disease	• Age • Renal function

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

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. 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).[9]

MICROARRAY-BASED GENE EXPRESSION PROFILE (GEP) ANALYSIS

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 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 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.

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.

Sky92 assesses 92 cancer genes to predict prognosis after a diagnosis of multiple myeloma.

REGULATORY STATUS

The MyPRS™/MyPRS Plus™ GEP70 test (Signal Genetics LLC), and SKY92 are examples of gene expression profile laboratory-developed tests. The laboratories performing these tests are accredited by the Centers for Medicare and Medicaid (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). MyPRS™/MyPRSPlus™GEP70 may be offered commercially through certain specialty commercial labs (e.g., Caris Life Sciences). SKY92 is currently perfomed and offered by SkylineDX.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature is used to describe variants found in DNA and serves as an international standard.[10] It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

Multiple myeloma is an invariably fatal disease.[11] 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.[5, 8] 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.[12, 13]

ANALYTICAL VALIDITY

The SKY92 assay is a prognostic risk stratification test for multiple myeloma that evaluates 92 genes. The SKY92 score is reported as high risk or standard risk for disease progression. Analytic validity was assessed using bone marrow specimens from 12 patients with multiple myeloma and 7 reference cell line specimens[14]. Analytic sensitivity using a minimum 100ng RNA as input material and >80% plasma cell purity was 100% for the high-risk reference specimens and did not exceed the delta threshold of 1.48. To assess analytic specificity, 33 microarray experiments were conducted using heparin, hemoglobin, EDTA and Ficoll as interfering substances. Using a high-risk reference specimen, all experiments demonstrated a high-risk SKY92 score and did not exceed the 1.48 delta threshold.

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 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).

CLINICAL VALIDITY

Chen (2022) published a retrospective, multinational study to compare GEP-based markers to ISS, revised ISS (r-ISS), and cytogenetic studies (CA) in a population of 155 multiple myeloma patients who were provided treatment outside a clinical trial.[15] The authors assert that most patients with multiple myeloma are not eligible for treatment trials, which limits the generalizability of GEP assessments. The GEP biomarker SKY92 and proliferation gene expression (PR)-cluster were independent prognostic factors for survival, with hazard ratios (HR) and 95% confidence interval (CI) of 3.6 [2.0-6.8] ($p<0.001$) and 5.8 [2.7-12.7] ($p<0.01$) for overall survival (OS). ISS, r-ISS, and CA were not associated with survival. Of note, ISS stage I and stage III were not significantly different in predicting survival (OS HR: 1.8 [0.7-4.8] ($p=0.24$); PFS HR: 1.0 [0.5-2.1] ($p=0.95$). There was generally overlap between SKY92 and the PR cluster, but only nine patients were in the PR cluster.

Mohan (2020) analyzed the predictive ability of the combination of chromosome 1q21 gain/amplification and GEP70 status on outcomes in 81 patients with relapsed/refractory multiple myeloma who were treated with daratumumab.[16] Gain or amplification of chromosome 1q21 has shown negative effects on progression-free survival (PFS) and OS in newly diagnosed and relapsed/refractory multiple myeloma. The authors analyzed predictive ability when GEP70 status was determined both at time of diagnosis and upon daratumumab treatment, given previous observations that GEP70 scores increase from presentation to relapse. At time of diagnosis, median PFS was significantly shorter in patients with versus without gain (1q21) ($p=0.004$), as was median OS ($p=0.002$). Median PFS was not significantly different based on GEP70 risk status, but median OS was significantly shorter in patients with

high-risk GEP70 status (p=0.01). When determined at time of daratumumab treatment, median PFS was shorter in patients with high-risk GEP70 status and median OS was significantly shorter in patients with high-risk GEP70 status (p<0.001).

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.[13] Two key publications reported 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.[17, 18]

In a widely cited validation paper by Shaughnessy 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).[17] 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 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 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) (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 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.[18] Patients with previously untreated multiple myeloma enrolled in the E4A03 trial were randomly allocated to lenalidomide and either standard-dose dexamethasone (40 mg days one -four, none-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 223 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.[17] 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 (2015) published an analysis of predictive factors for survival in patients with multiple myeloma.[19] 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.

CLINICAL UTILITY

Biran (2021) conducted a prospective study aimed at evaluating the clinical utility of the SKY92 test by assessing how knowledge of SKY92 risk stratification affected physician treatment decisions and confidence in their intended treatment plan.[20] The study enrolled 147 newly diagnosed multiple myeloma patients and their 30 hemato-oncologists. The primary endpoint was the percentage of patients the physicians would alter the treatment plan for (hypothetically) based on the SKY92 result. The secondary endpoint was physician confidence in the treatment plan. Based on usual clinical assessment methods 73 of 147 (50%) of patients were classified as high risk. Based on the SKY92 result alone 43 patients (29%) were stratified as high risk. Of those, 27 were initially classified as high risk and 16 were initially classified as standard risk. In the physician’s judgement, upon knowing the SKY92 result, 59 of the 147 patients (40%) were classified as high risk. Physicians reclassified 16 patients who had previously been deemed standard risk to be reclassified as high risk, and 30 patients were reclassified from high risk to standard risk. Of the 16 who were newly classified as high risk based on the SKY92 result physicians stated they would hypothetically recommend more aggressive therapy to 15 of them. Physicians would hypothetically de-escalate therapy for all 30 of the patients who were reclassified as standard risk. Further, physicians reported they would escalate therapy for 8 patients who were initially classified as high risk who were also stratified as high risk based on the SKY92 assay. Knowledge of the SKY92 result had a statistically significant impact on physician’s confidence in their treatment plan, primarily

leading to a shift from “confident” to “strongly confident” for 23% of treatment plans (p<0.001). The study is limited by its focus on physician intentions and not actual therapy administered, treatment response, or health outcomes.

Several review articles on GEP70 for risk stratification of MM uniformly stated this technology has not yet been proven to have clinical utility for this purpose.[21-24] No studies were identified which evaluated the clinical utility of the MyPRS™/MyPRS Plus™ tests.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) practice guidelines (V.2.2024) for multiple myeloma list “high-risk gene expression signature” as a factor “considered high risk” for multiple myeloma, but, no recommendation is made for the use of gene expression profile testing in any of the diagnostic or treatment algorithms.[25]

SUMMARY

It appears that gene expression profiling in select patients with multiple myeloma may guide clinical decisions. However, more research is needed to know for sure. There are no evidence-based practice guidelines that recommend the use of these tests. Therefore, microarray-based gene expression testing, including the MyPRS™/MyPRS Plus™ GEP70, and SKY92 tests, is considered investigational for all indications including the classification of multiple myeloma.

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CODES

Codes	Number	Description
CPT	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
	86849	Unlisted immunology procedure
HCPCS	None	

Date of Origin: *January 2014*