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NCCN Guidelines Panel: Multiple Myeloma-Smoldering

On behalf of Signal Genetics, Inc., I respectfully request that the NCCN Multiple Myeloma Panel review the enclosed data on the use of MyPRS® for patients with "Smoldering" Myeloma. MyPRS is a registered trademark of Signal Genetics, Inc.

Specific Changes:

Inclusion of MyPRS gene expression profile (GEP-70) as part of the initial evaluation of newly diagnosed patients with "smoldering" disease in order to accurately determine the patient's risk of progression to multiple myeloma and, thereby, determine which patients are at "high risk" and likely to benefit from early chemotherapy. Specifically, we would suggest including MyPRS in the "Initial Diagnostic Workup" of patients as may be found on page MYEL-1 in the current NCCN Guidelines (Ver. 3, 2016) using language, such as "… consider GEP-70 gene expression profiling".

Also, the addition of GEP-70 (MyPRS) as part of the definition of "high risk" smoldering myeloma would add universality, specificity and accuracy to paragraph four under "Primary Therapy for Smoldering (Asymptomatic) Multiple Myeloma" on page MS-7.

FDA Clearance:

MyPRS is a CLIA- and CAP-certified assay commercially available in the United States for which FDA Clearance is not required. It is also covered by Medicare at both initial diagnosis and relapse as stipulated in Coverage Decision L34796 (Novitas Solutions, Inc.) with an effective date of October 1, 2015.

Rationale:

The evolution of patient's with "high risk" smoldering myeloma to active (symptomatic) disease is estimated to be ~10%/ year (1). Gene expression profiling provides a single platform for identifying these patients without the failings in both accuracy and reproducibility associated with other methodologies and risk models employed worldwide (2,3,4). Thus, gene expression profiling using MyPRS provides a robust, commercially available universal standard for risk assessment for both individual patient care and stratification on clinical trials (5).

Supportive data can be found in several key citations. The MyPRS genomic assay was initially developed at the University of Arkansas Center for the Medical Sciences (UAMS) by Drs. Bart Barlogie, John Shaughnessy and co-workers (6). These clinical scientists are also the authors of the chapter on "Multiple Myeloma" in Williams Textbook of Hematology (8th edition, McGraw Hill Medical, New York, 2011).

The data generated from the SWOG 0120 prospective clinical trial of 361 patients with either AMM or MGUS indicates that those patients with a GEP-70 risk score > 0.26 (HR=5.85, $p<0.001$) had a 23.3% risk of progressing to clinical disease with potential organ damage within 2 years. If this risk score was combined with either an M spike > 3 gm% and/ or serum free light chains > 25 mg%, than this risk rose to 67% within 2 years (7). The authors conclude that the

GEP-70 score "… may be particularly important to identify a low-risk subset" of smoldering disease whose risk of conversion to clinical disease was "… similar to that in MGUS" (7). Similar results were reported by Khan et. al. in a cohort of 105 patients with smoldering disease (8). Those with a low risk score of $\leq$ 0.26 had a 15.7% likelihood of developing clinical disease (i.e. CRAB criteria) at two years versus a 49.9% risk if their GEP-70 risk score was > 0.26 ($p<0.0001$).

The benefit of risk assessment accrues from several publications in which a Phase II study of pamidronate plus thalidomide (9) and two Phase III studies of zolendronic w/wo thalidomide (10) or observation versus lenalidomide plus dexamethasone (11) significantly improved event-free survival and overall survival (60% and 91% at 4 yrs.), time to progression (1.2 vs. 2.4 yrs., $p=0.02$) or TTP and overall survival (21 mos. vs. NR, $p<0.001$ and 80% vs. 94% at 3 yrs., $p=0.03$), respectively, in patients with smoldering disease. These results support the "European Perspective" that "… more accurate identification of patients who would benefit from interventions needs to be performed" (12).

References:

1. Lopez-Corral L et. al., Genomic analysis of high-risk smoldering multiple myeloma. Haematologica 97: 1439-1443, 2012.
2. Cherry BM et. al., Modeling progression risk for smoldering multiple myeloma results from a prospective clinical study. Leukemia and Lymphoma 54: 2215-218, 2013.
3. Kyle RA et. al., Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia 24: 1121-1127, 2010.
4. Perez-Persona E et. al., New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. Blood 110: 2586-2592, 2007.
5. Van Laar R et. al., Translating a gene expression signature for multiple myeloma prognosis into a robust high-throughput assay for clinical use. BMC Medical Genomics 7: 25-37, 2014.
6. Zhan F et. al., Global gene expression profiling of multiple myeloma, monoclonal gammopathy of undetermined significance, and normal bone marrow plasma cells. Blood 99: 1745-1757, 2002.
7. Dhodapkar MV et. al., Clinical, genomic and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). Blood 123: 78-85, 2014.
8. Khan R et. al., Four genes predict high risk of progression from smoldering to symptomatic multiple myeloma (SWOG 0120). Haematologica 100: 1214-1221, 2015.
9. Barlogie B et. al., Seven year median time to progression with thalidomide for smoldering myeloma: partial response identifies subset requiring earlier salvage therapy for symptomatic disease. Blood 112: 3122-3125, 2008.
10. Witzig TE et. al., A Phase III randomized trial of thalidomide plus zolendronic acid versus zolendronic acid alone in patients with asymptomatic multiple myeloma. Leukemia 27: 220-225, 2013.
11. Mateos V-M et. al., Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma. N Engl J Med 369: 437-447, 2013.
12. Caers J et. al., The Changing Landscape of Smoldering Multiple Myeloma: A European Perspective. The Oncologist 21: 333-342, 2016.

Copies of all citations referenced are included in support of the above proposed changes.

Yours Sincerely,

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