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Submitted by:
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NCCN Guidelines Panel: Multiple Myeloma

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 newly diagnosed multiple myeloma (MM). MyPRS is a registered trademark of Signal Genetics, Inc.

Specific Changes:

Inclusion of MyPRS gene expression profile as part of the initial evaluation of newly diagnosed patients with MM in order to accurately determine the patient's risk of relapse and, thereby, ascertain which patients are truly "high risk" and unlikely to benefit from standard induction chemotherapy (eg. RVD). 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".

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 poor prognosis of patient's with "high risk" newly diagnosed multiple myeloma has prompted clinicians to suggest that such patients are best served by novel therapeutic approaches including new agents, clinical trials and allogeneic bone marrow transplantation. Gene expression profiling provides a single platform for identifying all myeloma-specific genetic aberrations without the failings in both accuracy and reproducibility associated with FISH testing (1). 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 (2).

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 (3). 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). Their initial discovery was subsequently validated on independent patient cohorts in both the United States (4) and Europe (5) demonstrating its robustness and universality. As such, we believe that performing both FISH (using selected probes, such as t(4:14) and del 17p) and MyPRS, which includes risk assessment, subgroup assignment and virtual FISH, would be the best way to accurately identify "high risk" patients (6,7). Further, GEP circumvents the 6% FISH failure rate experienced in the MRC Myeloma IX Trial which included 1069 newly diagnosed patients (8). In addition, the Mayo Clinic mSMART Guidelines (Ver. 2.0) includes gene expression profiling in their definition of "high risk" disease (9).

The clinical utility of gene expression profiling as an alternative or addition to conventional methods of risk assessment has been well demonstrated by Kuiper et. al (10) who evaluated 4750 patients treated at a number of centers in the EU and the UAMS and found MyPRS to have the highest hazard ratio of any metric for predicting overall survival. Indeed, recent work confirms that GEP "… can be used to identify high-risk profiles with significant prognostic significance" (11). The most recent IMWG Consensus Statement specifically states that "GEP profiling is useful for prognostication and may require bioinformatics support". Further, assignment of newly diagnosed patients to one of seven molecular subgroups may assist in confirming the importance of including a proteosome inhibitor in induction therapy and the utility of maintenance in prolonging both EFS and OS (12).

References:

1. Ross FM et. al., Report from the European Myeloma Network on Interphase FISH in multiple myeloma and related disorders. Haematologica 97: 1272-1277, 2012.
2. 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.
3. 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.
4. Zhan F et. al., The molecular classification of multiple myeloma. Blood 108: 2020-2028, 2006.
5. Broyl A et. al., Gene expression profiling for molecular classification of multiple myeloma in newly diagnosed patients. Blood 116: 2543-2553, 2010.
6. Shaughnessy JD et. al., A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. Blood 109: 2276-2284, 2007.
7. Zhou Y et. al., Prediction of cytogenetic abnormalities with gene expression profiles. Blood 119: e148-e150, 2012.
8. Boyd KD et. al., A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. Leukemia 26: 349-355, 2012.
9. Mikhael JR et. al., Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc 88: 360-376, 2013.
10. Kuiper R et. al., Prediction of high- and low-risk multiple myeloma based on gene expression and the International Staging System. Blood 126: 1996-2004, 2015.
11. Sonneveld P et. al. Treatment of Multiple Myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood (epub. ahead of print March 21, 2016).
12. Weinhold N et. al., The Clinical Value of Molecular Subtyping Multiple Myeloma Using Gene Expression Profiling, Leukemia (epub. ahead of print November 5, 2015).

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

Yours Sincerely,
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