ASSOCIATION FOR MOLECULAR PATHOLOGY
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November 15th , 2024

Meredith Loveless, MD
Attn: Medical Review
26 Century Blvd., Ste ST610
Nashville, TN 37214-3685
cmd.inquiry@cgsadmin.com

Dear Dr. Loveless,

On behalf of the Association for Molecular Pathology (AMP), we thank you for the opportunity to comment on the CGS Administrators, LLC (CGS) draft Local Coverage Determination (LCD) entitled DL40000 MolDX: Non-Next Generation Sequencing Tests for the Diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms.

AMP is an international medical and professional association representing approximately 3,000 physicians, doctoral scientists, and medical laboratory scientists (technologists) who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from academic medicine, hospital-based and private clinical laboratories, the government and the in vitro diagnostics industry.

AMP members are highly involved in the development, validation, and interpretation of molecular diagnostic tests. As such, we are concerned that the requirements for testing to be covered under this policy do not accurately reflect the current landscape of Non-Next Generation Sequencing Tests for the diagnosis of BCR-ABL Negative Myeloproliferative Neoplasms.

Specifically, we are concerned that the Coverage Guidance, under Indications and Limitations of Coverage, includes the requirement that "[t]he test is comprised of one or more highly sensitive single- or multi- gene assays (i.e. quantitative polymerase chain reaction [PCR], digital droplet PCR [ddPCR]) that can accurately detect a minimum variant allele frequency (VAF) of <1% for *JAK2* (and 1-3% for *CALR* and *MPL* when they are included in the testing)." Requiring tests to detect a minimum VAF of less than 1% for *JAK2* is not clinically relevant when completing a diagnostic work-up of BCR-ABL negative myeloproliferative neoplasms (MPNs) since 1% commonly understood to be the positive threshold[1][2][3][4]. Our evaluation of current clinical practice indicates that the draft LCD may restrict patient access to tests performed by laboratories who have appropriately validated their tests to the scientifically supported

[1] Cross NC. Genetic and epigenetic complexity in myeloproliferative neoplasms. *Hematology Am Soc Hematol Educ Program.* 2011. pp. 208–214. [PubMed]
[2] Kittur J, Knudson RA, Lasho TL, Finke CM, Gangat N, Wolanskyj AP, et al. Clinical correlates of JAK2V617F allele burden in essential thrombocythemia. *Cancer.* 2007;109:2279–2284.
[3] Wang YL, Vandris K, Jones A, Cross NC, Christos P, Adriano F, et al. JAK2 mutations are present in all cases of polycythemia vera. *Leukemia.* 2008;22:1289. [PubMed] [Google Scholar]
[4] Lippert E, Girodon F, Hammond E, Jelinek J, Reading NS, Fehse B, et al. Concordance of assays designed for the quantification of JAK2V617F: a multicenter study. *Haematologica.* 2009;94:38–45. [PMC free article] [PubMed] [Google Scholar]

threshold of one percent. Notably, within the coverage policy it states, "Patients with high suspicion of a BCR-ABL negative MPN who test negative by a non-NGS test for mutations in *JAK2* (including the detection of *JAK2* V617F at a VAF <1%), *CALR*, *MPL* and/or *CSF3R* may have a subsequent NGS panel performed for additional relevant mutations, as outlined in national or international consensus guidelines". This denotes that a result of less than 1% for *JAK2* as a negative result for the purposes of additional testing and thus further outlines that a VAF for *JAK2* of less than 1% is typically of uncertain clinical significance the setting of initial diagnostic testing.

AMP completed a survey of their members to better understand how they will be impacted. A large majority of our membership that completes *JAK2* testing validate their assays to a 1% VAF. Further, survey respondents noted that it would be too burdensome for laboratories to revalidate their testing to a less than 1% VAF to align with the requirements of the draft LCD which would likely force them to remove the test from their menu and limit testing options for patient care.

We acknowledge that NCCN guidelines **recommend** highly sensitive assays for the detection of *JAK2* V617F. However, there is no clinical significance between *JAK2* assays validated to 1% versus less than 1% and the clinical reasoning for this recommendation remains unclear. We are concerned that the recommendations made are not reflective of the current molecular testing landscape, which acknowledges that a positive *JAK2* result is 1%[1-4]. We would like to have a greater understanding behind CGS' decision to base this coverage policy off of this NCCN guideline recommendation.

AMP recommends that CGS change the language to: "***The test is comprised of one or more highly sensitive single- or multi- gene assays (i.e. quantitative polymerase chain reaction [PCR], digital droplet PCR [ddPCR]) that can accurately detect a minimum variant allele frequency (VAF) of 1% for JAK2 (and 1-3% for CALR and MPL when they are included in the testing)"*** in the draft LCD to reflect that there are many laboratories that complete accurate and clinically relevant *JAK2* testing at VAF of 1%.

Thank you again for the opportunity to review and comment on this draft policy. We are happy to be of assistance in providing additional clinical or other information to assist you with this draft LCD. Please direct your correspondence to Annie Scrimenti, Associate Director, Public Policy and Advocacy, at ascrimenti@amp.org.

Sincerely,

Maria E. Arcila, MD

President, Association for Molecular Pathology