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October 23, 2017

Seema Verma, CMS Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Hubert H. Humphrey Building, Room 445-G
200 Independence Avenue, SW
Washington, DC 20201

RE: Preliminary Determinations for Calendar Year 2018 (CY2018) for New and Reconsidered Services on the Clinical Lab Fee Schedule (CLFS), New Codes for CY2017, and Codes with No/Insufficient Private Payer Data.

Dear Ms. Verma:

On behalf of the Association of Molecular Pathology (AMP), thank you for the opportunity to submit comments on the Clinical Lab Fee Schedule (CLFS) on preliminary determinations for calendar year 2018 (CY2018) for new, reconsidered codes, codes new for CY2017, and codes with no/insufficient private payer data. AMP is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

CY2018 CLFS Preliminary Determinations for New and Reconsidered Codes

AMP presented public comment at the July 2017 CLFS meeting as well as provided written comments to CMS after the meeting[1]. We wish to thank CMS for recommending crosswalks for all of the new molecular pathology codes, however we are concerned that many of the preliminary recommendations provided by CMS differ vastly from both Advisory Panel recommendations and stakeholder input and, in many cases, do not represent the best options for crosswalks. We believe these were crosswalked incorrectly and should be adjusted using a crosswalk method that will more appropriately relate the new CPT codes to existing services already priced on the CLFS. When CMS chooses not to accept the Advisory Panel's recommendations, we ask that CMS provide a more detailed rationale as to why CMS has chosen a different code to crosswalk, allowing us to better respond to the agency's proposed changes.

As dictated by 42 CFR 414.508, crosswalking is used when it is determined that a new CDLT is comparable to an existing test, multiple existing test codes, or a portion of an existing test code.[2] In order to determine if this requirement is met, AMP analyzes and compares a number of factors to determine to most appropriate

[1] http://www.amp.org/publications_resources/position_statements_letters/documents/CLFSCY2018-AMPWrittenComments-FINAL.pdf
[2] https://www.law.cornell.edu/cfr/text/42/414.508

crosswalk, including the analytical methods employed, the overall resources utilized, the types of genetic variants tested (e.g., single nucleotide polymorphisms, deletions, duplications, etc.), and the amount of genetic material interrogated. A large number and wide spectrum of molecular pathology procedures now exist on the current CLFS, which allows for appropriate and streamlined crosswalking of new codes to existing codes. It's important to note that crosswalking based on a single criterion (e.g., the type of genetic variant tested) often will not yield the most appropriate crosswalk. For example, for a new code representing a full gene sequence procedure, a number of existing codes may appear to be a viable crosswalk candidate as a handful of full gene sequence codes exist on the CLFS. However, one must also consider other factors before choosing the most appropriate crosswalk as gene size and content can vary enormously, resulting in vast variability in the amount of resources utilized. It appears from our analysis that a large number of CMS's preliminary recommendations only account for one factor and thus may not be the most appropriate or applicable crosswalk for the new procedures. To assist CMS in finalizing the CY2018 determination, we provide a more detailed rationale for some of the new codes below and request that CMS reconsider and adopt the crosswalk recommendations provided by AMP, which are also supported by other stakeholders as well as the experts on the Advisory Panel.

Codes That Were New for CY2017 and for Which CMS Received No Applicable Information to Calculate Medicare Payment Rates Based on Weighted Median of Private Payor Rates

With regards to CY2017 codes of interest to our membership (81413, 81414, 81422, 81439, and 87483) AMP supports most of CMS's preliminary determinations, which maintain the crosswalk recommendations finalized in November 2016, and offers one recommendation concerning 2017 CPT code 81422 (fetal chromosomal microdeletion). There is now a code valued on the CLFS that is a more appropriate crosswalk than the crosswalk recommendation finalized in November 2016. AMP recommends CMS update the crosswalk recommendation for this code to 81420 (fetal chromosomal aneuploidy). 81420 did not have a value on the CLFS in 2016 and thus was not a viable candidate for a crosswalk recommendation. This recommendation reflects the similarities in analytical methods employed, the overall resources utilized, and the sample type analyzed between 81420 and 81422.

Codes With No Applicable Information to Calculate Medicare Payment Rates Based on Weighted Median of Private Payor Rates

AMP provided written comment in August 2017 as well as verbal recommendations to CMS during the Advisory Panel virtual meeting in September 2017 on the list of 60 Clinical Laboratory Fee Schedule (CLFS) test codes for which CMS received no (i.e., values of zero) and/or insufficient data to calculate a weighted median private payor rate.[3] We reiterate our sentiments expressed in previous letter that it is premature to remove any of these 60 codes from the CLFS because any perceived lack of data during the reporting period does not mean that these codes are not being used. We continue to recommend that CMS pursue recommendations by adding these codes to the agenda list for the next public meeting for the CLFS in 2018 and maintaining prices at the national limitation amount (NLA) where they exist until that time. We believe this will allow all interested stakeholders to provide meaningful input on the re-pricing of these codes and is within the agency's discretion when reported data is insufficient. Additionally, we are concerned about the process deployed to receive input on these codes, particularly the process to submit presentations for the September meeting, which were due a day before CMS released preliminary determinations for these codes. Stakeholders had little

[3] http://www.amp.org/publications_resources/position_statements_letters/documents/AMPCommentstoCMS-60CodeswithNoData7-17-2017FINAL.pdf

to no time to prepare responses or input on the CMS recommendations, which resulted in a suboptimal virtual meeting. This process reinforces our recommendation to add these codes to the agenda list for the next public meeting for the CLFS in 2018 and maintain prices at the national limitation amount (NLA) where they exist until that time.

If this is not acceptable to CMS, we request reconsideration of our original crosswalk recommendations submitted in August and presented again in September for the following molecular pathology procedures CPT codes on the list (81316, 81236, 81434, 81470, 81471). For these codes, the majority of Advisory Panel members voted in favor of supporting our recommendations at the virtual meeting. We urge CMS to reconsider their recommendations released in the preliminary determinations. As with the new CPT codes for CY2018, AMP analyzes and compares a number of factors to determine to most appropriate crosswalk, including the analytical methods employed, the overall resources utilized, the types of genetic variants tested (e.g., single nucleotide polymorphisms, deletions, duplications, etc.), and the amount of genetic material interrogated. A detailed rationale for each recommendation is provided in our original letter.[4]

AMP did not submit recommendations on the genome codes in our August letter (81425, 81426, 81427). However, AMP strongly believes the crosswalk to code 81445 is inappropriate. CMS's recommended crosswalk is a genomic sequencing procedure for a solid organ neoplasm and not for germline sequencing. Further, 81445 codes for 5-50 genes, when sequencing for the genome involves covering 20,000 and thus a direct crosswalk to 81445 here is woefully inappropriate. Sequencing of a genome is a far more extensive analysis both in terms of technical materials/reagents as well as interpretation and reporting. The code 81445 would need to be multiplied TIMES 20 to achieve a reasonable crosswalk value for each genome code. We urge CMS to reevaluate this crosswalk determination.

Specific Recommendations for New Molecular Pathology, Genomic Sequencing and Microbiology Procedures

2018 Molecular Pathology Procedures

81175 - ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndromes, myeloproliferative neoplasms, chronic myelomonocytic leukemia) gene analysis; full gene sequence

AMP, other commenters, and the Advisory Panel recommended a crosswalk to 81317 (PMS2). However, CMS proposes a crosswalk of 81295 (MSH2). Although, as CMS points out in the rationale for their recommendation, 81295 appears to use similar full gene sequencing methodology as does the new code 81175, the resource utilization of code 81317 is more similar to 81175 due to a few factors. 81175 and 81317 are similar in that the procedures assess a similar amount of DNA sequenced (e.g., there are a similar number of exons queried). Therefore, we ask CMS to reconsider this crosswalk recommendation and to adopt crosswalk to our original recommendation of 81317.

CMS uses the crosswalk of 81295 for the vast majority of the new codes that are full gene sequencing codes. Again, AMP cautions that adopting a single crosswalk recommendation across multiple codes may not yield the most appropriate or applicable crosswalk for some codes. Although 81295 is a full gene sequencing procedure, in many cases, additional factors such as the overall resources utilized and the amount of genetic material interrogated should also be taken into consideration. Moreover, AMP is reluctant to use 81295 (MSH2) as a

[4] http://www.amp.org/publications_resources/position_statements_letters/documents/AMPCommentstoCMS-60CodeswithNoData7-17-2017FINAL.pdf

crosswalk as it was originally valued via gapfill and was capriciously undervalued for a large gene with 21 exons; further the preliminary determination weighted median still does not appropriately account for the resources and amount of genetic material interrogated. Due to these reasons, 81295 is a suboptimal choice for a crosswalk recommendation in most cases.

81231- CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3,*4, *5 *6, *7)

CMS proposes a crosswalk of 81227 (CYP2C9), while AMP and the majority of the Advisory Panel members recommended a crosswalk of 81225 (CYP2C19). CMS's rationale for 81227 is that it appears to use similar sequencing methodology to identify specific known variants. While the methodology of 81227 is similar to new CPT code 81231 (CYP3A5), the number of common variants tested in 81227 is less similar than AMP's proposed crosswalk of 81225. 81231 tests for 6 common variants, 81225 tests for 5, while 81227 only tests for 4 variants. Thus, 81225 is a more direct crosswalk as it not only uses similar methodology but the number of variants is similar. AMP recommend CMS reconsider the crosswalk for 81231 and adopt a crosswalk of 81225.

81238 - F9 (coagulation factor IX) (eg, hemophilia B) full gene analysis

For 81238 (F9), CMS proposes a crosswalk of 81295 (MSH2). CMS's rationale for this recommendation states that 81295 appears to use a similar sequencing methodology to the new code 81238. AMP proposed a crosswalk of 81321 (PTEN) for this code, which is a more similar crosswalk than CMS's proposed crosswalk of 81295 because the resources required are more significant than those for 81295. The F9 gene spans a very large area (about 34 kb) with F9 containing 8 exons. Most of the testing is performed in females as the biochemical testing is not diagnostic. Carrier status is determined by identification of a heterozygous pathogenic variant in F9.[5] This is an X-linked disorder, so for females, this testing procedure is looking for mutations in both F9 genes, not one mutation as in an autosomal dominant disorder. Therefore due to the additional resources utilized and the amount of genetic material interrogated we recommend the more suitable crosswalk of 81321.

81248 - G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice) gene analysis; known familial variant(s)

For 81248 (G6PD), the proposed crosswalk recommended by CMS is 81322 (PTEN) as CMS believes that 81248 and 81322 appear to use similar sequencing methodology to identify familial variants. AMP, other professional organizations, and the Advisory Panel recommended a crosswalk of 81215 (BRCA1). 81215 is more similar to 81248 than the CMS proposed crosswalk as sequencing of BRCA1 includes both single nucleotide variants and deletion/duplication analysis, which is less common in the procedure for sequencing known familial variants of PTEN (81322) and thus requires more resources to perform. It's also important to note that the proposed crosswalk of 81322 was originally priced by gapfill and the value of that code (both the 2017 NLA and the PAMA preliminary determination) is well below the resources actually required to perform this procedure.

81249 - G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice) gene analysis; full gene sequence (13 exons)

Again, for new CPT code 81249 (G6PD) CMS recommended a crosswalk to 81295 (MSH2). AMP disagrees with this proposed crosswalk and urges CMS to adopt a final recommendation that is in line with the AMP recommendation and supported by other professional organizations, as well as a majority of the Advisory

[5] https://www.ncbi.nlm.nih.gov/books/NBK1495/

Panel members. AMP's crosswalk of 81321 (PTEN) is a more direct and appropriate crosswalk because in addition to type of genetic material sequenced, 81321 also is similar in the overall resources utilized and the amount of genetic material interrogated.

81258 - HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant

AMP recommended a crosswalk of 81215 (BRCA1) TIMES 2 for new code 81258 (HBA1/HBA2). While the CMS crosswalk of 81322 (PTEN; known familial variant) and AMP's crosswalk of 81215 TIMES 2 both assess a known familial variant, the method details make 81215 TIMES 2 a more appropriate crosswalk because the deletion and substitution types of variants tested between 81215 and 81258 are most similar. BRCA1 and HBA1/HBA2 known familial variants require PCR amplification followed by genotyping for single nucleotide variants and multiplex ligation-dependent probe amplification (MLPA) for deletion and duplication variants. AMP's recommendation uses a multiplier of 2 because alpha thalassemia is an autosomal recessive condition and thus two variants are tested. Further, the value of CMS's proposed crosswalk is much lower than the materials required to perform the test (e.g., MLPA reagents kits). AMP's proposed crosswalk of 81215 TIMES 2, which is also supported by other commenters and the majority of the Advisory Panel, is more similar to 81258 than CMS's proposed crosswalk of 81322 and we recommend CMS reconsider their preliminary determination in this case.

81259 – HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence

For 81259, AMP supports other commenters and the Advisory Panel's recommendation to crosswalk to 81321 (PTEN). The human alpha globin gene cluster spans a very large area (about 30 kb) and includes seven different loci, with HB1 and HB2 containing 6 exons each. The HBA2 and HBA1 coding sequences are identical, which further complicates sequencing. Due to nuances and requirements needed to perform this assay, AMP recommends 81321 as a more appropriate crosswalk than the one proposed by CMS.

81120 - IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)

AMP, other commenters, and the Advisory Panel recommended a crosswalk to 81275 (KRAS). However, CMS proposes a crosswalk of 81227 (CYP2C9). Although, CMS points out in their rationale for crosswalk to 81227 that 81227 appears to use similar sequencing methodology as the new code 81120, the resource utilization of code 81120 is more similar to 81275 due to a few factors. 81275 and 81120 are similar in the test purpose, method, and materials required. Both 81275 and 81220 assay two variants at the same or contiguous codons. Further, 81220 and 81275 test for somatic mutations found in cancers, while the CMS proposed crosswalk of 81227 assesses germline variants. AMP stresses that sequencing procedures amongst germline and somatic mutations vary significantly including in terms of the DNA extraction procedures employed and the increased sensitivity required of sequencing methods when assessing low level somatic alterations. Thus when assessing a viable crosswalk, it is imperative that one must assess the origin of the mutation and test purpose. We ask CMS to reconsider this crosswalk recommendation and to adopt crosswalk to our original recommendation of 81275.

81121 - IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)

Similar to 81220, AMP, other commenters and the Advisory Panel recommended a crosswalk to 81311 (NRAS) for new CPT code 81121. However, CMS proposes a crosswalk of 81227 (CYP2C9). Although, as CMS points out

in their rationale for their recommendation, that 81227 appears to use similar sequencing methodology as the new code 81121, the resource utilization of code 81227 is more similar to 81311 due to a few factors. 81311 (NRAS) and 81121 (IDH2) are also similar in the test purpose, method, and materials. Both 81311 and 81221 assay two variants in distant codons. Further, 81221 and 81311 test for somatic mutations in cancer, while the CMS proposed crosswalk of 81227 assesses germline variants. For the reasons outlined in the section above, it is imperative that one assess the origin of the mutation and test purpose. Therefore, we ask CMS to reconsider this crosswalk recommendation and to adopt crosswalk to our original recommendation of (81275).

81283 - IFNL3 (interferon, lambda 3) (eg, drug response), gene analysis, rs12979860 variant

AMP, other commenters and the Advisory Panel recommended a crosswalk to 81241 (F5). However, CMS proposes a crosswalk of 81322 (PTEN). Although, as CMS points out in their rationale for their recommendation, 81322 appears to use similar sequencing methodology as the new code 81283, the resource utilization of code 81283 is more similar to 81241 due to a few factors. This is a common variant in the population associated with drug response. Most assays are PCR amplification followed by a genotyping for single nucleotide germline variant and not known familial variant testing. Thus the clinical context and resources are more in line with AMP's proposed crosswalk of 81241.

81334 - RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy) gene analysis, targeted sequence analysis (eg, exons 3 – 8)

For new CPT code 81334 (RUNX1), CMS recommended a crosswalk of 81272 (KIT). AMP recommended a crosswalk of 81235 TIMES 2 (EGFR). 81235 TIME 2 is a more appropriate crosswalk and more similar to 81334 than 81272 because of the number of exons examined by each code. EGFR generally queries 3 exons, thus a multiplier of TIMES 2 was added for the 6 exons of RUNX1. A crosswalk to 81272 would be acceptable it if was TIMES a multiple of 1.5. This is because the amount of sequencing and effort in the analysis is more for RUNX1 analysis than for KIT gene analysis.

81362 - HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)

AMP recommended a crosswalk of 81215 (BRCA) TIMES 2 for new code 81362 (HBB). While the CMS crosswalk of 81322 and AMP's crosswalk of 81215 TIMES 2 both assess known familial variant, the method details make 81215 TIMES 2 a more appropriate crosswalk because the deletion and substitution types of variants tested are comparable to those employed for 81362. BRCA1 and HBB known familial variants require PCR amplification followed by genotyping for single nucleotide variants and multiplex ligation-dependent probe amplification (MLPA) for deletion and duplication variants. AMP's recommendation uses a multiplier of 2 because beta thalassemia is an autosomal recessive condition and thus two variants are tested. Further, the value of CMS's proposed crosswalk is much lower than the materials required to perform the test (e.g., MLPA reagents kits). AMP's proposed crosswalk of 81215 TIMES 2, which is also supported by other commenters and the majority of the Advisory Panel is more similar to 81362 than CMS's proposed crosswalk of 81322 and we recommend CMS reconsider the preliminary determination.

2018 Genomic Sequencing Procedures

81448 - Hereditary peripheral neuropathies panel (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, and SPTLC1)

For new CPT code 81448, AMP proposed a crosswalk of 81439 (Inherited cardiomyopathy). New CPT code 81448 includes sequencing of at least 5 genes, as does CMS's recommended crosswalk of 81445 (Targeted genomic sequence analysis panel). However, CMS's recommended crosswalk is a genomic sequencing procedure for a solid organ neoplasm and not a hereditary condition and thus is less similar to the crosswalk proposed by AMP, which is a direct crosswalk to another hereditary genomic sequencing procedure for at least 5 genes. AMP's crosswalk recommendation is also supported by other professional organizations as well as some of the Advisory Panel members. AMP's crosswalk recommendation is based on the type and amount of genetic material tested as well as the analytical method employed and overall resources utilized. Given the similarity in the relative resources required, we recommend that CMS adopt a straight crosswalk to existing 81439.

2018 Microbiology Procedures

87634 - Infectious agent detection by nucleic acid (DNA or RNA); respiratory syncytial virus, amplified probe technique

CMS proposes a crosswalk of 87798 (infectious agent detection; amplified probe technique, not otherwise specified). AMP recommended a crosswalk of 87801 (infectious agent detection; amplified probe technique; multiple organisms). AMP's recommendation was also supported and recommended by other commenters and the Advisory Panel. A crosswalk of 87801 is a more similar to new code 87634 than 87798 because the two subtypes of RSV (e.g., A and B) which typically cause disease must be assessed and this is similar in resource utilization to the multiorganism code of 87801.

87662 - Infectious agent detection by nucleic acid (DNA or RNA); Zika virus, amplified probe technique

CMS proposes a crosswalk of 87798 (infectious agent detection; amplified probe technique, not otherwise specified). AMP recommended a crosswalk of 87502 (infectious agent detection; amplified probe technique; influenza virus). This recommendation was also supported and recommended by other commenters as well as a majority of the Advisory Panel. A crosswalk of 87502 is a more similar crosswalk to new code 87634 than 87798 because the resources for Zika testing (e.g., kit costs and technologist time) is more similar, in terms of resources, to the NLA for the influenza code (87502) than for the NOS code.

Again, we thank you for the opportunity to submit these comments on the 2018 preliminary determinations for new, reconsidered codes, codes new for CY2017, and codes with no/insufficient private payer data. We are happy to answer any questions about our recommendations and provide follow up information. Please direct your correspondence to Tara Burke, AMP Director of Public Policy and Advocacy, at tburke@amp.org.

Sincerely,

Samuel K. Caughron, MD
Chair, Economic Affairs Committee
Association for Molecular Pathology