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July 20, 2015

Andy Slavitt, Acting 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

Dear Mr. Slavitt:

On behalf of the Association of Molecular Pathology (AMP), thank you for this opportunity to submit comments on the preliminary gapfill determinations. 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.

After a careful review of the preliminary determinations, we offer the following comments.

Codes Priced by Cahaba

We were pleased that Cahaba provided pricing for the services listed below. Doing so sets a positive example for the other Medicare Administrative Contractors (MACs), and we hope to see more MACs provide preliminary pricing for molecular diagnostic services. We offer the following specific comments:
Cahaba recommended that CPT codes 81435 and 81436 described below be priced at $795.95. We support this pricing and recommend that it be adopted by all of the MACs.

- 81435 Hereditary colon cancer syndromes (e.g., Lynch syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include analysis of at least 7 genes, including APC, CHEK2, MLH1, MSH2, MSH6, MUTYH, and PMS2 at

- 81436 Duplication/deletion gene analysis panel, must include analysis of at least 8 genes, including APC, MLH1, MSH2, MSH6, PMS2, EPCAM, CHEK2, and MUT

Cahaba also recommended that CPT codes 81445 and 81450 be priced at $90.

- 81445 Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

- 81450 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA and RNA analysis when performed, 5-50 genes (e.g., BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed

While we appreciate that Cahaba recommended a price, we cannot support pricing at this level. These procedures have become critically important to the management of cancer patients as evidenced by the increasing number of publications and abstracts describing the utility (From the recent 2015 ASCO annual meeting see (Von Hoff et al JCO 2010; 28 4877-4883, Tsimberridou et al., Clin Cancer Res 2014;20 4827-4836, Nadauld et al.,J Clin Oncol 33, 2015 (suppl; abstr e17641, Nadauld et al., J Clin Oncol 33, 2015 (suppl; abstr e17647).

We have obtained cost data from laboratories that provide services that fulfill these CPT codes (AMP's micro-costing project) which clearly identifies that costs are higher than $90. This, along with two other procedures that were costed in AMP's micro-costing project are explained in detail below.

Recommendations for Unpriced and Insufficiently-Priced Services

Microcosting analyses for codes 81445, 81430, and 81415

AMP initiated a micro-costing and health economic evaluation of genomic sequencing procedures (GSPs), CPT codes 81445, 81430, and 81415. They were selected as representative applications of GSPs reflect the spectrum of technology and data analysis. The goal of this project was to develop transparent cost data for representative procedures by collecting and analyzing the technical, analytical, post-analytical and interpretation costs. For a comprehensive analysis of the full costs of performing these GSPs, we also documented the development, validation, maintenance, quality control, and overhead costs from laboratories providing clinical testing.

Detailed microcosting analyses were performed on 13 protocols from nine laboratories performing clinical testing for one or more of the CPT based procedures. These laboratories represented both small and large academic medical centers as well as commercial reference laboratories so as to capture the array of testing methods and approaches to the bioinformatic analyses. One challenge in performing cost analyses for methods with multiple technology platforms and assay steps is the difficulty in determining a representative sample. To address this challenge laboratories performing clinical testing that met our definition of a representative laboratory were selected. All costs related to performing these procedures, including the direct costs of performing, analyzing and reporting patient samples; the expense of developing and validating the technical protocols; the development, validation, quality control, and maintenance of the informatics pipelines; data storage; and the institutional overhead were combined to calculate a total per sample per laboratory test cost. Individual laboratories were de-identified and the findings were aggregated for comparison and have been made publicly available (http://www.amp.org/committees/economics/NGSPricingProject.cfm).

For targeted genomic sequence analysis of DNA from solid tumor specimens, the results from five representative laboratories fulfilling the criteria for CPT code 81445, demonstrated costs ranging from $577.99 to $907.82 (Figure 1). Cost varied with platform, investment in laboratory-developed or commercial bioinformatics and validation expenses. These cost data should help to inform CMS of a more adequate price for this procedure and the related 81450 and 81455.

Cost data from two laboratories performing hearing loss genomic sequence analysis that fulfilled the criteria for CPT code 81430 were calculated ($1,949 and $1,890) (Figure 2). Their gene lists had a similar set of genes and the largest variance in cost was the bioinformatic analysis and clinical interpretation by group review.

Costs for exome sequence analysis (81415, single exome) ranged from $1,397.60 to $3,388.18, with data aggregated from three participating laboratories (Figure 3). Cost variability was observed for the technical sequencing and variant interpretation, even with the same platform and method, and appeared to be related to the extent of subsequent analysis (for example, through group review and interpretation vs. individual laboratory director review and sign out). Analysis of exome sequencing data can be considerably variable depending on the patient presentation and medical findings and the variety of genetic alterations detected by the assay. This is reflected in the greater variability in cost by these laboratories.

Figure 1: Microcosting data of targeted genomic sequence analysis of DNA from solid tumor specimens from five representative laboratories.

Sample Type/DNA Extraction Method		Tumor (Automated)	Blood (Manual)	Tumor (Manual)	Tumor (Manual)	Tumor (Automated)
Library Preparation Method		Ion AmpliSeq	Ion Ampliseq	Ion Ampliseq	Trusight Tumor	Trusight Tumor
Sequencing Platform		Ion Torrent	Ion Torrent	Ion Torrent	Illumina MiSeq	Illumina MiSeq
Bioinformatics/Data Analysis/Report Creation		Laboratory Director Review Custom Pipeline	Laboratory Director Review Custom Pipeline	Laboratory Director Review Custom Pipeline	Laboratory Director Review Custom Pipeline	Laboratory Director Review Commercial Pipeline
Total Labor Time	DNA Extraction	12	18.8	55	26	11
	Library Prep	31	26.62	44	34	25
	Sequencing	13	68	13	34	5
	Data Analysis	13	22	8	26	38
	Report Development	45	60	20	30	15
	Review/Sign-Out	9	8	8	10	15
Total Pre-Analytics/Analytics Consumables Cost	DNA Extraction	$ 6.28	$ 12.25	$ 10.21	$ 7.92	$ 5.47
	Library Prep	$ 207.68	$ 216.64	$ 181.87	$ 159.14	$ 163.08
	Sequencing	$ 85.30	$ 91.62	$ 75.56	$ 137.24	$ 180.25
Total Pre-Analytics/Analytics Equipment Cost	DNA Extraction	$ 0.15	$ 0.05	$ 0.23	$ 0.00	$ 0.09
	Library Prep	$ 3.12	$ 1.67	$ 10.22	$ 1.34	$ 7.56
	Sequencing	$ 6.21	$ 8.11	$ 6.89	$ 17.99	$ 21.46
Total Pre-Analytics/Analytics Labor Cost	DNA Extraction	$ 3.60	$ 5.64	$ 13.33	$ 13.71	$ 3.38
	Library Prep	$ 9.43	$ 7.99	$ 23.20	$ 18.29	$ 6.94
	Sequencing	$ 3.95	$ 20.34	$ 6.76	$ 18.29	$ 2.14
Total Bioinformatics / Data Analysis /Reporting Cost		$ 85.50	$ 243.49	$ 66.38	$ 110.00	$ 131.30
Total Validation Maintenance Overhead Cost		$ 287.34	$ 300.02	$ 194.77	$ 197.66	$ 56.31
Total Assay Cost (Per Sample)		$ 698.57	$ 907.82	$ 589.43	$ 681.58	$ 577.99

Figure 2: Microcosting data of hearing loss genomic sequence analysis from two representative laboratories.

Sample Type/DNA Extraction Method		Blood (Automated)	Blood (Manual)
Library Preparation Method		Agilent SureSelect	Agilent SureSelect
Sequencing Platform		Illumina HiSeq	Illumina HiSeq
Bioinformatics/Data Analysis/Report Creation		Group Review Custom Pipeline	Laboratory Director Review Custom Pipeline
Total Labor Time	DNA Extraction	4	12
	Library Prep	41	20
	Sequencing	6	3
	Data Analysis	276	175
	Report Development	90	120
	Review/Sign-Out	45	8
Total Pre-Analytics/Analytics Consumables Cost	DNA Extraction	$ 4.76	$ 7.66
	Library Prep	$ 157.92	$ 180.60
	Sequencing	$ 788.18	$ 984.82
Total Pre-Analytics/Analytics Equipment Cost	DNA Extraction	$ 0.96	$ 0.03
	Library Prep	$ 3.26	$ 8.85
	Sequencing	$ 101.84	$ 93.89
Total Pre-Analytics/Analytics Labor Cost	DNA Extraction	$ 1.05	$ 3.53
	Library Prep	$ 12.15	$ 0.12
	Sequencing	$ 1.80	$ 0.75
Total Bioinformatics / Data Analysis /Reporting Cost		$ 670.88	$ 255.75
Total Validation Maintenance Overhead Cost		$ 206.67	$ 354.29
Total Assay Cost (Per Sample)		$ 1,949.47	$ 1,890.27

Figure 3: Microcosting data of exome sequence analysis from three representative laboratories.

Sample Type/DNA Extraction Method		Blood (Automated)	Blood (Manual)	Blood (Manual)
Library Preparation Method		Agilent SureSelect	Agilent SureSelect	Agilent SureSelect
Sequencing Platform		Illumina HiSeq	Illumina HiSeq	Illumina NextSeq
Bioinformatics/Data Analysis/Report Creation		Laboratory Director Review Custom Pipeline	Group Review Custom Pipeline	Group Review Custom Pipeline
Total Labor Time	DNA Extraction	0	12	24
	Library Prep	128	72	149
	Sequencing	18	5	6
	Data Analysis	45	10	95
	Report Development	12	840	204
	Review/Sign-Out	4	13	25
Total Pre-Analytics/Analytics Consumables Cost	DNA Extraction	$ 3.30	$ 7.66	$ 2.80
	Library Prep	$ 420.22	$ 276.25	$ 431.78
	Sequencing	$ 314.90	$ 988.70	$ 806.20
Total Pre-Analytics/Analytics Equipment Cost	DNA Extraction	$ 3.30	$ 0.03	$ 10.00
	Library Prep	$ 1.33	$ 17.10	$ 2.41
	Sequencing	$ 135.53	$ 103.73	$ 64.10
Total Pre-Analytics/Analytics Labor Cost	DNA Extraction	$ 3.30	$ 3.53	$ 7.20
	Library Prep	$ 38.40	$ 21.60	$ 44.70
	Sequencing	$ 5.40	$ -	$ 1.80
Total Bioinformatics / Data Analysis /Reporting Cost		$ 61.71	$ 1,669.59	$ 659.10
Total Validation Maintenance Overhead Cost		$ 410.21	$ 300.00	$ 398.36
Total Assay Cost (Per Sample)		$ 1,397.60	$ 3,388.18	$ 2,428.45

Crosswalk Recommendations

For those procedures that the MACs did not price in the preliminary gapfill, AMP makes the following recommendations for pricing crosswalking to procedures that have already been priced. The following crosswalks for CPT codes 81246, 81313, 81287, and 81288 were chosen because they require similar levels of resource utilization and either the same number of variants or similar RNA expression analysis.

Code	CPT Descriptor	Test Purpose and Method	Crosswalk Recommendation
81246	FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836)	For patients with AML, test is used to predict prognosis and treatment. Typically PCR based fragment analysis.	81245. *FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (i.e., exons 14, 15)* This code has similar resource utilization, has the same number of variants and is in the same gene code family as 81245.

81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (e.g., prostate cancer)	Marker for prostate cancer. Quantitative reverse transcription PCR	81315. *PML/RARalpha, (t(15;17)), (PML-RARA regulated adaptor molecule 1) (e.g., promyelocytic leukemia) translocation analysis; common breakpoints (e.g., intron 3 and intron 6), qualitative or quantitative* This code uses identical types of resources with quantitative RNA expression analysis represented as a ratio of the target gene to a control as with 81315.
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (e.g., glioblastoma multiforme), methylation analysis	For patients with brain cancer; critical for therapy determination. Bisulfite DNA processing and DNA amplification.	81294. *MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants* This code has similar resource utilization as 81294.
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis	For patients with colorectal cancer with microsatellite instability; is used to determine whether they have sporadic CRC or hereditary Lynch syndrome which have different treatments and prognosis. Bisulfite DNA processing and DNA amplification.	81294. *MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants* This code has similar resource utilization, has the same number of variants and is in the same gene code family as 81294

Genomic Sequencing Procedures (GSPs)

Similarly, for those GSPs that were either not priced or were insufficiently-priced by the MACs, AMP is recommending crosswalks. These crosswalks are based on relativity and the similarity of resources to Tier 1 Molecular Pathology Procedures using a three component formula. The first component uses as a base the CPT code 81292 for sequencing of the *MLH1* gene, which is commonly performed and has a representative number of exons (21) and coding sequence (2271 base pairs) for a gene. We compared traditional Sanger sequencing methods to that of equivalently sized genomic sequencing procedures to demonstrate that GSPs are approximately one-fifth or 20% of the cost of traditional Sanger sequencing. We use this as the first component of the formula for determining the relative price.

The second component is that these services require significant bioinformatic analysis, which is not common for traditional Sanger sequencing, and therefore we recommend inclusion of CPT code 87901 (HIV Infectious agent drug susceptibility phenotype prediction using regularly updated genotypic bioinformatics). The method and resources of analyzing the nucleotide sequence to understand the alterations and predict the impact they may have overlaps very closely with the activity and resources involved in the bioinformatic analysis for GSPs and is relative to the amount of data being generated in the particular procedure.

To apply this formula to the GSP 81410, the minimum required genes for 81410 is 9 and totals 240 exons. 20% of 240 is 48 exons. This is approximately 2 times the number of exons for the *MLH1* gene in code 81292. Given this relationship which includes the cost savings of performing genomic sequencing, we recommend a crosswalk of 81410 to 81292 and 87901 both times 2.

Code	CPT Descriptor	Rationale	Recommendation
81410	Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK	Minimum of 9 genes (240 exons). 240 times 20% = 48 48 divided by 21 = 2.28	Crosswalk to 81292 x 2 plus 87901 x 2

The third component of the formula is that instead of using this math to calculate the minimum required exons per genomic sequencing procedure and applying a 20% reduction to determine the crosswalk, we identified that a there is a simple mathematical relationship using the natural log (ln) applied to the minimum number of genes for the particular GSP to determine the multiplier. In the above example for 81410 the natural log (ln) of 9 genes is 2.198. We recommended the multiplier of 2. Furthermore, we believe that resources for genomic sequencing procedures with greater numbers of gene targets do not increase linearly. Application of the natural logarithm takes this into account. We recommend scaling the resource increases with increasing numbers of genes using a natural logarithm scale to determine the multiply to apply to 81292.

For code 81430, a minimum of 60 genes is required. The natural log of 60 is 4.09 using the formula above. The resulting recommended crosswalk of 81292 and 87901 times 4 is similar in amount to the data from the cost analysis (presented above).

Code	CPT Descriptor	Rationale	Recommendation
81430	Hearing loss (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1	Min of 60 genes ln(60) = 4	Crosswalk to 81292 x 4 plus 87901 x 4

This same formula for determining the factor by which to multiply the base code is used for the rest of our recommendations.

Crosswalk Recommendations for Genomic Sequence Analysis Procedures: 81440, 81460, 81470

Code	CPT Descriptor	Rationale	Recommendation
81440	Nuclear encoded mitochondrial genes (e.g., neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP	Min of 100 genes ln2(100) = 4.6	Crosswalk to 81292 x 4.6 plus 87901 x 4.6
81460	Whole mitochondrial genome (e.g., Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection	Min of 37 genes ln(37) = 3.6	Crosswalk to 81292 x 3.6 87901 x 3.6
81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL,	Min of 60 genes ln(60) = 4	Crosswalk to 81292 x 4 87901 x 4

	KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2		

Crosswalk Recommendations for Targeted Genomic Sequence Analysis: 81450, 81455

Code	CPT Descriptor	Rationale	Recommendation
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA and RNA analysis when performed, 5-50 genes (e.g., BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed	Median number of genes is (27) ln(27) = 3.29	Crosswalk with multiplier 81292 x 3 87901 x 3
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed	Most laboratory GSPs include 100 genes ln(100) = 4.6	Crosswalk to 81292 x 4.6 plus 87901 x 4.6

GSPs – Duplication/Deletion

These tests are performed in conjunction with the genomic sequencing data from the base code in each family. We recommend using the base CPT code of 81294 and using a multiplier based on the natural logarithm of the number of genes to determine each of the matched GSP sequencing codes.

Code	CPT Descriptor	Crosswalk Recommendation
81411	Duplication/deletion analysis, panel must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1	Crosswalk with a multiplier 81294 x 1.4 Min of 4 genes ln(4) = 1.4
81431	Duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes	Crosswalk with a multiplier 81294 x 0.7 Min of 2 genes ln(2) = 0.7
81436	Duplication/deletion gene analysis panel, must include analysis of at least 8 genes, including APC, MLH1, MSH2, MSH6, PMS2, EPCAM, CHEK2, and MUTYH	Crosswalk with a multiplier 81294 x 2 Min of 7 genes Ln(8) = 2

81465	Whole mitochondrial genome large deletion analysis panel (e.g., Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed	81294 x 3.6 Min of 37 genes ln(37) = 3.6
81471	Duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2	Crosswalk with a multiplier 81294 x 4 Min of 60 genes ln(60) =4

Again, we thank you for the opportunity to submit these comments on the preliminary gapfill recommendations. We believe that the microcosting data and crosswalk recommendations described above will provide more accurate and equitable pricing for these services. We are happy to answer any questions about our recommendations and provide follow up information. Please direct your correspondence to Mary Steele Williams, AMP Executive Director, at mwilliams@amp.org.

Sincerely,

Janina A. Longtine, MD
AMP President