ASSOCIATION FOR MOLECULAR PATHOLOGY
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August 6, 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 written comments regarding new and reconsidered clinical diagnostic laboratory test codes for the Clinical Laboratory Fee Schedule (CLFS) for calendar year 2016 (CY2016). 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.

In alignment with our presentation at the CLFS meeting on July 16, 2015, we provide written recommendations to help CMS develop the CY2016 CLFS. Below, we provide rational and crosswalk recommendations for the 2016 CLFS molecular pathology procedures, the 2015 molecular pathology and genomic sequencing procedures reconsiderations, and the 2016 genomic sequencing procedures. Please note that there is one edit from our presentation: the recommendation to use code 87901 in the crosswalks is corrected to the 87900 code.

2016 CLFS Molecular Pathology Procedures

For the 2016 molecular pathology procedures, we provide crosswalk recommendations. The table below provides crosswalk to a code that has similar resource utilization and either the same number of variants or similar RNA expression analysis. The gray-colored CPT descriptor text represents the code information to which we recommend new codes be crosswalked.

Code	CPT Descriptor	Test Purpose and Method	Crosswalk Recommendation
81275 **81276**	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (e.g., carcinoma) gene analysis; variants in codons 12 and 13 ; additional variant(s) (e.g., codon 61, codon 146)	KRAS codon 61 and codon 146 variants which are important to identify in patients with colorectal cancer as the presence of these mutations is a contraindication for use of targeted anti-EGFR monoclonal	81275. *KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (e.g., carcinoma) gene analysis; variants in codons 12 and 13.*

		antibody therapy. Methods are typically PCR based.	This code has similar resource utilization, has the same number of variants and is in the same gene code family as 81275.
812XX	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (e.g., acute myeloid leukemia), gene analysis, full gene sequence	This testing is for somatic mutations in AML. Typically performed by sequencing and requires 4 amplicons to cover the entire gene due to the larger size of this one exon.	81235. *EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis; common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q).* This code has similar resource utilization as 81235.
812XX	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (e.g., acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain	For somatic mutations in CML which confer resistance to kinase inhibitors. It is done by sequencing and requires 6 amplicons to sequence the 6 exons of the gene that confer inhibitor resistance.	81235. *EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis; common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q).* This code has similar resource utilization as 81235.
812XX	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61)	NRAS activating mutations are important to identify in patients with colorectal cancer as the presence of these mutations is a contraindication for use of targeted anti-EGFR monoclonal antibody therapy. Methods are typically PCR based.	81275 times 1.5. *KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (e.g., carcinoma) gene analysis; variants in codons 12 and 13.* This code has 1.5 times more resource utilization as 81275.
812XX	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis; targeted sequence analysis (e.g., exons 8, 11, 13, 17, 18)	This testing is for somatic mutations in a number of different tumors. It is done by sequencing and requires 5 amplicons to sequence.	81235. *EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis; common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q).* This code has similar resource utilization as 81235.
813XX	PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (e.g.,	This testing is for somatic mutations in GIST (gastrointestinal stromal tumor)	81235.

	gastrointestinal stromal tumor [GIST]), gene analysis; targeted sequence analysis (e.g., exons 12, 18)	among other tumors which may confer resistance or sensitivity to kinase inhibitor therapy. It is done by sequencing and requires 5 amplicons to sequence.	*EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis; common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q).* This code has similar resource utilization as 81235.
812XX	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., mastocytosis), gene analysis, D816 variant(s)	This testing is for somatic mutations in mastocytosis among other tumors and confers resistance to kinase inhibitor therapy. Methods are typically PCR based similar to BRAF V600E testing.	81210. *BRAF (v-raf murine sarcoma viral oncogene homolog B1) (e.g., colon cancer), gene analysis, V600E variant* This code has similar resource utilization as 81210.
812X20	CALR (calreticulin) (e.g., myeloproliferative disorders), gene analysis, common variants in exon 9	This testing is for somatic mutations in myeloproliferative neoplasms to confirm diagnosis and determine prognosis. Methods are typically PCR based similar to FLT3 ITD mutation testing.	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 as 81245.
81211 **812xx**	BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) ; full sequence analysis and full duplication/deletion analysis	This testing is for hereditary mutations in breast, ovarian and prostate cancers. Methods are typically a combination of sequencing and dup/del testing.	81211 PLUS 81213. *BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)* *BRCA1, BRCA2; uncommon duplication/deletion variants* This code has similar resource utilization as 81211 plus 81213.

2015 Molecular Pathology Procedure Reconsideration Requests

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

2015 Genomic Sequencing Procedures

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 2015 Genomic Sequencing Procedures (GSPs)

For the 2015 Genomic Sequencing Procedures, 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 87900 (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. Please note that there is one edit from our presentation: the recommendation to use 87901 in the crosswalks is corrected to the 87900 code.

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 87900 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 87900 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 87900 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 In(60) = 4	Crosswalk to 81292 x 4 plus 87900 x 4

Following this relationship, for code 81415, approximately 20,000 genes are evaluated in performing exome analysis. The natural log of 20,000 is 9.9. We recommend a crosswalk of 81292 and 87900 times 9.9.

Code	CPT Descriptor	Rationale	Recommendation
81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis	~20,000 genes In(20,000) = 9.9	Crosswalk to 81292 x 9.9 plus 87900 x 9.9

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
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	Min of 7 genes ln(60) = 4	Crosswalk to 81292 x 2 plus 87900 x 2
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 87900 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 plus 87900 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, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2	Min of 60 genes ln(60) = 4	Crosswalk to 81292 x 4 plus 87900 x 4

Crosswalk Recommendations for Targeted Genomic Sequence Analysis: 81445, 81450, 81455

Code	CPT Descriptor	Rationale	Recommendation
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	Median number of genes is (27) ln(27) = 3.29	Crosswalk with multiplier 81292 x 3 plus 87900 x 3

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 plus 87900 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 87900 x 4.6

2015 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,	Crosswalk with a multiplier 81294 x 4 Min of 60 genes

	FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2	ln(60) =4

Recommendations for 2016 Genomic Sequencing Procedures

For the 2016 Genomic Sequencing Procedures, AMP is recommending crosswalks. We recommend using the same rationale described for the 2015 Genomic Sequencing Procedures. The resources required for performing other genomic sequencing procedures was estimated based on the genetic content being evaluated and recommendations are based on this similarity of resource utilization.

Code	CPT Descriptor	Rationale	Crosswalk Recommendation
814XB	Ashkenazi Jewish associated disorders (e.g., Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1	Min of 9 genes ln(9) = 2.2	Crosswalk to 81292 x 2.2 plus 87900 x 2.2
814XL	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11, and TP53	Min of 14 genes ln(14) = 2.6	Crosswalk to 81292 x 2.6 plus 87900 x 2.6
814XM	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11	Min of 5 genes ln(5) = 1.6	Crosswalk to 81292 x 1.6 plus 87900 x 1.6
814XP	Hereditary retinal disorders (e.g., retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A	Min of 15 genes ln(15) = 2.7	Crosswalk to 81292 x 2.7 plus 87900 x 2.7
814XE	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma; genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL	Min of 6 genes ln(6) = 1.8	Crosswalk to 81292 x 1.8 plus 87900 x 1.8
814XF	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma; duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL	Min of 4 genes ln(4) = 1.4	Crosswalk to 81292 x 1.4 plus 87900 x 1.4

814XD	Noonan spectrum disorders (e.g., Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1	Min of 12 genes ln(12) = 2.5	Crosswalk to 81292 x 2.5 plus 87900 x 2.5

Recommendations for 2016 Genomic Sequencing Procedures- Duplication/Deletion Analysis

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
814x06	duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL	Crosswalk with a multiplier 81294 x 1.4 Min of 4 genes ln(4) = 1.4
814x13	duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11	Crosswalk with a multiplier 81294 x 1.6 Min of 5 genes ln(5) = 1.6

Again, we thank you for the opportunity to submit recommendations to help CMS develop the CY2016 CLFS. 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