ASSOCIATION FOR MOLECULAR PATHOLOGY
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July 1st, 2024

The Honorable Chiquita Brooks-LaSure
Administrator
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: 2024 Preliminary Gapfill Payment Determinations

Dear Administrator Brooks-LaSure:

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 2,900 physicians, doctoral scientists, and medical laboratory scientists (technologists) who perform or are involved with laboratory testing based on knowledge derived from infectious disease, molecular biology, and genetics and genomics. Membership includes professionals from the government, academic medicine, private and hospital-based clinical laboratories, and the in-vitro diagnostics industry.

We are concerned that the preliminary gapfill median rates do not accurately represent the value of the work performed for the procedures described by CPT codes 81457, 81458, 81459, 81462, 81463, and 81464.

Analysis of 2024 Preliminary Gapfill Determinations for GSP CPT Codes (81457-59 and 81462-64)

In Table 1 below, we have outlined the CPT codes and the preliminary gapfill median rates of interest to AMP's members. We have determined that these preliminary median rates do not adequately account for the level and complexity of the work and resources required to provide these diagnostic and prognostic tests for cancer patients.

Table 1: Description of CPT Codes and CMS Preliminary Gapfill Median Rate

Code	Descriptor	Gapfill Median Rate
81457	Solid organ neoplasm, genomic sequence analysis panel,	$896.87

	interrogation for sequence variants; DNA analysis, microsatellite instability	
81458	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability	$1,046.35
81459	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements	$2,989.55
81462	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements	$1,195.83
81463	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability	$1,345.31
81464	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements	$3,288.51

Under 42 C.F.R 414.508(b)(1), Medicare regulations state that MACs are required to consider the following criteria when establishing gapfill rates:

(b) Gapfilling. Gapfilling is used when no comparable existing test is available. (1) In the first year, carrier-specific amounts are established for the new test code using the following sources of information to determine gapfill amounts, if available:

(i) Charges for the test and routine discounts to charges;
(ii) Resources required to perform the test;
(iii) Payment amounts determined by other payers; and
(iv) Charges, payment amounts, and resources required for other tests that may be comparable or otherwise relevant.

AMP is concerned that these factors have not been fully considered because the preliminary median rates for 81457-59 and 81462-64 do not account for the resources required to perform these tests. These codes represent a variety of genetic alterations and variants (see Table 2) which reflect the work and resources involved. Specifically, the variants specified by the code descriptors entail months of validation studies in a high-complexity clinical laboratory, reagents, stringent quality control, proficiency testing, capacity of the instrumentation, and bioinformatic resources to run multiple algorithms for accurate reporting. Furthermore, the new Genomic Sequencing Procedure codes reflect new assays involving the analysis of Tumor Mutational Burden (TMB) and Microsatellite Instability (MSI), work

previously unaccounted for by Category 1 CPT codes. **For these reasons, AMP strongly urges that the gapfill rates be revised to ensure work and resources are appropriately accounted for 81457, 81458, 81459, 81462, 81463, and 81464.** To further inform the establishment of a gapfill rate, AMP provides the following information about different features of the assays these codes represent.

Additional Information on Resources/Work Involved

Table 2: Comparison of Oncology GSP CPT code (codes recommended by AMP highlighted in blue)

Code	Specimen Source			Panel Type	Nucleic Acid	Sequence Variants	Copy Number Variants	Micro-satellite Instability	Tumor Mutation Burden	Rearrangements
	Solid Organ	Hemato-lymphoid	Cell Free							
81445	•		No	Targeted 5-50 genes	DNA or DNA/RNA	•	•			•
81449	•		No	Targeted 5-50 genes	RNA	•	•			•
81450		•	No	Targeted 5-50 genes	DNA or DNA/RNA	•	•			•
81451		•	No	Targeted 5-50 genes	RNA	•	•			•
81455	•	•	No	Targeted ≥51 genes	DNA or DNA/RNA	•	•			•
81456	•	•	No	Targeted ≥51 genes	RNA	•	•			•
81277	•		No	Genomic Sequence	DNA or DNA/RNA		•			
81457	•		No	Genomic sequence	DNA or DNA/RNA	•		•		
81458	•		No	Genomic sequence	DNA or DNA/RNA	•	•	•		
81459	•		No	Genomic sequence	DNA or DNA/RNA	•	•	•	•	•
0244U	•		No	Genomic Sequence	DNA	•	•	•	•	•
81462	•		Yes	Genomic sequence	DNA or DNA/RNA	•	•			•
81463	•		Yes	Genomic sequence	DNA or DNA/RNA	•	•	•		
81464	•		Yes	Genomic sequence	DNA or DNA/RNA	•	•	•	•	•

Next Generation Sequencing

Next generation sequencing is a high throughput approach to DNA sequencing using the concept of massively parallel processing. This is also used for sequencing an individual's entire genome. Once DNA is extracted from the sample of choice, a DNA library is prepared, and next generation sequencing is completed. The resulting sequencing data can be used by a molecular professional for analysis of copy number variants (CNVs), microsatellite instability (MSI), or tumor mutational burden (TMB).

Copy Number Variants

CNVs are structural changes in the genome composed of large deletions or duplications. CNVs can be found in the germline but can also occur in somatic cells.

Microsatellite Instability

The term MSI reflects a change that occurs in certain cells in which the number of repeated DNA bases in a microsatellite is different from what it was when the microsatellite was inherited. To evaluate MSI, microsatellites are excised and analyzed for insertion and deletion events from the tumor sample to detect replication errors.[6] Reliable assessment of MSI by sequencing methods requires evaluation of sufficient microsatellite loci, typically only achievable with larger panels, i.e., those over 50 genes.

Tumor Mutational Burden

TMB is a complex biomarker analysis that requires significant bioinformatics, development and validation requirements. Due to the amount of DNA required to analyze TMB (300 or more genes)[1], it is measured in mega-bases rather than the number of genes. TMB is defined in the 2024 CPT code book in the Preface of the GSP section as "the number of somatic mutations detected per million bases, or megabase (Mb) of genomic sequence investigated from a cancer specimen. It is usually obtained from analysis using a next generation sequencing method." The TMB value indicates the total number of mutations in the analyzed genomic region. While assessing the value of TMB, molecular pathologists usually count somatic mutations in the entire region of interest.

Formalin-Fixed Paraffin-Embedded Tissue and Cell-Free Nucleic Acid Testing

The abovementioned GSP codes represent assays using two different sample types, formalin-fixed paraffin-embedded (FFPE) tissue and cell-free nucleic acid testing (cfDNA) assays. Using cfDNA testing is more labor intensive and more expensive than FFPE. Kits that isolate cfDNA for analysis cost more than kits to isolate DNA from FFPE.[2,3] Furthermore, there is an increased level of work and expertise of the molecular pathologist to interpret results for cfDNA that is required as the depth of sequencing is an order of magnitude higher than FFPE tissue, i.e. cfDNA requires 10,000x depth of sequencing versus FFPE tissue with 100-1,000x. We appreciate that the median gapfill rates for 81462, 81463, and 81464 are higher than the corresponding codes for tests involving FFPE, however, these rates do not fully encompass the resources involved in cfDNA testing.

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[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7710563/#:~:text=TMB%20can%20be%20assessed%20using,present%20within%20the%20entire%20exome.

[2] https://www.qiagen.com/us/products/discovery-and-translational-research/dna-rna-purification/dna- purification/cell-free-dna/qiaamp-circulating-nucleic-acid-kit

[3] https://www.qiagen.com/us/products/discovery-and-translational-research/dna-rnpurification/dna-purification/genomic-dna/qiaamp-dna-ffpe-tissue-kit

Our Recommendations regarding the Genomic Sequencing Procedure Codes

Below, we have provided information about "charges, payment amounts, and resources required for other tests that may be comparable or otherwise relevant". These benchmarks may be used to guide gapfill amounts. Additionally, we provide recommended payment rates for 81457-59 and 81462-64 based on the work and resources needed to complete the testing.

1. **CPT Code 81457** *Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability*

   Recommendation:

   The work involved for 81457 is equal to that of 81455 less the work of 81277 because 81457 does not include copy number variant analysis.

   81457 = 81455 – 81277 = $1759.60

   Rationale/Additional Considerations

   We believe that the work necessary to complete 81457 is equal to **81455 less than 81277**. The code 81457 does not include copy number variants detection and analysis within its code description, and we therefore recommend using 81455 with a subtraction of **81277.** AMP believes that the code 81277 reflects the work of copy number variants and have subtracted it from the 81455 to reflect what is the most accurate reflection of work and resources needed to complete an assay under the code description of CPT code 81457.

Code	Descriptor
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis.
81277	(Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities).

2. **CPT Code 81458** *Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability*

   Recommendation: 81455 is the most similar to 81458 in terms of work and resources and as such, adequately accounts for the work required to complete this testing.

   81458 = 81455= $2919.60

   Rationale/Additional Considerations:

   81455 uses similar work and resources as it also involves the analysis of tumor alterations

(sequence variants, copy number variants and microsatellite instability) to match the patient to the best therapies based on clinical evidence in peer-reviewed literature and professional guidelines.

Code	Descriptor
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis.

3. **CPT Code 81459** *Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements*

Recommendation: 0224U is the most similar to 81459 in terms of work and resources and adequately accounts for the work required to complete this testing.

81459= 0224U=$3500.00

Rationale/Additional Considerations:

0244U is relevant as the code descriptors include the same attributes and therefore it uses similar work and resources.

Code	Descriptor
0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor- mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue.

4. **CPT Code 81462** *Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements.*

Recommendation: 81455 is the most similar to 81462 in terms of work and resources. Additionally, this requires a sample change from FFPE to cfDNA and AMP recommends a multiplier of 1.25 to adequately account for the work required to complete this testing.

81462= 81455 * 1.25= $3549.50

Rationale/Additional Considerations:

81455 is a relevant code because both assays are designed to analyze tumor alterations

(sequence variants, copy number variants and rearrangements) to match the patient to the best therapies based on clinical evidence in peer-reviewed literature and professional guidelines. However, 81455 involves the use of FFPE. A payment adjustment should be applied to adequately reflect the work and resources used for cfDNA. Due to the sequencing depth able to be achieved in cfDNA testing. AMP suggests a multiplier of 1.25 to reflect the proper amount of work and resources used.

Code	Descriptor
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis.

5. CPT Code 81463 *Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability*

Recommendation:

81455 is the most similar to 81463 in terms of work and resources. We believe a multiplier of 1.25 accounts for the sample change from FFPE to cfDNA to adequately accounts for the work required to complete this testing.

81463= 81455 * 1.25= $4375.00

Rationale/Additional Considerations:

81455 (code descriptor below) is a relevant code because the two assays are designed to analyze tumor alterations (sequence variants, copy number variants and microsatellite instability) to match the patient to the best therapies based on clinical evidence in peer-reviewed literature and professional guidelines. However, 81455 involves the use of FFPE. A payment adjustment should be applied to adequately reflect the work and resources for cfDNA. Due to the sequencing depth able to be achieved in cfDNA testing. AMP suggests a multiplier of 1.25 to properly reflect the work and resources used.

Code	Descriptor
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis.

6. **CPT Code 81464** *Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements*

   Recommendation:

   0244U is the most similar to 81464 in terms of work and resources. We believe a multiplier of 1.25 accounts for the sample change from FFPE to cfDNA.

   81464= 0244U * 1.25= $4375

   Rationale/Additional Considerations:
   0244U Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue. 0244U is a relevant code because both assays are designed to analyze tumor alterations (copy number variants/alterations, sequence variants, rearrangements, microsatellite instability, and tumor mutational burden) to match the patient to the best therapies based on clinical evidence in peer-reviewed literature. However, 0244U involves the use of FFPE. A payment adjustment should be applied to adequately reflect the work and resources for Cell-Free Nucleic Acid Testing. Due to the sequencing depth able to be achieved in cfDNA testing. AMP suggests a multiplier of 1.25 to accurately reflect the amount of the work and resources used.

Based on the information above, AMP urges the gapfill rates to be revised as recommended to ensure that **81457-59**, and **81462-64** are given appropriate assessment and reflect the actual resources and work required to perform the testing for cancer patients.

<u>Improving Transparency in the Gapfill Process</u>

AMP remains concerned by the lack of detail in the rationale that is provided to the public about how the Medicare Administrative Contractors (MACs) arrive at a particular gapfill rate. It is difficult for the public to fully analyze and constructively respond to preliminary gapfill values given the lack of transparency in how the preliminary pricing is determined. We understand that CMS relies on the MACs to be the primary operational contacts between the Medicare fee-for-service program and providers across the country. Consequently, MACs must serve as equitable intermediaries, thoroughly and conscientiously considering the input of physicians and stakeholders who are practicing in these rapidly evolving fields of research, science, and medicine. Having an open dialogue between CMS, MACs, and stakeholders is necessary to ensure that Medicare patients receive the benefit of and access to the most up-to-date clinical science and receive safe and effective care. Transparency and stakeholder engagement are critical to ensuring that the gapfill process results in appropriate and fair pricing assessments. We understand that the median gapfill rate is largely dependent on the rate reported by Palmetto GBA which is calculated using their Equitable Pricing Model. This model is a "proprietary algorithm developed and used by Palmetto GBA® and other contractors affiliated with the MolDX®

program to establish Gapfill pay rates"[4]. We understand that Palmetto is required to use the criteria defined by CMS regulation when determining a gapfill rate, however, there is little detail about the Equitable Pricing Model, the data considered when the model is used, and how that data is weighted.

AMP requests that CMS further improve its process for establishing gapfill payment rates, increase transparency, and require more substantial information be reported to the public on how information is used by each MAC to calculate a gapfill rate as well as the methods employed to arrive at the reported payment rate.

Again, we thank you for the opportunity to submit these comments on the preliminary gapfill recommendations. We believe that the 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 Annie Scrimenti, AMP Associate Director, Public Policy and Advocacy, at ascrimenti@amp.org.

Sincerely,

Maria Arcila, MD
President, Association for Molecular Pathology

[4] https://palmettogba.com/palmetto/moldxv2.nsf/DID/CQ8P1FBUXO