August 6, 2018

Mr. Glenn McGuirk
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Submitted via email: glenn.mcguirk@cms.hhs.gov

Dear Mr. McGuirk,

The American Clinical Laboratory Association (ACLA) submits these written comments on the 2018 Proposed Clinical Laboratory Fee Schedule (CLFS) Gapfill Determinations.

At the outset, ACLA reiterates its long-standing concern about a lack of transparency in the gapfilling process and the failure by the Centers for Medicare and Medicaid Services (CMS) to adhere to its own regulations regarding providing an explanation for preliminary payment determinations. At a minimum, the agency is to provide the public with an explanation of the payment rate for the test, the reasons for each determination, the data on which the determinations are based, and how it took into account the recommendations of the Advisory Panel on CDLTs. 42 C.F.R. § 414.506(d). In the final rule implementing the Protecting Access to Medicare Act of 2014, the agency expressed its intention to provide these explanations, yet it does not appear that CMS has provided any of this information with its preliminary payment rates. The agency must explain to stakeholders why it did not adhere to its own regulation and provide this information with the preliminary payment rates.

When the final rates are released, CMS must meet its statutory obligation to "make available to the public an explanation of the payment rate for [each gapfilled] test," including how it took into consideration the charges for the test, the resources required to perform the test, payment amounts determined by other payors, and charges and resources for other similar tests, and which of these factors it did not take into consideration. 42 U.S.C. § 1395m-1(c). Congress gave CMS clear direction on how the gapfilling process is to become more transparent, and the agency must comply with that directive.

Absent even the minimal information the agency is to provide for each determination indicated above, ACLA offers the following specific input by category.

1. **MAAA Codes**

ACLA is providing the following information on 0009M – fetal aneuploidy (trisomy 21, and 18) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as risk score for trisomy of particular relevance in the gapfill process.

HCPCS	New National Limit	Descriptor	ACLA Recommendation
0009M	$132.86	Fetal aneuploidy (trisomy 21, and 18) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as risk score for each trisomy	This is a LabCorp test that no longer is being offered. LabCorp plans to submit an application to the AMA for deletion of this code. Since the testing is no longer being performed, ACLA would suggest that this code not be priced on the CLFS.

2. **SEPT9 (Septin9) Methylation Analysis**

ACLA supports the preliminary determination (shown below) for this test.

HCPCS	New National Limit	Descriptor
81327	$192.00	SEPT9 (Septin9) (eg, colorectal cancer) methylation analysis

3. **Genome Sequence Analyses**

HCPCS	New National Limit	Descriptor	ACLA Recommendation
81427	$24.50	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)	See below
81425	$349.00	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis	See below
81426	$349.00	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)	See below

The proposed preliminary gapfill amounts are woefully inadequate and need to be increased significantly to reflect the costs and value of running these types of assays. ACLA's rationale and recommendations to remedy this substantial undervaluing are as follows:

a. CMS Has Underpriced Clinical Genome Services

In June 2018, CMS proposed pricing for Whole Genome Sequencing (WGS) codes (below at right). These proposed rates are currently considerably lower than the NLAs associated with the three HCPCS/CPT

codes for Whole Exome Sequencing (WES), reviewed by CMS in November 2017 and reported on the 2018 CLFS (shown below at left). The proposed rates are far below the actual cost of the resources used to perform this very complex technical and evaluative service. ACLA recommends revising this proposed rate as outlined below to appropriately reimburse for the cost of this important testing.

Whole Exome Sequencing (Fixed, 2017/2018)				**Whole Genome Sequencing** (Proposed for Comment)		
CPT Code	**Code Description**	**CMS Price**		**CPT Code**	**Code Description**	**CMS Price**
81415	Clinical Exome Seq	$ 4,780		81425	Clinical Genome Seq	**$349**
81416	Comparator (EACH)	$12,000		81426	Comparator (EACH)	**$349**
81417	Reinterpretation	$ 320		81427	Reinterpretation	**$ 24.50**

b. Preliminary Gapfill Determinations Far Below Newly Documented WGS Costs

According to a 2018 systemic review of literature, WGS performance costs were up to $24,810 (Schwarze *et al., Genet Med*, 2018) per analysis; while the cost analysis was not fully transparent, the reported cost of WGS was two to five times the cost of WES. CMS's own fee schedule for exome sequencing (left) validates the cost range for WES reported in this publication. The proposed pricing for WGS grossly under-reimburses providers far below the cost of WGS testing.

c. WGS Health Economic Evidence Supports its Use in Clinical Practice

While currently the use of WGS in clinical practice is limited, studies that carefully evaluate the health economics landscape, including cost effectiveness and clinical outcomes, support the use of WGS in clinical practice. [1-3]. Supporting testing with appropriate reimbursement is important for appropriate utilization in clinical practice.

In their study, Stavropoulos et al demonstrated that whole-genome sequencing (WGS) can expand diagnostic utility and improve clinical management in pediatric medicine and has the potential to capture multiple classes of genetic variation in one test[1]. In this prospective study, WGS with comprehensive medical annotation was used to assess 100 patients referred to a pediatric genetics service was compared to the diagnostic yield from standard genetic testing. WGS identified genetic variants meeting clinical diagnostic criteria in 34% of cases, representing a fourfold increase in diagnostic rate over CMA (8%; P value = 1.42E − 05) alone and more than twofold increase in CMA plus targeted gene sequencing (13%; P value = 0.0009). WGS identified all rare clinically significant CNVs detected by CMA. In 26 patients, WGS revealed indel and missense mutations presenting in a dominant (63%) or a recessive (37%) manner. Four subjects had mutations in at least two genes associated with distinct genetic disorders, including two cases harboring a pathogenic CNV and SNV. When considering medically actionable secondary findings in addition to primary WGS findings, 38% of patients would benefit from genetic counselling. The findings from this study suggest that clinical implementation of

[1] Stavropoulos et al Whole-genome sequencing expands diagnostic utility and improves clinical management in paediatric medicine, Genomic Medicine 2018.

WGS as a primary test will provide a higher diagnostic yield than conventional genetic testing and potentially reduce the time required to reach a genetic diagnosis.

Schuh *et al*. reported results from PCR-free WGS of fresh frozen tumors and germline DNA in patients with cancer[2]. The WGS results helped to clarify an uncertain histopathological diagnosis in one case, led to informed or supported prognosis in two cases, leading to de-escalation of therapy in one, and indicated potential treatments in all eight. Overall 26 different tier 1 potentially clinically actionable findings were identified using WGS compared with six SNVs/indels using routine targeted NGS. These initial results demonstrate the potential of WGS to inform future diagnosis, prognosis, and treatment choice in cancer and justify the systematic evaluation of the clinical utility of WGS in larger cohorts of patients with cancer.

Farnaes *et al.* highlight that genetic disorders are a leading cause of morbidity and mortality in infants, and that rapid whole-genome sequencing (rWGS) can diagnose genetic disorders in time to change acute medical or surgical management (clinical utility) and improve outcomes in acutely ill infants[3]. In their retrospective cohort study of acutely ill inpatient infants in a regional children's hospital, the rate of clinical utility of rWGS (31%, thirteen of 42 infants) was significantly greater than for standard genetic tests (2%, one of 42; P = .0015). Eleven (26%) infants with diagnostic rWGS avoided morbidity, one had a 43% reduction in likelihood of mortality, and one started palliative care. In six of the eleven infants, the changes in management reduced inpatient cost by $800,000–$2,000,000. These findings demonstrated improved outcomes and net healthcare savings, and suggest that WGS merits consideration as a first tier test in this setting.

d. Recommendations for WGS Price

Given the current costs of WGS in clinical practice, we recommend that existing WES CMS Pricing be applied to WGS, using CPT 81415 as follows:

> 81425: Because the cost of WGS is two to five times the cost of WES, we recommend a price twice the rate established for HCPCS/CPT Code 81415.
>
> 81426: A comparator WGS should be roughly equivalent to the cost of a Clinical Genome Sequencing, since comparator genomes need to be sequenced and analyzed. We recommend a price to be the same as the recommended price for 81425 proposed above.
>
> 81427: Clinical reinterpretation of existing WGS still requires significant effort. While reinterpretation does not require the re-sequencing of the data itself, the original data are reanalyzed through bioinformatics and leveraging significant analysis time for PhD Clinical Variant Scientists, Genetic Counselors, and Laboratory Medical Directors. These services account for approximately half of the costs of the full service. This needs to be accounted for in the

[2] Schuh et al Clinically actionable mutation profiles in patients with cancer identified by whole-genome sequencing. Cold Spring Harb Mol Case Stud 4 2018.

[3] Farnaes et al Rapid whole-genome sequencing decreases infant morbidity. Genomic Medicine 2018.

proposed rates. We recommend that 81427 be half the recommended price for 81425 proposed above. This would essentially be the amount of 81415.

Given this information, we recommend that the proposed prices be adjusted accordingly.

Whole Exome Sequencing (Fixed, 2017/2018)			**Whole Genome Sequencing**				
CPT Code	**Code Description**	**CMS Price**	**CPT Code**	**Code Description**	**CMS Price**	**Recommendation**	**Recommended Price**
81415	Clinical Exome Seq	$ 4,780	81425	Clinical Genome Seq	$349	81415 x 2	$9560
			81426	Comparator (EACH)	$349	81415 x 2	$9560
			81427	Reinterpretation	$24.50	81415	$4780

Thank you for your consideration. Should you have questions or need additional information, please do not hesitate to contact me at swest@acla.com or (202)637-9466.

Sincerely,

Sharon L. West
Vice President, Legal and Regulatory Affairs