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July 30, 2015

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Centers for Medicare & Medicaid Services
7500 Security Boulevard
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Public Comment on the 2015 Clinical Laboratory Fee Schedule Public Meeting

Dear Director Hartstein:

Thank you again for the opportunity to present at this month's public meeting. In response to statements made by other speakers, I would like to rebut several inaccurate and misleading assertions and expand upon a few aspects of my presentation. This letter will address:

- The regulatory basis for selecting crosswalking codes
- Demonstrably inaccurate statements by Mr. Conroy
- Further data on the actual cost and performance of Cologuard and its components

Please note that Cable Car supports crosswalking code 815XB to the reconsidered payment amount for code G0464. Cable Car requests that the reconsidered payment amount for code G0464 be based on a crosswalk to code 82274 plus an additional code intended for population health screening purposes.

Crosswalking codes must be "comparable" to the new test

Mr. Michael Beebe, a paid consultant to Exact Sciences, stated in his remarks that he believes "pharmacoeconomic models, value based models, cost analyses, and the impact on the Medicare program" are "irrelevant" considerations that may not inform the determination of payment levels on the Clinical Lab Fee Schedule. This assertion has no basis in law. Although CMS has often chosen comparator assays with primary reference to their underlying methodology (as a proxy for cost to the lab), there is ample justification for consideration of other factors such as test purpose in determining an appropriate crosswalk. For example, much of the afternoon's discussion of substance abuse assays centered on the importance of reimbursing screening and confirmatory drug tests differently.

Code of Federal Regulations §414.508(a), which establishes crosswalking as a means of determining payment for a new clinical diagnostic laboratory test, is succinct: "*crosswalking is used if it is determined that a new test is comparable to an existing test, multiple existing test codes, or a portion of an existing test code.*" Nothing in this text requires CMS to base the selection of comparable tests on test methodology alone, and nothing in the regulation prohibits CMS from considering all available

information in choosing the most comparable assay or assays. Mr. Beebe would have CMS disregard overwhelming evidence that the crosswalk is too high, in favor of a formulaic approach designed to maximize financial returns for a self-interested sponsor.

The law provides wide latitude to establish payment levels based on multiple test codes or even portions of a test code, while requiring CMS to crosswalk only to existing tests that are "comparable." For reasons detailed in the presentation, the two diagnostic DNA assays in the current crosswalk are not comparable to Cologuard.

The reconsideration request is not limited to the example Tier 2 code identified in the request

Mr. Beebe further notes that there is no NLA for Tier 2 codes such as 81401, the suggested replacement for code 81315 in the crosswalk. However, there are local payment amounts established by Medicare contractors such as Palmetto, as noted in the request. At no time during the process have CMS staff indicated that Tier 2 codes are unacceptable for a crosswalking analysis, nor need they be as long as local fee schedule amounts can be determined. CFR §414.508(a)(2) reads: "Payment for the new test code is made at the lesser of the local fee schedule amount or the national limitation amount."

Cable Car has suggested code 81401 because it is an example of a DNA methylation assay intended for population health screening. Prior to the public meeting last year, Exact Sciences had identified 81401 in an investor presentation as a possible crosswalking code for the DNA methylation portion of Cologuard. In any case, the reconsideration rationale provided is not specific to the inclusion of code 81401. The recommendation is to place greater emphasis on the test's intended purpose in screening and the associated costs rather than on the steps required to perform the analyses.

In the event CMS required a code with an established NLA, there are several other codes that represent screening tests on the Clinical Lab Fee Schedule. For example, Code G0103 for PSA screening is indisputably "comparable" to code G0464 because both are preventative oncological screening tests. If code G0103 alone does not adequately compensate for the "work" involved in DNA methylation, a roughly 4x multiple of code G0103 to reflect the test sponsor's actual unit costs (discussed later) would be a suitable adjustment.

To reiterate, CMS has a great deal of discretion in determining the appropriate crosswalk. Cable Car's request is to encourage a comprehensive reassessment of the available evidence, not to presuppose an all-or-nothing crosswalk. Please crosswalk code G0464 to 82274 plus your choice of an appropriate code that reflects the costs and purpose of screening. If using a Tier 2 code presents technical challenges, please consider this recommendation to be 82274 PLUS 4 TIMES G0103 instead.

There is no evidence Cologuard achieves superior compliance over other screening methods

Mr. Kevin Conroy, CEO of Exact Sciences, made several representations in his remarks that appear to be inconsistent with the facts, which this letter will address in turn. On the subject of adherence, Mr. Conroy stated, "The cost effectiveness models you saw do not take into account compliance." Actually, they do. The AHRQ/CMS Technology Assessment by Dr. Zauber, et al. cited in the request

assumed a base case 50% adherence for all screening methods and included several adherence scenario analyses. Cost-effectiveness for stool-based DNA screening was only achieved in a scenario where it exhibited significantly better adherence than other screening modalities (e.g. 25-50 percentage points higher than FIT). There is insufficient evidence that Cologuard achieves any better compliance than other screening methods, even with extensive follow-up efforts and patient financial incentives which CMS cannot separately reimburse.

Mr. Conroy quoted a 73% compliance rate for Cologuard, but this is an internal productivity metric that does not account for unfulfilled physician orders. In the 9 months since FDA approval, there have been approximately 35,000 tests completed out of about 80,000 tests ordered. That represents 44% adherence. At its Investor Day on June 25, 2015, Exact Sciences attributed many of the unfulfilled orders to patient address errors and insurance coverage issues, which could be temporary. However, the company acknowledged that other hurdles to patient compliance remain, and COO Maneesh Arora stated, "Over time, we expect somewhere between 55-60%" of physician orders to result in a completed test. This aspiration, from 44% today, is what should be compared to adherence of other screening tests. The 73% compliance rate is a misleading apples-to-oranges comparison.

In his remarks, Mr. Conroy compared Cologuard to a 38% compliance rate for screening colonoscopy, rather than much higher compliance rates for other stool-based alternatives. He may have been referring to a 2012 *Archives of Internal Medicine* article by Dr. John Inadomi, et al. entitled "Adherence to Colorectal Cancer Screening: A Randomized Clinical Trial of Competing Strategies," which found that 38% of patients recommended a colonoscopy without any further intervention completed screening within 12 months, versus 67% who were recommended FOBT. Notably, the highest compliance rate (69%) was among the control group of patients given the choice between colonoscopy and FOBT. Assuming FIT has similar adherence characteristics to FOBT, early data on Cologuard compliance does not suggest the potential for superior adherence.

Furthermore, other studies have demonstrated significantly higher adherence to colonoscopy when the patient is more actively managed. Despite its title, a 2015 *Digestive Diseases & Sciences* article by Michael Greenspan, et al., "Patient Non-adherence and Cancellations Are Higher for Screening Colonoscopy Compared with Surveillance Colonoscopy," found that 279 (83.3%) of 335 participants adhered to a planned screening colonoscopy within one year of it being scheduled. This result reflects the possibility that high levels of compliance with screening protocols may be achievable through patient monitoring and follow-up.

Similar research has demonstrated the potential for other recommended screening modalities to achieve exceptionally high compliance through physician intervention. The recent ADherence to Minimally Invasive Testing (ADMIT) trial (pre-publication) comparing FIT to the Septin9 blood test demonstrated an 88.1% adherence rate for FIT. In short, there is simply no justification for Cologuard compliance rates to influence the crosswalk analysis.

Cologuard has a variable cost per test of only $88 or less at current volumes

In response to a question about the gross margins highlighted on slide 11, Mr. Conroy presented different information to CMS than his colleagues have conveyed to the financial community. At the public meeting, Mr. Conroy said: "The data that [Mr. Ma-Weaver] cites are what could occur in the future at specific volumes. Today with about 80,000 test orders, the costs of Cologuard are approaching $400 per test today. That could change in the future with significantly different volumes."

Just four days after the Public Meeting, Bill Megan, SVP of Exact Sciences, said on the company's earnings call for the quarter ending June 30, 2015: "We reported $384 in terms of cost per test [in Q1 2015], and it moved down smartly this quarter, and it's a function of capacity utilization….as we move through the year, we expect [cost per test] to continue to move down as we get higher volumes."

According to public filings with the Securities and Exchange Commission, during the three months ended March 31, Exact Sciences reported approximately 11,000 tests completed at a cost of goods sold of $4.2 million, the $384 per test referenced by Mr. Megan. Using the same methodology, in the second quarter, Exact Sciences reported about 21,000 tests completed at a cost of $5.1 million, or about $242 per test. The reduction in cost per test is due to spreading the fixed costs of the lab over a larger number of tests.

Furthermore, simple arithmetic illustrates the variable cost per incremental test. The increase in cost of goods sold between quarters was approximately $882,000, while the increase in the number of tests completed was approximately 10,000. Accordingly, the variable cost per incremental test is currently about $88. Note that this figure includes a roughly $15 per test royalty paid to a third party which would be proportionally reduced if the reimbursement were lower. It may also include additional costs for financial reporting purposes, such as expedited shipping and handling, which CMS does not separately reimburse.

Notwithstanding Mr. Beebe and Mr. Conroy's emphasis on the amount of "work" required to perform the DNA methylation and mutation analyses, it is apparent that Exact Sciences already has a very efficient lab that processes an incremental test at a time and materials cost of $73 or less ($88 minus $15).

For reference, the statement on the October 27, 2014 conference call referred to in the presentation described anticipated costs as follows: "We had previously talked about numbers between $100 and $110 per test at scale…our forecast for that is now higher based upon the preliminary payment determination from Medicare that will change our cost of goods sold. And the reason for that is that a piece of cost is a royalty payment and part of our royalty payments are linked to revenue numbers. So I think a fair way to think about costs is in the neighborhood of a $115 to $125 at scale. So again probably two years or so to get to that scale number on the way up, we are learning right now what that's going to be. But the ramp is going to be much lower margin to begin with and then into that run rate over the course of say the next 24 months." Mr. Megan was noting that the royalty amount payable on Cologuard is higher because it is based on a percentage of revenue, and the payment level set by CMS during last year's process was significantly higher than the company's own prior expectation.

Mr. Conroy references an unpublished study that does not refute the cited, peer-reviewed literature

On the subject of cost-effectiveness, Mr. Conroy claimed: "As part of the NCD process, Exact Sciences sponsored research by Archimedes…which found that even at $600 per test Cologuard is cost-effective." No such study was referenced in the NCD Decision Memo (CAG-00440N), and no such study has been published or released to the public for review. CMS should not rely on unverified oral descriptions of an unpublished analysis, especially one whose findings are contradicted by several peer-reviewed papers. The Decision Memo cited both the Zauber et al. analysis referenced earlier and the 2013 Skally, et al. literature review, "Cost-effectiveness of fecal DNA screening for colorectal cancer: a systematic review and quality appraisal of the literature," which was also cited in Cable Car's October 2014 comment letter. The literature review did not identify a single study which found fecal DNA screening to be cost-effective.

Mr. Conroy also attempted to discredit the CISNET analysis by suggesting that it is outdated. While there have been refinements to the underlying models over time, the trend in treatment costs since the study's publication has been such that other screening methods are now more cost-effective than before. Due to the high number of Cologuard false positives in the Medicare population, increases in the cost of colonoscopy actually improve the relative cost-effectiveness of more specific non-invasive tests. As discussed at length in Cable Car's October 2014 comment letter, the version 2.0 test examined in the analysis actually had more cost-effective sensitivity and specificity characteristics than Cologuard.

Prior to the Public Meeting, Cable Car confirmed with Dr. Zauber that her analysis was properly represented in the comment letter and reconsideration request. Cable Car also publicly offered to withdraw the reconsideration request if Exact Sciences were to publish data that demonstrated superior cost-effectiveness among Medicare beneficiaries at the current payment level. No such study has been published.

Mr. Conroy mischaracterized the cost of colonoscopy

Although comparison between the cost of colonoscopy and the cost of Cologuard is not directly relevant to the crosswalk determination, it is noteworthy that Mr. Conroy also overstated the cost to Medicare of colonoscopy in his remarks. He said, "The cost of colonoscopy that Medicare pays all-in is about $1,700, and that's an important part of the consideration we made when we priced Cologuard." Since a positive test result on Cologuard leads to a referral to colonoscopy, Cologuard should not be considered a substitute for colonoscopy or priced with reference to colonoscopy instead of other non-invasive screening tests. In any case, the cost-effectiveness studies just mentioned already account for the all-in costs of colonoscopy to Medicare.

A 2014 BMC Health Services Research publication by Bruce Pyenson, et al., "Costs and repeat rates associated with colonoscopy observed in medical claims for commercial and Medicare populations," assessed the 6 most commonly used billing codes for colonoscopy. The study found that the average allowed cost for an episode of colonoscopy in 2010, the latest period for which comprehensive data was available, was $1,071 in the Medicare population, with average cost sharing of $275. After cost sharing,

the cost to Medicare, which includes associated charges such as bowel preparation and polypectomy, was $796, less than half the figure cited by Mr. Conroy.

Exact Sciences' own analysis supports removing KRAS from the crosswalk

Mr. Conroy's response to a question regarding the additive value of the DNA components of Cologuard described in slides 9-10 of the presentation was to accuse: "Mr. Ma-Weaver either misunderstands or mischaracterizes the data." No portion of the comment letters or reconsideration request has in any way mischaracterized any of the data from the DeeP-C trial, and Cable Car takes exception at the suggestion. The receiver operating characteristic (ROC) curve assessing the contribution of the Cologuard FIT component and DNA components separately was a third-party analysis conducted by FDA staff, and the presentation acknowledged the incremental benefit of the DNA component in detecting precancerous adenomas. The mathematical claim on slide 9 is provable: the algorithm returns a positive result when the DNA values are at a minimum but the hemoglobin level is sufficiently high.

Mr. Conroy stated, "The FIT component detects about 70% of cancers, and the DNA component detects about 70% of cancers." That is not what the FDA's analysis shows. Please refer to pp. 23-25 of the FDA Executive Summary from the Molecular and Clinical Genetics Panel meeting. According to the ROC graph excerpted on slide 10, the headline sensitivity of Cologuard's FIT component was in line with commercial FIT at approximately 74%, not 70%. However, this reflects significantly higher specificity than Cologuard. Using a hemoglobin cutoff equivalent to the specificity of Cologuard, its FIT component would have detected approximately 83% of cancers. The incremental sensitivity to CRC contributed by the DNA component at that level of specificity was approximately 10 percentage points.

Put differently, if Cologuard had been required to maintain the same high specificity as the comparator FIT, its sensitivity to CRC would have been only 80%, not statistically distinguishable from the performance of its FIT component.

To reiterate, the incremental benefit of Cologuard's DNA component over FIT is attributable to its ability to detect precancerous adenomas that are not bleeding but are shedding methylated DNA. This is a real and valuable contribution to the menu of screening alternatives, but it does not justify the inclusion of extremely expensive comparator assays in the crosswalk. Cable Car's proposed reconsidered crosswalk would reimburse Cologuard at a payment level over 5x that of FIT.

The 70% figure Mr. Conroy referenced may have been referring to Exact Sciences Chief Science Officer Graham Lidgard's 2010 internal modeling exercise, which first hypothesized that the addition of FIT could improve the sensitivity and specificity of the early methylation assay. According to Exact Sciences' June 25, 2015 investor presentation, the DNA components were expected to achieve 67% sensitivity with 93% specificity. Even in this hypothetical model, KRAS had a negligible contribution to the assay's sensitivity of only 3%. The slide is reproduced below:

Exact Sciences R&D:
Proven approach through a multi-marker assay

Modeling Sensitivity/Specificity for Colon Cancer (2010)

Marker	Sensitivity	Contribution	Additive Sensitivity	Specificity	Contribution to False Positives	Subtractive Specificity
Methylation	64%	64%	64%	94%	6%	94%
Hemoglobin	64%	16%	87%	98%	3%	91%
KRAS	27%	3%	90%	99%	1%	90%

The DeeP-C trial ultimately demonstrated that both Cologuard's FIT component and commercial FIT have significantly higher sensitivity to fecal hemoglobin. The modeling, however, suggests that KRAS offered limited incremental contribution to the test's performance and only 27% sensitivity to cancer. Even if it were not already statutorily excluded from coverage for screening purposes, 81275 should not be part of the crosswalk because it is not sensitive for colorectal cancer. An assay that contributes only 3% of the sensitivity of Cologuard should not represent 40% of its reimbursement.

CMS should carefully evaluate all of the available data in choosing comparable tests

Mr. Conroy asked the audience in closing: "So I ask you, what test would you want to have for you and your family and for the citizens of the US – one that detects 94% of curable stage cancers or one that detects 70%?" This comparison of FIT and Cologuard presents an entirely artificial dilemma. There is no dispute over whether Cologuard offers incremental sensitivity compared to FIT. No one has suggested that Cologuard not be offered to anyone's family. The FDA has already approved Cologuard and CMS has already issued a national coverage determination. The reconsideration request simply asks CMS to reassess whether Cologuard currently has the right payment amount.

Cable Car strongly encourages CMS to examine the complete factual and academic record regarding the appropriate payment level for code G0464. The cost-effectiveness literature cited in the request and comments, the FDA analysis of the DeeP-C study, the comments of Drs. James Allison and J. Sanford Schwartz during the NCD process, and the arguments developed at the Public Meeting should be reviewed in full. I have my own family history of colorectal disease that I have avoided discussing; I hope you will base your decisions on the facts, not appeals to emotion.

Thank you very much for the opportunity to comment.

Sincerely,

Jacob Ma-Weaver, CFA