

Cable Car Capital LLC
1449 Washington Street #6
San Francisco, California 94109

October 24, 2014

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

Re: Basis for and amount of payment for Code G0464

Dear Mr. McGuirk:

Cable Car Capital LLC (“Cable Car”) is a registered investment adviser based in San Francisco with a concentrated, hedged approach to value investing. Cable Car appreciates the opportunity to comment on the proposed payment for the G0464 (Colorectal cancer screening) code in the Preliminary Determination for the CY 2015 Clinical Laboratory Fee Schedule published on October 9, 2014. As previously disclosed in its September 10 public comment¹ supporting CMS coverage for Cologuard, Cable Car holds a short position on behalf of clients in the common stock of Exact Sciences.

After careful review of the extensive cost-benefit literature on colorectal cancer (“CRC”) screening, Cable Car believes the preliminary payment amount for G0464 is too high. Based on 2014 National Limitation Amounts, the proposed crosswalk to codes 81275, 81315, and 82274 would result in payment of \$502.01 per screening test, 23x the payment for fecal immunochemical tests (“FIT”). At this level, stool-based DNA screening is dominated by all other screening modalities in terms of the cost of life-years gained. The payment amount proposed in the preliminary determination threatens to impose substantial additional costs on taxpayers. Cable Car strongly urges CMS to consider the available pharmacoeconomic evidence in its determination of an appropriate payment level for code G0464.

Accordingly, Cable Car recommends CMS adopt gapfill pricing for code G0464. In recent years, CMS has consistently recommended that new molecular tests be gapfilled, including as part of the preliminary CY 2015 determinations at issue.² Notwithstanding the introduction of a new G code for stool-based DNA screening, Cologuard is a new molecular test. Gapfill pricing would be consistent with past practice. If CMS determines to retain crosswalking as the basis for payment, the chosen crosswalk comparator assays should distinguish between tests intended for screening as opposed to diagnostics. In that event and as more fully set forth below, Cable Car recommends a crosswalk to code 82274 plus an appropriate Tier 2 methylation analysis code such as 81401.

¹ Ma-Weaver, J. September 10, 2014 public comment. Available at <http://www1d.cms.gov/medicare-coverage-database/staticpages/public-comment.aspx?commentID=28083&ReportType=nca>

² CLFS Preliminary Determinations for CY 2015 Codes. The rationale provided for gapfilling codes 81246, 81288, and 81313 given was: “As we have done with past molecular codes, we are recommending that this series of new Tier 1 molecular pathology codes be gapfilled for 2015. This will allow CMS and its contractors the opportunity to gather current information about the manner in which the tests are performed and the resources necessary to provide them, so that ultimately CMS can set an appropriate payment rate for these tests.”



I. Stool-based DNA screening for CRC is not cost effective

The cost-effectiveness of stool-based DNA screening for CRC is well-studied. During the long development process for Cologuard, numerous studies have examined the potential costs and benefits of stool-based DNA tests in comparison to other recommended screening modalities such as colonoscopy and FIT. Academics worldwide have utilized diverse modeling approaches to examine both early and idealized versions of the test. Studies computed the discounted costs of life-years gained from screening in various healthcare systems, including the Medicare population in the United States. According to a 2013 literature review, not a single study found fecal DNA screening to be cost-effective in comparison to existing alternatives.³ Authors generally found fecal DNA screening to be better than no screening at all, but even at prices significantly below the proposed reimbursement for code G0464, alternative modalities dominated fecal DNA screening.

Notably, positive results on a DNA test or FIT lead to referral to colonoscopy, which remains the standard of care. This dynamic limits – or should limit – the potential payment for screening tests because of the high incremental cost of false positives. These effects may be particularly pronounced for Cologuard given the significantly lower specificity in the over-65 population reported by the sponsor.⁴

Among the most thorough of the analyses in the literature review was a technology assessment⁵ by the Cancer Intervention and Surveillance Modeling Network (“CISNET”) commissioned by CMS. Because it focused exclusively on the Medicare population, was created expressly for the purpose of informing decisions by CMS, and is both unbiased and comprehensive, the CISNET report is the best available resource for determining the true cost-effectiveness of stool-based DNA testing. CMS should make use of its insights in determining an appropriate level of reimbursement for code G0464.

Although the underlying cost data used by CISNET may have changed since the study, the general trend has been towards higher costs for CRC treatment, increasing the value of all effective screening methodologies. In some cases, alternative screening costs have actually declined while the cost of colonoscopy has risen.⁶ While the CISNET analysis will hopefully be updated using the more recent inputs, the relative costs of different screening methodologies have not changed for the benefit of stool-based DNA testing. For this reason, the report’s analysis of threshold costs at which stool-based DNA testing could be cost effective remains instructive.

³ Skally M, Hanly P, Sharp L. Cost-Effectiveness of Fecal DNA Screening for CRC: A Systematic Review and Quality Appraisal of the Literature. *Appl Health Econ Health Policy* (2013) 11:181-192.

⁴ 83.8% in the over-65 cohort versus 89.8% in the broader trial. As reported in CMS Decision Memo (CAG-00440N). Available at <http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=277&NcaName=Screening+for+Colorectal+Cancer+-+Stool+DNA+Testing>

⁵ Zauber AG, Lansdorp-Vogelaar I, Wilschut J, Knudsen AB, van Ballegooijen M, Kuntz KM. Cost-Effectiveness of DNA Stool Testing to Screen for Colorectal Cancer. *AHRQ Technology Assessment*, December 2007. Available at <http://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id52TA.pdf>. Later published in *Annals of Internal Medicine* as Lansdorp-Vogelaar I, et al. Stool DNA Testing to Screen for Colorectal Cancer in the Medicare Population: A Cost-Effectiveness Analysis. *Ann Intern Med*. 2010; 153:368-377.

⁶ E.g. FIT (code 82774) reimbursement has declined from \$22.22 at the time of the study to \$21.70 in 2014.



The CISNET report examined a hypothetical version 2.0 of the DNA test, which actually assumed more favorable test characteristics from a cost perspective than Cologuard ultimately demonstrated. According to data from its sponsor, Cologuard achieved 92.6% sensitivity for CRC and 44.6% sensitivity to advanced adenomas with 83.8% specificity in the Medicare-age population.⁷ The CISNET version 2.0 model assumed higher specificity (85%), which would result in fewer costly false positives, and higher sensitivity to advanced adenomas (55%), which would result in more cost-saving early interventions, only partially offset by slightly lower CRC sensitivity of 90%. Using these parameters, CISNET conducted a threshold analysis to determine the Medicare reimbursement rate under a range of assumptions. They computed threshold costs using two models and three approaches,⁸ which represent the cost at which the test would be the most cost-effective screening method (ICER), at least as good as one alternative (ACER), and the price at which it would be cost-neutral with no screening. While the CISNET report should be read in full, its threshold cost conclusions are summarized in Table 11, reproduced below. CISNET explicitly calculated the maximum CMS reimbursement rate, assuming a 3-year screening interval, which would result in cost-effective screening. In order for stool-based DNA screening to be the best strategy (on the efficient frontier), reimbursement could be at most \$80. Reimbursement above \$191 would result in stool-based DNA screening being dominated by all other screening strategies.

Table 11. Threshold analysis from modified societal perspective: unit costs for DNA stool test resulting in equal cost-effectiveness (ACER and ICER) compared to current recommended CRC screening strategies for modified societal perspective

	Total Threshold costs (includes co-payments and patient time costs)			CMS reimbursement rates (excludes co-payments and patient time costs)		
	sDNA (v1.0)	sDNA (v1.1)	sDNA (v2.0)	sDNA (v1.0)	sDNA (v1.1)	sDNA (v2.0)
<i>5-year DNA stool testing</i>						
On efficient frontier	<i>NT, 54[‡]</i>	<i>105[‡], 151</i>	<i>50, 110</i>	<i>NT, 37</i>	<i>88, 134</i>	<i>33, 93</i>
Cost-neutral vs. no screening	<i>NT, 25</i>	<i>97, 151</i>	<i>36, 110</i>	<i>NT, 8</i>	<i>80, 134</i>	<i>19, 93</i>
Equal to highest ACER	<i>31, 131</i>	<i>239, 254</i>	<i>232, 243</i>	<i>14, 114</i>	<i>222, 237</i>	<i>215, 226</i>
<i>3-year DNA stool testing</i>						
On efficient frontier	<i>NT, 35[‡]</i>	<i>90, 133</i>	<i>56, 97</i>	<i>NT, 18</i>	<i>73, 116</i>	39, 80
Cost-neutral vs. no screening	<i>NT, 23</i>	<i>83, 133</i>	<i>21, 97</i>	<i>NT, 6</i>	<i>66, 116</i>	4, 80
Equal to highest ACER	<i>44, 118</i>	<i>212, 213</i>	<i>201, 208</i>	<i>27, 101</i>	<i>195, 196</i>	191, 184

ACER = average cost-effectiveness ratio compared with no screening (calculated using discounted costs and life-years gained)

ICER = incremental cost-effectiveness ratio (calculated using discounted costs and life-years gained)

NT = no threshold found (i.e., negative DNA stool test cost)

* MISCAN values in plain text; SimCRC values in italics

[‡] DNA stool test strategy is on the frontier as the least effective and least costly non-dominated strategy if the cost is at most this amount

⁷ CMS Decision Memo (CAG-00440N) op cit.

⁸ Zauber, et al. op cit. explains: “While calculating ICERs for competing alternatives is the theoretically correct approach for optimizing the health of a population under constrained resources... we also determined threshold costs for the DNA stool test such that the test strategy has the same average cost-effectiveness ratio (ACER) as at least one other recommended CRC screening strategy. ACERs represent the incremental cost per life-year saved of each strategy relative to no screening. We calculated the per-test cost that would allow a DNA stool test strategy to have the same ACER as the non-DNA stool test strategy with the lowest and highest ACER values.”

The substantial body of evidence demonstrating lack of cost-effectiveness in stool-based DNA screening has already led some commercial payors not to cover stool-based DNA tests at all, e.g. Harvard Pilgrim in a decision reaffirmed in April 2014.⁹ CMS has already decided to cover stool-based DNA tests; it should now set a payment level for G0464 that would result in cost-effective screening.

II. Pharmacoeconomic research should factor in the payment decision

On a May 1, 2014 conference call with financial analysts, Kevin Conroy, CEO of the test sponsor, suggested that the independent coverage and payment decisions could not both consider cost-effectiveness data:

“There are two groups within CMS. One is the coverage group, and the coverage group typically looks at cost-effectiveness as part of their coverage determination. We have provided very detailed, thorough cost-effectiveness data to CMS that they will use as part of the decision to cover Cologuard. That is very different than what is presented to the payment group. The payment group, as you know, it looks at new molecular tests. With the new approach that was first laid out in 2012 in collaboration with the AMA, there were codes issued for individual DNA markers, and payment levels have been ascribed to those markers through a robust process that included the AMA, CMS national and the regional MACs. That is a way to create a more standard approach to CMS paying for molecular tests. We are very pleased with that process and believe that we can get very good value out of it. That process does not include the cost-effectiveness analysis that is provided to the coverage group. And that's an important distinction that has to be made when looking at this and sometimes people get confused about that.”¹⁰

Conroy correctly observes that the NCD for Cologuard may have considered cost-effectiveness data.¹¹ Since there exists a price, i.e. \$80, below which Cologuard would be the most cost-effective screening modality for CRC, the coverage decision is unsurprising. However, there is no basis for the payment group to ignore important cost-effectiveness information in determining an appropriate payment level.

There is nothing in Section 414 prohibiting the Secretary from considering pharmacoeconomic evidence in establishing payment for a new test. Indeed, if it is determined that there is no comparable existing test, as this letter suggests, the gapfill process allows CMS to consider “payment amounts determined by other payers” and “payment amounts...for other tests that may be comparable or otherwise relevant.”¹² The CISNET analysis of other screening tests would be an important data point in any gapfill analysis. Even when crosswalking, CMS may determine that a new test is comparable to a single test or “a portion of an existing test code,”¹³ providing wide latitude in establishing payment levels.

⁹ Harvard Pilgrim Health Care Medical Policy on Fecal DNA Testing for CRC. Available at https://www.harvardpilgrim.org/pls/portal/docs/PAGE/PROVIDERS/MEDMGMT/STATEMENTS/FECAL_DNA_TESTING_0414.PDF

¹⁰ Exact Sciences Q1 2014 earnings call. Response to a question from Brian Weinstein of William Blair & Co.

¹¹ CMS Decision Memo (CAG-00440N) op cit. states, “As permitted by §1861(pp)(1)(D) of the Act, we may consider the appropriate frequency and payment level in determining whether to expand coverage for new CRC tests. CMS has commissioned such analyses in all past determinations (FIT, stool DNA, and computed tomography (CT) colonography) and will reanalyze using the test parameters of Cologuard.”

¹² Section 414.508(b)(iii-iv). [71 FR 69786, Dec. 1, 2006, as amended at 72 FR 66401, Nov. 27, 2007]

¹³ Ibid.



This letter cannot opine on any cost-benefit data provided by Exact Sciences to the coverage group, as that analysis has not yet been released to the public. However, any such analysis should also be included in the payment determination, with appropriate consideration of potential bias from its financially-interested sponsors. Such financial interests are significant. News of the unexpectedly high preliminary payment determination increased the market value of Exact Sciences by over \$500 million on October 10.

At a minimum, it is in the public interest for CMS to make use of its own commissioned research in order to avoid imposing unnecessary additional costs on taxpayers. Given the CISNET findings, any payment amount above the \$80-191 range of potential cost-effectiveness should require a very compelling justification.

For the foregoing reasons, Cable Car believes a process which explicitly considers costs and benefits in the context of Medicare's overall budget would be the optimal way to determine the basis for payment for code G0464. CMS should consider whether the gapfill process might best establish a payment level consistent with cost-effectiveness research. Alternatively, choosing more reasonably priced comparator assays could allow for a similar outcome through crosswalking. The remainder of this comment letter discusses potential shortcomings of the preliminary crosswalk determination and recommends alternative comparisons.

III. Diagnostic tests are not directly comparable to screening tests despite similarities in function

The preliminary determination proposes to adopt a crosswalk to the sum of FIT and two expensive companion diagnostic tests, “based on similarities in function of these tests with the components of the new test.”¹⁴ Indisputably, Cologuard is not a single molecular test. Instead, it is composed of several component assays that generate a combined algorithmic result. As the test sponsor concedes, Cologuard includes two pre-existing component assays within its algorithm, FIT and KRAS, along with a proprietary DNA methylation analysis. Although the analogous function of FIT and KRAS as standalone tests and within Cologuard is self-evident, it is imperative to consider not only the *function* of these tests, but also their *purpose*. Crosswalking solely on the basis of functional similarities could give rise to many of the same potential abuses of code-stacking that CMS has sought to reduce since 2012. As a general principle, the performance of additional steps or assays should not necessarily result in a higher payment unless they contribute to the purpose of the test. In selecting a comparator assay, CMS should not consider only the “resources required to perform the test,” which is a gapfill criterion, but instead look to the test’s intended usage in a healthcare setting. By this criterion, both the KRAS code (81275) and the DNA methylation code (81315) are wholly inapposite.

In the case of code G0464, the purpose of the test is broad-based population health screening for CRC. This is a completely distinct purpose from KRAS testing. KRAS, in contrast to FIT and the proposed G0464 code, is indicated solely as a companion diagnostic to help determine treatment options for patients with pre-existing CRC or non-small-cell lung cancer diagnoses.¹⁵ Genetic tests such as KRAS are expressly prohibited from being reimbursed by Medicare for screening purposes, unless specifically

¹⁴ CMS Preliminary Determinations, op cit. Rationale for code G0464.

¹⁵ Quest Diagnostics. http://www.questdiagnostics.com/testcenter/testguide.action?dc=TS_KRAS



authorized by statute.¹⁶ The NCD for stool-based DNA testing authorized reimbursement for a stool-based DNA screening test, but it did not authorize the use of standalone KRAS testing as a screening methodology. Using KRAS as a crosswalk comparator implies otherwise, despite the fact that KRAS would not be reimbursed at all in a screening context.

Similarly, the proposed comparison to code 81315 is inappropriate for a test intended for *screening*, not *diagnosis*. Code 81315 is used for a confirmatory diagnostic test for acute promyelocytic leukemia (“APL”). APL affects only about 1000 patients annually and is one of the most treatable forms of leukemia.¹⁷ The rarity of the disease and the effectiveness of timely intervention are factors which would support a high reimbursement rate, yet have no bearing on stool-based DNA *screening*, even if the process of methylation analysis is similar. Just as it would be inappropriate to reimburse for APL screening in the general population using code 81315, it is not appropriate to include the full, substantial cost of this assay in the payment for an unrelated CRC screening test.

Moreover, Cologuard’s combination of multiple existing assays into a single, algorithmically determined test raises the question of whether it is in fact a Multianalyte Assay with Algorithmic Analyses (“MAAA”). Cable Car does not have a position on the ideal basis for payment for MAAA tests in general, but cautions that treatment of Cologuard should be consistent with past practice. An additional argument in favor of gapfill analysis is that, as with other MAAAs, it would be ideal to collect further data on cost-effectiveness and realized payment decisions by third party payors before establishing a payment level for a new MAAA code.

One risk in basing a crosswalk analysis directly on the component assays in a multi-assay test is that it provides test developers with an undesirable incentive to add unnecessary procedures to a test. Logically, if Cologuard included an additional component assay that did not increase its efficacy, should that automatically result in higher reimbursement? It is not possible to determine the contribution of each component assay to the composite score from the binary test result, and there is no way to assess from the clinical trial data whether Cologuard would have performed equally well without any one of its component assays. Basic statistical reasoning supports the observed result that the combination of a proven diagnostic test (i.e. KRAS) with a proven screening test (i.e. FIT) should be at least as sensitive to CRC as the screening test alone. However, CMS does not currently reimburse for the combination of FIT and KRAS for screening because diagnostic tests are not reimbursed for screening purposes. If combining diagnostic tests with a screening test creates a new screening test, it is illogical to simply add up the costs of each component, which would not have qualified for separate reimbursement for the same purpose.

Only one of the three proposed crosswalk codes involves a test with a payment based on its intended screening purpose. It is no accident that the payment for FIT (code 82274) is much lower than the purely-diagnostic codes. FIT, like code G0464, is intended for a broad screening population. At high volumes, it would not be cost effective to reimburse FIT at a higher payment level.

Because of its use in screening, code 82274 is an appropriate comparator for G0464. Payment for the methylation analysis (including both the proprietary DNA biomarkers and KRAS) component of

¹⁶ Department of Health and Human Services. <https://oig.hhs.gov/oei/reports/oei-07-11-00011.pdf>

¹⁷ Medscape. <http://emedicine.medscape.com/article/1495306-overview>



Cologuard, on the other hand, should not be based on diagnostic tests. Even new diagnostic methylation analyses have historically been gapfilled, e.g. code 81287 which currently has a National Limitation Amount of zero. Instead, CMS should look to other screening tests where possible. Tier 2 codes may be appropriate for this purpose. For example, a competing CRC screening test in development is a blood-based assay for Septin-9, a DNA biomarker that may be predictive of CRC. The FDA has not yet approved the Septin-9 test for use in CRC screening, and as a result the test is currently statutorily excluded from coverage. However, Palmetto currently pegs payment for code 81401 (SEPT9 methylation analysis) at \$90.59 through the MoDX program.¹⁸ Codes tagged ‘methylation analysis’ in the MoDX program are currently paid amounts ranging from \$73.22 (81331) to \$112 (81401).¹⁹

Cable Car respectfully submits that in the absence of gapfilling, the most appropriate crosswalk for code G0464 would be 82774 PLUS 81401 (SEPT9 methylation analysis).²⁰ Based on the 2014 National Limitation Amounts and Palmetto data, that would result in a payment of \$112.29 for code G0464. At such a level, stool-based DNA screening would be among the most cost-effective screening strategies. Medical practitioners could safely encourage widespread adoption without burdening the healthcare system.

Thank you very much for your time and attention to this important public health discussion. Please do not hesitate to contact me if you should have any questions about this letter.

Sincerely,



Jacob Ma-Weaver, CFA

¹⁸ “MoPath Claims Submission Guidelines”. Palmetto. Available at [http://www.palmettogba.com/Palmetto/Providers.Nsf/files/MoPath_Claims_Submission_Guidelines.pdf/\\$File/MoPath_Claims_Submission_Guidelines.pdf](http://www.palmettogba.com/Palmetto/Providers.Nsf/files/MoPath_Claims_Submission_Guidelines.pdf/$File/MoPath_Claims_Submission_Guidelines.pdf)

¹⁹ Ibid.

²⁰ Prior to substituting the inapt 81315 code in its formal request, Exact Sciences investor materials indicated plans to request a crosswalk to 2 times code 81401. For the same cost-benefit reasons given previously, the presence of multiple biomarkers in the assay should not multiply the reimbursement amount. Additional biomarkers do not result in a one-for-one increase in test cost or a provably proportional increase in screening effectiveness.

