



CABLE CAR CAPITAL

CLFS Annual Laboratory Public Meeting
July 16, 2015

Reconsideration Request

G0464: Colorectal cancer screening; stool-based DNA and fecal occult hemoglobin (e.g., KRAS, NDRG4 and BMP3)

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Recommended crosswalk



Cologuard Component	CY2015 Crosswalk	CY2016 Crosswalk (Proposed)	Reconsideration Rationale	Current Payment (CLFS 2015 NLA)	Proposed Payment (CLFS 2015 NLA)
Fecal Hemoglobin	82274 <i>FIT</i>	82274 <i>FIT</i>	Code directly describes test method <u>and purpose</u>	\$21.65	\$21.65
2 DNA Methylation Markers	81315 <i>ML/RARalpha</i>	81401 <i>Methylation analysis</i>	Similar based on steps involved in methylation <u>and intended use in screening</u>	\$282.12	\$90.59 <i>(e.g. Septin 9)</i>
7 DNA Mutation Markers (KRAS)	81275 <i>KRAS</i>	None	<u>Diagnostic test statutorily excluded from reimbursement for screening</u>	\$196.99	\$0.00
DNA Normalization Markers	N/A	N/A	Quality assurance marker not separately paid by CMS	N/A	N/A
Collection Kit, Algorithm, Compliance	N/A	N/A	Not separately reimbursable	<i>-1.7% adjustment</i>	N/A
Total				\$492.72	\$112.24

What is Cable Car Capital?



- Cable Car Capital LLC is a San Francisco-based investment adviser founded in 2013 and managed by Jacob Ma-Weaver, CFA
- Cable Car implements a concentrated, hedged value investing strategy through separately managed accounts
- Not here to attack test sponsor. Support improved CRC screening but believe lower payment rate is in the public interest.

Who is Jacob Ma-Weaver?



Qualifications

- MA in Statistics from Columbia University
- CFA charterholder
- Experienced healthcare investor and portfolio manager
- Studied CRC screening modalities in detail since 2012

Biases

- Short position in Exact Sciences
- Reimbursement for new tests should be cost-effective

Recommended crosswalk: 81401+82274



- Cable Car recommends a crosswalk based on similarities in test *purpose*, not just method
- CY2015 crosswalk included payment for KRAS, a diagnostic test not intended for screening
- Proposed CY2016 crosswalk is to 81401 methylation analysis + 82274 fecal immunochemical test for hemoglobin (FIT)
- G0464 would retain the highest payment level for any non-invasive CRC screening test

Code G0464's purpose is CRC screening

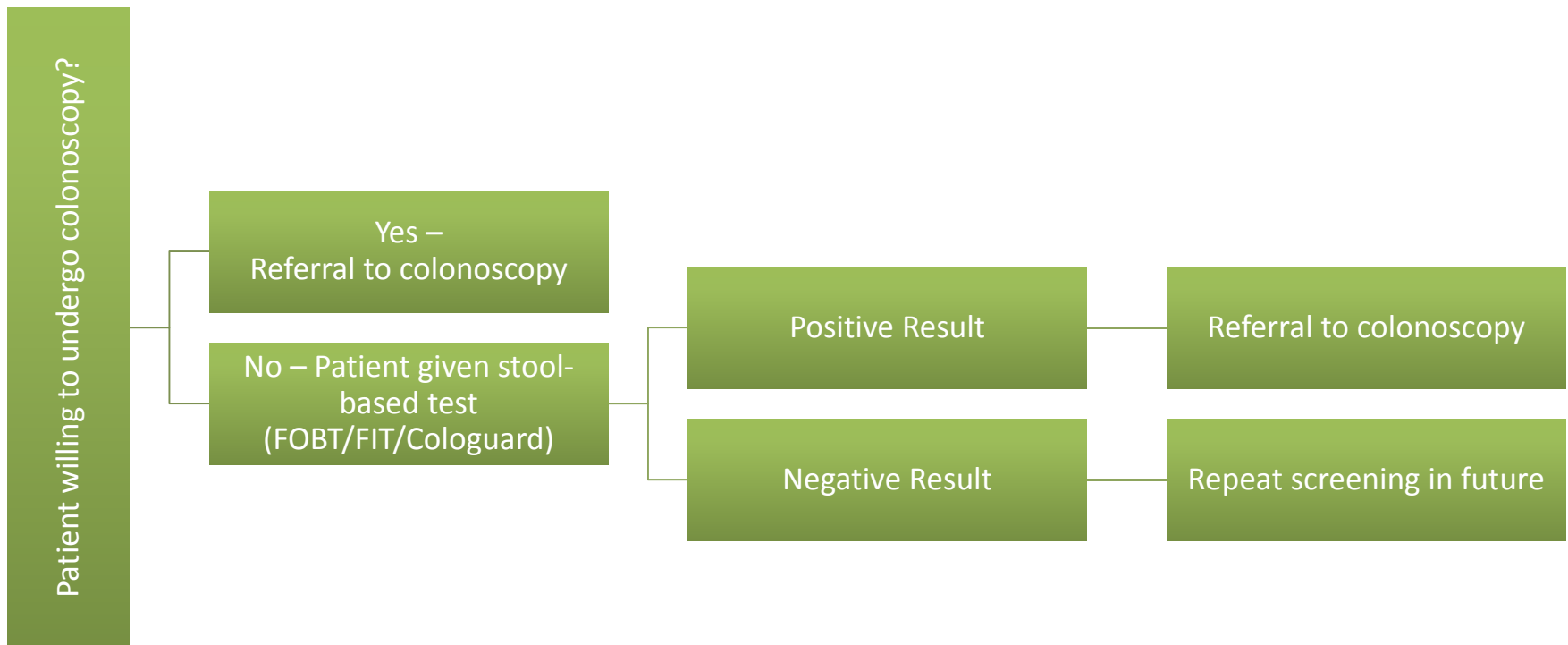


- G0464 covers Cologuard, a stool-based DNA and fecal occult hemoglobin assay intended for colorectal cancer (CRC) population health screening. **Cologuard is not a diagnostic test.**
- Cologuard was the first test approved by the FDA and CMS under Parallel Review
- In public comments, Cable Car supported CMS coverage but argued that the reimbursement amount is too high for a screening test

Colonoscopy is the standard of care

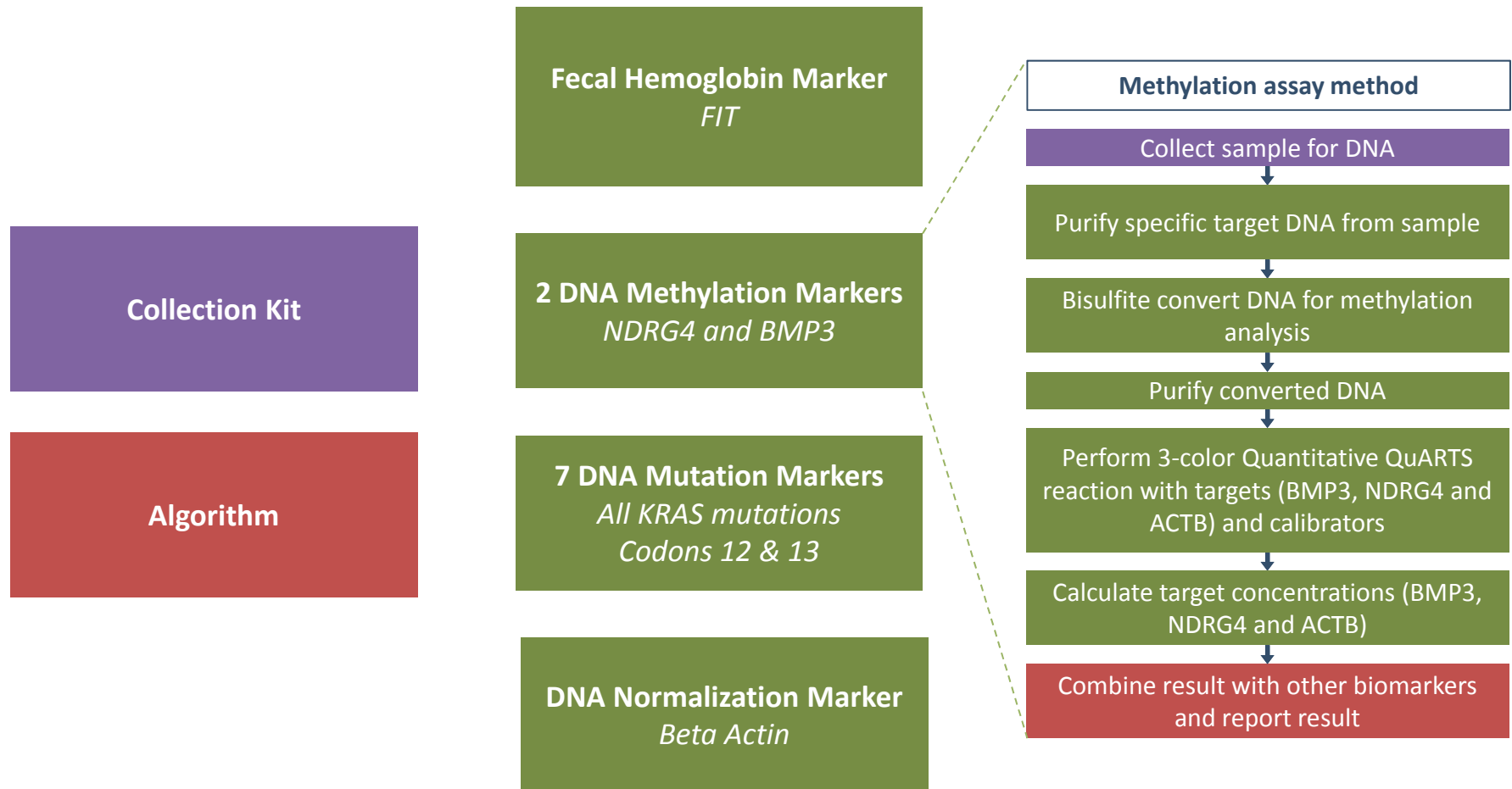


Simplified CRC screening decision tree



Positive result leads to referral to colonoscopy for confirmation and treatment

Cologuard combines FIT with DNA assays



Positive FIT is sufficient for positive Cologuard



Figure S2. Multi-target sDNA Algorithm – Composite Score Calculation

		Multi-target stool DNA QuARTS assay for methylation markers			Multi-target stool DNA QuARTS assay for Kras mutation marker			Multi-target stool DNA assay for fecal hemoglobin
Logistic Score inputs and calculations*	Biomarker Strand Counts or fecal hemoglobin in ng/ml buffer**	BMP3 strands	NDRG4 strands	β-actin (ACTB ANB) strands	Kras 1 strands	Kras 2 strands	β-actin (ACTB Kras) strands	Fecal hemoglobin ng/ml
	Weighting factors	X1 = 0.090944082	X2 = 0.790758888	X5 = -0.302462543	X3 = 1.119802381	X4 = 0.428424885		X6 = 0.008894834
	Logistic Score formula	$X1 * \text{Log}10(\text{BMP3 strands} + 1) + X2 * \text{Log}10(\text{NDRG4 strands} + 1) + X3 * \text{Log}10(\text{KRAS1 strands} + 1) + X4 * \text{Log}10(\text{KRAS2 strands} + 1) + X5 * \text{Log}10(100 / (\text{ACTB ANB strands} + 1)) + X6 * \text{Hemoglobin ng/ml} - 2.796044521$						
Sum of Scores inputs and calculations	DNA marker scores in the Sum of Score Formula are either 0 or 10: BMP3_Score, NDRG4_Score, Kras_1_Score, Kras_2_Score	If :Log10 BMP3 strands $\geq \text{Log}10(0.029294806)$ + Log10 ACTB ANB strands, 10, else 0	If :Log10 NDRG4 strands $\geq \text{Log}10(0.112083742)$ + Log10 ACTB ANB strands, 10, else 0		If :Log10 KRAS1 strands $\geq \text{Log}10(0.043660902)$ + Log10 ACTB KRAS strands, 10, else 0	If :Log10 KRAS2 strands $\geq \text{Log}10(0.074733554)$ + Log10 ACTB KRAS strands, 10, else 0		
	Sum of Scores formula	Sum of Scores = Logistic Score + BMP3_Score + NDRG4_Score + KRAS1_Score + KRAS2_Score						
Composite Score inputs and calculations	Composite Score formula	$(e^{\text{Sum of Scores}}) / (1 + e^{\text{Sum of Scores}}) * 1000 = \text{multi-target stool DNA Composite Score}$						
Multi-target stool DNA result determination	Reference range: Negative <183	If the Composite Score <183, result as "Negative; If Composite Score \geq 183 result as "Positive"						

* Quality Measures:

1. If β-actin (ACTB ANB or ACTB KRAS) < 2.301 log strands, the sample is invalid as there is insufficient human DNA for accurate analysis
2. If Log10 ACTB KRAS - Log10 ACTB ANB < -0.52 or > 1.04, the sample is invalid as there has been a recovery of error for β-actin (ACTB)

** The dynamic range of the DNA assays is 10-300,000 strands. If the DNA marker value is below the dynamic range (<10 strands), the biomarker value is set to 0 for the Logistic Score calculation. If the DNA marker value is >300,000 strands, the biomarker value is set to 300,000 for the Logistic Score calculation. The dynamic range of the fecal hemoglobin assay is 6ng/ml - 500 ng/ml. If the fecal hemoglobin level is below 6 ng/ml, the value is set to 0 ng/ml and if the hemoglobin value is >500 ng/ml, the hemoglobin value is set to 500 for calculating the Logistic Score.

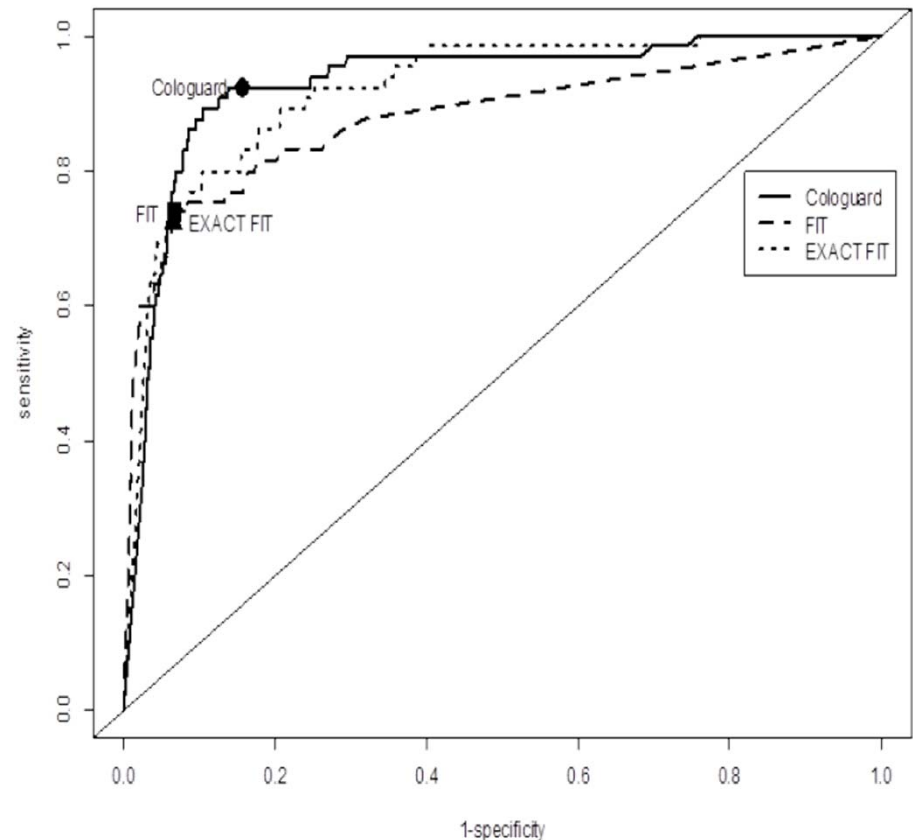
Sum of scores > -1.49615 results in a positive Cologuard score. Assuming zero KRAS, BMP3, and NDRG4 strands and the minimum level of β-actin, hemoglobin levels of > 188 ng/mL generate a positive result. In general, significant fecal bleeding, as would be detected by FIT or FOBT alone, triggers a positive Cologuard result even if no DNA methylation or KRAS mutation is detected. Conversely, the presence of sufficient DNA strands alone results in a positive reading. Source: Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal cancer screening. N Engl J Med. DOI: 10.1056/NEJMoa1311194.

http://www.nejm.org/doi/suppl/10.1056/NEJMoa1311194/suppl_file/nejmoa1311194_appendix.pdf

DeeP-C did not demonstrate value of DNA



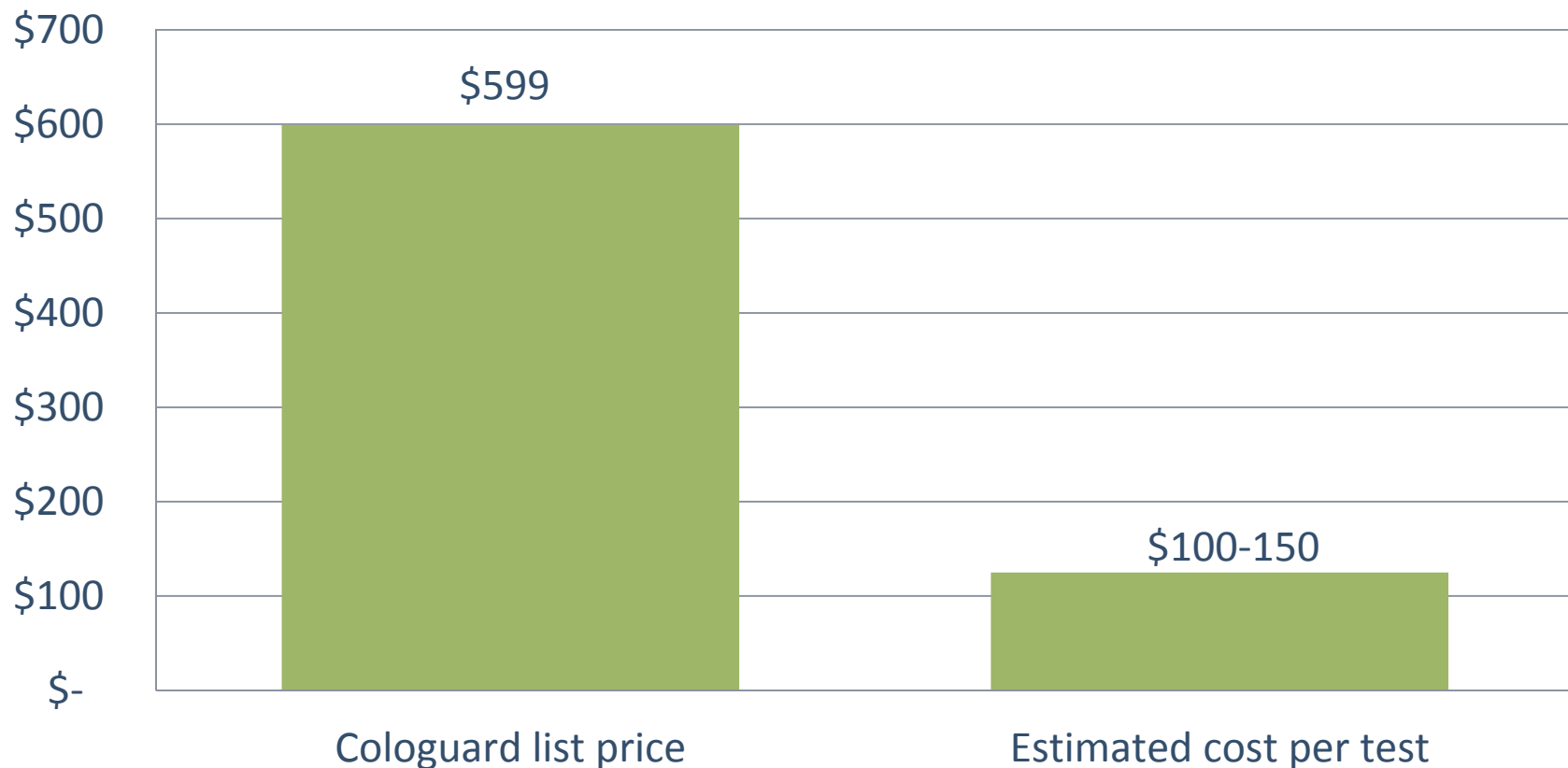
- Cologuard FIT component alone outperforms competing commercial FIT
- Cologuard sensitivity would be only ~80% at specificity level of commercial FIT
- DeeP-C provided insufficient evidence that DNA components improve CRC detection over FIT component alone
- Curve represents “probability that a randomly selected CRC patient has a test value greater than a randomly selected non-CRC patient”
- AUC was significantly greater for Cologuard than competing FIT ($p = 0.0496$), significantly greater for Cologuard FIT alone than competing FIT ($p = 0.0292$), but not significantly greater for Cologuard than Cologuard’s FIT component ($p=0.5507$)
- Cologuard had a modest benefit over its FIT component alone for pre-cancerous neoplasia (which do not bleed)
- Sensitivity to pre-cancers was <50%, which does not justify population screening using expensive DNA tests



Costs and charges imply very high margins



CY2015 NLA of \$492.72 greatly exceeds test costs

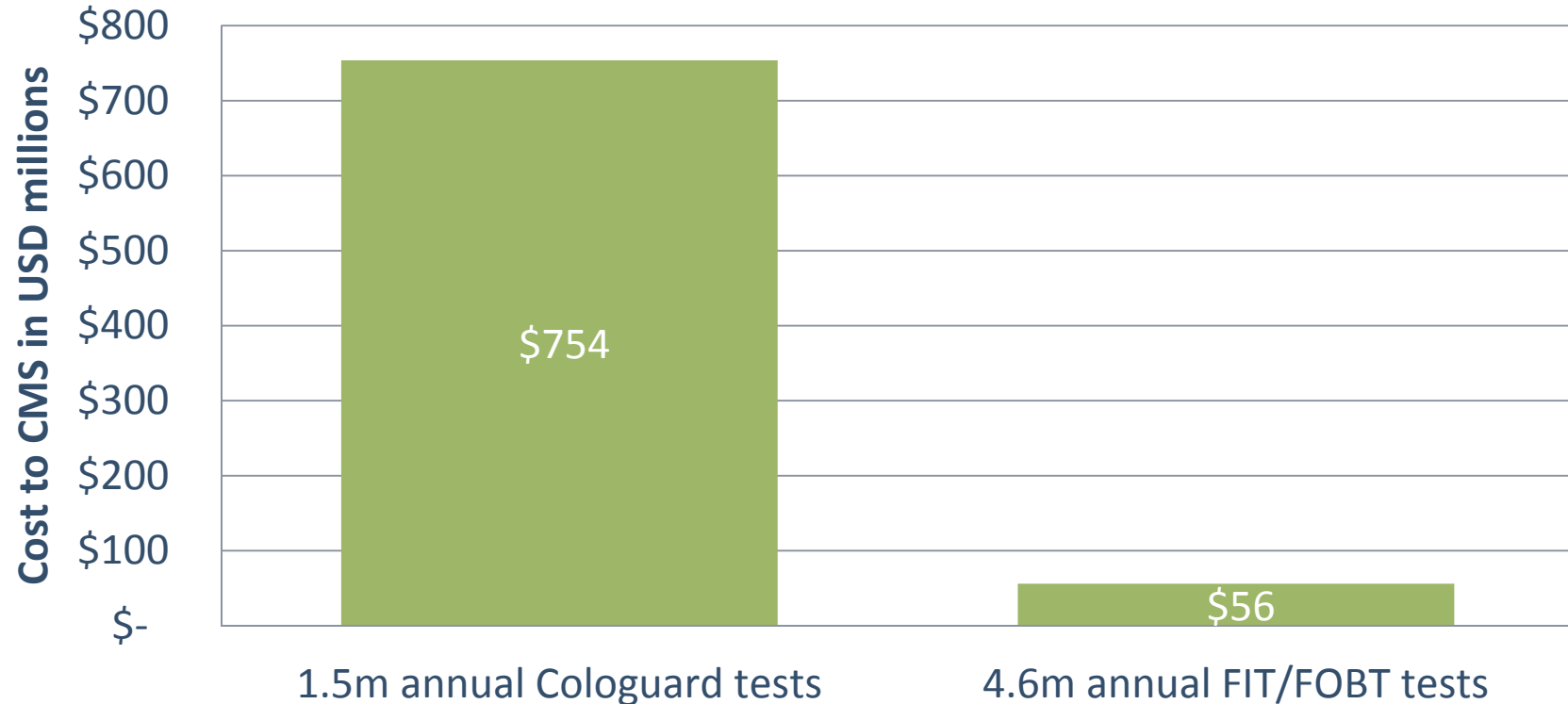


Estimated cost per test based on Exact Sciences conference call commentary and sellside analyst estimates assuming ca. 70% gross margins at scale. Cost estimates include charges not reimbursable by CMS such as compliance follow-up and shipping and handling.

Cologuard would raise screening costs 13x



Replacing FIT/FOBT with Cologuard would cost CMS
\$700 million per year at the current NLA



Source: Exact Sciences estimated FIT/FOBT market size citing Aileron Solutions. Assumes 45% of 10.2 million annual US FIT/FOBT test market is covered by Medicare and reimbursed at 2015 NLA for CPT codes 82274 (\$21.65) and 82271 (\$4.43). Assumes 3-year interval for Cologuard.

Cologuard is not cost-effective



A CMS-commissioned study by CISNET found that even with superior specificity and pre-cancer sensitivity (v2.0), Cologuard is less cost-effective than no screening above \$80, and less cost-effective than all other screening methods above \$191.

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>	<i>39, 80</i>
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>	<i>4, 80</i>
Equal to highest ACER	<i>44, 118</i>	<i>212, 213</i>	<i>201, 208</i>	<i>27, 101</i>	<i>195, 196</i>	<i>191, 184</i>

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

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. Please see full comment letter for further discussion. Zauber, et al. analysis available at <http://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id52TA.pdf>. 13

Crosswalking should consider test purpose



- Current crosswalk compares Cologuard to DNA tests that are similar in methodology, but which have very different applications
- Crosswalking comparators should be tests intended for screening, especially CRC screening, such as FIT and Septin 9 methylation analysis.

Thought experiment: suppose Cologuard also included a circulating tumor cells assay like CellSearch, which could marginally increase its late-stage CRC sensitivity. Would it be appropriate to add CPT code 86152 with a \$334.37 NLA to the existing crosswalk?

Recommended crosswalk



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KRAS is not reimbursable for screening



- KRAS is a companion diagnostic genetic test suitable for patients “with CRC or NSCLC who are being considered for treatment with an EGFR antagonist”
- KRAS is not recommended for population health screening, and it is priced accordingly
- 2012 OIG opinion: “Medicare does not pay for preventive screening tests except for those specifically authorized by statute. Since CMS considers predictive tests to be screening tests, genetic tests for this purpose are not covered by Medicare”
- Cologuard as a whole is authorized for screening, but KRAS as a component is not

81315 is not an appropriate comparator



- CPT 81315 uses Real-Time Reverse Transcriptase Polymerase Chain Reaction, which is similar to the methodology of the Cologuard DNA methylation assay
- However, 81315 is indicated for the diagnosis of acute promyelocytic leukemia, a rare disease affecting ~1,000 patients annually
- Reimbursing a high-volume screening test at the cost of an uncommon diagnostic assay will impose unnecessary costs on the health system
- Tier 2 methylation analysis codes for screening purposes such as 81401 share similarities in function *and* purpose with Cologuard

Sources: Quest Diagnostics, <http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=14994>; Medscape

G0464 local payment amounts are lower



- Unusually, 13 of 57 CMS localities established payment levels 22-47% lower than the NLA
- Only Jurisdiction 6 matters due to sponsor lab location; WI 06302 level equals NLA of \$492.72
- Jurisdiction K payment amounts determined by same MAC (NGS) are between \$262.07-\$268.54
- Cable Car was unable to learn rationale for lower payment level despite multiple requests
- Possibility MAC rationale for payment levels may support reasoning given in this presentation



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For more details, read the full 10-page reconsideration request and comment letter online at:

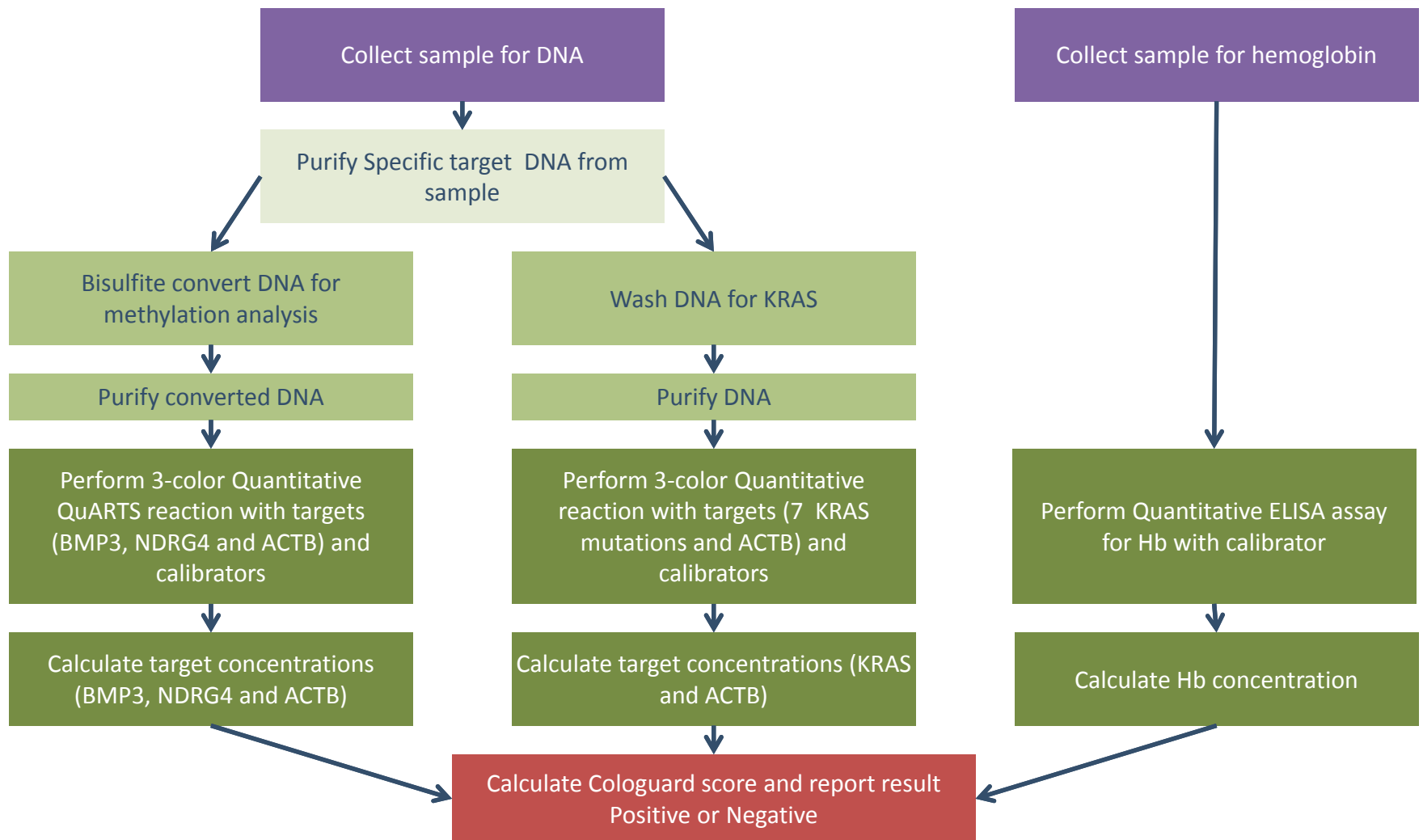
[http://www.cablecarcapital.com/
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Appendix: Cologuard Detailed Method



Source: Exact Sciences/ADVI 2014 public meeting presentation