Initiating Coverage on Exact Sciences Corporation (NASDAQ:EXAS) - Strong Sell

Testing Negative for Future Revenue

Date: April 30, 2014
Price: $11.96/Share
Market Capitalization: $1.1bn

Legal Disclaimer

Summary

Exact Sciences Corporation ("EXAS") is an extremely timely and compelling short, with an imminent catalyst that we believe will cause shares to plummet as much as 75% in the near future. EXAS has one product in its pipeline, Cologuard, which is a non-invasive test for colorectal cancer that requires patients to deposit fecal matter into a jar, administer a preservative to the feces, and ship the jar to EXAS' laboratory where EXAS evaluates the feces and diagnoses for colorectal cancer ("CRC"). Cologuard combines an existing non-invasive test, the fecal immunochemical test ("FIT"), with additional tests for DNA markers to increase sensitivity[1] to cancer and large polyps at the cost of specificity[2]. In our discussions with investors, we have found that the consensus is that the current bear thesis for EXAS is predicated on a failure for EXAS in marketing Cologuard (similar to its predecessors, PreGen-Plus and ColoSure), while bulls believe Cologuard will achieve substantial market penetration. While we are very skeptical of Cologuard's marketability, we view that as immaterial to our thesis and already well-covered by others, and we will refrain from making it a focal point of this report. We have no doubt that Cologuard will be approved by the FDA. However, we also believe that investors will soon find that FDA approval is a meaningless victory.

Soon after the FDA decision (potentially even the same day), the Centers for Medicare and Medicaid Services ("CMS") will announce its preliminary National Coverage Determination ("NCD") for Cologuard. We believe the eventual CMS national reimbursement limit for Cologuard will be below EXAS' gross cost per test—effectively making Cologuard unsellable for EXAS. Based on extensive diligence and consultations with industry experts (including a former senior CMS employee), we are confident that CMS and its Medicare Administrative Contractors ("MACs") will establish a reimbursement rate for Cologuard that is at least 70-80% lower than the ~$500 rate EXAS has projected to investors due to CMS using a gap-fill process to price the test rather than the crosswalk analysis EXAS has repeatedly claimed will be used. We also think there is a meaningful probability that CMS may simply decide to issue a negative NCD and refuse to cover Cologuard, as CMS did in 2009 with the CT colonography ("CTC") when it became clear that while CT colonographies were capable of diagnosing cancer and allowing physicians to detect polyps, they were far from being cost-effective at the reimbursement prices required to make the test economical for practitioners.

There are two methods for CMS to determine reimbursement rates for diagnostic laboratory tests: crosswalk analysis and gap-fill. A crosswalk analysis is a cost-stacking approach where CMS adds up the reimbursements for the various components of a procedure/test to arrive at a reimbursement rate for the procedure/test. Crosswalk analyses are intended for procedures/tests that represent logical combinations of pre-approved procedures/tests that are already in use. The gap-fill process involves assigning a new test code, and allowing MACs to establish carrier-specific reimbursement rates for the first year of coverage. Gap-fill reimbursement rates depend heavily on cost-effectiveness data when it is available, and FITs serve as an excellent and relevant precedent for Cologuard.

In 2003, CMS evaluated FITs after Enterix (a pioneer in the FIT space) requested reimbursement from CMS of $28 per FIT. CMS priced FITs using the gap-fill process, and commissioned a cost-effectiveness study from the Agency for Healthcare Research and Quality ("AHRQ", a HHS subsidiary) yielding a range of cost-effective prices (-$4.22 to $29.02) based on a range of inputted assumptions. The assumptions used to produce the prices at the very top and bottom of that cost-effective range were overly optimistic and pessimistic, respectively, and included sensitivity and specificity figures outside the range of appropriately-powered published results. Ultimately, CMS issued a national reimbursement limit for the test of approximately $22, which reflected the top of the cost-effective range for published results.

To justify its ~$500 price target, EXAS requires CMS to price Cologuard's reimbursement using a crosswalk analysis. That is, EXAS added up CMS reimbursements for the separate test components within Cologuard, and arrived at a total sum of approximately $500. Analysts have inputted reimbursements ranging from approximately $300 to $500 into their

[1] Sensitivity is the rate of correct positive readings; if sensitivity is 90%, then, on average, 90% of the positive cases would be correctly interpreted as positive while 10% of positive cases would be incorrectly interpreted as negative

[2] Specificity is the inverse rate of false positive readings; if specificity is 90%, then, on average, 10% of the negative cases would be incorrectly interpreted as positive

models, and used those assumptions to churn out valuations in the $15/share to $25/share range for EXAS.[3] This analysis is completely flawed, and we are confident that CMS will base its reimbursement rate off of a cost-effectiveness analysis instead. **As we confirmed with a former senior CMS employee with more than a decade of experience working on CMS reimbursements and policies, the assumption that CMS will use a crosswalk analysis is fundamentally wrong for two reasons:**

1) The DNA tests contained within Cologuard, which account for over 95% of the value in EXAS' hypothetical crosswalk analysis, were explicitly **banned** by the Department of Health and Human Services ("HHS", parent bureau of CMS) in 2012 from being reimbursed as diagnostic tests (as they would be used in Cologuard). See below for relevant text from the HHS memorandum (emphasis added):

   > "The Social Security Act provides that no Medicare payment may be made for expenses incurred for items or services that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. Consistent with this, Medicare does not pay for preventive screening tests except for those specifically authorized by statute (e.g., prostate-specific antigen test). **Since CMS considers predictive tests to be screening tests, genetic tests for this purpose are not covered by Medicare.**"[4]

   While certain DNA tests for cancerous markers are covered by CMS, due to the expensive nature of such tests, they are almost exclusively used as "companion diagnostics" for patients who have already been diagnosed with cancer in order to determine proper treatments—they are NOT approved to diagnose cancer itself in normal, asymptomatic patients and it is well-known that they are not cost-effective for such purposes. For instance, the most expensive component of Cologuard is the KRAS test (currently sold as therascreen KRAS PCR Kit). This test is being reimbursed by Medicare, but only for patients who are already known to have colorectal cancer in order to determine whether or not EGFR inhibitors (such as cetuximab and panitumumab) would be appropriate treatments.[5] It is NOT reimbursed as a diagnostic tool for patients without symptoms to determine whether or not they should be referred for a colonoscopy. We encourage investors to visit the MolDX website to review further information regarding caveats for genetic test reimbursements.[6]

   The genetic tests EXAS uses within Cologuard (KRAS, NDRG4, and BMP3) are not new or novel, and CMS is not permitted to reimburse for any of those tests individually as screens for colorectal cancer. It makes no sense for HHS to contradict itself by suddenly electing to make an exception for Cologuard, and this would open the gates for companies to push for the dozens of existing genetic tests to be independently approved for screening for various cancers.

2) Calculating the reimbursement rate via crosswalk analysis has no relation at all to the true value of Cologuard. Crosswalks are only used in cases where the test components are used together in practice and combining them represents a logical, cost-effective combination. That is not the case for the DNA tests within Cologuard—none of which are currently being reimbursed as screening tests for CRC. Again, the DNA tests within Cologuard that EXAS is seeking reimbursements for are only used in practice to check for specific mutations within patients who are already known to have cancer in order to determine proper courses of treatment.

   Given that Cologuard is a screening test for CRC, it is especially ridiculous to assume that CMS will price Cologuard via crosswalk as opposed to using gap-fill (cost-effectiveness). First, there are numerous alternative tests spanning a wide range of sensitivities/specificities available to screen for CRC which allow for an easy cost-effectiveness analysis. Second, CMS has consistently relied on established cost-effectiveness models in order to

[3] The exception is Maxim Capital, which was rightfully suspicious regarding EXAS' prospects and has issued a Sell rating on EXAS with a current price target of $8
[4] Link
[5] Link
[6] Link

determine appropriate reimbursement rates for CRC screening tests. CMS has commissioned a cost-effectiveness report for every single CRC diagnostic test it has reviewed in the past decade. Finally, pricing Cologuard using a crosswalk would open the floodgates for biotech companies to stack on as many expensive DNA tests as possible without regard to practicality or efficiency.

Imagine if a competitor created a new test that combined a dozen random DNA tests for markers linked to different types of cancer, and then asked for a $5,000/test reimbursement from CMS based on a crosswalk analysis of those tests. Would this new test be able to detect (to an extent) different types of cancer without harming patients? Sure, but only to a very limited extent—most cases of cancer would be missed since specific DNA markers are typically found in a relatively small portion of total patients with any given type of cancer. Would the new test be a cost-effective use of healthcare dollars? Not at all. Cologuard can be boiled down to a combination of FIT (a CRC test with a CMS national reimbursement limit of $21.70) with additional DNA marker tests (KRAS, NDRG4, and BMP3). As we will show in this paper, the incremental value of those additional DNA tests does not even come close to justifying EXAS' asking price. Breaking out the sensitivity of the FIT by itself based on the DeeP-C results, we find that at least 80% of the total sensitivity to cancer provided by Cologuard can be directly attributed to Cologuard's embedded FIT (which carries a national reimbursement limit of $21.70). To put it simplistically, 80% of Cologuard's cancer detection ability is already available for $21.70 per test. EXAS is claiming that it will be reimbursed an additional $450+ per test for the 20% of the cancer sensitivity provided by the DNA tests simply because those DNA tests are ordinarily billed that much, despite that fact that those prices are associated with completely different uses that affect a much smaller patient population.

We believe that CMS will price Cologuard using the gap-fill process instead of crosswalk, meaning that MACs will calculate reimbursement rates largely based on a cost-effectiveness analysis commissioned by CMS. **A prior cost-effectiveness report published by CMS shows that a theoretical test dominating Cologuard in every single aspect of sensitivity and specificity, many of them by a wide margin, warranted a reimbursement rate of $179 - $247/test.**[7] Therefore, Cologuard cannot possibly achieve a reimbursement higher than $247/test. **We have constructed an internal cost-effectiveness model based on thorough assessment of published colorectal cancer ("CRC") detection cost-effectiveness modeling, and our model shows that the most likely cost-effective reimbursement price will be between $100 and $150 per Cologuard test: approximately 70-80% less than EXAS' proposed rate.** However, a complex model is not even necessary to see that this is the case—it is clear from published CMS data that we will discuss in this paper that even a $150/test reimbursement rate for Cologuard is a major stretch. We also find it very telling that EXAS has been unable to find any partners for Cologuard and has not published its own cost-effectiveness study for Cologuard despite purportedly "working" on one since 2011.

Cologuard is EXAS' second attempt at getting CMS approval for a CRC test. CMS previously reviewed Cologuard's predecessor, PreGen-Plus, which was a different fecal test for CRC that also relied on DNA markers. CMS rejected it due to lack of FDA approval—but not before commissioning a cost-effectiveness analysis showing that the cost-effective price for PreGen-Plus would be $34 to $60 per test—well below the $300/test that EXAS was asking for. Let's assume that $300 was representative of the reimbursements for the DNA test components of PreGen-Plus. While CMS technically did not use gap-fill to price PreGen-Plus because it was rejected, ask yourself this: do you think CMS would have been willing to reimburse $300/test when cost-effectiveness showed that the test was only worth $34-$60/test? Do you think CMS will reimburse at $500/test for Cologuard when cost-effectiveness modeling shows that the test is only worth $100-$150? Exactly. **Using a crosswalk analysis in the case of Cologuard is especially inappropriate given the huge discrepancy between the cost-effective price for Cologuard and the price calculated using a crosswalk.**

Due to the high gross costs associated with its Cologuard test (estimated by sell-side analysts to be between $150 - $250 per test and implied to be $165+/test based on EXAS executives' comments during earnings calls and EXAS' 2013 Investor Fact Sheet[8]), EXAS needs to achieve reimbursements in excess of $150 to even turn a profit. **To put it bluntly,**

[7] See *CMS CRC Screening Precedents & How CMS Will Get to $100-$150/Test*
[8] Link

we believe that following FDA approval, EXAS will be unable to sell its Cologuard test at a gross profit. Barring any new radical developments in its pipeline this leaves EXAS worth little more than the cash on its balance sheet (a little over $3/share).

Again, the two problems with a crosswalk analysis are that 1) such a reimbursement rate has no relation at all to the true value of the EXAS DNA test and 2) the DNA tests contained within Cologuard are explicitly banned from being reimbursed as diagnostic tests for patients with no symptoms (as they would be used in Cologuard). A crosswalk analysis ignores the actual cancer detection rate or prevalence of type 1/type 2 errors (sensitivity and specificity) and completely ignores the other currently available methods for colorectal cancer detection. **Crosswalk pricing is only applicable in cases where the proposed test/procedure represents a logical combination of other reimbursable tests/procedures that would be used in conjunction with each other during the ordinary course of care, which is not the case for Cologuard's DNA marker tests.** While genetic tests could technically be used to detect cancer, using them for such a purpose is not cost-effective. The reimbursement rates for KRAS, NDRG4, and BMP3 (the DNA marker components of Cologuard) were set by MACs for detecting mutations in patients already known to have cancer in order to determine the proper treatments. EXAS' proposed crosswalk analysis takes the reimbursement rates for the DNA tests contained within Cologuard completely out of the context of established reimbursement rates. **In addition, performing cost-effectiveness analyses to determine coverage/reimbursement rates for colorectal cancer screening tests has been CMS policy for the past decade.** Every single innovation within colorectal cancer screening that came up for CMS review regarding National Coverage Determination has been subject to an extensive cost-review paper ordered by CMS—this includes a report on Fecal Immunochemical Tests commissioned in 2003, a report on Cologuard's predecessor PreGen-Plus commissioned in 2007, and a report on CT colonographies commissioned in 2009. We strongly encourage investors to review the relevant papers, which we have posted in the Appendix to this report.

On top of all this, EXAS has grossly misrepresented the relative benefit of Cologuard to investors. EXAS' pivotal DeeP-C trial results are extremely misleading when comparing Cologuard with FITs because EXAS intentionally used a high cut-off level (100 ng/mL) for hemoglobin levels in the FITs it was comparing Cologuard to, which made the FITs seem less capable of diagnosing cancer/large polyps than they really are. FITs work by measuring levels of human hemoglobin in a fecal sample provided by the patient and comparing them to a predetermined "cut-off level" to determine whether or not a patient should be referred for a colonoscopy. The presence of human hemoglobin in feces indicates bleeding in the colorectal passage, which could be caused by polyps and/or cancer. The higher the cut-off level, the more likely the FIT will miss cases of advanced adenomas or cancer and the less likely the FIT will show false positives. The lower the cut-off level, the more likely the FIT will catch advanced adenomas or cancer, but the more likely the FIT will also show false positives for patients who do not have CRC or advanced adenomas. **In this report, we show that a well-powered 2012 trial using the exact same brand of FIT as EXAS used in the DeeP-C trial showed that adjusting the cut-off point for that FIT down to 50 ng/mL as opposed to the 100 ng/mL level EXAS used in DeeP-C accounted for nearly all of the difference in sensitivity between the FIT and Cologuard observed in DeeP-C, while maintaining superior specificity.** Because EXAS took so long to develop and get Cologuard approved, technological advancements in the machines responsible for interpreting FITs have allowed FITs to achieve comparable results to Cologuard.

Finally, we think the addressable market for Cologuard is approximately 70% smaller than EXAS claims and is in decline. A paper published on March 17, 2014 shows that the majority of patients (approximately 70%) using FITs/FOBTs are also concurrently having colonoscopies every 10 years, and used the non-invasive tests as a secondary detection test for CRC. The author explicitly stated that "dramatic declines in incidence in recent years have been largely attributed to the uptick in colonoscopy because it is the only test for which use increased from **2000 to 2010; use of fecal immunochemical testing and sigmoidoscopy declined during that time period."** Given the price point EXAS is targeting, no payer would be willing to cover their test in tandem with colonoscopies unless the colonoscopy were medically necessary based on the results of a Cologuard test. As a result, we believe the true addressable market would be thos patients who are exclusively using FITs/FOBTs: approximately 2.7mm patients. Assuming 30% market share (as EXAS Management has), we arrive at 810,000 patients. Assuming uniform discrete distribution over three years, this comes out to 270,000 patients per year. Even if EXAS were to achieve their theoretical reimbursement of $500/test

(which we view as impossible), peak revenue would only be $135mm/year (compared to the billion dollar market that bulls and analysts are predicting).

We believe that the unfavorable CMS reimbursement decision will be followed by EXAS unsuccessfully attempting to convince private insurers to pay a price above its gross costs. While we, like many others, also believe that adoption by patients would be low regardless of reimbursement and that both patient compliance/acceptance and total market size for Cologuard are grossly overestimated,[9] these issue are ultimately irrelevant. These issues are secondary to the much larger problem: a failure to achieve a reimbursement price in excess of the gross cost of each Cologuard test. We believe this will prevent the test (regardless of how many patients want to use it) from ever generating a profit.

[9] Link

CMS CRC Screening Precedents & How CMS Will Get to $100-$150/Test

First, it is helpful to review how EXAS arrives at its proposed reimbursement price. EXAS claims that CMS will use a crosswalk analysis summing the reimbursements of the different elements of Cologuard in order to calculate Cologuard's reimbursement price. Below is a reproduction of a table from a recent EXAS investor presentation (included in the Appendix to this report) showing how EXAS arrived at a theoretical price of ~$500/test for Cologuard:

Descriptor	Code	Rate
KRAS	81275	$198.97
FIT	82274	$21.86
NDRG4	81401	$128.00
BMP3	81401	$128.00
Total		**$476.83**

This analysis is completely irrational—by claiming that CMS will calculate reimbursement based on a crosswalk analysis, EXAS/analysts are effectively claiming that the reimbursement rate for the test is merely a sum-of-the-parts calculation and has **no** relation at all to the actual cancer/polyps detection rate or sensitivity/specificity (prevalence of type 1/type 2 errors). That type of policy would encourage EXAS and other companies to bundle as many DNA tests as possible to drive up the cost, regardless of end benefit to patients. **It makes no sense and this is not how CMS calculates reimbursements for colorectal cancer diagnostic tests!** As we highlighted in the *Summary* section, the US Department of Health and Human Services (parent agency to CMS) has explicitly stated that Medicare will **not** cover genetic tests as a screening test for patients without signs or symptoms (emphasis added):[10]

> "The Social Security Act provides that no Medicare payment may be made for expenses incurred for items or services that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. Consistent with this, Medicare does not pay for preventive screening tests except for those specifically authorized by statute (e.g., prostate-specific antigen test). **Since CMS considers predictive tests to be screening tests, genetic tests for this purpose are not covered by Medicare.** However, genetic tests used to diagnose or determine treatment in the presence of signs and symptoms of disease can be covered by Medicare."

The CEO of EXAS, Kevin Conroy, would have investors believe he is doing CMS a huge favor by asking for reimbursement based on a crosswalk analysis (emphasis added):

> "Our test is so…fortunately, a very straightforward test with a limited number of biomarkers in it. And we, unlike other new molecular tests, are **not looking to be reimbursed based upon the value of an algorithm, rather we are looking to be reimbursed for these specific codes**, which have been fortunately listed in these Tier 1 and Tier 2 codes that have been created. So I think that is part of thought process on the part of CMS."
> -EXAS CEO Kevin Conroy, Q3 2013 Earnings Call

Unfortunately for Kevin, the CMS process for reimbursing CRC diagnostic tests is much more sophisticated than merely adding up component prices, and value plays a major role in CMS decisions when it can be accurately determined.

Every time CMS has been approached to make a National Coverage Determination ("NCD") for a new CRC detection test in the past decade, it has commissioned a report from the Agency for Healthcare Research and Quality ("AHRQ", a Department of Health and Human Services subsidiary). The AHRQ reports evaluate the cost-effectiveness of the

[10] Link

proposed test, and determine the appropriate price for the test such that the test would lie on the efficient frontier of available tests.[11] Tests evaluated by AHRQ include the FIT, a prior iteration of EXAS' DNA stool-based test (PreGen-Plus), and CT colonographies. We have provided all of the relevant reports in our Appendix to this report posted on www.gravityresearchgroup.com.

1) **Fecal Immunochemical Test (FIT)**: CMS commissioned a cost-effectiveness report from AHRQ in 2003 to determine the appropriate reimbursement rate for FIT tests. The original creator of FIT tests, Enterix, proposed a price of $28/test. At the time, the sensitivity and specificity of FITs were significantly better than the sensitivity and specificity of FOBTs (the primary non-colonoscopy alternative). In its request, CMS explicitly asked AHRQ to 1) compare FIT to FOBT in terms of cancers detected, cancer deaths averted, and costs, 2) Assess cost-effectiveness, and 3) estimate reimbursement levels of FIT at which cost-effectiveness would be equal to FOBT at current Medicare reimbursement. The AHRQ report showed that the appropriate reimbursement rate (threshold price where the cost effectiveness of FIT would be equal to the cost-effectiveness of FOBT) for FIT was between -$4.22 and $29.02 depending on assumptions/modeling. The assumptions used to produce the prices at the top and bottom of that cost-effective range were overly optimistic and pessimistic, respectively, and included sensitivity and specificity figures outside the range of appropriately-powered published results. Based on the cost-effectiveness study, local CMS carriers set a median reimbursement of approximately $22 (which ultimately became the national limit): well below the reimbursement rate Enterix was asking for but within the range presented in the AHRQ report.

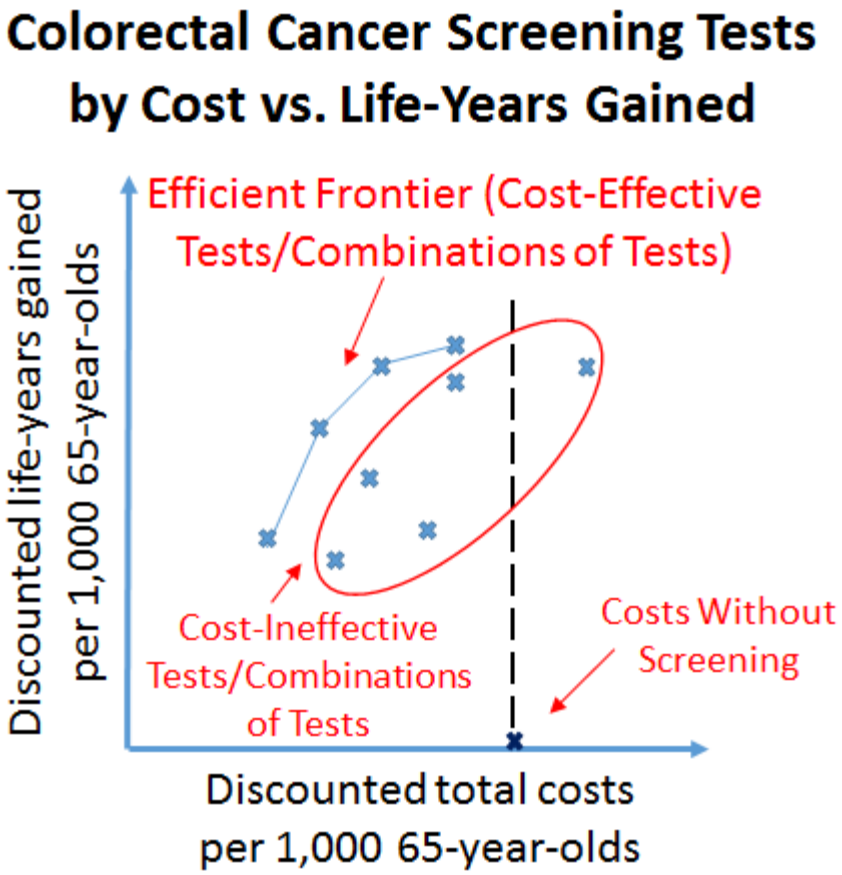
2) **PreGen-Plus**: CMS commissioned a cost-effectiveness report from AHRQ in 2007 to determine the appropriate reimbursement rate for PreGen-Plus, for which EXAS was requesting $300/test. AHRQ modeled out that the cost-effective price for PreGen-Plus would be $34 to $60 per test—well below what EXAS was asking for. Ultimately, CMS elected not to cover the test due to lack of FDA approval. However, because one of the aims of this paper was to determine the cost-effective price for ColoSure (PreGen-Plus' successor) even though the performance of ColoSure was unknown at the time, the paper also included an analysis for a wide range of potential sensitivities and specificities—including theoretical diagnostic tests that completely dominate Cologuard.

3) **CT Colonography**: CMS commissioned a cost-effectiveness report from AHRQ in 2009 to determine the appropriate reimbursement rate for CT colonographies. The study showed that CT colonographies could be cost-effective at per-test cost of $108 to $205 per scan (well below the $488 average cost per test cited in the study). Ultimately, CMS decided not to cover CT colonographies due to "lack of sufficient clinical evidence". However, at the time, two separate large-scale studies confirming CT colonographies as an effective method of diagnosing CRC had been completed: the Department of Defense study (which enrolled 1,233 subjects) and the National CT Colonography Trial (which enrolled approximately 2,600 subjects). **As we confirmed in discussions with a former senior CMS employee, it is clear that CMS' real reason for rejecting CT colonographies almost certainly stemmed from the fact that the cost-effectiveness of CT colonographies had been shown in the cost-effectiveness paper commissioned by CMS to be significantly below the average cost per CT colonography test. As a result, we believe there is a meaningful probability that Cologuard will suffer the same fate as CTCs.**

There are already numerous tests (FIT, FOBT, sigmoidoscopy, colonoscopy, etc.) available to test for colorectal cancer and precancerous polyps. The availability of these tests makes it possible to produce reliable cost-effectiveness analyses that focus on comparative cost-effectiveness with other solutions rather than being forced to attempt to quantify the value of extra years of human life. In cost-effectiveness analyses, these existing diagnostic tests for CRC make up the

[11] Links to all reports can also be found here: link

cost-efficient frontier, which is quantified as the tests which provide the highest life-years gained for equivalent total cost. The cost-effectiveness analysis is performed using three well-established models (the MISCAN-Colon, SimCRC, and CRC-SPIN models) that are used for calculating cost-benefit of CRC detection test. Below is a graphical depiction of the cost-efficient frontier used in AHRQ papers for colorectal cancer detection tests. Note that actual placement of different tests/combinations of tests will vary depending on the model used:



The graph above shows the cost-effectiveness of each test/combination of tests. Each point in the graph represents a different diagnostic test/procedure or combination of diagnostic tests/procedures, and the cost-effectiveness of each test is measured as the life-years gained in exchange for total additional costs. "No screening" yields zero benefit in life years (hence the Y-coordinate is zero) and carries significant cost due to the costs associated with treating colon cancer.

Within the efficient frontier graph, the (x,y) coordinates for each test are determined by the test's benefit in terms of life-years (that is, how many life-years patients using the test gain on average) and the total costs of the tests (including costs subsequent to the test). The total costs include not only the cost of the test but also the cost of resulting procedures/events (including for Type 1 and Type 2 errors), such as colonoscopies, polyp removals, potential complications, and treatments for colon cancer. In the case of a Type 1 error (a false positive), the test incorrectly determines that the patient has colorectal cancer, and requires a colonoscopy to find and remove the malignant polyp and assess what further treatment may be required. The rate of Type 1 errors is calculated as: 100% - (specificity). For instance, the specificity of the FITs used in EXAS' DeeP-C trial was 95%, while the specificity of Cologuard in the same trial was 87%. The rate of Type 1 errors is therefore 5% in FITs and 13% in Cologuard based on the DeeP-C trial results. Lower specificity means increased probability of unnecessary colonoscopies, increasing the effective cost of the test. **Cologuard's low specificity (high rate of Type 1 errors) relative to all other testing options is the key reason that,**

despite having high cancer/polyp sensitivity (low rate of Type 2 errors) relative to existing noninvasive tests, it is not cost-effective for CMS to pay anything near the premium EXAS is claiming the test deserves.

In the AHRQ studies we reviewed, the top right point of the efficient frontier (maximum life-years gained) was either colonoscopies or flexible sigmoidoscopies every five years combined with FOBTs every year, while the bottom left point of the efficient frontier is FOBTs once each year. A separate cost-effectiveness graph is produced for each of the three accepted models: MISCAN-Colon, SimCRC, and CRC-SPIN. The models each have slight nuances that affect the discounted costs per life-year, including 1) the value of detecting pre-cancerous polyps and 2) the "dwell time" estimates (that is, how long it takes for pre-cancerous adenomas to evolve into cancer). It is impossible to know how fast the progression from precancerous adenomas to cancer actually occurs because reaching such a conclusion would require identifying such polyps 10+ years in advance of them turning cancerous and monitoring those specific polyps in a large population for decades, which is impractical and unethical in real life. Higher dwell time, lack of polyp bifurcation (keeping it such that every polyp is capable of becoming cancerous rather than only certain polyps being capable of becoming cancerous), and continuous modeling of adenomas (compared to discrete modeling) all increase the life-years per dollar gained through CRC diagnostic tests, but lower the incremental benefit of increased screening frequency. Below are comparative summaries of the three models used for calculating cost-effectiveness of CRC screening methods:

1) **MISCAN-Colon**: This model assumes that there are two types of adenomas: progressive adenomas (which can progress to cancer) and non-progressive adenomas (which can never progress to cancer). In this model, the dwell time is estimated to be approximately 10 years on average before clinical diagnosis (significantly shorter than in the other two models). MISCAN assumes a distribution of adenomas throughout the colorectal passage that is the same as the distribution of colorectal cancer cases, which causes an increased percent of adenomas (approximately 30%) to be located in the rectal passage compared to the 8-10% suggested by data from autopsy studies. This causes MISCAN-Colon to estimate higher cost-effectiveness for testing strategies involving sigmoidoscopy when compared to SimCRC and CRC-SPIN due to a modeling a larger proportion of adenomas being within the reach of the sigmoidscope.

2) **SimCRC**: This model assumes that all adenomas have the ability to progress to cancer, though most will not during the lifespan of an individual. In this model, the dwell time is estimated to be approximately 22 years on average before clinical diagnosis (close to the CRC-SPIN estimate, and significantly longer than in the MISCAN model). Contrary to the MISCAN model, SimCRC assumes that approximately 8-10% of adenomas are located within the rectum, decreasing the cost-effectiveness of testing strategies involving sigmoidoscopies.

3) **CRC-SPIN**: This model assumes that all adenomas have the ability to progress to cancer, though most will not during the lifespan of an individual. CRC-SPIN also models continuous size of adenomas rather than discrete stages of adenoma size that are used in the MISCAN and SimCRC models. In this model, the dwell time is estimated to be approximately 25 years on average before clinical diagnosis (close to the SIM-CRC estimate, and significantly longer than in the MISCAN model). Contrary to the MISCAN model, CRC-SPIN assumes that approximately 8-10% of adenomas are located within the rectum, decreasing the cost-effectiveness of testing strategies involving sigmoidoscopies.

For each of the three models, there are three major inputs: sensitivity (probability of detecting cancer/adenoma among patients who have cancer/adenoma) to different sizes of pre-cancerous polyps, sensitivity to colorectal cancer, and specificity (probability of positive reading being correct rather than a false positive). Sensitivity to pre-cancerous polyps can be sub-divided into sensitivity to polyps less than 5mm, sensitivity to polyps between 5 mm & 10 mm, and sensitivity to polyps greater than 10 mm. When EXAS was seeking CMS coverage for the first iteration of its test (PreGen-Plus), AHRQ published a cost-effectiveness paper for CMS that modeled the maximum cost-effective prices for numerous

ranges of sensitivity and specificity for precancerous polyps and CRC since, at the time, it was not clear what the actual sensitivity and specificity for PreGen-Plus and its successor (ColoSure) were. That paper, along with other similar cost-effectiveness papers written by authors of that paper, provides a maximum cost-effective price of $247 for a test that completely dominates Cologuard in every respect (and by a wide margin in most of them). See below for a table summarizing the cost-effective prices collected from published papers commissioned by CMS regarding potential new diagnostic tests for CRC (the dominant test is Test E, although Test F is also a dominant test):

		Sensitivity by Adenoma Size/CRC					Cost-Efficient Price			
							MISCAN	SimCRC	MISCAN	SimCRC
Reference Name	Test[1]	<5 mm	5-10 mm	>10 mm	CRC	Specificity	3-Year	3-Year	5-Year	5-Year
Test A	sDNA (v1.1)	4%	12%	43%	70%	96%	$40	$60	$34	$51
Test B	sDNA (v1.1) + 10%	13%	20%	48%	73%	96%	$79	$87	$85	$85
Test C	sDNA (v1.1) + 25%	27%	33%	57%	77%	97%	$102	$118	$117	$128
Test D	sDNA (v1.1) + 50%	51%	55%	71%	85%	98%	$140	$167	$163	$187
Test E	sDNA (v1.1) + 75%	75%	77%	85%	92%	99%	$179	$247	$215	$250
Test F	sDNA (v1.1) +100%	100%	100%	100%	100%	100%	$237	$302	$239	$264
Test G	sDNA (v2.0)	15%	22%	55%	90%	85%	$17	$41	$2	$31
CTC A	CTC DoD 3D	0%	84%	92%	92%	80%	NA	NA	$122	$199
CTC B	CTC NCTC 2D/3D	0%	57%	84%	84%	88%	NA	NA	$108	$183
FIT A	FIT (AHRQ)	5%	10%	22%	70%	95%	Max. Reimbursement - $21.70			
FIT B	OC FIT-CHEK (DeeP-C)	NA	NA	24%	74%	95%	Max. Reimbursement - $21.70			
FOBT	Hemoccult SENSA	8%	12%	24%	70%	93%	Max. Reimbursement - $4.44			
	Cologuard	**20%**	**32%**	**42%**	**92%**	**87%**	**NA**	**NA**	**NA**	**NA**

Sources: AHRQ papers and DeeP-C trial (see Appendix for all sources)

Notes:

1 sDNA (v1.1) and sDNA (v2.0) refer to prior iterations of EXAS' stool-based DNA test. The percentages (i.e. "+ 10%") denote the increase of the difference between the v1.1 test sensitivity/specificity and 100%

The stool-based DNA test ("sDNA") figures from the above table can be verified through the tables on pages 28 and 37 of the file labeled *CMS Cost-Effectiveness Report – sDNA* in the Appendix to this report. Again, this was a cost-effectiveness study requested by CMS in order to determine proper pricing. **As it states in the report, the sensitivity and specificity figures provided in the table above are the only independent inputs for each test when computing cost-effectiveness.** There are no other confounding variables impacting cost effectiveness that we are leaving out that would obscure the data. As such, even without building an independent model, one can review the table and gain a very good sense of the range of reimbursements Cologuard can realistically expect.

The fact that the maximum reimbursement price for Test E as determined by AHRQ is $247/test implies that the maximum reimbursement price for Cologuard will be lower since Test E is equal to or superior to Cologuard in every single measure. How much lower will Cologuard's reimbursement be? Take a look at Test G: sDNA (v2.0) has much more similar characteristics to Cologuard, with lower sensitivity for small adenomas, higher sensitivity for large adenomas and slightly lower sensitivity for colorectal cancer and slightly lower specificity, **yet has a maximum reimbursement of $41**! **We can say with certainty that the reimbursement rate for Cologuard will be below $247/test. Given that the sDNA (v2.0) test is much closer to having similar sensitivity/specificity figures than Test E, we believe that Cologuard's reimbursement rate will be closer to $41 than to $247—based on our internal model, we believe that the ultimate reimbursement will be, at best, between $100 and $150.** However, compared with the data provided by precedent CMS publications in the above table, even our estimates appear very optimistic. Bulls may argue that some of the data used in the cost-efficient price modeling is old, and that inputs have changed. This is correct, but the changes in inputs all adversely affect the cost-effective reimbursement for Cologuard! The maximum

reimbursement will be even lower using current data than using the data previously used in the AHRQ models because 1) CMS reimbursement rates have **declined** since the AHRQ paper was published, 2) the sensitivity and specificity of FIT was shown to be higher in every single measure through the DeeP-C trial than the authors of prior cost-effectiveness papers assumed it to be, and 3) advances in the ability of FIT processing machines to reliably detect lower levels of hemoglobin make them nearly as effective as Cologuard with a CMS reimbursement rate of $21.70 (see next section for more on this). See below:

		CMS Max	Sensitivity		Specificity
Source	Test	Reimbursement	Large Adenomas	Cancer	Overall
Prior AHRQ Paper	FIT	$22.22	22%	70%	95%
DeeP-C Trial	FIT (100 ng/mL cut-off)	$21.70	24%	74%	95%
Wijkerslooth et al	FIT (50 ng/mL cut-off)	$21.70	35%	88%	92%

As a result, the cost-effective pricing for Cologuard today is even lower than it would have been when the AHRQ papers were written. **Again, the published papers show definitively that the cost-effective price for Cologuard is between $17 and $247, and our internal modeling produces a likely reimbursement price between $100 and $150 per test, which is generous when compared to the published figures for tests with comparable specificity and sensitivity figures.**

We have found in the course of our research that many investors appear to have a gross misperception of CMS reimbursement rates for alternatives to Cologuard (other CRC screening tests). For instance, a short-seller estimated the cost of colonoscopies at $2,777 based on commercially available data in a Seeking Alpha article.[12] However, this is way too high. In reality, colonoscopies and sigmoidoscopies, which offer the highest available sensitivity and specificity to cancer and large adenomas (well in excess of Cologuard on all measures), are only reimbursed $100-$700 by CMS. EXAS is proposing a reimbursement rate within this range for an inferior test that would require a colonoscopy to verify positive test results. See below for 2014 CMS reimbursements of variations of the two procedures:

[12] Link

2014 Medicare Colonoscopy/Sigmoidoscopy Reimbursement Rates[1]

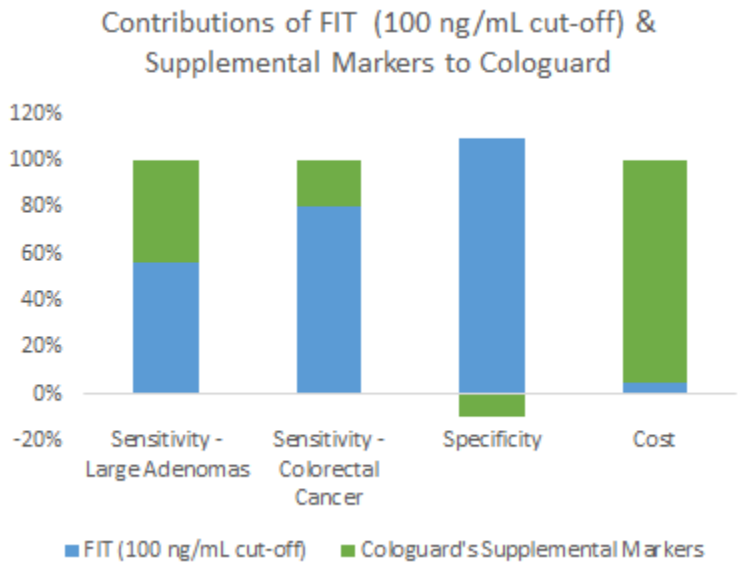
Average Reim.	Max Reim.	Code	Details
$270.31	$485.72	45378	Colonoscopy, flexible, proximal to splenic flexure; diagnostic, with or without collection of specimen(s) by brushing or washing, with or without colon
$476.63	$578.64	45380	Colonoscopy, flexible, proximal to splenic flexure; with biopsy, single or multiple
$579.08	$695.70	45383	Colonoscopy, flexible, proximal to splenic flexure; with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique
$476.81	$574.45	45384	Colonoscopy, flexible, proximal to splenic flexure; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps or bipolar cautery
$537.83	$648.40	45385	Colonoscopy, flexible, proximal to splenic flexure; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
$362.09	$446.96	44388	Colonoscopy through stoma; diagnostic, with or without collection of specimen(s) by brushing or washing
$407.17	$503.41	44389	Colonoscopy through stoma; with biopsy, single or multiple
$452.33	$553.55	44392	Colonoscopy through stoma; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps or bipolar cautery
$517.54	$627.13	44393	Colonoscopy through stoma; with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique
$510.47	$623.88	44394	Colonoscopy through stoma; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
$140.30	$175.61	45330	Sigmoidoscopy, flexible; diagnostic, with or without collection of specimen(s) by brushing or washing
$167.88	$209.72	45331	Sigmoidoscopy, flexible; with biopsy, single or multiple
$305.69	$385.94	45333	Sigmoidoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps or bipolar cautery
$327.77	$408.50	45338	Sigmoidoscopy, flexible; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
$351.79	$428.81	45339	Sigmoidoscopy, flexible; with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique

Note:

1 Rates vary by region; figures in this table are inclusive of all US regions

Why Cologuard is Not as Remarkable as Investors May Think

Cologuard is merely combining a currently-available non-invasive test (FIT) with extra tests for DNA markers. However, the DNA markers provide only marginal incremental benefit, and, in fact, sabotage the specificity of the test. See below for a performance and price breakdown of the FIT and the supplemental tests included in Cologuard based on the results of the DeeP-C trial:



Cologuard's Biggest Contribution: Cost

The above chart shows what percentage of sensitivity, specificity, and cost can be allocated to the FIT within Cologuard versus Cologuard's supplemental DNA markers, and is scaled to 100% (that is, the total sensitivity/specificity of Cologuard are not actually 100%, but the chart shows the percent contribution of FIT and EXAS' supplemental markers). The figures used are based on EXAS' proposed cost for Cologuard and the results of its DeeP-C trial. It is true that Cologuard nearly doubles the sensitivity to precancerous polyps, but precancerous polyps are a secondary characteristic of diagnostic tests—the most important factor (obviously) is the test's ability to detect colorectal cancer.

Cologuard's DNA tests have a very limited impact on sensitivity to cancer (the more important sensitivity measure) and actually **negatively** impact the specificity by roughly 8%. Further, this graph plainly shows that the proposed increase in cost far outweighs the increased benefit. EXAS is estimating reimbursement for Cologuard at $476.83 in a recent investor presentation. EXAS is asking for a 2,000%+ premium to FIT, while providing much lower relative increases in terms of sensitivity and a negative impact on specificity.

Returning to the point we discussed in the *Summary*, we believe that even the above breakdown graph is egregiously overestimating Cologuard's relative value over available FITs because EXAS chose an artificially high cut-off rate (100 ng/mL) for positive FIT readings in its pivotal trial. A trial published in the American Journal of Gastroenterology (*Wijkerslooth et al*) showed that lowering the cut-off rate from 100 ng/mL (which EXAS used in its trial) to 50 ng/mL would have reproduced nearly the entire difference between Cologuard and the comparator FIT EXAS used in its trial. Compare the sensitivities and specificities for the 50 ng/mL FIT with Cologuard in the table below (see outlined sections):

DeeP-C vs. Wijkerslooth et al, 2012[1]

	Sensitivity	Specificity
Wijkerslooth - FIT (50 ng/mL cut-off)		
Advanced Adenomas	35%	93%
Colorectal Cancer	88%	91%
Wijkerslooth - FIT (100 ng/mL cut-off)		
Advanced Adenomas	29%	97%
Colorectal Cancer	75%	95%

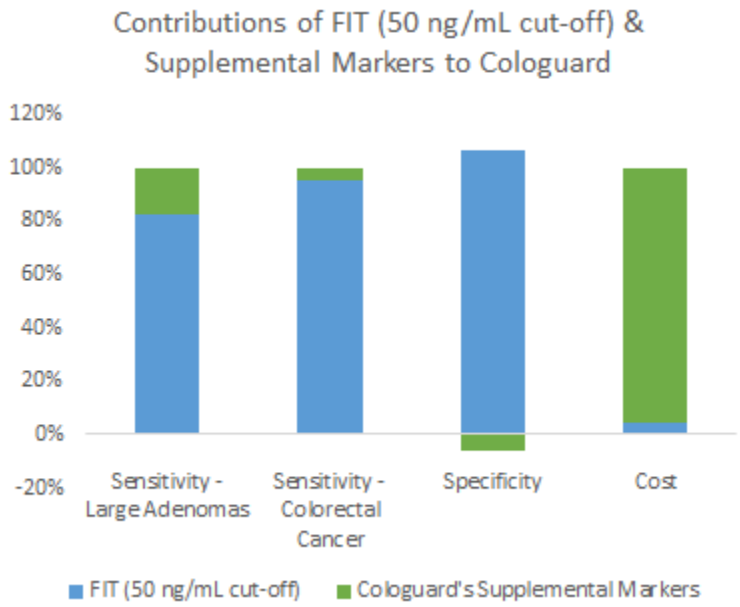
	Sensitivity	Specificity[2]
EXAS' DeeP-C Trial - Cologuard		
Advanced Adenomas	42%	87%
Colorectal Cancer	92%	87%
EXAS' DeeP-C Trial - FIT (100 ng/mL cut-off)		
Advanced Adenomas	24%	96%
Colorectal Cancer	74%	96%

Notes:

1 *Wijkerslooth et al* included 1,256 test subjects

2 Specificity figures from EXAS' trial only provided for both advanced adenomas and cancer; not for AA and cancer independently of each other

As the above table shows, *Wijkerslooth et al* produced very similar results to the reference FIT in EXAS' DeeP-C trial results using a cut-off for positive results of 100 ng/mL, with all figures within 1% of each other except for sensitivity to advanced adenomas (which showed a 5% difference). Reducing the cut-off level for the FIT from 100 ng/mL of hemoglobin to 50 ng/mL, we find that the sensitivities and specificities for the FIT are within spitting distance of Cologuard. Adjusting the contribution chart from the prior page to reflect the *Wijkerslooth et al* results for a 50 ng/mL cut-off for positive results, we find that the FIT is capable of producing 83% of the sensitivity to large polyps and 95% of the sensitivity to colorectal cancer when compared to Cologuard:



The link between the reduction in hemoglobin cut-off levels and increased sensitivity/decreased specificity should be obvious, and makes perfect sense: as the FIT cut-off declines, the test becomes more sensitive to hemoglobin in stool samples. However, hemoglobin is not necessarily attributable to cancer or advanced adenomas (though most of the time, it is), and as a result, the specificity decreases when the cut-off level is reduced. We further confirmed the link and the ability to improve sensitivity using FIT beyond the levels achieved in DeeP-C through other published studies. Below is a table taken from a meta-analysis published in February 2014 that compiled completed trials to provide a more complete picture of the relationship between cut-off values for FITs and sensitivity and specificity:

Table 3. **Sensitivity Analysis: Summary Estimates of Subgroups After Removing Discontinued FITs**

Variable	Studies, *n*	Sensitivity (95% CI)	I^{2*}	Between-Study Variance in Logit Sensitivity	Specificity (95% CI)	I^{2*}	Between-Study Variance in Logit Specificity	Positive LR (95% CI)	I^{2*}	Negative LR (95% CI)	I^{2*}
FIT sample											
1-sample	11	0.78 (0.65–0.87)	58.1	0.63	0.94 (0.92–0.95)	98.2	0.17	12.8 (10.8–15.1)	85.9	0.23 (0.14–0.38)	49.8
2-sample†	4	0.77 (0.59–0.89)	61.1	0.43	0.93 (0.90–0.95)	98.7	0.17	11.2 (6.5–19.5)	89.0	0.25 (0.13–0.49)	73.9
3-sample	6	0.80 (0.66–0.89)	5.2	0.07	0.93 (0.89–0.95)	97.7	0.30	11.3 (7.4–17.5)	88.4	0.21 (0.12–0.38)	0
FIT cutoff value for a positive test result											
<20 μg/g	9	0.89 (0.80–0.95)	26.4	0.32	0.91 (0.89–0.93)	94.9	0.12	10.2 (8.3–12.3)	75.2	0.12 (0.06–0.22)	14.5
20–50 μg/g	5	0.70 (0.55–0.81)	0	0.10	0.95 (0.95–0.96)	82.0	0.03	15.3 (12.5–18.8)	0	0.32 (0.21–0.49)	0
>50 μg/g	4	0.67 (0.59–0.74)	33.2	0.00	0.96 (0.94–0.98)	99.2	0.24	18.7 (11.7–29.8)	92.2	0.34 (0.27–0.43)	37.6
FIT brand											
OC-Micro/Sensor	5	0.86 (0.68–0.95)	0	0.28	0.91 (0.87–0.94)	95.5	0.21	9.7 (6.8–13.9)	54.4	0.16 (0.06–0.38)	0
OC-Light	4	0.93 (0.83–0.97)	26.6	0.07	0.91 (0.88–0.92)	95.9	0.06	9.9 (8.0–12.2)	85.7	0.08 (0.03–0.20)	9.99
Reference standard											
Colonoscopy	10	0.77 (0.65–0.86)	45.7	0.60	0.93 (0.91–0.95)	98.2	0.21	11.6 (9.6–14.0)	78.9	0.25 (0.16–0.39)	27.1
2-y follow-up‡	5	0.91 (0.78–0.97)	0	0.52	0.94 (0.91–0.96)	97.9	0.25	15.6 (10.8–22.7)	88.0	0.09 (0.03–0.25)	0

FIT = fecal immunochemical test; LR = likelihood ratio.
* Inconsistency index minus the measure of heterogeneity.
† Unable to do a sensitivity analysis because of the lack of data sets/studies.
‡ At least a 2-y longitudinal follow-up with medical records or cancer registry.

Source: *Ann Intern Med.* 2014; 160(3):171-181 (Link)

As the outlined section in the table above shows, comparing the sensitivities and specificities for different cut-off ranges (from >50 μg/g to <20 μg/g) showed increases in sensitivity and decreases in specificity at each step, with sensitivity increasing by nearly 1/3 when comparing the highest cut-off range with the lowest cut-off range. This is consistent with the results from *Wijkerslooth et al*. When reviewing the table above, please note that the units were all converted to μg/g, and the exact conversion rates will differ depending on the exact brand of FIT used, some of which use varying amounts of buffer solution. Below is a break-out of the different trials included in the meta-analysis results outlined above:

Compilation of FIT Results Using Varying Cut-Offs						
Date	FIT Product	Patients	Sensitivity[1]	Specificity	Study	Cut-Off (µg/g)
2007	FlexSure OBT	5,356	86%	97%	Allison et al, 2007	300
1996	HemeSelect	7,493	69%	94%	Allison et al, 1996	100
2005	MagStream HemSp	21,805	66%	95%	Morikawa et al, 2005	67
2005	MagStream HemSp	7,421	86%	94%	Launoy et al, 2005	67
1999	Monohaem	4,611	56%	97%	Nakama et al, 1999	20
1996	Monohaem	3,365	83%	96%	Nakama et al, 1996	20
2005	OC-Hemodia	3,794	25%	99%	Sohn et al, 2005	20
1996	OC-Hemodia	27,860	87%	95%	Itoh et al, 1996	10
2006	OC-Hemodia	3,090	53%	87%	Nakazato et al, 2006	16
2002	OC-Light	7,411	88%	91%	Cheng et al, 2002	10
2010	OC-Light	1,756	100%	93%	Parra-Blanco et al, 2010	10
2013	OC-Light	8,822	85%	92%	Chiu et al, 2013	10
2011	OC-Light	2,796	96%	87%	Chiang et al, 2011	10
2011	OC-Micro	1,204	100%	88%	Levi et al, 2011	14
2007	OC-Micro	80	67%	83%	Levi et al, 2007	15
2010	OC-Micro	770	77%	94%	Park et al, 2010	20
2012	OC-Micro	1,256	75%	95%	de Wijkerslooth et al, 2012	20
2013	OC-Micro	2,235	73%	96%	Brenner and Tao, 2013	6.1
2013	Ridascreen Haemoglobin	2,235	60%	95%	Brenner and Tao, 2013	24.5

Source: *Ann Intern Med.* 2014; 160(3):171-181

Note:

1 Sensitivity to colorectal cancer

Based on our review of available literature, the trials used in this meta-analysis represent a comprehensive summary of significant trials evaluating FIT to date. Note that the OC-Light (outlined above) used the lowest cut-off values. We produced a table showing that, based off of significant cumulative studies with a more than double the patient pool of the DeeP-C trial, OC-Light appears to achieve sensitivity to CRC that is nearly as high as Cologuard with superior sensitivity. **OC-Light's superior sensitivity performance in the trials is clearly attributable to the fact that it used the lowest cut-off values:**

Sensitivity & Specificity Weighted Averages by FIT				
	Total Patients	CRC Sensitivity	Specificity	Total Clinical Studies
OC-Light	20,785	89%	91%	4
FlexSure OBT	5,356	86%	97%	1
OC-Micro	5,545	80%	94%	5
OC-Hemodia	34,744	77%	95%	3
MagStream HemSp	29,226	71%	95%	2
HemeSelect	7,493	69%	94%	1
Monohaem	7,976	67%	97%	2
Ridascreen Haemoglobin	2,235	60%	95%	1
Cologuard	**9,989**	**92%**	**87%**	**1**

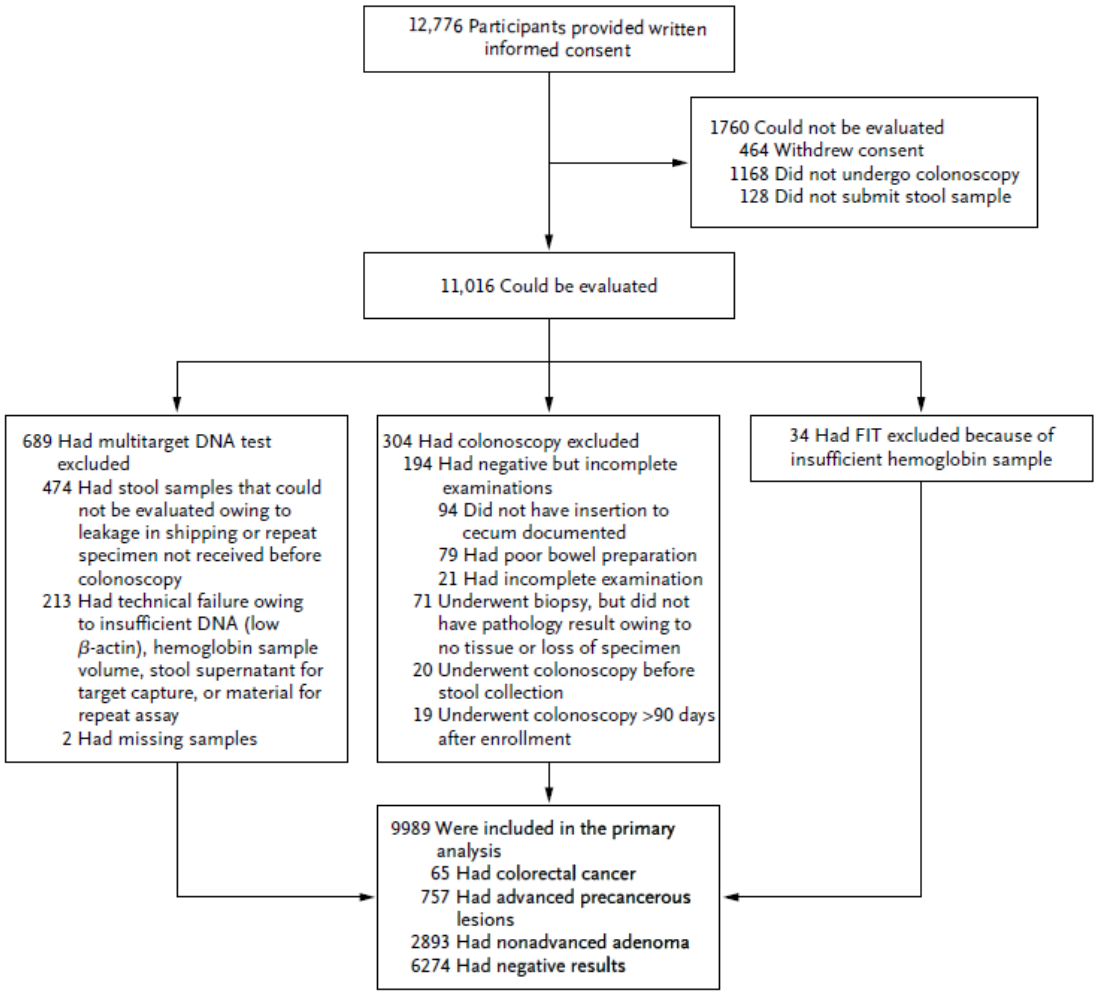
Source: *Ann Intern Med.* 2014; 160(3):171-181, DeeP-C trial results

Bull Counterpoints and Our Preemptive Rebuttals

Bull Counterpoint #1: But Cologuard Will Drive Increased Compliance Which Will Drive Higher Cost-Effectiveness!

In order to help justify its ridiculous reimbursement target, EXAS has also pushed the notion that compliance with its stool-based test will be greater than existing non-invasive solutions owing to a "compliance engine" that it intends to build out involving mailings and calls to patients who have received stool kits to increase the rate at which those patients return stool samples. It is virtually certain that, when (or if) EXAS publishes the cost-effectiveness analysis it claims to have produced, the analysis will rely heavily on Cologuard having significantly higher compliance than alternatives in order to justify high reimbursement rates. However, there are three reasons we believe this will not help drive higher reimbursements from anyone:

1) **EXAS' benchmark DeeP-C trial results completely betray the "higher compliance" conviction—if anything, everyone should be assuming that compliance with Cologuard will be LOWER than compliance with existing FITs.** This is plainly shown in the article discussing the DeeP-C results published recently in the New England Journal of Medicine. On page four of the article, Figure 1 shows a breakdown of the enrollment and outcomes from the trial. Within the chart, you can see that of the 11,016 eligible participants enrolled in the trial, 687 Cologuard samples provided by patients were excluded because of leakages in shipping, failure to receive specimens from participants, or due to technical failure. Of the 11,016 participants, 34 had FITs excluded from the results due to insufficient hemoglobin sample. To put it together, this means that within the DeeP-C trial, **patients using Cologuard were 20x more likely to fail to return the test or have an unsuccessful test than patients using FIT.** See below for the relevant diagram from the NEJM article:



On top of that, multiple authors responsible for modeling out the cost-effective prices of colorectal cancer detection methods in prior cost-effectiveness paper commissioned by CMS stated in a 2010 paper that they believe adherence to stool DNA tests (Cologuard) was unlikely to be greater than adherence to existing tests due to the fact that both tests are non-invasive.[13] We agree, and though the authors did not comment on this, we believe that the "ick" factor increases exponentially with a test such as Cologuard where patients are forced to handle/ship a meaningful amount of feces as opposed to trace amounts of feces that can be brushed onto a sheet. This is likely to adversely impact compliance rates.

2) **The 70% compliance rate at Kaiser Permanente that EXAS claims to investors it can replicate is completely implausible because the primary driver of the increased compliance at Kaiser Permanente that EXAS cites was the fact that the insurance company was preemptively sending out test kits to at-risk patients—NOT additional calling/mailing after patients received the test kits.** EXAS' claims that it will be able to achieve increased compliance rates due to its "compliance engine" from the national average of 59.1%[14] to 70% by pointing to the success experienced by Kaiser Permanente's success is extremely misleading. The increased compliance was largely driven by the fact that patients were mailed initial tests, which is something EXAS would have no power to do. In order to participate in such a system (which would involve mailing out tests to all customers), payers would have to have financial incentive—but there would be none if the price of Cologuard already reflects the benefit of higher compliance and EXAS is pocketing the incremental benefit!

3) **Historical precedents show that CMS refuses to reimburse for non-lab procedures (including a compliance engine) under its clinical diagnostic laboratory fee schedule; therefore, any actual benefit derived from the "compliance engine" will not be reflected in reimbursement prices.** For instance, there are numerous multi-analyte assays that require algorithmic analyses—meaning that after the assays are completed, algorithms are run to analyze the results and to reach the appropriate conclusion. Despite the fact that algorithm analyses are required to yield actionable results, CMS declined to reimburse for the algorithmic analyses because "Medicare does not recognize a calculated or algorithmically derived rate or result as a clinical laboratory test". Similarly, EXAS' proposed "compliance engine" is not going to be acknowledged as a clinical laboratory test. Below is CMS' commentary from its preliminary decision for Multi-Analyte Assays with Algorithmic Analyses ("MAAAs"). Emphasis added:[15]

> ***"CMS Preliminary Payment Decision***
> *CMS uses other codes for payment of the underlying clinical laboratory tests on which the MAAA is done and does not recommend separately pricing the MAAAs codes.*
>
> ***Rationale***
> *A MAAA is a numeric score(s) or a probability (i.e., "p-score") based on the results of laboratory tests and, in some cases, patient information.* ***Medicare does not recognize a calculated or algorithmically derived rate or result as a clinical laboratory test*** *since the calculated or algorithmically derived rate or result alone does not indicate the presence or absence of a substance or organism in the body. Medicare uses other codes for payment of the underlying clinical laboratory tests on which the MAAA is done and we continue to recommend not separately pricing the MAAAs codes"*

[13] Ann Intern Med. 2010 September 21; 153(6): 368–377
[14] CA Cancer J. Clin. 2014;64:104–117
[15] Link

Bull Counterpoint #2: But Given Imaging is getting reimbursed ~$1,000/test for PillCam Colon 2! Therefore, $500/test for Cologuard is not unreasonable.

PillCam Colon 2 ("PillCam") is completely different from Cologuard. **PillCam is only reimbursed for patients who are unable to have conclusive colonoscopies, and is in fact only indicated for such patients by the FDA**.[16] For such patients, there is no other currently-available method backed by significant clinical results that is capable of locating adenomas/polyps throughout patients' entire colons. Colonoscopies are the gold standard for locating and removing polyps, and there are no generally accepted alternatives with clear prices for patients who were unable to receive complete colonoscopies. As a result, using an efficient market pricing model to determine the fair price based on alternatives does not work. On the other hand, Cologuard is one of several methods of merely diagnosing patients with colorectal cancer and precancerous polyps. Cologuard does not identify polyp locations, while PillCam does.

Second, the reimbursement decision for Cologuard must come via a national coverage determination ("NCD") from CMS, where CMS sets a national limit for reimbursements for Cologuard. This is the case for all clinical diagnostic laboratory procedures. PillCam is not a clinical diagnostic laboratory procedure, and is reimbursed on a local coverage determination basis, with no NCD from CMS.

Bull Counterpoint #3: But the CRC Detection Market is Large and Some Payers Will Pay $500/Test Regardless of the CMS Decision!

Even ignoring the "ick" factor of Cologuard and the difficulties EXAS will run into marketing the test due to its impracticality compared with alternatives, the addressable market for Cologuard is approximately 70% smaller than EXAS claims and is in decline. A paper published on March 17, 2014 shows that the vast majority of patients (approximately 70%) using FOBTs/FITs are also concurrently having colonoscopies every 10 years, and used the non-invasive test as a secondary diagnostic test for CRC. See below for the relevant table:

[16] Link

TABLE 6. Colorectal Cancer Screening Among Adults Aged 50 Years or Older, United States, 2010

CHARACTERISTIC	FOBT*	ENDOSCOPY†	EITHER FOBT or ENDOSCOPY‡
Sex			
Men	9.0	57.4	60.2
Women	8.6	55.6	58.3
Age, years			
50-64	8.0	52.3	55.2
65+	9.7	61.2	63.7
Race/ethnicity			
White (non-Hispanic)	9.2	58.5	61.5
Black (non-Hispanic)	8.4	53.0	55.5
Asian§	6.9	44.5	45.9
American Indian/Alaska Native¶	6.1	46.5	48.1
Hispanic/Latino	5.6	45.3	47.0
Education, years			
≤11	5.8	42.1	43.9
12	6.8	51.9	54.2
13 to 15	11.0	59.5	63.1
16+	10.4	66.7	69.2
Health insurance coverage			
Yes	9.2	59.4	62.2
No	1.6	17.8	18.8
Immigration			
Born in US	9.2	58.0	60.9
Born in US territory	4.7	53.3	55.6
In US <10 years	1.7	24.1	25.3
In US 10+ years	6.5	46.5	48.4
Overall	8.8	56.4	59.1

The author of the paper stated that "dramatic declines in incidence in recent years have been largely attributed to the uptick in colonoscopy because it is the only test for which use increased from **2000 to 2010; use of fecal immunochemical testing and sigmoidoscopy declined during that time period."** Given the price point EXAS is targeting, no payer would be willing to cover their test in tandem with colonoscopies. As a result, we believe the true addressable market would be approximately 2.7mm patients. Assuming EXAS can achieve its proposed 30% market share among those patients, we arrive at 810,000 patients. Assuming uniform discrete distribution over three years, we arrive at 270,000 patients per year. Even if EXAS were to achieve their theoretical reimbursement of $500/test (which is highly improbable), peak revenue would only be $135mm/year. At a more realistic estimate of $150/test, that figure falls to total peak revenue of only $40.5mm/year. This is a somewhat pointless exercise though, because $150/test would represent a negative gross margin for EXAS.

EXAS' Gross Margins

Below are two quotations from 2013 earnings calls discussing expected pricing and margins (emphasis added):

Q2 2013 Earnings Call:

> "Yes, Brian, that's very, very consistent with how you should think about it and how we've thought about it. What we've always said is we expect gross margins 65% or better at launch -- not at launch, excuse me, but at a run rate. **And so you could expect over time us to get to that -- so let's say, by year 3, us to be able to attain that 65% -- with some modest inefficiencies as we approach that.** So as we get closer to launch, we'll be discussing that in more detail. But the best way to think about it is still consistent with what we've said about that 65% gross margin once it is penetrated into year 3, and approaching that, it would be modest inefficiencies, but not far from that."
> -EXAS CFO

Q3 2013 Earnings Call:

> "At the end of September, CMS released 2014 National Limitation Amounts or NLAs for Tier 1 molecular pathology codes. It has yet to issue final payment rates for Tier 2 codes. Cologuard contains components in both tiers. CMS issued a rate for KRAS testing at $199. It had previously issued its rate for FIT testing at $22. Together, these 2 codes amount to $221. In addition, we believe that the agency will eventually issue rates for the detection of methylated DNA. Presently, Cahaba, a regional Medicare administrative contractor, has priced single-methylated variant detection at $140. Cologuard has 2 methylation markers: NDRG4, and BMP3. **Assuming CMS sets the National Limitation Amount for a single-methylated variant at $140, the total reimbursed value of Cologuard would be $501.** The final payment level will be determined by HAPG."
> -EXAS CEO

Combining the two comments, we get to a peak run-rate gross cost per test of approximately $175. Using a lower target reimbursement price ($476.83) from a January 2014 investor presentation (see below), we arrive at a peak-efficiency gross cost of $166.89 per test:

Cologuard CMS crosswalk analysis

Descriptor	Code	Rate
KRAS	81275	$198.97
FIT	82274	$21.86
NDRG4	81401	$128*
BMP3	81401	$128*
Total		$476.83

*Tier 2 code – Palmetto pricing per analyte for 19 analytes. Final reimbursement not yet established.

Conclusion

As we discussed in the *Summary*, the root of the mispricing of EXAS equity is the misconception by analysts and shareholders that Cologuard will be reimbursed based on the cost of its DNA test components as opposed to the cost-effectiveness of Cologuard. Despite Management's insistence that CMS will use a crosswalk analysis to price Cologuard, we believe that EXAS has been well-aware for a long time that the reimbursement rates for Cologuard will depend heavily on cost-effectiveness studies. EXAS has previously acknowledged that cost-effectiveness was critical to achieving its target reimbursements: see below for an excerpt from EXAS' 2010 Letter to Shareholders:

> "Among the most important marketing activities during 2011 will be the initiation of studies that will measure Cologuard's cost effectiveness. These studies are important to our efforts to achieve the desired reimbursement level for the test. If we can demonstrate a significant economic influence on the prevention, diagnosis and care of colorectal cancer, the reimbursement rate for the test should reflect that contribution."[17]

In the same letter, EXAS assigned a $500 price target to Cologuard:

> "Our market analysis also has helped us value the market opportunity we're pursuing. There are at least 80 million Americans who are at average risk of colon cancer and eligible for screening today. Assuming a 30 percent penetration rate and current reimbursement rates, we estimate the market for our screening test to be $1.2 billion."[18]

Multiplying 80 million by 30%, we get 24 million patients. Dividing $1.2 billion by 24 million, we get an average price of $500 per test. It seems that Management believed, at the time, that Cologuard would perform well enough in the DeeP-C trial to elicit a $500/test reimbursement.

Unfortunately, EXAS reported its unfavorable top-line results in April 2013, and after reporting the data, EXAS stock dropped approximately 20% over the next few trading days. The primary endpoint targets were 85% cancer sensitivity, 50% pre-cancerous polyps sensitivity, and 90% specificity. The reported Deep-C results show that Cologuard achieved 92% cancer sensitivity, 42% detection of pre-cancerous polyps, and 87% specificity—effectively missing two out of three primary endpoints. However, we do not think this will preclude Cologuard from being approved by the FDA. We do, on the other hand, believe that it will make it impossible for Cologuard to achieve the reimbursement rate investors are expecting.

Prior articles published on EXAS have scratched the surface regarding EXAS' problems, but have largely ignored or incorrectly addressed the elephant in the room: reimbursement rates. For instance, the article published by Reed Research values EXAS at $8-9 based on the assumption of a price of $300/test, which the author got from a prior CMS paper.[19] It is likely that the author was referring to the following excerpt when stating that the study "gave a range of between $200 to $300 for a 3 year interval test":

> "The threshold costs of the DNA stool test version 1.1 at 3-yearly intervals were…$237-$302 if the DNA stool test had perfect test parameters."[20]

However, the $237-$302 range is for tests with perfect test parameters! That is, the test would have 100% sensitivity to cancer and all large adenomas, and 100% specificity. Cologuard is far from perfect, and the $237-$302 range

[17] Link
[18] Id.
[19] Link
[20] Id. (see bottom of p. 6 of the link above)

represents a cap on how much EXAS could get reimbursed if it were perfect—**not** a range of likely reimbursement prices! While we commend the author for his work, the article overestimates the potential range of prices for Cologuard.

Because Cologuard is a non-invasive diagnostic test that provides useful metrics, and poses no potential threat to patients, there is no reason for the FDA not to approve Cologuard—determining practicality and cost-effectiveness is not within the FDA's wheelhouse. However, we also think that Cologuard is as close as you can get to a guaranteed flop, with reimbursements at least 70-80% lower than EXAS has communicated to investors and little doctor or patient interest in selecting this test over other non-invasive alternatives due to the cost and the "ick" factor. The conventional fecal immunochemical test (FIT) requires patients to use a brush to scrape fecal samples onto a card that is then mailed back and processed by a lab. Cologuard requires patients to return a minimum of 8 grams of fecal matter in a container as well as a separate fecal sample for hemoglobin sampling, and offers sensitivity and specificity that are comparable to existing FITs. We doubt any patients will be rushing to try to get test kits.

Marketability aside, we believe that following imminent FDA approval, it is very likely that EXAS will be unable to sell its Cologuard test at a profit on a gross basis. We think it is very telling that EXAS has been unable to find any partners and has not published a cost-effectiveness study for Cologuard despite purportedly "working" on one since 2011. Barring any new radical developments in its pipeline, we believe EXAS is worth nothing more than the cash on its balance sheet (a little more than $3/share). We rate the stock a "Strong Sell", and we are short. **EXAS shareholders are encouraged to reach out to us at info@gravityresearchgroup.com with any questions you may have regarding EXAS or the content of this report.**