EXAS’ Cologuard the Preferred Test for Patients Refusing Colonoscopy

Companies: ABT, BDX, BIOC, BSX, CHEK, CPHD, DGX, EXAS, FMI, GIVN, GSK, IRWD, RHHBY

August 14, 2015

Research Question:

Will Exact Sciences’ Cologuard become physician’s screening test of choice for colon cancer?

Summary of Findings

- Exact Sciences Corp.’s (EXAS) Cologuard has high clinical value, but it is unlikely to become physicians’ cancer screening test of choice, according to all 21 sources.

- Cologuard can expect strong adoption in the one-third of 50-year-old patients who are recommended to get a colonoscopy but who refuse it or are unable to undergo the preparation and procedure.

- Cologuard’s clinical results, potential to increase the number of patients screened for colon cancer, and reasonable cost compared with a colonoscopy ($649 vs. $1,500 to $7,000) are its strengths.

- Sources admired Exact Sciences’ partnerships with the Mayo Clinic and The University of Texas’ MD Anderson Cancer Center and the quick approval its Cologuard received from the FDA and CMS. Also, its direct-to-consumer and general practitioner sales and marketing campaign are expected to drive Cologuard’s adoption.

- However, Cologuard is up against the colonoscopy, a medical gold standard. Also, it requires a stool collection process and lacks awareness in the medical community. Sources said a blood test would be the ideal screening for cancer.

- Exact Sciences hopes to expand Cologuard’s indication for use in 40- to 49-year-olds, for whom colon cancer rates have risen.

- The field of molecular diagnostics is expected to expand further during the next five to 10 years. Key companies include Abbott Laboratories (ABT), Roche Holding AG (RHHBY), Cepheid (CPHD), Becton, Dickinson & Co. (BDX), Caris Life Sciences, Foundation Medicine Inc. (FMI), Guardant Health Inc., GlaxoSmithKline plc (GSK) and Biocept Inc. (BIOC).

<table>
<thead>
<tr>
<th>Silo Summaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Physicians and Related Medical Professionals</td>
</tr>
<tr>
<td>All six sources said Cologuard is unlikely to become the colon cancer screening test of choice, but they added that it does have an important clinical application. Patients who refuse or are inappropriate for a colonoscopy based on a medical condition are the primary Cologuard candidates. Sources said Cologuard will not replace the colonoscopy in younger patients, who are an at-risk group. Exact Sciences is expected to heavily market Cologuard directly to consumers and to general practitioners instead of to gastroenterologists, who favor the use of a colonoscopy and run the risk of reduced procedure revenue if Cologuard penetrates this market. Reimbursement has not been an issue.</td>
</tr>
<tr>
<td>2) Medical Sales Professionals</td>
</tr>
<tr>
<td>Three of these five sources said 25% to 60% of the 50-year-old-plus patient population facing a colonoscopy might opt for Cologuard if given the choice. The other two sources said the test is appropriate for patients who refuse the colonoscopy. Still, all sources acknowledged Cologuard’s clinical value as it could increase the number of patients screened for cancer. Exact Sciences’ direct-to-consumer (DTC) education and marketing to general practitioners will be needed to drive Cologuard’s adoption, which is expected to build slowly.</td>
</tr>
<tr>
<td>3) Third-Party Payers/Insurance</td>
</tr>
<tr>
<td>Two sources from the CMS and two sources representing the health insurance industry said their organizations reimburse for the Cologuard test. They did not discuss the extent of Cologuard use, but acknowledged the test’s clinical value. CMS sees high value in the home test for elderly rural patients; the organization’s goal is to reduce the reimbursement rate of colonoscopies and some endoscopy procedures by 19% in 2016, and expects Cologuard to assist in that goal. Insurer sources said Cologuard increases screening compliance and is less costly than a colonoscopy.</td>
</tr>
<tr>
<td>4) Industry Specialists</td>
</tr>
<tr>
<td>These six sources had a wide range of reactions to Cologuard’s adoption and offered the following beliefs: Within two to three years consumer demand will drive the test’s adoption; Cologuard will be the method of choice for patients who refuse a colonoscopy; 10% of the one-third of patients who refuse a colonoscopy (2 million tests) might be its market; the less than desirable collection process will limit adoption; and the test is filling a diagnostics need. A blood test is expected to increase the number of patients screened for cancer. Exact Sciences is expected to heavily market Cologuard directly to consumers and to general practitioners instead of to gastroenterologists, who favor the use of a colonoscopy and run the risk of reduced procedure revenue if Cologuard penetrates this market. Reimbursement has not been an issue.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Colguard Primary Cancer Test</th>
<th>Colguard Secondary Cancer Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians/Medical Professionals</td>
<td>![Down Arrow]</td>
<td>![Up Arrow]</td>
</tr>
<tr>
<td>Medical Sales Professionals</td>
<td>![Down Arrow]</td>
<td>![Up Arrow]</td>
</tr>
<tr>
<td>Third-Party Payers/Insurance</td>
<td>![Down Arrow]</td>
<td>![Up Arrow]</td>
</tr>
<tr>
<td>Industry Specialists</td>
<td>![Down Arrow]</td>
<td>![Up Arrow]</td>
</tr>
</tbody>
</table>
Exact Sciences Corp.’s Cologuard

Background

Exact Sciences’ second-quarter revenue was reported at $8.1 million, a 90% increase over the first quarter. The company claimed growth was due to the CMS’ October approval of Cologuard, a self-administered molecular diagnostics noninvasive colorectal cancer test, and to an increased number of sales personnel selling the product. By the end of the 2015, Exact Sciences expects a headcount of 800 salespeople, up from 430 in its first quarter.

Cologuard’s major advantage over a colonoscopy for screening cancer is its much lower price point and ease of use. Later this year the CMS is expected to decide on Cologuard’s universal CPT code, which would increase payers’ order efficiency. Exact Sciences is seeking the FDA’s approval to market Cologuard to 40- to 49-year-olds, and it also intends to grow internationally and develop tests for lung, pancreatic and esophageal cancer.

Exact Sciences’ lofty valuation of $2.2 billion appears to be ahead of itself given its 2015 revenue projection could fall short of $50 million, and most of its international and other cancer-testing ambitions are just beginning to be developed or only exist on paper. Patients using Cologuard who test positive for colon cancer still must then undergo a colonoscopy. One gastroenterologist recommended that patients instead consider the fecal immunochemical test, aka FIT, a much less expensive ($6 to $25), insurance-covered colon cancer screener better at identifying false-positive patients.

Current Research

Blueshift Research assessed whether Exact Sciences’ Cologuard would be widely adopted and become physicians’ colon cancer screening test of choice. We employed our pattern mining approach to establish five independent silos, comprising 21 primary sources (including one repeat source) and eight relevant secondary sources focused on molecular diagnostics and specifically colon cancer screening:

1) Physicians and related medical professionals (6)
2) Medical sales professionals (5)
3) Third-party payers/insurance (4)
4) Industry specialists (6)
5) Secondary sources (8)

Next Steps

Blueshift Research will monitor the use of Cologuard to see if it becomes the go-to test for patients who refuse a colonoscopy. We will research Exact Sciences’ expanded direct-to-consumer and general practitioner sales and marketing efforts to determine the adoption rate of Cologuard. Finally, we will try to determine how Cologuard sales are affected by a possible expanded indication to 40- to 49-year-old patients.

Silos

1) Physicians and Related Medical Professionals

All six sources said Cologuard is unlikely to become the colon cancer screening test of choice, but they added that it does have an important clinical application. Patients who refuse or are inappropriate for a colonoscopy based on a medical condition are the primary Cologuard candidates. Sources said Cologuard will not replace the colonoscopy in younger patients, who are an at-risk group. Exact Sciences is expected to heavily market Cologuard directly to consumers and to general practitioners instead of to gastroenterologists, who favor the use of a colonoscopy and run the risk of reduced procedure revenue if Cologuard penetrates this market. Reimbursement has not been an issue. One source said Exact Sciences handled all of the paperwork regarding payment. Challenges facing Exact Sciences are the length of time it takes to get test results and a conservative medical community committed to long-standing procedures. Molecular diagnostics is five to 10 years from mainstream use, but the market is ramping up. Abbott and Roche are advancing in the molecular diagnostics field.
Exact Sciences Corp.’s Cologuard

Key Silo Findings

Adoption of Exact Sciences’ Cologuard
- None of these 6 expects Cologuard to become the colon cancer screening test of choice.
- 6 do think the test has clinical value for older patients and patients who can’t tolerate the colonoscopy prep or procedure.

Molecular Diagnostics Market’s Competitive Landscape
- Abbott and Roche are known to be advancing in the molecular diagnostics field.

Molecular Diagnostics Market’s Adoption and Growth
- Adoption of molecular diagnostics is 5 to 10 years out.
- Still, the field is ramping now. Molecular diagnostics tests are available for Clostridium difficile (Cdiff) and methicillin-resistant Staphylococcus aureus (MRSA) detection, along with patient drug response tests.

Miscellaneous
- Exact Sciences is expected to heavily market directly to consumers and general practitioners instead of gastroenterologists, who are conservative and risk the loss of colonoscopy procedure revenue.

1) RN for three gastroenterologists at a large clinic

Cologuard is useful for the elderly or people who have had difficulties with previous colonoscopies, but it is not for routine screening. People would like to see a noninvasive test replace the colonoscopy, but this will not occur for a number of years. The clinic does not screen patients under 50 years of age. The source has not heard of any other upcoming molecular tests, but thinks molecular diagnostics will take at least five to 10 years to ramp up.

Adoption of Exact Sciences’ Cologuard
- “I have ordered 10 Cologuard tests for about three gastroenterologists. We have several other gastroenterologists in the office, and it could be that others have ordered the test as well, but I wouldn’t know.”
- “Only one of these patients had a positive test and required a colonoscopy, but I don’t know what the results of the colonoscopy were.”
- “I had no problems ordering the test. One time a patient called for his results, but we didn’t get them. They claimed there was a fax mix-up.”
- “I couldn’t say what percentage of our patients would qualify for the Cologuard. I think is really varies.”
- “Cologuard is useful for some people who have had problems with previous colonoscopies or as a recheck. It is not used as a routine screening.”
- “All of our patients were over 50. We used the Cologuard for various reasons—some because they were elderly and would possibly do poorly with a colonoscopy. A few had had previous difficult colonoscopies, so we used Cologuard as an alternative to a virtual colonoscopy, a CT [computerized tomography] colonoscopy. We did one routine follow-up that was low-risk. I don’t think any of the patients refused to have a colonoscopy; we didn’t use it for that.”
- “I know that people would really like to see the Cologuard used as the primary test because it is noninvasive. But we won’t see this for a while. Maybe this is something in the future, a number of years down the road.”
- “I would assume that you’d use the Cologuard test because it is more sensitive or more accurate than the FIT test, but I really don’t know for sure.”
- “We don’t screen for patients under 50 years, so I doubt if we would use the test on younger patients. Possibly if they have a family history, but then they would probably benefit from a colonoscopy.”
- “Insurance may be a problem. I’m not sure about reimbursement because the patients are reimbursed by their insurance companies. I haven’t heard of any problems, but I really don’t know. But the company was very good about working with insurance. The patients don’t need to do it themselves.”

Molecular Diagnostics Market’s Competitive Landscape
- “I don’t know about companies.”
Exact Sciences Corp.’s Cologuard

Molecular Diagnostics Market’s Adoption and Growth
- “I haven’t heard of any other tests coming out. That’s not to say there aren’t some, but we focus on gastroenterology.”
- “This will take a while, maybe five to 10 years down the road.”

Miscellaneous
- “Most physicians feel they need a visual scope.”

2) MD and RN at a large gastroenterology clinic in the Midwest

Patients who do not want a colonoscopy are asking this GE clinic, which also does primary exams, for a Cologuard test. These orders vary, and it is difficult to estimate the percentage of patients who would qualify for the test. Patients are carefully screened to ensure they qualify as a candidate. Cologuard may be a prime noninvasive test, but it will never replace the colonoscopy. It may be preferable to the FIT test because it offers the DNA component. These sources have heard that blood tests beyond cancer markers are being developed for cancer diagnosis.

Adoption of Exact Sciences’ Cologuard
- “We have used the Cologuard more than 10 times in our small section of the clinic. I don’t know how frequently the other physicians use the test. But I think usage will vary, at least in our section.”
- “It would be difficult to estimate the percentage of patients who would be candidates for the test.”
- “Last year we had patients calling us and telling us about the test. It was advertised somewhere. We had numerous requests before the test even came out. Patients also come to us for their yearly general, which is why the patients were calling us and not a general practitioner. Most of the requests came from people who did not want to do a standard colonoscopy. But to take the Cologuard, the patients had to meet certain criteria, without a history of polyps and cancer. It all depends on their family history. A positive history would exclude them from the Cologuard.”
- “If they have a positive Cologuard, then we would recommend that they pursue a colonoscopy. I don’t know what our patients’ results were, if any were positive or not.”
- “The Cologuard offers the DNA component, which is not offered by the occult blood test alone. This is an interesting part of the test and will allow us to understand colon cancer a bit more.”
- “Cologuard is becoming a prime noninvasive test now. Whether that continues will depend on the outcome of long-term studies and how our patients fare. But this is not to say that it will replace the colonoscopy as the only colon test. It has a place in what we can offer the patients.”
- “I would rather doubt that we would use Cologuard on younger patients. If there is an issue at that age, a colonoscopy might be the best decision.”
- “As far as I know, we haven’t had any issues with ordering. Results are faxed to us in a few months, I believe. We encourage the patients to call their insurers and see if the test is covered. I have not heard of any issues with insurance.”

Molecular Diagnostics Market’s Competitive Landscape
- “I believe there are several companies developing a blood test for cancer, but I don’t know their names.”

Molecular Diagnostics Market’s Adoption and Growth
- “The blood test for cancer is the only diagnostics that comes to mind. But keep in mind that if any of these tests come back positive for colon cancer, those people would still need to have a colonoscopy.”
- “[Molecular diagnostics] will take a number of years before it becomes common. I believe the tests are still in clinical trials, and some are still in development.”

3) Gastroenterology RN at a large medical center on the West Coast

ColoGuard is becoming a prime noninvasive test now. Whether that continues will depend on the outcome of long-term studies and how our patients fare. But this is not to say that it will replace the colonoscopy as the only colon test. It has a place in what we can offer the patients.

MD and RN at a large gastroenterology clinic
Midwest, USA
A section of this large clinic has used Cologuard only once, with a patient who could not tolerate the preparation for a colonoscopy. The source is uncertain how often or even if the center would use Cologuard again. Cologuard might become more popular among people without polyps or a family history of colon cancer. Generally the test would be prescribed by a primary care physician, not a gastroenterologist, who would lose money by offering the test.

Adoption of Exact Sciences’ Cologuard

- “We have used the test once on a gastrointestinal patient with a history of esophageal cancer. The colonoscopy test prep would not have been good for him. I brought the Cologuard test to the attention of the general care provider, and we decided to use it. Someone else in the department may be using the test, but I’m not sure.”
- “I do not know if we will be using the test again; it could be this was a one-time, special usage. So I couldn’t say a percentage [of our population who might be candidates] for the test.”
- “Cologuard is a great idea for someone who cannot tolerate the colonoscopy prep or procedure. This gives us another option to use. Eventually it may be the way to go for people without polyps or a family history of colon cancer.”
- “When I read about Cologuard, the study showed that it was better than the current tests out there.”
- “I don’t know about reimbursement, so it is possible that could be an issue for some.”

Molecular Diagnostics Market’s Competitive Landscape

- “I couldn’t comment on companies involved in this field. I really don’t know.”

Molecular Diagnostics Market’s Adoption and Growth

- “We are hearing more about molecular diagnostics, but just that term in general. I don’t know specific areas.”

Miscellaneous

- “I would think that the primary care doctors would be the ones to order this test, not the GI folks. This test would actually take business away from the GI, but it is good to know about it.”

4) Gastroenterologist at a major academic center

Cologuard is an excellent noninvasive test with impressive clinical results. However, it must only be used by patients who refuse colonoscopies, and any use as a preventive test carries a potential liability for physicians. Potential use among patients scheduled for follow-up colonoscopies is promising. Although the source thinks few GPs are turning to Cologuard, he expects to continue to use it. Still, he has had some difficulty receiving test results on a handful of patients. Exact Sciences is improving its communication system and is reassessing a fee charged to non-Medicare patients.

Adoption of Exact Sciences’ Cologuard

- “I personally think the Cologuard is the best noninvasive test of this type. ... The company is a very good one, and I think they’re doing a good job. I had some trouble in getting results on some of my patients. I talked to one rep and then another, but nothing happened. And then with reps with Ironwood Pharmaceuticals Inc./IRWD—Ironwood is a pharma company they got to co-promote, even though they don’t have colon cancer knowledge and had to be trained on it. Finally I got a call from Wisconsin, and things started to happen. They’re instituting a weekly email update system so I can see the status on patients I’ve ordered it on. They’re trying to improve.”
- “Who should use [Cologuard]? Patients should be offered a colonoscopy and, if they decline, then go to Cologuard. But first is, why did they decline? If it’s because they don’t want invasive, or the prep or any pain, then Cologuard. It could be they don’t want to do it in three years or if they won’t take bowel prep. But if it’s because they’re on Coumadin or have difficult anatomy, a virtual colonoscopy might be better because it can find more polyps.”
- “Where it might get some use is when patients get scared about having another colonoscopy after five years, so I can see [increasing] use there. It has to find its niche. Primary docs are not ordering very many, because [the few who do want to order it] call me to get the phone number.”
 Exact Sciences Corp.’s Cologuard

- “In any practice, this would be offered to those who have been offered and refused a colonoscopy. It’s not a preventive test and never will be. If it’s marketed as an alternative to colonoscopy, that’s fraudulent.”
- “There are two methods: cancer detection and cancer prevention. Colonoscopy is a cancer prevention test. I don’t know how this one is marketed … but it hasn’t been designed as a cancer prevention test. On the whole this is a cancer detection, not a cancer prevention test. Even though it can find polyps, but they have to be big. The 43% sensitivity was for larger 2-cm adenomas—that’s a huge polyp.”
- “In terms of technology, it has 92% sensitivity compared to 76% for FIT—although it’s unclear which FIT test they used in their study. … Did they use the very best FIT test? Some people think they used a secondary one so it wouldn’t test high. But the study was incredible.”
- “Kaiser does 5,000 FIT tests a day, especially with the goal to screen 80% of Americans by 2018. About 60% of Kaiser patients complete it because Kaiser has a dedicated system. If positive, they get in for a colonoscopy within two weeks. If they want a colonoscopy [otherwise], it’s a two-year wait. Kaiser just can’t afford to give everyone a colonoscopy, I don’t think the VA will use [Cologuard]. Kaiser won’t use it.”
- “If a primary care doctor recommends a Cologuard to a patient without recommending a colonoscopy, and they test negative but then two years later they have metastatic cancer, that doctor is liable because they didn’t offer a colonoscopy. You can’t recommend it unless you’re not appropriate or decline a colonoscopy. … There’s no incentive for a primary care doc to do Cologuard. Medicare pays for screening colonoscopy, and the major insurance companies have already built colonoscopies into the cost.”
- “I haven’t heard about [a possible indication for patients ages 40 to 49]. I don’t deny we’re having an epidemic of cancer among 30- to 35-year-olds, but there’s clinically no active screening guidelines for 40- to 49-year-olds who are low- or medium-risk. That would be [Exact Sciences’] own advocacy. Certainly Medicare doesn’t cover that population.”
- “Regarding reimbursement [Exact Sciences does] everything. You fax the form to them and everything is taken care of. Except they didn’t send me the results. [The kit is] totally covered with Medicare patients. Commercial insurance patients have paid $50 by credit card to get sent the kit, but that $50 gets reimbursed when you send the kit in. It’s a big bucket, not a little test like the FIT test. So you’re getting a bucket in the mail. But [Exact Sciences has] had second thoughts; I heard they were going to stop the $50 payment because you’re expecting the patient to be non-compliant, which is a bad way to start out a relationship.”

Molecular Diagnostics Market’s Competitive Landscape

- N/A but see below

Molecular Diagnostics Market’s Adoption and Growth

- “I think every cancer will be molecular-typed; many are to some extent already. No doubt that trend will continue. And then there’s a test [called the Cobas] by Roche, for example, that tests for three to four, such as Cdiff and MRSA. I think [molecular diagnostics are] ramping now and will be continuing.”

Miscellaneous

- “Cologuard is a third generation of what is a dual fecal FIT test put in with a DNA test. It’s either positive or negative. You don’t know if positive because of FIT or DNA. It was the first test to be coapproved with FDA and CMS. The various markers indicate cancer and certain polyps. It has some ability to pick up polyps over 2 cm.”
- “Colonoscopy prices range widely, but it’s about a $1,800 charge for the patient. The doctor gets paid $250, and there might be a $1,200 facility fee.”
- “Basically the incidence of colon cancer in the U.S. is 0.7%, so one in 153 people is walking around with colon cancer. So if I do this test, there’s a 99.9% chance you don’t have colon cancer. If the test is negative, 99.3% goes to 99.9% you don’t. You’ve gained about 0.6% to 0.7% certainty. If you walk in the door and the test is positive, 95% still don’t have cancer. It goes from 99.3% to 95% you don’t have it. … The point is there are false positives, but the vast majority who have a positive test still don’t have colon cancer.”
- “Another way of looking at this is [with a 70% or so sensitivity with the FIT test] out of 1,000 FIT patients, five of seven people will be found by FIT, compared to 6.3 out of 1,000 will be found with Cologuard. The absolute yield for this test is 1.3 persons out of 1,000. So this is a $600 test with an absolute yield of 1.3. Its negative predictive value makes people feel great, but [there are other aspects to it.]”
5) Gastroenterologist at a major academic medical center

Cologuard will not become a screening test for physicians because of its cost and low sensitivity in detecting precancerous lesions. The CMS approval was surprising and potentially a positive if the organization also covers colonoscopies that result from positive Cologuard tests. The source does not expect Cologuard to get approval for testing in patients ages 40 to 49 because those who are high-risk should undergo a colonoscopy. Molecular diagnostics tools that determine therapeutic response are the biggest growth area.

Adoption of Exact Sciences’ Cologuard

- “Here we use it next to none because we’re a tertiary center. Will it fly [elsewhere]? They’re marketing to primary care docs and others, but the real issue is cost. … I’ve only had referral from a positive [Cologuard] test, probably because it’s new. I would have liked to know which segment of the test was positive.”
- “Cologuard is more sensitive than FIT but not much better for adenomas. In most of the world it wouldn’t replace FIT, but [Exact Sciences is] not marketing it as a replacement but as an option for a patient who doesn’t want a colonoscopy. Will that be enough to switch? Certainly if CMS approved it; that’s a big thing. [Use among physicians] will probably range widely.”
- “They want to get a niche for commercial viability: those who refuse colonoscopies. For a screening it won’t fly as a replacement for FIT.”
- “I don’t think it will get [approval for use in patients ages 40 to 49]. Why use it in that population when they’re considering a colonoscopy because of family history? They’re high-risk. … That person needs a colonoscopy, not a two-step test.”
- “Their large pivotal trial showed the sensitivity for detecting colorectal cancer was 92%. The sensitivity for detecting advanced ‘precancerous’ lesions was 42%. … They also marketed it at $600, about what a colonoscopy costs. They need to recoup their costs. But they were able to get their application through FDA approval, which is pretty hard. After the approval there was a lot of interest, so they then got investors. The other issue is subtle, but how much is FIT and how much is from the DNA portion? They don’t tell you which. The real issue from a commercial standpoint is cost. The sensitivity for cancer [is good] but less for adenoma when you want to pick up everything.”
- “It[s success] also depends on the insurers. … I was surprised by the CMS approval. They wouldn’t even approve CT colonography or virtual colonoscopy. It depends if CMS also pays for a colonoscopy [if the test is positive]. Let’s say they do; then maybe it will be more successful.”

Molecular Diagnostics Market’s Competitive Landscape

- “I haven’t kept up enough to know, but [of the large companies, Eli] Lilly [& Co./LLY] has no interest in diagnostics while Abbott and Roche are [taking part in the market].”

Molecular Diagnostics Market’s Adoption and Growth

- “There are molecular diagnostics for screening, for prognosis and for being predictive of response to therapy. I think the most growth potential is in determining response to therapeutics. If you look at certain drugs there are markers if they work or not.”
- “An ideal test would be a blood test that can pick up the markers. For a blood test you need to have a precursor or early stage, and that marker has to be able to get out into the blood.”
- “I think the use of molecular diagnostics will jump. There’s a lot of interest with some companies, while others have said they’re not interested in diagnostics because it’s so hard to get through FDA.”

Miscellaneous

- “Basically they’ve been trying to come up with a colorectal test for a long time since colon cancer arises from genetic alterations. If reflected in stool in shed DNA or cells it should be detected. So they looked at a panel of DNA markers, which were disappointing for a couple reasons, including technical reasons that they overcame and the performance wasn’t ideal. What’s used around the world is the two-stage fecal occult blood and the FIT test. What Cologuard is, is a combination of FIT—one particular one that is good—and a panel of DNA markers.”
"I’ve developed a blood test that is picking up markers for some advanced adenomas. But diagnostics is hard to change, and it’s difficult to get FDA approval. ... If our blood tests works, it may have more value outside the U.S. But international patents are expensive.”

6) Two primary care physicians at a private practice; one repeat source

Cologuard is not a replacement for the colonoscopy, which identifies both size and location of various tumors in addition to different forms of serious disorders and cancers. This six-physician office has used the Cologuard test once, on the request of a patient. The test was easy to order, but the results were slow to arrive. Getting reimbursement was not a problem. The physicians would consider using Cologuard on patients with no colon cancer concerns, but not on a regular basis. The test may be beneficial for the elderly not at risk for colon cancer. They also would not consider using the test for patients under 50 years old. Molecular diagnostics was not a topic discussed at a recent family practice conference. Sources said at least five to 10 years will pass before molecular diagnostics ramps up.

Adoption of Exact Sciences’ Cologuard

- “[One physician at our office] has used it once, and that was at the request of an ex-patient of another doctor. Before the patient came in asking for the test, [the doctor] had never heard of it.”
- “He would use the test again but not regularly and not primarily. He would probably use it on a patient that he didn’t have any concerns about colon cancer.”
- “He did not have any problems ordering the test, but he did not get the results in a timely manner.”
- “I suppose the Cologuard offers more than just an occult blood test. I have used the guaiac test before on some patients. It depends on their family history. If I had a better test, then I would go for the Cologuard.”
- “The test would be better than no screening at all. Sure, you’d have to recommend the colonoscopy, but if the patient doesn’t want one, you’d have to note that in the chart. I don’t think there would be a need for a release form.”
- “[Cologuard] may be a top noninvasive test, but I disagree that it is a replacement for a colonoscopy. Could the Cologuard pick up on other problems? By what percentage? I suppose the test is a tool, but it would not be seeing everything.”
- “Symptoms for ulcerative colitis and Crohn’s disease start at a younger age, but there are other disorders, such as angiodysplasia and diverticulitis, which can occur without symptoms. I order a colonoscopy to identify other problems with my patients. With the scope, you can see the number of diverticuli that will be a problem.”
- “I’d also want to know how much of a tumor mass a patient has to have to get a positive test. Will young tumors be missed? Of course, it’s not 100%, and neither is a colonoscopy. Sometimes they miss cancers too.”
- “If you have a positive Cologuard test, then I’d assume that you still need to have a colonoscopy to identify location and staging. You need to know where the tumor is and how big it is. You need to have the colonoscopy for diagnosis and treatment.”
- “In certain high-risk groups, you’d want to do a test earlier, in the 40s. But I think in those cases you would need to do a colonoscopy. We would not use the Cologuard test for people 40 to 49 years old.”
- “We did not have problems with reimbursement for the one test we ordered. But reimbursement is always the big roadblock. Do you know how many insurers cover the test? Of course, insurance companies always want to save money, and this would save them money.”

Molecular Diagnostics Market’s Competitive Landscape

- “We have no idea about any molecular diagnostics companies.”

Molecular Diagnostics Market’s Adoption and Growth

- “I just returned from a family practice meeting, and there was nothing mentioned about molecular diagnostics. I don’t recall any seminars on it.”
- “I’ve heard about genomic testing for specific gene tumor markings on the radio, but that’s about it. We don’t know of anything else.”
- “Unless there is more information that comes down the pipe, it will be a while for adoption, five to 10 years.”

Miscellaneous

- “I would assume the company markets to primary care physicians, not to gastroenterologists, who would lose money because of the test.”
- “Primary care physicians are usually the ones who prescribe a colonoscopy. Usually patients see primary care first; then they are recommended to a specialist.”
3) Battery Street, 2nd Floor, San Francisco, CA 94111 | www.blueshiftideas.com

Exact Sciences Corp.’s Cologuard

- “I would be concerned that the company would push this test as the best thing since sliced bread. Would they sell it as a test you have to have before a colonoscopy?”
- “Seventy-year-olds should have a colonoscopy. I would not push a colonoscopy on an 80-year-old unless they have a family history of colon cancer. I may encourage 80-year-olds to do this test rather than a colonoscopy, however, if I were worried about something.”

2) Medical Sales Professionals

Three of these five sources said 25% to 60% of the 50-year-old–plus patient population facing a colonoscopy might opt for Cologuard if given the choice. The other two sources said the test is appropriate for patients who refuse the colonoscopy. Still, all sources acknowledged Cologuard’s clinical value as it could increase the number of patients screened for cancer. Sources were split on its value in a younger patient population. Exact Sciences’ direct-to-consumer (DTC) education and marketing to general practitioners will be needed to drive Cologuard’s adoption, which is expected to build slowly. Cologuard is not well known in the gastroenterology community, which would lose colonoscopy procedure revenue if it were to adopt the test. Molecular diagnostics adoption is expected to take five to 10 years. Roche, Cepheid, Becton Dickson, Caris Life Sciences, Foundation Medicine, Guardant Health and Biocept were discussed as leaders in the field.

Key Silo Findings

Adoption of Exact Sciences’ Cologuard
- 3 of 5 expect Cologuard to be used by 25% to 60% in the nonrisk 50-and-older population.
- 2 think it will be used for patients who refuse a colonoscopy.

Molecular Diagnostics Market’s Competitive Landscape
- Roche, Cepheid, Becton Dickson, Caris, Foundation Medicine, Guardant and Biocept are leaders in the field.
- Diagnosis and targeted drug therapy in oncology are a growing molecular diagnostics application.

Molecular Diagnostics Market’s Adoption and Growth
- Adoption is expected to take place during the next 5 to 10 years.

1) Colonoscopy/endoscopy supply sales representative

A simple at-home test for colon cancer screening could expand the percentage of people over 50 who are screened. DTC education will drive adoption. Growth in molecular testing is most likely in those cases in which traditional cancer screening is difficult or unpleasant.

Adoption of Exact Sciences’ Cologuard
- “I expect that approximately one-third of the 50-and-older population, without existing risk factors, would be good candidates for the Cologuard test. These are the people who are very uncomfortable with the traditional colonoscopy procedure or find it too inconvenient to schedule. When there is no blood in the stool, many people are not motivated. A high-sensitivity/specificity, at-home test could improve colon cancer screening.”
- “It makes complete sense to market Cologuard directly to general practitioners, but Exact Sciences will need an aggressive sales force able to change behavior. Many general practice physicians will have their own GI specialists, whom they trust for reliable colonoscopy testing. It will take a strong and convincing educational effort to get them to shift to a simple diagnostics test.”
- “Gastroenterologists will be tougher to convince. A test like Cologuard is taking money out of their pockets.”
• “Public awareness will definitely drive adoption. When patients are asking for a specific test directly, utilization will increase, particularly where there is adequate reimbursement.”

Molecular Diagnostics Market’s Competitive Landscape
• N/A

Molecular Diagnostics Market’s Adoption and Growth
• “Molecular diagnostics has space to grow, particularly in difficult-to-identify cancers [such as prostate, breast and testicular]. Molecular diagnostics manufacturers would be well served to identify those screening opportunities that are inadequately served presently.”

Miscellaneous
• “Most people are aware that a routine colonoscopy is recommended for people 50 years and older. Awareness is a result of extensive public relations efforts. If/when earlier screening is generally recommended and the public is made aware of the new standards, earlier screening will eventually be adopted. Having an indication for the younger population in such a case would definitely be advantageous.”

2) Molecular diagnostics sales representative

Given Cologuard’s reliable sensitivity and specificity, up to 60% of patients may prefer the test over the traditional colonoscopy. Cologuard also may appeal to people who otherwise would not be screened. Marketing to the general practitioner makes the most sense as gastroenterologists will be reticent to change and forgo the revenue of their “bread-and-butter” procedure. Having an indication for a younger population should be a welcome change for patients, but the relatively low sensitivity for precancerous polyps will limit medical support. The biggest opportunity in molecular diagnostics lies in the identification of antibiotic-resistant microorganisms.

Adoption of Exact Sciences’ Cologuard
• “I am not familiar with any specific institution that has adopted the Cologuard test.”
• “Given the sensitivity and specificity is reliable, there are so many positives to a test like Cologuard compared with traditional colonoscopy, I would expect 50% to 60% of patients would prefer it.”
• “Colonoscopy is the bread-and-butter for gastroenterologists. It will be difficult to change their behavior. But if public demand is sufficient, and the Cologuard test gets people who would otherwise refuse the procedure to get screened, there may be a place for it in their practice.”
• “Marketing to the general practitioner makes a lot of sense. Cologuard is a test they can prescribe. The price differential between it and the FIT test should not be an issue as long as there is reimbursement.”
• “Patients want to be informed about cancer screening recommendations. They want peace of mind and are interested in catching early stages as soon as possible to avoid more radical treatments later. Having an indication for a younger population would, therefore, be favorable for Exact Sciences and potentially improve adoption.”

I expect that approximately one-third of the 50-and-older population, without existing risk factors, would be good candidates for the Cologuard test. These are the people who are very uncomfortable with the traditional colonoscopy procedure or find it too inconvenient to schedule. When there is no blood in the stool, many people are not motivated. A high-sensitivity/specificity, at-home test could improve colon cancer screening.

Colonoscopy/endoscopy supply sales representative

Colonoscopy is the bread-and-butter for gastroenterologists. It will be difficult to change their behavior. But if public demand is sufficient, and the Cologuard test gets people who would otherwise refuse the procedure to get screened, there may be a place for it in their practice.

Molecular diagnostics sales representative
Sciences, but if the test has poor sensitivity for precancerous polyps, it may not find support in the medical community for that indication.”

**Molecular Diagnostics Market’s Competitive Landscape**

- “Leaders in molecular diagnostics include Cepheid, Roche, and Becton Dickinson.”
- “Academic institutions are very supportive of molecular testing for oncology. Consumer demand is also a driver. But these tests have historically ramped up more slowly than the infectious disease assays.”

**Molecular Diagnostics Market’s Adoption and Growth**

- “Infectious diseases are the main growth opportunity for molecular testing. The need to identify antibiotic-resistant bacteria as quickly and reliably as possible is critical to the healthcare system. These bugs cost medical facilities a lot of money. Utilization and adoption are driven by the providers and infection control professionals.”
- “Gonorrhea is a superbug now. Resistance is a big driver for new molecular tests.”
- “Adoption of new molecular infectious disease tests can ramp pretty quickly if there is demand from the medical community, reimbursement exists, and the manufacturer and testing platform is trusted.”
- “Different assays ramp differently. Factors include demand, cost-benefit analysis, what problem the new test solves, and the time and ability to validate the new test.”

3) Molecular diagnostics sales trainer

Approximately one-quarter of the 50-and-older population likely would choose Cologuard over traditional colonoscopy. DTC advertising will educate the public and general practitioners alike and will drive demand. As long as reimbursement is adequate, the test’s cost should not be a significant factor. An indication for the 40- to 49-year-old population is a great idea. This group likely is anxious about the recommendation to screen at 50 and is comfortable with the reliability of molecular tests. The future of molecular testing lies in personalized medicine: identifying gene mutations to guide targeted therapy in oncology. Wide adoption of a new test takes a concerted effort to prove efficacy, convince discriminating physicians, and find inclusion in industry-respected guidelines.

**Adoption of Exact Sciences’ Cologuard**

- “I am not familiar with this test specifically or any lab currently performing the Cologuard analysis. That said, any lab performing molecular tests should be readily equipped to add the test.”
- “There are different types of patients. One group will always want to follow the guidelines and be screened with the traditionally accepted gold standard. These folks (and their physicians) will need to be completely convinced of the science. Other folks avoid preventative medicine altogether, whether from fear, inconvenience or apathy. These people wait until they have symptoms. Having a simple noninvasive screening method may sway them to get screened. In my opinion, probably 20% to 25% of the 50-plus population would opt for the Cologuard test if they were aware of it.”
- “Direct-to-consumer advertising can be very effective. It helps to educate both consumers as well as physicians because patients begin to demand specific brands, and even doctors who refuse to see sales representatives are forced to familiarize themselves with new methods.”
- “As long as a new test like Cologuard is reimbursed, cost is not an issue. It really does not play into the decision.”
- “An expanded indication to the 40- to 49-year-old population is a great idea. These people are probably already experiencing some level of anxiety because they know colonoscopy is recommended at 50. This group is also more likely to be aware of molecular testing and feel comfortable with its reliability. Cologuard could provide peace of mind earlier.”

**Molecular Diagnostics Market’s Competitive Landscape**

- “Companies like Caris Life Sciences and Foundation Medicine use a variety of molecular technologies to drive personalized approaches to the best cancer treatment options.”
- “Companies including Guardant Health and Biocept that offer molecular blood tests that function like biopsies are at the cutting edge.”

**Molecular Diagnostics Market’s Adoption and Growth**
“It may seem counterintuitive, but community physicians are often the first to adopt new test methods. They do not have access to the academic institution support and generally do not need the abundant clinical evidence to try a promising new technology. In some cases, lack of reimbursement may not be a barrier to use. Wide adoption requires a great deal of education, reimbursement and the blessing of the National Comprehensive Cancer Network.”

“The whole future of medicine lies in molecular testing. Much of the growth is in prognosis and targeted therapy based on gene mutations. Oncology is the most compelling field; it is what everyone fears. For example, in the case of colon cancer, a colorectal cancer mutation panel is used to predict response to EGFR-targeted immunotherapy in patients with metastatic colorectal cancer.”

Miscellaneous

“I spoke with an oncologist today who mentioned that he read about Cologuard and asked his local hospital if they could order it for a patient who refused a colonoscopy. The hospital wasn’t familiar with it and didn’t know how to order it. As a side note, he thinks the best utility for it is to use Cologuard in combination with an imaging test to replace colonoscopies. That way, you can still detect precancerous polyps.”

4) Sales representatives at two different locations of a large endoscopy company

Cologuard and other noninvasive stool tests will never replace the visualization and biopsy ability of colonoscopies. Also, Cologuard currently is not widely discussed among gastroenterology clinics. If the test is prescribed for those who refuse a colonoscopy, those patients will need to be educated on what the noninvasive test can and cannot detect. Even if Cologuard is given an indication for a younger population, high-risk patients still should have a colonoscopy. Reimbursements are a roadblock to new medical tests. DNA testing will need at least five years before it becomes commonplace.

Adoption of Exact Sciences’ Cologuard

“I have been working in this field for several years, and I talk with the GE folks all the time. I have never heard anyone mention Cologuard. Not once.”

“No one in my territory has brought it up. I’m not exactly sure what it does.”

“I can’t imagine that it could replace the colonoscopy. That is the gold standard for diagnosing colon cancer. The doctor has to get in there and actually see what is going on, take a biopsy. You cannot do that with a stool sample. It is important to see what is going on.”

“I can’t imagine a gastroenterologist prescribing either the Cologuard or FIT test. A colonoscopy will give all the information needed.”

“No one wants to have a colonoscopy. ... The prep is the worst part. So if you have patients who simply refuse a colonoscopy, then I imagine they would do the stool test [required by Cologuard]. I guess it is better than nothing, right? Maybe that is what they are thinking. However, they will need to do a lot of patient education, so the patient knows exactly what they are getting and what they aren’t getting.”

“Doctors will need to educate the patients on the risks of not getting a colonoscopy and exactly what the other tests do and don’t do.”

“For the average-risk person, the current guideline is a colonoscopy starting at age 50. I’m not sure why they would want to reduce that age limit, unless you are high-risk. And if you are high-risk, you need to have a colonoscopy.”

“It sounds like the test is reimbursed by insurance companies. That is a big roadblock for most new tests right there. I don’t know if reimbursement has been an issue for people. It would be interesting to find out.”

Molecular Diagnostics Market’s Competitive Landscape

“I imagine all the companies want to get in on this. Couldn’t name names.”

Molecular Diagnostics Market’s Adoption and Growth

“Cancer is certainly the big area for diagnostics. You want to get in there and find out what is going on as soon as you can. Then the survival rates are higher.”
“DNA testing will continue to grow, but it will take a number of years—at least five, maybe more. Insurance companies need to reimburse for the tests, and they need to check and ensure that the tests are accurate. Those trials take time.”

“I believe Europe is ahead of us on this one. Europe is a leader on a number of medical tests and pharmaceuticals.”

Miscellaneous
“‘It is the rub of sales to get a new technology adopted. You can have something very cutting-edge, such as a new endoscope, but then you meet resistance.”

5) President and director of sales for a small endoscopy and medical supply company

Cologuard may be beneficial if a patient refuses a colonoscopy, but long-term studies are needed to prove the test’s effectiveness. Receiving approval for a younger age group is contradictory; most likely younger people requiring colonoscopies are at high-risk and would require a full colonoscopy. This source talks with gastroenterologists throughout the United States and has never once heard Cologuard mentioned. Genetic tests are becoming more common and will be used more frequently in 10 years.

Adoption of Exact Sciences’ Cologuard
“I have not heard of Cologuard. We deal with gastroenterologists all over the country, all day long, and not one doctor or clinic has mentioned the test.”

“A colonoscopy is the most accurate for diagnosis of colon cancer. Some people do a sigmoidoscopy, but it is not as accurate. You have to see the whole inside of the colon to diagnose cancer. I don’t think you can just rely on a stool test. How would you know where the cancer was?”

“Under-screening for colon cancer is a problem. Most people do not want to do a colonoscopy. So maybe this test is better than nothing. But they should have long-term studies to back up their claims, and it should only be used as a last resort—when someone refuses a colonoscopy.”

“Colonoscopies are recommended for age 50 and above, earlier if you are high-risk. If a colonoscopy is done on a younger patient, that means they are at risk and have a family history. They need to have a colonoscopy. Why would [Exact Sciences] need to get approval for a younger age group? Sounds like they just want to sell more tests.”

“I would think that insurance reimbursement may be a roadblock.”

Molecular Diagnostics Market’s Competitive Landscape
“I don’t know the companies involved in this field.”

Molecular Diagnostics Market’s Adoption and Growth
“Genetic risk assessment is becoming more popular, so I can see this field growing by leaps and bounds in a few years. By 10 years we will all be doing gene tests.”

Miscellaneous
“This company better be very careful, or they could find themselves in a heap of problems.”

3) Third-Party Payers/Insurance

Two sources from the CMS and two sources representing the health insurance industry said their organizations reimburse for the Cologuard test. They did not discuss the extent of Cologuard use, but acknowledged the test’s clinical value. CMS sees high value in the home test for elderly rural patients; the organization’s goal is to reduce the reimbursement rate of colonoscopies and some endoscopy procedures by 19% in 2016, and expects Cologuard to assist in that goal. Insurer sources said Cologuard increases screening compliance and is less costly than a colonoscopy. One insurer added that it usually take two to three years post–FDA approval for an new molecular test to gain clinical traction. Two sources praised Exact Sciences for its partnerships with the Mayo Clinic and the MD Anderson Cancer Center. One source expect the company to be profitable in four to five years. Molecular diagnostics is gaining acceptance, and new tests are expected to emerge

Under-screening for colon cancer is a problem. Most people do not want to do a colonoscopy. So maybe this test is better than nothing. But they should have long-term studies to back up their claims, and it should only be used as a last resort—when someone refuses a colonoscopy.

President and director of sales for a small endoscopy and medical supply company

301 Battery Street, 2nd Floor, San Francisco, CA 94111 | www.blueshiftideas.com
Exact Sciences Corp.’s Cologuard
during the next five to 10 years. GlaxoSmithKline is viewed as a leader.

Key Silo Findings
Adoption of Exact Sciences’ Cologuard
- The 2 CMS sources said they reimburse for Cologuard tests.
- The 2 insurers also reimburse for Cologuard tests.
- Adoption levels were not discussed, but sources acknowledged the test’s clinical value.

Molecular Diagnostics Market’s Competitive Landscape
- GlaxoSmithKline was discussed as a molecular diagnostics leader.

Molecular Diagnostics Market’s Adoption and Growth
- Molecular diagnostics will gain acceptance over the next 5 to 10 years.

Miscellaneous
- 1 praised Exact Sciences for partnering with MD Anderson and the Mayo Clinic.
- The CMS has a goal to reduce colonoscopy procedures by 19% in 2016; this could help Cologuard adoption.

1) Billings and claims advisor at the CMS and a technical advisor at a CMS support branch
For patients who have Part B coverage, CMS reimburses for the Cologuard test every three years. Depending on each case, CMS may or may not reimburse for a colonoscopy following a positive Cologuard test. Lowering the age for the Cologuard test will not affect people on Medicare, who must be 65 years or older; however, it may affect some people on Medicaid. The CMS does not necessarily reimburse every test or exam that is approved by the FDA. The organization is proposing to cut colonoscopy rates by up to 19% starting in January 2016, which may affect reimbursements for Cologuard. Three gastroenterology societies are fighting these proposed cuts.

Adoption of Exact Sciences’ Cologuard
- “Given that insurances are covering this test, doctors are probably using it, but I couldn’t say how often it is being used.”
- “Medicare reimburses for the Cologuard test every three years, given certain specifications. It is covered under Part B, so you must have Part B coverage.”
- “The patient must meet certain specifications. As long as the patient is qualified for the test, Medicare covers it. There should not be a problem.”
- “Right now, unless a patient is at high-risk, they would not need a colonoscopy before age 50, so I’m not sure why they want to approve the test for an earlier age group. I’m not sure what this means. But the Medicare patients are all 65 years or older. That wouldn’t affect them. Not sure how it would affect Medicaid patients, who are younger.”
- “It would seem that Medicare would cover what the FDA approves, but that is not always the case. FDA approval is the start to getting Medicare approval. It is the first of a long line of steps. But there are probably medical tests, exams that have been approved by the FDA, but are not covered by CMS.”
- “I can’t say if Medicare would cover a colonoscopy if a patient has tested positive for the Cologuard test. That would be hard to say. It would depend on the circumstances, the patient, what the doctor says. The doctor would have to let us know why. Yes, it makes sense that someone may need a colonoscopy after a positive test, but I can’t say for certain if the colonoscopy would be covered by Medicare. Maybe it would be covered or not covered in some cases. I can’t answer nitty-gritty coverage questions because one situation is different from another.”
- “Reimbursement is always a big roadblock for any new test, but this one is already cleared for reimbursement.”
- “CMS reimbursement rates vary by location around the country. CMS will be cutting endoscopy rates starting in January 2016. This may affect Cologuard reimbursement, but the codes do not list brand names of tests so I couldn’t say for sure.”

Billings and claims advisor at the CMS and a technical advisor at a CMS support branch
**Exact Sciences Corp.’s Cologuard**

**Molecular Diagnostics Market’s Competitive Landscape**
- “I really couldn’t answer questions about new devices or their companies. I don’t know anything about that.”

**Molecular Diagnostics Market’s Adoption and Growth**
- “Any new test that has the potential to be effective and save money is generally considered a good thing. We are all about keeping people healthy and trying to save money.”

2) **Project manager of Medicare cases for an insurer in the Northeast**

Insurers cover diagnostics tests, such as Cologuard, because they meet evidence-based practice guidelines and Medicare approval. Third-party payers welcome convenient at-home tests that do not require special handling to meet the needs of elderly people living in rural areas. Diagnostics blood tests would be very convenient.

**Adoption of Exact Sciences’ Cologuard**
- “Cologuard was approved by someone in Medicare, so then we picked it up. One of CMS’ requirements is regular colonoscopy testing, and a test like Cologuard helps ensure that more members are tested.”
- “This is relatively new, and I’m not sure of the numbers yet—how many people have used the test and why.”
- “I’m not sure if Cologuard will become the primary noninvasive test. It’s still new.”
- “Because we work with clients 65 years and above, we wouldn’t be involved with covering people of younger ages. I’m not sure what advantage a younger age would offer given that it is outside of the standard guidelines of 50 years.”
- “Insurers pay on evidence-based practice; they look at specific guidelines, the consequences and best evidence. Most insurers look at the U.S. Preventive Services Task Force and CDC websites to determine what is experimental and what isn’t. We look at what the science says and what parameters are given to determine what we should cover. This goes back into the same issue with mammograms a few years back.”
- “For the general public, the FIT test is not an expensive proposition. But if you target a specific profile, then the Cologuard test seems more appropriate.”
- “The cost of everything is the big roadblock.”

**Molecular Diagnostics Market’s Competitive Landscape**
- N/A

**Molecular Diagnostics Market’s Adoption and Growth**
- “Blood tests for cancer are fabulous. I hear that MD Anderson is working on a lung cancer diagnostic using a blood test.”
- “We are looking for a test in the home that doesn’t need to be chilled or rushed to the lab. Something that can be done off-site and require little special handling. We heard of one for kidney function, but it didn’t work because it required [special handling]. We are still waiting for another kidney test to come out.”

**Miscellaneous**
- “We are looking for quality at-home testing for Medicare Advantage members. We are trying to cover as many screening tests as possible in the home. Not all of our members want to go to a doctor or have access to a doctor, especially in the rural areas. Some of them don’t drive anymore, and the doctor is more than a 10- to 20-minute drive away. So I’m always looking for what I can offer members in the home. We don’t offer home tests to everyone but to specific individuals.”
- “We are trying to address to our clients about why we have screening, why it is important. We encourage our clients by a verbal reach out or phone call; we send a publication reminder that it is a free screening. We reach out in various ways. Often we don’t talk enough to the public about the rationale for a test.”
- “We are trying to get to know each individual member, to find out what it is they are afraid of. We want our clients to have ease and comfort. The more knowledge they have, the less frightened they will be.”
- “Insurance needs to be integrated. Then it is easier to work with hospitals, specialists.”

3) **Former executive for an insurance company in the Midwest**

One of CMS’ requirements is regular colonoscopy testing, and a test like Cologuard helps ensure that more members are tested.

*Project manager of Medicare cases for an Insurer Northeast, USA*
ColoGuard’s roadblock of calendar-based evidence will be cleared in four to five years, possibly less; then Exact Sciences will start making money. Time is the company’s largest liability. ColoGuard is easier for patients, increases compliance, and comes with lower price point. The gastroenterology (GE) community is traditional and accepts change slowly, but Exact Sciences understands this and is gradually working at educating clinicians and patients. Some GE doctors are pushing for testing in younger patients because the current 50-year-old standard is arbitrary. Lung and pancreatic cancers are the next breakthrough areas. Molecular diagnostics will need four to five years to take off.

**Adoption of Exact Sciences’ ColoGuard**

- “We were one of the first health plans to adopt ColoGuard. We looked at our clients and ColoGuard from a consumer’s standpoint and a business or price standpoint, and what wasn’t to like? Not only was it easier to do than a colonoscopy, it was cheaper, and patients were more likely to do the test. And it is equivalent or superior to a colonoscopy. ColoGuard is great for patients, and it increases compliance.”
- “The average fee for a colonoscopy is anywhere from $4,000 to $7,000, depending on where you live. What is not to like about the $600 ColoGuard test?”
- “But the GE docs are slow to change, and they don’t want to lose money. There is a resistance to ColoGuard embedded in the GE community. They squawk about it. But Exact Sciences has got it. They are the real deal, and they understand the old doctors’ club.”
- “In the GE doc circles, there is a sense that earlier may be better across the board. Having a first colonoscopy at 50—that was an arbitrary number determined a while ago. The fact the Exact Sciences is questioning this number [and looking at 40 years instead] is evidence of how quickly the company is willing to challenge the old thinking.”
- “Exact Sciences didn’t have a simultaneous rollout campaign when they received FDA approval. They had to build up. And they need to get in with key payers. Again, this is calendar-based, but they need to slow superior outcomes compared to the FIT.”

**Molecular Diagnostics Market’s Competitive Landscape**

- “Look at GlaxoSmithKline and the other pharma companies.”
- “There are lots of companies out there; all you have to do is Google them.”

**Molecular Diagnostics Market’s Adoption and Growth**

- “Lung cancer is next, and pancreatic cancer in 10 years. It will take four to five years for molecular diagnostics to take off. Physicians have a duty to look at evidence-based results.”
- “Exact Sciences is on the calendar now. It will take time to show the results. Within four to five years—after this next clinical trial—maybe even two to three years, they will show improved rates and alignment with other clinical tests, and they will start making money. Time is the largest liability they face right now.”
- “Exact Sciences is in the early stages of additional screening for early lung cancer. They are looking at noninvasive ways to achieve patient compliance. The macroeconomics is staggering when you think about it.”

**Miscellaneous**

- “I worry that they are getting too big, too quick. They have a strong presence in Europe, which has a different regulatory environment.”
- “Exact Sciences is hitting it out of the park. Ethically, they feel good. They are not some fly-by-night-and-flip-in-two-years company. They have discipline and cadence; they are not going after the fast buck.”
- “They don’t pick lightweight partners. They have aligned with true, platinum-level business partners, Mayo and MD Anderson. Their first big hurdle was getting FDA approval, and Mayo helped them nail that one. They also have huge cash coming. The analysts are seeing the light, and this changes the paradigm of cancer screening.”
- “They have a huge marketing staff to work with the all GEs and primary care staff. They are pushing ColoGuard with an awareness campaign. They know the docs won’t change quickly, and they are going to health plans and working on the clinical uptake rate by reaching out to physicians and patients. The docs need to take time to study the test. Exact Sciences isn’t going to do this like the pharmaceutical sales reps did. Their competition is still traditional delivery.”

---

*We were one of the first health plans to adopt ColoGuard. We looked at our clients and ColoGuard from a consumer’s standpoint and a business or price standpoint, and what wasn’t to like? Not only was it easier to do than a colonoscopy, it was cheaper, and patients were more likely to do the test. And it is equivalent or superior to a colonoscopy. ColoGuard is great for patients, and it increases compliance.*

*Former executive for an insurance company*

*Midwest, USA*
“Exact Sciences relocated to Madison, near the university and all the scientists. Now the city is helping them with new downtown headquarters.”

4) Medical director at a Midwest health plan

Colonoscopy remains the ideal test for screening and the only effective prevention; however, Cologuard gives providers another option at this integrated health plan. While more expensive, Cologuard carries advantages over FIT, and this plan’s guidelines for its use reflect Medicare’s and the FDA approval.

Adoption of Exact Sciences’ Cologuard

- “We work closely with our clinical partners to determine the best course of action to determine colon cancer. Sometimes that is using the new test, Cologuard, which we do cover.”
- “FIT or FOBT remain appropriate and are more cost-effective for screening a population, but are ineffective in prevention. Cologuard is a reasonable alternative for screening, but is also not prevention. Cologuard has advantages over FIT as demonstrated in the NEJM articles and FDA submissions. The cost for Cologuard is materially higher than FIT/FOBT but less than colonoscopy.”
- “[As for how each test is used] the issue is complex and nuanced by factors of clinical effectiveness, cost-effectiveness, availability/access, patient acceptability, false positive and/or false negative consequences. We have chosen not to impose a one-size-fits-all approach. The patient and provider are in the best position to engage in meaningful and personalized shared decision making to arrive at a conclusion and act for cancer risk mitigation.”
- “Guidelines [at our health plan] for Cologuard do exist and mirror Medicare guidelines and FDA approval labeling in most respects.”
- “[We have] elected not to mandate FIT/FOBT testing as the required primary method of colorectal cancer screening. Clinically, I would prefer that all appropriate patients undergo colonoscopy despite the higher price.”
- “Colonoscopy is the only screening approach that also has been proven to preventing colon cancer, through premalignant polyp removal/destruction. Colonoscopy is, therefore, preferred for screening in appropriate patients despite its substantial cost and patient demands. Some patients decline to undergo screening colonoscopy.”

Molecular Diagnostics Market’s Competitive Landscape

- N/A

Molecular Diagnostics Market’s Adoption and Growth

- N/A

Miscellaneous

- “The most important goal is to see that screening is done. Any of the evidence-based screening procedures and regimens are superior to no screening. Many patients never get screening of any type completed and subsequently present with advanced cancer.”

4) Industry Specialists

These six sources had a wide range of reactions to Cologuard’s adoption and offered the following beliefs: Within two to three years consumer demand will drive the test’s adoption; Cologuard will be the method of choice for patients who refuse a colonoscopy; 10% of the one-third of patients who refuse a colonoscopy (2 million tests) might be its market; the less than desirable collection process will limit adoption; and the test is filling a diagnostics need. A blood test is considered the most desirable cancer screen but is not yet available. Sources cited value in using Cologuard in younger patients given this age group’s growing rate of colon cancer. Two sources also said the test could be of interest to men of certain ethnic groups often opposed to colonoscopies. The lack of awareness of Cologuard and the gastroenterology community’s resistance will challenge its use and adoption. Molecular diagnostics is expected to gain traction over the next five years. One source said Roche has been active in this market.
Exact Sciences Corp.’s Cologuard

Key Silo Findings

Adoption of Exact Sciences’ Cologuard

- I expect widespread adoption.
- I expect Cologuard to be test of choice for patients who refuse a colonoscopy.
- I expect 10% of the one-third of patients who refuse a colonoscopy (2 million) to use Cologuard.
- I expect limited adoption because of the undesirable stool collection process.
- I said Cologuard fills a diagnostics need.

Molecular Diagnostics Market’s Competitive Landscape

- I discussed Roche’s efforts in this market.

Molecular Diagnostics Market’s Adoption and Growth

- 5 to 10 years will pass before use of molecular diagnostics is widespread.

1) GI medical device executive

Cologuard will be adopted. Educational efforts should be focused on the public and general practitioners. Gastroenterologists are slow to change and will resist the loss of procedural revenue. As long as Cologuard has reimbursement, it is likely to replace FIT testing. Oncology is a good fit for molecular testing. Two to three years generally go by before a new test is widely adopted.

Adoption of Exact Sciences’ Cologuard

- “Based on my conversations with physicians, the short answer is yes, Cologuard will be adopted.”
- “With regard to traditional colonoscopy for low-risk screening, Cologuard adoption will be driven more by psychological preference than science. Colonoscopy has a nasty reputation, and although it is largely outdated because preparation is much less onerous than it once was, people dread the process. For a lot of people, Cologuard could obviate the need for the procedure.”
- “It will take an extensive consumer education effort on the part of Exact Sciences, because the rate of adoption will largely be a function of consumer demand.”
- “GI physicians are less likely to embrace the switch from traditional colonoscopy. A molecular test that can be accomplished at home negatively impacts procedure revenue. And if the decreased sensitivity for precancerous polyps proves problematic, the gastroenterologists with have more reason to resist adoption.”
- “Exact Sciences should focus their professional marketing efforts on the general practitioner and concierge physicians. These providers have nothing to lose and everything to gain by recommending the Cologuard test. Their patients will be happier with the less invasive screening, and the physician keeps the patient directly under their care longer, potentially eliminating the need for a specialist altogether.”
- “As long as reimbursement is adequate, Cologuard is well positioned to replace FIT. Fecal occult blood testing is a 40-year-old technology. The additional sensitivity and specificity of the molecular test makes it a sensible transition for those who will not/cannot undergo traditional colonoscopy.”

Molecular Diagnostics Market’s Competitive Landscape

- N/A

Molecular Diagnostics Market’s Adoption and Growth

- “There is positively a shift toward the higher sensitivity and specificity provided by molecular methods. Oncology is a sensible area to incorporate these noninvasive screening assays. Generally speaking, it will take two to three years post-approval for a new molecular test to gain significant traction into traditional workflows.”
- “Gastroenterologists are slow to change—definitely not early adopters.”
Exact Sciences Corp.’s Cologuard

2) Executive for a colon cancer screening advocacy organization

Cologuard will become the method of choice “for those unable or unwilling to undergo traditional colonoscopy.” Colonoscopy holds a particular stigma in the African-American male population. An indication for the 40-to-49 age group makes sense as the fastest increase in colon cancer diagnosis is in the younger population. Most third-party payers will follow suit with the CMS reimbursement.

Adoption of Exact Sciences’ Cologuard

- “Although I am not in the position to predict adoption, Cologuard has the advantages of high sensitivity and specificity. I think it will become a preferred option for those unable or unwilling to undergo traditional colonoscopy.”
- “The percentage of patients of people physically unable to undergo colonoscopy is small. Cologuard provides an option for those who refuse the procedure. The stigma of colonoscopy is particularly acute among African-American males.”
- “Although I was unaware of expanded indication effort, the fastest increase in colon cancer diagnoses is in younger patients. Our organization recommends screening at 45 years for the African-American population.”
- “I expect Cologuard will be reimbursed by most providers as they tend to follow CMS approval for Medicare. Moreover, under the Affordable Care Act, colonoscopy screening must be covered without copay. Cologuard is significantly more cost-effective.”

Molecular Diagnostics Market’s Competitive Landscape

- N/A

Molecular Diagnostics Market’s Adoption and Growth

- “Molecular diagnostics utilization is sure to expand. I know there is a DNA-based blood test under development. But we believe more simple, at-home tests are needed to maximize the percentage of the population that are screened early.”
- “We would like to get to the point that screening for colon cancer is as routine as other health screening in general practice.”

Miscellaneous

- “One-hundred people die of colon cancer every day in the United States, but 90% to 95% of these deaths would have been prevented if caught early. Although there is no awareness problem, more than one-third of high-risk patients never get screened. They perceive colonoscopy as the only option, but attitudes about the invasive procedure keep them from getting screened.”

3) President of a medical consulting company

Cologuard is filling a colon cancer diagnostics need. Medical diagnostics must be improved, and specific treatments should be identified and available for each patient. Currently, diagnosis often comes too late, and existing treatments are habitually ineffective for a large part of the population. Molecular diagnostics should be well on its way in five years, and quantum leaps will be made in research in the next five to 10 years. The target should be pancreatic and ovarian cancers, which often are not diagnosed until it is too late.

Adoption of Exact Sciences’ Cologuard

- “Cologuard was adopted by an insurance company I worked with. This was an area that needed and still needs improved diagnostics.”

Molecular Diagnostics Market’s Competitive Landscape

- “Everyone wants to work in this field right now because there is so much going on. It is easy to identify these candidates by looking on the Internet. I don’t have those names in front of me.”

Molecular Diagnostics Market’s Adoption and Growth

- “What is missing is early diagnosis and to have a specific treatment identified for a patient. The diagnostics piece needs to be improved. Eventually they will end up with most of the markers for cancer. Emphasis should be placed on pancreatic and ovarian cancers because people don’t know they have these cancers until it is too late.”
Exact Sciences Corp.’s Cologuard

- “The way things are moving, molecular diagnostics should be well on its way in five years. All is moving that way, the treatment patterns, genome and DNA identifications.”
- “Ten years ago they used to come out with a new drug after significant Phase I research; the program took six, seven, eight years. They would test the toxicity of the drug. But once the drug was approved, only 12% to 15% of the patients responded well to the drug. But dramatically over the last five years, we have the ability to use tissue samples to identify who will respond to a drug. We have weaned patients who don’t respond to a treatment from 500 to 15. Before we’d use a regimen on someone, and it would weaken them. Now we have more personalized oncology.”
- “Tissue and blood samples are now banked to use later. We will make quantum leaps in research in the next five to 10 years as we start putting together the whole molecular piece.”

4) Isolated statements made from six individuals in the field

Cologuard is the top noninvasive colon cancer test; the hope is that eventually it will be replaced by a very accurate blood test. Cologuard may be a good test to use between colonoscopies, especially for someone at-risk. A lower screening age also may be a good idea, especially for patients with a family history of colon cancer. Third-party payers usually cover CDC recommendations, and a test or procedure is no longer investigational when it receives FDA approval. Noninvasive diagnostics tools are needed.

Adoption of Exact Sciences’ Cologuard
- “I doubt if Cologuard will ever replace the colonoscopy. Will it become the primary noninvasive test? Maybe right now or in a few years, once it has proven itself. But we are hoping it will be replaced eventually by a blood test, a very accurate one.”
- “We usually cover what the CDC recommends. They will cover annual FOBT tests for some patients. If something is FDA-approved, it is usually not considered investigational.”
- “You could use the Cologuard on off years. Say you had a colonoscopy every 10 years but had polyps: Maybe the Cologuard test every three to five years would be a nice preventative.”
- “The colonoscopy is not 100% accurate. I’m sure there is a percentage that is missed. And then you have the risk of perforation. Cologuard’s 92% accuracy looks pretty good.”
- “Even if Cologuard is only 85% effective, that is better than no testing at all. At least the patients are being screened.”
- “Colonoscopies used to be done every five years, but that recommendation was upped to every 10 years. It really depends on the patient’s history and family history.”
- “If there is no reason to think you have a problem, the Cologuard could be very useful.”
- “Even 20-year-olds can be high-risk and have symptoms. I know someone who had colon cancer at 29 years. Maybe starting younger would be good.”
- “We don’t usually do a colonoscopy on anyone over 75 years unless they are at-risk.”
- “I think earlier is always a good idea, definitely if you have a family history.”
- Five physician and medical centers: “I’ve never heard of Cologuard.”
- Three physician and medical centers: “We learned about it from a patient.”
- “For all of these tests, reimbursement depends on if the patient meets certain criteria. The patient needs to check with their payer.”

Molecular Diagnostics Market’s Competitive Landscape
- “I have heard some interesting things about Roche.”

Molecular Diagnostics Market’s Adoption and Growth
- “If you have a patient that refuses a colonoscopy, and that is the same with mammograms, then there is the need for noninvasive alternatives.”
- “Exact Sciences is working on test for other cancers such as pancreas, stomach and esophagus. They are also trying to get approval for Cologuard or a variation for ulcerative colitis and Crohn’s disease.”

Miscellaneous
- “If you have a patient that refuses a colonoscopy, and that is the same with mammograms, then there is the need for noninvasive alternatives.”
“We have daily requests for a virtual colonoscopy, called a colonography. We do 40 to 50 procedures a month. Many people have this procedure covered in their company health plan as a benefit.”

“You have to do the same prep for a colonography as you do for a colonoscopy. The next day you come in and have a computerized tomography scan. It just takes 20 to 30 minutes, and you are not sedated so you don’t miss another day of work. Some people cannot handle the sedation. Others cannot do a colonoscopy for different reasons.”

“The CT scan is usually used on patients with symptoms.”

“The colonography is just as effective as the colonoscopy. You can see where the polyps are, but if you have a polyp 4 mm or bigger, then you have to have a colonoscopy to have it removed and biopsied.”

“The [Given Imaging Ltd./GIVN] PillCam is popular in Europe, but not so much here in the United States. It is used mostly on a patient whose colonoscopy was unsuccessful or had to be stopped and not completed. Of course, if these was a major problem, they might want to do a colonography instead.”

5) Executive of a patient advocacy association

Cologuard is not an optimal alternative to colonoscopy due to its low sensitivity for precancerous polyps and the unpleasant fecal collection process. Gastroenterologists will not support the test. Indication for the 40- to 49-year-old category could offer a cost-effective, reimbursable option for this group, which has experienced the fastest increase in colon cancer diagnoses. With proper marketing to generate demand, Exact Sciences could convert approximately 10% of the one-third of patients who refuse a colonoscopy. A better, noninvasive alternative will be developed within 10 years.

Adoption of Exact Sciences’ Cologuard

“Gastroenterologists will not recommend Cologuard. Colonoscopy is their cash cow. But colonoscopy also allows them to identify and remove precancerous polyps. Cologuard has poor sensitivity for precancer, and early detection is really the purpose of a screening test. They will never be convinced of a better alternative.”

“Marketing directly to general practitioners and patients is probably the best strategy, but the collection is a problem. When I watch their collection video, I ask myself whether the average person would be willing to do this. I suspect they will continue to avoid screening altogether. I do not think it will become a primary alternative.”

“Cologuard fecal collection is unpleasant. The Quest [Diagnostics Inc./DGX] ColoVantage offers a simple and desirable blood test alternative, but the sensitivity is not very high [70%]. The virtual colonoscopy has not been widely adopted, nor is reimbursement available. An optimal alternative simply has not been developed as yet, but one will come. I tell people to get their last colonoscopy, because in 10 years I believe there will be a good alternative.”

“People looking for an alternative to colonoscopy will likely go for the FIT test or ColoVantage. These are the easiest and most convenient. These are the people who are not intimately concerned about sensitivity levels or formal medical guidelines. No way will most people opt to collect and handle feces if there is another option.”

“Colonoscopy is still the gold standard and will be the patient test of choice for those who are interested in following formal guidelines.”

“Getting the indication for 40- to 49-year-old screening is a good idea. This group has seen the greatest increase in colon cancer diagnoses, but colonoscopy is not covered by insurance since the screening guidelines begin at 50. Intestinal problems under 50 are generally attributed to IBS, diet, allergies, stress and the like. Cologuard would provide for a more comprehensive workup in the absence of a much more expensive colonoscopy.”
“It is pretty remarkable that Cologuard got CMS reimbursement coverage so quickly. But I have never understood why so much money has been invested in Exact Sciences. All the enthusiasm seems based on a single clinical trial.”

“There is still not a lot of awareness about Cologuard in the medical community.”

“Impressively, Cologuard was recommended by the U.S. Preventive Services Task Force before it was approved by FDA. The Task Force recommendations are very influential on organizations like the American Cancer Society and third-party insurers.”

“Cologuard does eliminate a lot of the traditional barriers to undergoing colonoscopy. So, if demand is generated within the one-third who refuse colonoscopy, perhaps Exact Sciences could capture 10%, or 2 million tests. That alone is significant. But they will need to be clever to get beyond the distasteful collection.”

**Molecular Diagnostics Market’s Competitive Landscape**
- N/A

**Molecular Diagnostics Market’s Adoption and Growth**
- N/A

**Miscellaneous**
- “All of us involved in colon cancer prevention want to increase the screening rate. Currently the goal is to achieve 80% screened, but it is not going to happen until there are new, reliable, noninvasive alternatives. In the short term, one-third of people will continue to refuse due to psycho/social or physical reasons. This is particularly true in the African-American and Hispanic populations where there are strong social stigmas.”
- “A tremendous amount of money has been poured into Exact Sciences, but Cologuard is not a desirable alternative.”

Cologuard is only a marginally better test than FIT, and its collection process will be a turnoff for patients. What is wanted is a blood test, but the biology is not there. Exact Sciences has a good story, but Cologuard is not an optimal solution. Nonetheless, the company has garnered enthusiasm from the investment community.

**Adoption of Exact Sciences’ Cologuard**
- “What everyone wants is a blood test to screen for colon cancer, but the biology for it does not work.”
- “Cologuard is only marginally better than the FIT test, which itself is only marginally better than the fecal occult test.”
- “Not many people are going to want to deal with the collection. The kit requires collecting and handling about half a kilo of feces.”
- “Transport of samples in one trial resulted in approximately 60% lost in transit. That is likely to be very problematic.”
- “Exact Sciences is spending a lot on sales and marketing to try to drive demand, but ultimately I do not believe the test will capture a significant amount of market share.”

**Secondary Sources**
The following eight secondary sources discussed a Cologuard indication for 40- to 49-year-olds, physicians’ acceptance of Cologuard, and the test’s addressable market.
A study found an increasing occurrence of colorectal cancer in patients under the age of 50. A lead physician in the study advocated for screening tests like FIT and Cologuard for younger people. Another study supported testing in the 40- to 50-year-old bracket since 11% of those were found to have colonic adenomas—not much less than the 16.4% of the 50- to 59-year-old bracket.

April 10 The Asco Post article
A study found colorectal cancer was increasing in patients under the age of 50. Physician-related delays have been estimated to occur in 15% to 50% of young-onset colon cancer cases. A lead physician in the study supported noninvasive screening tests like FIT and Cologuard for the younger population.

- “While colorectal cancer predominantly occurs in people over 50 years old, rates are increasing among younger patients. It is important for physicians not to ignore symptoms in patients who are young, ‘simply because they are young,’ Jason A. Zell, DO, MPH, told The ASCO Post. Dr. Zell is the corresponding author of a recent study finding that colorectal cancer is significantly increasing among younger adults.”
- “Individuals under 50 who have symptoms that may be consistent with colon cancer need to seek medical attention so the appropriate testing can be done and deserve a prompt and thorough examination,’ according to the Never Too Young Coalition. ‘Physician-related delays (eg, missed symptoms, initial misdiagnosis) have been estimated to occur in 15% to 50% of young-onset colon cancer cases,’ a coalition fact sheet noted.
- “The Never Too Young Coalition’s aim is to educate the public about colon cancer among people younger than 50 and reduce the number of late-stage cases diagnosed among younger adults. The study coauthored by Dr. Zell found that colorectal cancer in young adults ‘was more likely to be diagnosed at an advanced stage and therefore less likely to be cured.’”
- “Because it is already a test that we don’t optimally deliver for screening,’ Dr. Zell noted, colonoscopy does not seem a workable approach to detect colorectal cancer earlier in younger patients. Colonoscopies ‘are very expensive, and 50% to 60% of eligible patients are not being screened, either because they don’t like the test or because there are not enough gastroenterologists to do all the procedures,’ Dr. Zell said.”
- “But we are currently able to benefit from advantages in screening with tests such as the fecal immunochemical test [FIT] and the multitarget stool DNA test,’ Dr. Zell said. The Cologuard test uses an immunochemical test similar to FIT as well as DNA biomarkers that have been found in colorectal cancer and precancerous advanced adenoma.”
- “These tests ‘have been shown in prior reports to have excellent results in determining who has colon cancer and who doesn’t when compared with colonoscopy,’ Dr. Zell stated. ‘We don’t have the outcomes data that will inform us if they predict death from colorectal cancer, which is the ultimate goal of any screening test. But we have two very good tests. They pick up colon cancer at a very high rate. They are also more cost-effective.’”
- “Having these two tests available to help detect colorectal cancer ‘does change the conversation a little bit,’ Dr. Zell said. ‘Adherence to these new tests is much better, because you don’t have to undergo the colonoscopy procedure, and that may be more suitable to a younger population.’”

August BioPortfolio article
11.2% of 40- to 49-year-olds and 16.4% of 50- to 59-year-olds have tested positive for adenomas in a colonoscopy study in which individuals lacked any lower gastrointestinal symptoms. The study determined that colorectal cancer screening could be recommended to some adults under 50 years old.

- “According to current guidelines, screening colonoscopy begins at 50 years for the average-risk population, although there are not enough data on the incidence of precancerous lesions of individuals in the preceding decades. To evaluate the prevalence of colorectal polyps including potentially premalignant lesions in asymptomatic, average-risk individuals aged 40-49 versus 50-59 years, we offered total colonoscopy screening to individuals without any lower gastrointestinal symptoms. The primary end point was the prevalence of colorectal adenoma in two age groups.”
- “Of a total of 737 studies, 333 participants were 40-49 years old and 407 participants were 50-59 years old. The overall prevalence of adenomas was 11.2 and 16.4% in the group of 40-49 and 50-59 year olds, respectively. Advanced adenoma was more common in 50-59 year olds (1.2 vs. 2.9%). Malignancy was not reported in these groups. Furthermore, 77.5 and 68.6% of adenomas were observed in the distal colon in the groups of 40-49 year olds and 50-59 year olds, whereas in the proximal colon, 22.2 and 57.1% of adenomas in the groups of 40-49 year olds and 50-59 year olds, respectively, were advanced adenomas. In our study, male sex showed an association with adenoma. However, importantly, there was no significant association between age and colorectal adenoma.”
“Although the prevalence of colorectal adenoma was similar in the two age groups investigated, the rate of advanced adenoma was higher in the group of individuals who were 50-59 years old, suggesting that colorectal cancer screening could be recommended at an age younger than 50 years.”

**Physicians’ Acceptance of Cologuard**

Exact Sciences believes Gastroenterologists who profit from colonoscopies still would not resist using Cologuard since they would realize its application in the large percentage of patients who refuse colorectal screening. Cologuard’s adoption rate might not accelerate quickly because of the growing amount of new medical information. A physician columnist explained his reasons for supporting colon cancer test kits like Cologuard.

March 6 *Forbes* article

Exact Sciences claimed many gastroenterologists would not resist Cologuard since a large percentage of the population refuses screening via colonoscopies. The company faced a bigger battle trying to convince insurance carriers to cover Cologuard. Its test needs to compete for awareness amid the stream of new medical information that often overwhlems physicians.

- “Last year the *New England Journal of Medicine* reported a study involving over 12,000 research subjects, nearly 10,000 of whom underwent both Cologuard testing and colonoscopy, at 90 institutions. In that study, which was sponsored by Exact Sciences, Cologuard predicted over 92 percent of colorectal cancers that were identified by colonoscopy. For pre-cancerous conditions, the sensitivity ranged from 42 to 69 percent (depending on the type of abnormality).”
- “The [NCI lists](https://www.cancer.gov/about-cancer/diagnosis-staging/screening/screening-fecal-occult-blood-testing) several methods for screening. I reviewed new reports on what most doctors considered the two standard” methods in 2012: colonoscopy and testing the stool for trace amounts of blood (fecal occult blood testing, FOBT). The latter includes guaiac tests and what some doctors call hemoccult.”
- “In 2015 many U.S. physicians, particularly internists and specialists in cities, favor colonoscopy. But that invasive procedure involves an unpleasant prep and does have some risks; it usually involves light anesthesia, and there is a very small chance of a perforation of tear. As I have said before, colonoscopy depends a lot on the skills of the doctor, usually a gastroenterologist, who does the procedure.”
- “I asked Maneesh K. Arora, Chief Operating Officer at Exact Sciences, about possible resistance to Cologuard testing among gastroenterologists—doctors who often derive income from colonoscopies. “It varies,” he responded. “The GI community understands that a big proportion of the population refuses to get screened.” Many recognize this can be helpful, he said in a phone interview.”
- “The biggest challenge today is lack of commercial coverage,’ Arora said. ‘Coverage can be limiting,’ he considered.”
- “Changing the practice of medicine, even with great technology, is very hard. Because there is so much new information going to primary care physicians, it can be hard to keep up,’ Arora considered. ‘But the key factor will be adoption by commercial payers,’ he emphasized. ‘We believe that (coverage) will be the key driver for physicians. That plus education and awareness that it’s available. Many physicians don’t know about it yet.’”
- “We’re seeing wide-scale appeal,’ Arora said. ‘Patients want it, physicians want it. But changing the practice of medicine is hard.’”
- “We won’t cure cancer by doing this, but we would significantly, significantly reduce the burden if an extra 25 or 30 percent of the population got screened,’ [Dr. Sasson, professor at University of Nebraska Medical Center] said.”
- “Screening, even by colonoscopy, isn’t perfect,’ he admitted. Occasionally gastroenterologists fail to detect polyps. But the ‘miss’ rate generally runs below 10 percent, he suggested. Some types of benign polyps, such as flat adenomas and those on the right side of the colon can be hard to visualize, Sasson said. ‘Detecting those is the new buzz for gastroenterologists.’”
- “It’s a way to capture patients who aren’t getting their colonoscopies,’ Sasson said. A positive result will push some who are disinclined toward screening. ‘And it’s so sensitive that if you’re truly negative on Cologuard, you might not need a colonoscopy,’ he added.”
- “What I’d hate to see is people forgoing colonoscopy because there is Cologuard,’ he added. ‘But there doesn’t have to be one answer. There are places where people don’t have access to great colonoscopy,’ he considered. ‘Having other options available is worthwhile.’”

May 14 *St. Louis Post-Dispatch* article

A physician columnist voiced support for home colon-cancer testing kits, and preferred Cologuard over FIT.
“Dear Dr. Roach: Do home colon-cancer testing kits really help in the diagnosis of colon cancer? Do you recommend them?—E.F.”

“Answer: I strongly recommend colon cancer screening for healthy people ages 50-70. Based on other risk factors, some people need testing at a younger age, and for some, it may be appropriate to continue testing beyond age 70. Home tests have the potential to screen people who might otherwise be unable or unwilling to get screened in a doctor’s office.”

“The home test that combines a screen for colon cancer DNA and blood (multitarget test) is better than the fecal immunochemical test (FIT), based on a 2014 study showing better sensitivity. The multitarget test identified 92 percent of the cancers found by colonoscopy. The home test isn’t perfect: Of all the positive test results, only about half had cancer or polyps, and the remainder had no abnormalities.”

“Colonoscopy remains the best test, because it can find cancers and polyps, and they can be biopsied or even removed at the same time, thus preventing some polyps from ever becoming cancer in the first place. However, there are many people who live in areas where routine screening colonoscopy isn’t available. There also are still some people who should, but don’t want to, get a colonoscopy. For these two groups, I recommend home testing, preferably with a multitarget test (such as Cologuard), as an alternative.”

**Cologuard’s Addressable Market**

Exact Sciences hopes to expand the standard indication of Cologuard to 40- to 50-year-old patients and to expand its business in Europe as well. Approximately 20 million people per year could seek some form of colorectal screening in the United States; 132,700 cases of colorectal cancer are reported each year, and an increasing number of physicians are ordering Cologuard. 15 million colonoscopies occur in the United States per year.

**Exact Sciences’ 2014 Annual Report**

GI related cancers accounted for 145,000, or 25%, of all U.S. cancer deaths. Exact Sciences hopes to expand Cologuard outside the standard indication and market to the 40- to 50-year-old bracket. The company also wants to expand in Europe, which had an addressable market of 136 million people aged 50 to 75.

• “We plan on continuing to collaborate with MAYO on future products related to early detection of gastrointestinal (GI) cancers specifically in the areas of esophageal and pancreatic cancers. GI cancers account for 145,000 or 25% of all U.S. cancer deaths annually and represent a significant market opportunity for future products.”

• “For colorectal cancer, we will focus on expanding the indications of Cologuard for screening outside of the standard indication for Cologuard. There may be a significant opportunity for Cologuard in patients between the ages of 40-50. In addition, there may be an opportunity for Cologuard to be used with high risk patients such as those with inflammatory bowel disease who may refuse colonoscopy. Additional research and development efforts will be necessary to evaluate and pursue these opportunities.”

• “Our initial efforts for international expansion are focusing on the European launch of Cologuard. There is a significant unmet need in the European market as it relates to colorectal cancer screening. There are 152,000 deaths annually in Europe and the screening rates for colorectal cancer are only ~20%. There are 136 million people aged 50-75 years old which we believe is a large, addressable market. We received a CE mark for Cologuard in December 2014, which is a mandatory conformity marking for certain products sold within the European Economic Area. Our initial launch into Europe in 2015 will be limited and focused.”

**Nov. 4, 2014, Seeking Alpha article**

More than 32% of the U.S. population is older than 50, making the addressable market for Cologuard a surplus of 100 million people. A closer analysis showed potentially 20 million people per year might screen for colorectal cancer.

• “The addressable market for Cologuard is tremendous. The target market is any individual over the age of 50 at average risk for colon cancer. According to Wikipedia, more than 32% of the U.S. population is over the age of 50. This amounts to nearly 100 million people in the U.S. alone that fall into Cologuard’s addressable market. With the aging baby boomer population, this number is expected to continue growing for the foreseeable future. The current guideline is to repeat screening every five years starting at the age of 50. According to an article published in the New York Times, compliance with the screening guidelines hovered around 60% utilizing previous methods. Exact Sciences hopes that Cologuard can bring that compliance closer to 100%.”
“Let’s dive further into the numbers and try to estimate future volumes. Following the guidelines, the total addressable market comes out to about 20 million individuals per year on average. As mentioned earlier, this number is anticipated to climb with the aging baby boomer demographic.”

“I realize these numbers will not be perfect, but I feel this is a good starting point. NIPT and Cologuard are facing the same obstacle in replacing the gold standard screening methodology. NIPT and Cologuard are lower-cost and less-invasive methodologies. When applying the NIPT percentages to the target population for Cologuard the volumes are astonishing.”

<table>
<thead>
<tr>
<th>Year</th>
<th>Percent Tested</th>
<th>Target Population</th>
<th>Estimated Sample Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>3.1%</td>
<td>20 mil</td>
<td>0.62 mil</td>
</tr>
<tr>
<td>Year 2</td>
<td>12.3%</td>
<td>20 mil</td>
<td>2.45 mil</td>
</tr>
<tr>
<td>Year 3</td>
<td>19.8%</td>
<td>20 mil</td>
<td>3.96 mil</td>
</tr>
<tr>
<td>Year 4</td>
<td>21.7%</td>
<td>20 mil</td>
<td>4.33 mil</td>
</tr>
</tbody>
</table>

“Additional factors that could positively affect the revenue/profit for Exact Sciences Corporation include:
- Cologuard becoming the standard of care for colon cancer screening
- Rapid uptake starting in year one, effectively shifting the growth curve
- Expanding the target population from age 50 to age 45 or younger
- Decreasing the interval between screenings, currently five years
- Increased reimbursement amounts for Cologuard”

Aug. 11 Seeking Alpha article
132,700 new cases of colorectal cancers are reported in the United States each year. The number of physicians ordering Cologuard has increased exponentially.

“There are approximately 132,700 new cases of colorectal cancers reported in the U.S. each year, of which 93,090 are colon and 39,610 are rectal [1]. Colorectal cancer causes approximately 49,700 Americans to die annually, and is the third most commonly diagnosed cancer in males and second in females [1]. This is a significant societal ailment with an equally significant addressable market. The estimated annual cost of treating colorectal cancer in the U.S. is approximately $6.5 billion including both preventable medical costs and lost productivity [3].”

“Cologuard tests were completed 21,000 times—a more than 90% quarter over quarter increase. 14,700 ordering physicians—a 77% quarter over quarter increase, and is accelerating this growth is exponential, and the company’s revenue will compound similarly.”
Exact Sciences Corp.’s Cologuard

- “The number of physicians ordering greater than or equal to 20 Cologuard tests increased by 290% between Q4 of 2014 to the end of Q1 this year. (No figure was reported in the Q2 call) This describes the Cologuard’s ‘product stickiness’ and retention rate. (No surprises here, given that its competition pales in comparison).”

Endoscope article
30 million colonoscopies are performed each year; 15 million occur in the United States alone.

- “The large and ever expanding colonoscopy market is characterized by:
  - Approximately 30M procedures per year worldwide (15M in US, < 1.5M in Korea)
  - Aging population
  - Increasing awareness of the need for the CRC screening
  - Rapid rise in the CRC cases in developing countries due to diet change
  - Primary driver of the Screening Colonoscopy market - Eligible population
  - Projected consumer adoption pattern of new technology/service - Similar to Convenient Care Clinic case”

Additional research by Renee Euchner, Linda Richards and Pam Conboy.

The Author(s) of this research report certify that all of the views expressed in the report accurately reflect their personal views about any and all of the subject securities and that no part of the Author(s) compensation was, is or will be, directly or indirectly, related to the specific recommendations or views in this report. The Author does not own securities in any of the aforementioned companies.

OTA Financial Group LP has a membership interest in Blueshift Research LLC. OTA LLC, an SEC registered broker dealer subsidiary of OTA Financial Group LP, has both market making and proprietary trading operations on several exchanges and alternative trading systems. The affiliated companies of the OTA Financial Group LP, including OTA LLC, its principals, employees or clients may have an interest in the securities discussed herein, in securities of other issuers in other industries, may provide bids and
Exact Sciences Corp.’s Cologuard

offers of the subject companies and may act as principal in connection with such transactions. Craig Gordon, the founder of Blueshift, has an investment in OTA Financial Group LP.

© 2015 Blueshift Research LLC. All rights reserved. This transmission was produced for the exclusive use of Blueshift Research LLC, and may not be reproduced or relied upon, in whole or in part, without Blueshift’s written consent. The information herein is not intended to be a complete analysis of every material fact in respect to any company or industry discussed. Blueshift Research is a trademark owned by Blueshift Research LLC.