Effective colorectal cancer (CRC) screening programs have the potential to save lives through prevention and early intervention; however, a large percentage of the eligible US population either is not up-to-date with CRC screening or has never been screened at all.

A number of emerging companies are developing patient-friendly, cost-effective cancer screening technologies and risk-assessment tools, many with an eye, at least initially, on the CRC market. Three are profiled here: VolitionRx, Medial EarlySign, and Check-Cap.

All of these companies have generated promising data and are moving toward US and OUS commercialization. However, in the US they, like others before them, will likely face a high hurdle when it comes to gaining widespread acceptance and payor coverage.

Exact Sciences is a case in point. ColoGuard, its DNA stool test, is highly sensitive and noninvasive, but the company hit a wall with the US Preventive Services Task Force, which declined to group it among recommended CRC screening options in its recent draft guidelines.

Cancer management is leading the charge toward more personalized healthcare, thanks to our rapidly expanding knowledge of (and ability to map out) patient- and tumor-specific genetic mutations associated with various cancers, and the introduction of new biologic drugs that target those mutations. This paradigm shift is also helping to intensify interest in early detection and treatment, which greatly improves a cancer patient’s chances of disease remission and long-term survival. But the key to early detection is the development of screening tests and tools that are highly accurate, cost-effective, and widely acceptable to both patients and physicians—a tall order for medtech companies, but one that is being pursued by a growing number of small, innovative firms.

Colorectal cancer (CRC) is one of the first targets for many of these companies. The third most common cancer diagnosed in the US (excluding skin cancers) and the second leading cause of US cancer deaths (when both sexes are combined), CRC progresses through slow, well-characterized, and readily detectable/treatable precancerous and early cancerous stages (see Figure 1). Thus, effective CRC screening programs have the potential to save lives through prevention and early intervention. Of course, the operative word is “effective.” No matter how good the screening technology, patients won’t benefit if they don’t get screened, and in the case of colorectal cancer, screening rates in the US (and worldwide) still fall far short of ideal.
**Figure 1**

**Colorectal Cancer At a Glance**

**Colorectal Cancer**

<table>
<thead>
<tr>
<th>Stages of Colorectal Cancer</th>
<th>2016 Estimates:</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLYP</td>
<td>US Incidence</td>
</tr>
<tr>
<td>Most colorectal cancers develop from these noncancerous growths.</td>
<td>134,490</td>
</tr>
<tr>
<td><strong>IN SITU</strong> Cancer has formed, but is not yet growing into the colon or rectum walls.</td>
<td>90%</td>
</tr>
<tr>
<td><strong>LOCAL</strong> Cancer is growing in the colon or rectum walls; nearby tissue is unaffected.</td>
<td><strong>5-YEAR SURVIVAL RATE IF FOUND AT THE LOCAL STAGE</strong></td>
</tr>
<tr>
<td><strong>REGIONAL</strong> Growth is into tissue or lymph nodes, beyond the colon or rectum walls.</td>
<td>80%</td>
</tr>
<tr>
<td><strong>DISTANT</strong> Cancer has spread to other parts of the body, such as liver or lungs.</td>
<td></td>
</tr>
</tbody>
</table>

Sources: American Cancer Society; data on cancer screening rates from an Exact Sciences presentation (originally from the CDC)
According to a survey conducted in 2012 by the US Centers for Disease Control and Prevention (CDC), 30% of US adults age 50-75 reported they had never been screened for CRC with any type of test. Of those who had undergone colonoscopy—the current gold-standard screening test—only 62% said they were up-to-date with screening guidelines (colonoscopy is recommended once every 10 years in average-risk patients). And compliance appears to be even worse for less effective annual tests that look for signs of blood in the stool.

Researchers estimate that at least two-thirds of CRC cases and at least 50% of deaths from CRC could be prevented if all eligible patients were screened with colonoscopy. However, there are many barriers that keep patients from getting screened. In the case of colonoscopy, the procedure can involve substantial out-of-pocket costs in the US, even with insurance coverage, and it is inconvenient—patients must take a day off of work and they cannot drive themselves home afterwards. However, it is the perceived risk, discomfort, and invasiveness of colonoscopy, as well as fear of the pre-procedure bowel prep, that keep most patients away.

Some of these issues are being tackled by companies developing more patient-friendly, next-generation colonoscope systems (see “Colon Cancer: Technology Advances Seek to Close Screening & Prevention Gap,” The MedTech Strategist, February 13, 2015); while other emerging companies—including VolitionRx Ltd., Medial EarlySign Ltd., and Check-Cap Ltd., profiled below—are working on innovative new technologies that are intended to offer highly accurate, less-invasive(noninvasive), and cost-effective solutions to screening and risk assessment. (In addition to these companies, start-up Personal Genomic Diagnostics is focused on providing a comprehensive platform of advanced genomic analyses for the oncology space, based on pioneering work in colorectal and other cancers performed at Johns Hopkins University and elsewhere—see “Personal Genomic Diagnostics: One-Stop Cancer Genome Testing,” this issue.)

Although obtaining widespread payor coverage in the US for a new cancer screening test is no small feat, as Exact Sciences Inc. has discovered recently with its Cologuard stool DNA test (see sidebar, “USPSTF Sets High Bar for Cancer Screening Tests”), the unmet need is generating continued interest in novel CRC technologies with the potential to impact patient compliance, reduce costs, and save lives.

One emerging company developing a new blood-based test platform that it believes could revolutionize cancer screening and diagnosis—not only for patients with colorectal cancer, but for a range of cancers and other conditions—is VolitionRx Ltd.

VolitionRx: Redefining Blood-Based Cancer Screening and Diagnosis

Publicly traded, with its laboratory located in Namur, Belgium, VolitionRx’s lead product is a blood test for CRC that detects epigenetic alterations in nucleosomes, the building blocks of chromosomes, using only a single drop of blood and standard ELISA (enzyme-linked immunoassay) technology. According to the company, the test potentially can be adapted to run in nearly any clinical setting, including at the point of care.

As Jake Micallef, PhD, VolitionRx’s chief scientific officer, explains, a nucleosome consists of a short strand of DNA wrapped around four pairs of histone proteins. When a cell dies, the chromosomes inside the nucleus are broken up into their mono-nucleosome components and some of these nucleosomes are shed into the blood (see Figure 2).

Both the histones and the DNA that comprise nucleosomes are susceptible to a variety of genetic mutations as well as epigenetic changes that control gene expression. These changes alter the structure and chemical make-up of the nucleosomes, producing patterns that can be detected in the blood. Since the rate of cell death in patients with cancer is elevated, and since the body cannot locally metabolize all of the increased cell debris, nucleosome concentrations are more abundant in the blood of cancer patients, making these alterations easier to identify in a small blood sample using standard, low-cost laboratory techniques.

VolitionRx’s NuQ assay technology is capable of distinguishing several different categories of nucleosome features in the blood. Altogether, there are tens of thousands of unique structural and chemical alternations that can occur in the nucleosome, says Micallef, and certain patterns of alterations, or signatures, are associated with disease. In cancer, “the pattern of how the nucleosomes look, the attached proteins, are all in the wrong proportions,” he explains. “We’ve looked at these structural possibilities and we’ve found specific combinations that are actually very good at differentiating different cancers.”

Moreover, the test offers a cost-effective alternative to current screening options, adds Cameron Reynolds, VolitionRx’s president and CEO. “Healthcare markets are looking for simple, low-cost, highly compliant tests, not more and more expense to get to the same solution. In stark contrast to just about every other [CRC] test out there, this is not a complicat-ed or expensive test. We’re able to detect early-stage cancer with the same sensitivity as late-stage, and we’re also defining pre-cancers extremely well. So, I think we have something extremely unique—we tick all the boxes.”
Indeed, the test does not require expensive and time-consuming gene amplification and sequencing technology, as do many so-called “liquid biopsies” under development that are looking at DNA circulating in the blood. In fact, notes Micallef, most of those tests target the same nucleosomes as VolitionRx, but they extract the DNA and throw the rest of the nucleosome away. “So they’re probably looking at only 50 base pairs in the three billion base pairs of DNA that make up the human genome, and that’s why these things are expensive—you need big amplification.”

“We’re doing something very different,” he notes, based on an idea that everyone else seems to have missed. Adds Reynolds, “We pretty quickly realized that we were the only company in the world looking at the nucleosomes themselves, which we found very surprising.” And, he continues, the company has “just scratched the surface. There are thousands of different nucleosome structures and only a couple hundred have been looked at to see if they’re different in cancer.”

The idea of detecting cancer by looking at nucleosomes in the blood originated with a company called Chroma Therapeutics in the UK, which Micallef says was developing cancer treatments based on reversing or preventing epigenetic changes. Chroma scientists were the first to realize that these structurally altered chromosome fragments circulating in the blood might provide a good way of detecting cancer, he notes, and they filed patents on the idea. However, since the company was focused on therapeutics, it wasn’t ideally set up to develop the concept into a commercial diagnostic assay. At the time, Micallef was working at ValiRx, a UK-based cancer diagnostics and therapeutics firm. He thought the concept held promise and licensed it into ValiRx, where it was held in the company’s Belgian subsidiary. In early 2010, the Nucleosomics technology, as it is known, changed hands again when Reynolds gathered together a group of investors and purchased the IP, along with the laboratory facility in Belgium, with Micallef on board to head-up the development work.
VolitionRx went public on the over-the-counter market in October 2011 and began trading on the New York Stock Exchange in February 2015. Over the past few months, the company has received three issued US patents on the technology covering the measurement of cancerous changes to the nucleosomes, the detection of cancer-related proteins bound to nucleosomes, and nucleosome detection. Its total IP portfolio includes nine patent families of issued and pending patents in markets worldwide.

The firm has been working to clinically validate the technology in a variety of cancers, with the majority of the work thus far focused on CRC. Its NuQ CRC blood test is expected to consist of a panel of four to six individual ELISA assays that it says could easily be ordered alongside other common blood tests performed during a routine medical check-up.

As VolitionRx conducts clinical studies, it continues to refine the make-up of the CRC assay panel in order to produce the highest accuracy and detection rates, and results obtained thus far are very encouraging. In the company’s first completed prospective CRC clinical trial, an age-adjusted study of 121 patients who were symptomatic for CRC or were at high-risk, a four-assay NuQ panel detected 91% of CRC cases at 90% specificity, and accuracy was equally good for early- and late-stage cancers. The test panel also detected 67% of high-grade pre-cancerous polyps, according to the company, which reported the results in December. In addition, in February, the firm released results of a 430-subject, double-blind, age-adjusted study conducted in Denmark, which found that a four test panel accurately detected 75% of high-risk pre-cancerous adenomas and 86% of stage-1 colorectal cancers. Specificity in that study was 78%.

Large CRC trials involving both screening and symptomatic populations are ongoing, including a 4,800-patient retrospective study of symptomatic patients in Denmark and a 14,000-patient prospective screening study in Denmark. Interim data from the 4,800-subject Danish study showed that a panel of NuQ assays was able to detect 81% of early- and late-stage colorectal cancers at 78% specificity and 67% of high-risk adenomas, which compares favorably to other CRC tests (see Figure 3).

Commercial release of the multi-assay CRC test in Europe is slated for late this year (the company now has CE marks for the first three of its CRC assays). The firm may also launch a laboratory developed test (LDT) for CRC in the US.

Figure 3
Colorectal Cancer - Comparative Data

<table>
<thead>
<tr>
<th>Emerging IVD Technologies</th>
<th>Current Industry Standards</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VolitionRx (NuQ®)</strong></td>
<td>Epigenomics (Epi proColon)</td>
</tr>
<tr>
<td><strong>CRC Sensitivity</strong></td>
<td>81%¹</td>
</tr>
<tr>
<td><strong>Pre-Cancer Polyp Sensitivity</strong></td>
<td>63-75%²</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>78%¹</td>
</tr>
<tr>
<td><strong>Price (Physician/Lab)</strong></td>
<td>Low cost allows for price flexibility</td>
</tr>
</tbody>
</table>

1. Interim data release from 4,800 patient retrospective study released on September 9, 2015
2. Press release dated February 17, 2016
3. Canaccord research report
5. Gastroenterology, Aug. 2005 (Morikawa)

Sources: VolitionRx; data on Epi proColon specificity from Epigenomics
this year through licensing agreements with US CLIA certified laboratories; however, ultimately, it is aiming for FDA PMA approval for the test, a milestone that will take several more years to achieve. While VolitionRx pursues PMA approval, the company intends to seek FDA 510(k) clearance as an adjunct test for high-risk or symptomatic individuals, which it hopes to achieve in 2017. (Applied Proteomics Inc. is also targeting symptomatic, high-risk patients with a lab-based test, SimpliPRO Colon, which uses proprietary algorithms to measure and analyze 11 protein markers in the blood that are associated with CRC and advanced adenomas to help identify patients most likely to benefit from a diagnostic colonoscopy.)

Reynolds acknowledges that the US market will be more challenging for the company than markets outside the US (OUS), in large part because colonoscopy is so accurate and so widely accepted in the US, although “it’s crippling expensive.” However, it is not a common screening test used OUS—most countries in Europe rely on the Fecal Occult Blood Test (FOBT) or Fecal Immunochemical Test (FIT), both of which look for blood in the stool, as a first-line screening tool. “There are about 600 million people in the EU zone and about 150 million of screening age,” notes Reynolds, “and there’s zero chance the European governments are going to spend that kind of money on a screening test [colonoscopy]. So I think we have a very easy case in the rest of the world because we’re not competing with colonoscopy’s accuracy, we’re competing with FIT and FOBT, which suffer from low compliance and low accuracy rates.” There are some 84 million people of screening age in the top five EU countries and only about 30% have been screened with fecal tests, according to the company (see Figure 4).

VolitionRx is also investigating NuQ blood tests for the detection of other diseases, including lung, pancreatic, and prostate cancers, as well as some non-cancerous disorders (nucleosome blood levels also are elevated in immune and inflammatory diseases). Initial results from one of the company’s prostate cancer clinical studies will be presented later this month at the annual meeting of the American Association for Cancer Research. In pancreatic cancer, outcomes from a second preliminary study showed the test, used in conjunction with CEA testing (a traditional cancer biomarker), detected 95% of pancreatic cancer cases at 84% specificity. The company plans to move forward with one or more large, dedicated pancreatic cancer studies and expects pancreatic cancer to be its second commercial target indication, after CRC.

In the area of lung cancer, the company released interim data last November on 73 patients enrolled as part of a 240-patient prospective study being conducted in Belgium. The results included 29 patients with non-small-cell lung cancer, 22 with chronic obstructive pulmonary disease (COPD), and 22 healthy subjects. The interim analysis found that a four-panel NuQ assay, combined with information on the patient’s smoking history, accurately detected 93% of the lung cancer cases, with a 91% specificity. Full results of the study are expected to be available later this year, along with results from a separate 600-subject lung cancer trial conducted in collaboration with Bonn University Hospital in Germany. Meanwhile, the firm’s first pilot

---

**Figure 4**

**Global Colon Cancer Market Potential**

<table>
<thead>
<tr>
<th>Age Range*</th>
<th>Screening Pop. (mil.)</th>
<th>% Screened</th>
<th>Current FIT (mil)</th>
<th>Non FIT Compliant</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK 60-75</td>
<td>10</td>
<td>60%</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>France 50-74</td>
<td>19</td>
<td>42%</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Germany &gt;56</td>
<td>28</td>
<td>18%</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Italy 50-69</td>
<td>16</td>
<td>27%</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Spain 50-69</td>
<td>11</td>
<td>14%</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>30%</strong></td>
<td><strong>25</strong></td>
<td><strong>59</strong></td>
</tr>
<tr>
<td>USA 50-74</td>
<td>89</td>
<td>8%</td>
<td>7</td>
<td>82</td>
</tr>
<tr>
<td>Asia Pacific</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan &gt;40</td>
<td>75</td>
<td>17%</td>
<td>13</td>
<td>62</td>
</tr>
<tr>
<td>China 40-74</td>
<td>564</td>
<td>1%</td>
<td>6</td>
<td>558</td>
</tr>
<tr>
<td>India 50-69</td>
<td>175</td>
<td>2%</td>
<td>4</td>
<td>172</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>814</strong></td>
<td><strong>3%</strong></td>
<td><strong>22</strong></td>
<td><strong>792</strong></td>
</tr>
<tr>
<td>Total Worldwide</td>
<td>987</td>
<td>54</td>
<td>933</td>
<td></td>
</tr>
</tbody>
</table>

*Defined by the age range obtained from identified sources for national screening programs or recommendations.
Source: From a presentation by VolitionRx; original data from GlobalData Pharma eTrack database
study outside of the cancer arena was aimed at idiopathic pulmonary fibrosis (IPF), and preliminary data, released last month, showed that a single NuQ biomarker assay was able to detect 86% of non-treated IPF patients with a specificity of 80%.

“We’ve spent in the region of $16 million over four years and we’ve opened up a whole new area of science. No one’s ever done any of this before.”

—Cameron Reynolds, CEO VolitionRx

Notes Reynolds, “We’ve spent in the region of $16 million over four years and we’ve opened up a whole new area of science. No one’s ever done any of this before.” And, coming largely from outside the space, as the team has, is actually a benefit, he asserts, because the company has not been hobbled by the typical “groupthink” and biases. “Everyone else said, ‘that’s not the way you do it.’ Well, why?” he asks. “These things are easy—it costs a couple of dollars per test to make; there are hundreds of targets, which is very unique; and it’s blood based. It’s a great idea for a whole lot of reasons.”

Medial EarlySign: Applying Big Data Analytics to Cancer Risk Assessment

Another young company taking a unique road in the battle to detect cancer earlier is Medial EarlySign (formerly Medial CS), based in Israel. A pioneer in algorithm-based Big Data analysis, Medial EarlySign is using its expertise to help identify patients who are at high risk of CRC and other cancers. But, rather than developing a test that is run directly on blood samples, the company is applying a sophisticated algorithm to data that is readily available in the patient’s medical and insurance records, including data collected from one of the most common tests performed today—the complete blood count (CBC).

The company’s MeScore CRC provides a personalized indication of whether or not a patient is at high risk of having CRC. It is based on a sophisticated algorithm that looks at subtle variations in the patient’s CBC results (including trends over time), along with other patient-specific demographic data, to detect patterns that suggest the patient is at high risk of CRC and should undergo further testing.

According to company CEO, Ori Geva, key parameters from the CBC that help assess CRC risk include hemoglobin and hematocrit levels, although other red cell counts, platelets, and white cell count also contribute to the determination. In addition, the company’s risk assessment also takes into account patient-specific information, such as patient age and sex. The firm is currently working on a second-generation algorithm model that builds in additional parameters to create a layered approach that could further narrow the high-risk population. But the data parameters vary depending upon the disease of interest, Geva says. For example, a risk algorithm for lung cancer that the firm is developing also incorporates data on the patient’s smoking history.

The final result obtained from the MeScore CRC separates those at normal risk for colorectal cancer from those at high risk so that the latter can be effectively referred for screening tests. According to Geva, “We’re looking at this as a platform for finding individuals with a high or extremely high probability of harboring cancer—I’d say 20-, 30-, or 40-times more than the average person. So we’re narrowing down to a much smaller population where it’s more cost-effective to go and invest the additional resources [for screening tests such as colonoscopy].” The firm also believes the algorithm may be able to identify some patients with precancerous lesions, something that is currently being tested in a study ongoing at the University of Calgary, Canada, which is investigating how well the algorithm model works in average patients who come in for a screening colonoscopy.

Much of the clinical validation work on the CRC risk score has been performed at Maccabi Healthcare Services, Israel’s second-largest HMO, which has been working in collaboration with Medial EarlySign to help develop the test. Explains Geva, early population-based research conducted at Maccabi found that patients in the HMO who were diagnosed with CRC demonstrated a decline in hemoglobin levels on the CBC test about two to three years prior to their CRC diagnosis. However, Maccabi was unable to put that knowledge to use for individual patients, which is the goal of Medial EarlySign. Maccabi prepared an anonymized data set that contained clinical information on over 800,000 patients over the age of 40, and Medial EarlySign used this data to build out its algorithm, incorporating CBC data as well as age and gender. Eventually, Geva says, the company was able to build a model that showed good separation between individuals who were diagnosed with CRC and those who didn’t develop the cancer. Maccabi was then able to validate that model using individual data from its electronic records.

Last year, Maccabi began using the test as a way to routinely follow patients who are not compliant with CRC screening.
screening recommendations. Their goal, says Geva, is to identify very high-risk patients who are not up to date with their screening, with the ultimate aim of being able to use colonoscopy resources more wisely. Each time a patient who is not up to date with screening has a routine blood test, they automatically run the score, he says. If the score is very high, then the patient’s primary care physician is notified that this individual is potentially at much higher risk and should be encouraged to get a colonoscopy or go to a gastroenterologist for further assessment.

“So it’s sort of a safety net that is working in the background,” notes Geva. The algorithm has been able to “pick up a nice percentage of [high-risk] people who are still asymptomatic,” he continues, “or their clinical indicators are not showing something that is worrying, and there’s a nice percentage of CRC cases that can be flagged by the device and then detected still in the early stages. These are really curable stages—we might be able to aid in their earlier detection and potentially save lives.” (Geva points out that another potential use for the test involves assessing patients between regular screening intervals—for example, if FOBT is employed every two years, or colonoscopy every 10 years, what happens during that interval? “Cancers are still found there,” he notes, “and these individuals are completely under the radar.”)

To make sure the test works just as well on populations outside of Israel, the company turned to the UK, where it had access to a data set representing about eight million people in the general population, and was able to achieve “very comparable results,” says Geva (the test was CE marked about two years ago). Medial EarlySign is currently conducting validation studies in several countries worldwide, including the US, where it is working with Kaiser Permanente. The firm hopes to use the data generated from these studies to further support the risk-assessment model and serve any regulatory needs (although US regulatory requirements have not yet been definitively determined). It is seeking additional mutually beneficial partnerships worldwide that will help the company increase awareness and move forward with its commercialization plans.

Medial EarlySign has an interesting history. Established about six years ago, it is the first spin-out from The Medial Institute, a stealthy research institution based in Israel that was founded by Nir Kalkstein, a high-wealth Israeli stock trader and world-renowned expert in the field of algorithmic prediction and data mining. Kalkstein started a company in 2001 called Final Financial Algorithms, which pioneered the concept of using algorithms to enable high-frequency stock trading. Some nine years later, Kalkstein and Ofer Ariely (founder of the first Startup Factory fund in Israel) founded The Medial Institute. The Institute’s goal is to launch companies seeking to apply similar complex computer algorithms, based on Big Data analysis, to the field of healthcare to aid in diagnostic and therapeutic decision-making. Kalkstein continues to personally fund the work being performed in the research arm of the Institute, according to Geva, who says the Institute acts like a nonprofit—all profits obtained by the Institute are put back into founding and supporting the commercial companies.

As The Medial Institute’s first commercial entity, Medial EarlySign has a lot to prove. And, Geva believes it will—in fact, he says the company’s work could have implications far beyond risk-assessment in CRC. The data being collected in medical records today “might hold hidden signals for all kinds of things” that patients might face in the future, says Geva. The company’s vision, he says, is to “use this approach for other diseases [beyond CRC], such as lung cancer, gastric cancer, and perhaps other life-threatening diseases,” something the firm is doing in parallel to its work in CRC. (Outside the cancer arena, the firm is conducting US studies to detect ICU patients at high risk of early deterioration and cardiac intervention patients at risk of post-procedure complications.)

“I really believe,” he continues, “if we look at the less prevalent diseases and cancers that is where this is really a game-changer.” He points to gastric cancer as one example. Very few countries have a screening program for gastric cancer, he says. “But what if we could run this in the background and find individuals who are at higher probability of having this cancer, and it’s almost zero cost? I think this is the big promise, where we can really leverage what we see as an underutilized resource—the electronic medical records—to indicate individual risk.”
The first such device to reach the US market was Medtronic’s PillCam Colon 2, which was FDA cleared in February 2014 (the PillCam was developed by Given Imaging, which Covidien—now a unit of Medtronic—acquired in February 2014 for $860 million). PillCam Colon 2 is a vitamin-sized capsule equipped with two miniature color video cameras, a battery, and an LED light source. Following a bowel preparation, the patient swallows the capsule, which captures images of the colon as it moves naturally through the GI tract.

PillCam Colon 2 was initially cleared by FDA for use only in patients with an incomplete colonoscopy. However, late last month, Medtronic announced that the device had received an expanded indication from FDA for use in patients with evidence of lower GI bleeding who have major risks for colonoscopy or sedation, but who could tolerate a colonoscopy procedure if the PillCam identified a significant abnormality.

According to Vafa Jamali, president, Early Technologies in Medtronic’s Minimally Invasive Therapies Group, the expanded indication gives physicians some discretion as to risk determination, but low-risk patients who simply refuse colonoscopy would not qualify. Examples of major risk groups, says Jamali, include a patient who is taking an anticoagulant drug and thus is at higher risk of bleeding during and after a colonoscopy procedure, or someone who has chronic obstructive pulmonary disease and is not a good candidate for moderate sedation. But both would need to have documented evidence of lower GI bleeding (such as a positive FOBT test) before they would be eligible to undergo the PillCam Colon procedure.

Jamali notes that of the 14 million colonoscopies performed annually in the US today, about 24% are diagnostic procedures prompted by evidence of lower GI bleeding. Moreover about 20% of patients who undergo colonoscopy have comorbidities that increase their risk, which adds up to a sizeable potential patient population for the device. Over the past five years, some 20,000 PillCam Colon procedures have been performed worldwide. However, Jamali says the total potential patient population approaches 700,000 in the US alone.

As for payor coverage for this new indication, Jamali says insurance claims for PillCam Colon are currently evaluated on a case-by-case basis (the capsule costs $625, but total costs, including procedure and physician costs, are higher). The device has a Category 3 CPT code; however, Medtronic plans to apply for a Category 1 code in the near future. The company also will continue its efforts to further expand FDA indications for PillCam Colon 2, he says.

Check-Cap: A New Concept in Capsule-Based GI Imaging

While Medtronic works to bring the PillCam Colon to more patients, emerging Israeli competitor Check-Cap Ltd. believes it has come up with a better idea: a swallowable capsule that images the colon using ultra-low-energy X-rays. Importantly, the device is able to “see through” stool and thus does not require the dreaded bowel prep.

Check-Cap was founded in 2005 by Yoav Kimchy, PhD, currently the company’s chief technology officer. Prior to founding Check-Cap, Kimchy worked as an algorithm specialist and technical project leader in an Israeli government contract company, served as the Director of Cardiovascular Research in a biomedical start-up, and was VP of R&D at a medical device start-up company working in the field of nuclear molecular imaging technology. Kimchy, who has a family history of CRC, had family members who were still reluctant to get a colonoscopy—primarily because of the bowel prep. As a result of this personal experience, explains Bill Densel, Check-Cap’s CEO, he recognized “a significant need to develop a technology that could do a
Kimchy worked independently on the concept for several years. His efforts ultimately led to the current Check-Cap system, which consists of three components: a 30 X 11 mm swallowable device (roughly the size of the PillCam Colon) that contains an X-ray source with a short half-life and X-ray detectors (see Figure 5); a capsule positioning system worn on the patient’s back that retrieves data from the capsule (via radiofrequency telemetry) and tracks the capsule’s passage through the GI tract; and a work station that takes the data from the capsule positioning system and creates a high-resolution, 3D map of the inside of the colon.

Notes Densel, “This is the first X-ray we are aware of where the X-rays don’t pass from a source through your body into a detector, such as a screen or a film. Everything is contained in the capsule. So it really is an incredible technology.” (Average total X-ray exposure during the test is 0.03 mSv, which is about the same as a single chest X-ray.)

As the capsule travels through the digestive tract, patients are required to swallow a small amount (about 15 ml) of standard contrast material with each meal, which mixes with the contents in the colon and enables the system to reconstruct the surface topography. When the capsule enters the colon, a rotating electric motor enables it to scan in a 360-degree angular view, Densel explains. The image obtained relies on two physical phenomena: X-ray fluorescence from the contrast material and Compton backscatter, which occurs when photons bounce off the walls of the colon (or any other structure present) and then are received back in the capsule. “When we combine those two phenomena,” he continues, “we’re able to estimate the distance from the capsule to the colon wall. As we continue to take scans based on motion as the capsule moves, we’re able to create a topographical map of the inside of the colon. Features like polyps will be evident because they’re an asymmetrical feature and the distance from the capsule to those features differs along the colon wall.”

Once the capsule has traveled the full length of the GI tract and is eliminated, the physician receives a 3D, computer-generated image of the entire colon, from the cecum to the rectum, enabling them to determine the size and location of each polyp present. Explains Densel, the physician can look at that image in either a tubular view, as if it were a colonoscopy, or a “fillet” view, which opens up the colon to produce a flat image so it looks like a map. They can also move through the image in “fly-through” mode, looking up or down, or moving backwards.

Densel says the firm’s ultimate intent is to obtain an approved indication for the device for screening medium-risk patients with no prior history of CRC, which covers most people currently indicated for a screening colonoscopy in the US. “But who we’re really focused on,” he says, “are the 40% of Americans who are not current with their screening for CRC under any means. The number-one reason why they don’t get a colonoscopy is the bowel preparation, and then of course, there’s the invasive nature of the procedure, the embarrassment factor, the fact that you have to get anesthesia and potentially get driven home, take time off of work—all those things combined. We’re trying to develop a screening technology that’s acceptable to them, so those patients will get screened.” According to the company, targeting the 36 million patients in the US who are not willing to undergo a future colonoscopy amounts to a $4 billion an-

---

**Figure 6**

Potential US Market Opportunity for Check-Cap

<table>
<thead>
<tr>
<th>Not willing to undergo future colonoscopy</th>
<th>Willing to undergo future colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>36M Patients</td>
<td>$4B Annual US Market Opportunity*</td>
</tr>
<tr>
<td>43%</td>
<td>57%</td>
</tr>
</tbody>
</table>

*For patients screened once every five years at average Check-Cap System price of $600
Source: Check-Cap Ltd.
As for the challenges involved in bringing physicians on-board with the new screening paradigm, Densel says the scans will be read and interpreted by gastroenterologists—the same physicians that currently perform colonoscopies. But even though colonoscopy is their bread-and-butter procedure, there is an incentive for them to embrace the Check-Cap test. “The patients we’re going to appeal to,” he asserts, are the ones who are not showing up for a colonoscopy now.” So there’s an opportunity to not only improve screening rates, he explains, but there’s a larger group of patients—maybe 20-25% of those who undergo a Check-Cap procedure—in whom pre-cancerous polyps may be discovered and who may need a follow-up therapeutic colonoscopy. Thus, a capsule screening would bring a certain number of new colonoscopy patients into the system.

The company is currently conducting a multi-phase clinical study OUS that will culminate in a CE mark application, which is anticipated in the second half of this year. (The initial human experience involving 49 cases was published last December in Gut [Gluck, N. et al]—the system clearly showed pedunculated and sessile polyps that were validated by subsequent colonoscopy.) The firm also has plans to initiate an FDA-approved US trial and anticipates that US market approval will require either the de novo 510(k) or PMA regulatory pathways. The company went public on the NASDAQ exchange in February 2015 and Densel joined last May. It now has 20 granted patents on the technology, one allowed, and 34 pending.

Densel acknowledges that gaining widespread acceptance and coverage in the US market for a new CRC screening test presents a challenge, but he believes the benefits of the Check-Cap technology will win out in the end. Even though colonoscopy is the gold-standard in the US and provides a one-stop procedure, he points out that “after tremendous progress over more than 15 years of effort and a lot of education on the need to get screened for CRC, we still have only about 60% of the eligible population getting screened. There are barriers we think we can take out of the way with Check-Cap.”
USPSTF Sets High Bar for CANCER SCREENING TESTS

Researchers have been working for many years to make CRC screening more patient friendly. However, the solutions developed to date have thus far failed to make much of a dent in the US screening compliance rate, for a variety of reasons, and chief among them is the difficulty companies often have convincing payors to provide coverage and reimbursement.

The first such advance to reach the US market, computed tomography (CT) colonography, provides a good example of the many potential pitfalls involved for those seeking to innovate in this arena. CT colonography is a noninvasive imaging test that can be used to screen for colorectal cancer; however, uptake has been slow due to concerns about radiation exposure and limited advantages to patients. Unlike colonoscopy, CT colonography does not require sedation, so patients can return to work immediately afterward. It also has a much lower risk of bowel perforation and is less costly than colonoscopy. However, patients must still undergo a full bowel prep before the test to clear the colon of any debris that might obscure the image, and the colon must be insufflated during the procedure, which can be uncomfortable.

CT colonography also is not as effective as colonoscopy at detecting certain types of lesions, particularly flat polyps, and it provides no preventive treatment option. Patients with suspicious results or clinically significant polyps detected on CT colonography must still undergo a follow-on colonoscopy (requiring another bowel prep). And, since a follow-on colonoscopy is typically classified as a diagnostic procedure rather than a screening test, the out-of-pocket cost is likely to be higher than if the patient had undergone a screening colonoscopy in the first place.

USPSTF’s final recommendation is important to the CRC screening market because the Affordable Care Act mandates that US insurers cover all screening tests that receive an “A” or “B” rating from the agency.

As a result, it is not universally covered by payors, including Medicare, as a routine screening test. And updated screening recommendations due out this year from the US Preventive Services Task Force (USPSTF) are unlikely to help. A draft proposal issued by USPSTF last October failed to list CT colonography as a recommended screening test, saying it found “no studies that assessed the impact of screening with CT colonography on cancer incidence, morbidity, quality of life, or mortality.” Moreover, “evidence is still lacking to bound the potential harms of this technology, particularly in regard to incidental findings,” the document said. Instead, USPSTF relegated CT colonography to a new “Alternative Test” category, stating it “may be useful in select clinical circumstances.”

USPSTF’s final recommendation, expected to be released this year (possibly by summer), is important to the CRC screening market because the Affordable Care Act mandates that US insurers cover all screening tests that receive an “A” or “B” rating from the agency. Those that don’t could face an uphill battle when it comes to gaining widespread coverage and reimbursement. At this point, it is unclear from the new draft recommendations exactly what rating CT colonography will receive in the final document, although it appears likely that the test will not be grouped with the four other well-established screening strategies the agency deemed “effective”: fecal immunochemical blood tests (FIT), traditional fecal occult blood tests (FOBT), flexible sigmoidoscopy, and colonoscopy.

It its draft proposal, the Task Force also declined to recommend routine use of Exact Sciences Corp.’s Cologuard multi-target DNA stool test for
CRC screening, placing Cologuard in the “Alternative Test” category as well. (The previous USPSTF recommendations, released in 2008, placed both Cologuard and CT colonography in the “I” category, indicating there was insufficient evidence to assess their benefits and harms.)

Cologuard was FDA approved in August 2014 and received a positive National Coverage Determination from the Centers for Medicare and Medicaid Services (CMS), establishing Medicare coverage for the test, which retails for $649. It is also included in a recommended list of CRC screening options issued by the American Cancer Society (ACS). FDA approval of Cologuard was based on Exact Sciences’ 90-site, 10,000-patient pivotal trial, the results of which were published in March 2014 in the New England Journal of Medicine. However, although the firm says physician interest in Cologuard is on the rise (in January, management said physicians are coming on board at a rate of about 2,000 new doctors per month, according to Mark Massaro, an analyst with Canaccord Genuity), the company has struggled to obtain nationwide private payor coverage. Thus far, Exact Sciences has managed to win national coverage from Anthem Blue Cross Blue Shield and regional coverage from some 25-30 additional plans; but the company has filed lawsuits against at least two regional insurers (Blue Cross Blue Shield of North Carolina and Humana in Kentucky) for refusing to pay (North Carolina and Kentucky are among 18 states with laws requiring insurers to cover any test included in the ACS’ colon cancer screening guidelines).

USPSTF’s reluctance to fully embrace the test apparently centers on concerns about Cologuard’s lower specificity compared with FIT tests and the risk that patients with false-positive results on Cologuard will undergo unnecessary, and potentially harmful, follow-up colonoscopies. Cologuard has a higher sensitivity (92%) than FIT, but a lower specificity (87%), which means it can detect more cancerous and high-grade precancerous lesions, but it also produces more false-positive results. And, according to the draft guidelines, “empiric evidence is lacking on appropriate follow-up of abnormal results” following Cologuard screening.

Exact Sciences’ executives have pointed out that the Task Force only considered once-yearly testing with Cologuard, whereas the company has new modeling data showing that testing every three years may be sufficient, an interval that would reduce the frequency of unnecessary follow-ups. However, it is unclear whether or not this information will influence the agency’s final decision. USPSTF could overhaul its final recommendations based on public comments (Exact Sciences executives said recently that the agency received a large number of comments about the draft decision); however, that would be a rare move and seems improbable at this point. Still, Exact Sciences’ President and CEO, Kevin Conroy, told analysts recently that although the firm doesn’t anticipate a major change to the final guideline wording, the company does believe Cologuard will be “deemed A rated” once the final guidelines are re-
leased, since the draft gave an A rating to colon cancer screening overall for those age 50 to 75.

In spite of the reimbursement challenges it has faced, Exact Sciences says 2015 was a “strong first year of commercialization” for Cologuard. A total of 104,000 of the tests were completed in 2015, bringing in $39.9 million in revenue, and about 24% of the 80 million Americans eligible for CRC screening are now covered for Cologuard under insurance contracts. The company expects 2016 revenues to reach $90-100 million, with over 240,000 tests completed this year, according to comments made during the firm’s Q4 earnings call in February.

Based on his experiences in the trenches, Conroy had some cautious words during the call for other companies working to bring screening tests to the US market, particularly those developing blood-based tests. He told analysts that following its difficult experience with the Task Force guidelines for Cologuard, Exact Sciences decided to terminate its collaboration with MD Anderson Cancer Center to develop blood-based screening and diagnostic tests for lung cancer. The pathway to get a screening test to the US market leads directly through the Task Force, he said, and the amount of evidence the agency requires for a new screening modality “is so incredibly high that even one large study may not have been enough—and that study could have cost $50+ million.” This is a “significant barrier” to the US market, he continued. “We believe that for the fundamental industry to be altered, the regulatory pathway has to be altered. Until that happens, I think companies that spend hundreds of millions of dollars trying to develop blood-based screening tests probably are in for a rude awakening.”

One company with a blood-based test for CRC that has already felt the challenges of the US regulatory system is molecular diagnostics company Epigenomics AG, based in Berlin, Germany, and Germantown, MD. FDA twice requested more data from the company to support its pre-market approval (PMA) submission for Epi proColon, a blood-based CRC screening test that utilizes PCR gene sequencing technology and the company’s proprietary DNA methylation biomarkers to qualitatively detect Septin9 gene methylation in cell-free DNA shed into the blood. According to the company, cytosine residues of the Septin9 gene are methylated in CRC but not in normal colon mucosa and “have been demonstrated in multiple clinical studies to be a reliable indicator of the presence of CRC.” In its pivotal trial, the test met its 65% sensitivity target, but it did not meet the 85% specificity target (specificity was 79%), and FDA expressed concern about the possibility of false positive patients going on to get needless additional testing. However, the company argued, and FDA eventually agreed, that the test deserved approval because of its potential to increase the number of patients who get screened and to direct patients to guideline-recommended screening methods (i.e., colonoscopy). (This argument has also been used successfully by Exact Sciences for Cologuard—see Figure SB-1.)

Epi proColon is not as sensitive or specific as Cologuard (sensitivity improves as cancer stage increases), and the test finds only about 20% of precancerous polyps, although the company points out it is not designed for adenoma detection. However, it has the distinct advantage of enabling patients to be screened with just a simple blood test, rather than requiring them, as Cologuard does, to collect and ship back a complete bowel movement, a process that some patients may find objectionable.

In November, Epigenomics appealed FDA’s most recent data request, and in January of this year, it received a positive response—FDA notified the firm that the data it had already obtained and submitted would be enough for a final determination on the test’s safety and efficacy. The company received final FDA PMA approval just this month, making Epi proColon the first blood-based CRC screening test to reach the US market (it will be marketed jointly with Polymedco, Epigenomics’ commercialization partner). The test is FDA approved for colorectal cancer screening in average-risk patients who choose not to undergo screening by guideline-recommended methods such as colonoscopy and FIT. Convincing US payors (and the USPSTF) of the test’s benefits in order to obtain insurance coverage will be Epigenomics’ next major hurdle. (Epi proColon is also marketed in Europe, China, and selected other countries.) The company will conduct a post-approval study in the US to investigate the test’s long-term benefits.

—Mary Thompson