EDISON

VolitionRx

Clinical outlook

Big EU trials on deck

Pharma & biotech

In September 2017, VolitionRx announced its European development plan for the Nu.Q™ colorectal cancer (CRC) frontline screening test. It will run two clinical trials (of 4,300 and 10,000 samples), which are expected to initiate in Q118 and Q218, respectively, supporting an expected CE mark and launch in Q318. VolitionRx is also participating in a three-year, 13,500-person US clinical trial including Nu.Q™ assays to support a US launch.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/15	0.0	(9.7)	(0.54)	0.0	N/A	N/A
12/16	0.0	(12.3)	(0.53)	0.0	N/A	N/A
12/17e	0.0	(14.1)	(0.53)	0.0	N/A	N/A
12/18e	0.3	(17.6)	(0.64)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortization of acquired intangibles, exceptional items and share-based payments.

European development plan

The two planned European clinical trials intend to use banked blood samples from Danish patients. The sets of samples will be constructed to include confirmed CRC patients, fecal immunochemical test (FIT) negative patients, and FIT positive patients who are CRC negative in ratios similar to those found in national screening populations. The first trial (4,300 samples) will be used to hone the final Nu.Q™ panel to be used in the larger 10,000 sample trial and to be used for CE marking.

Triage test setbacks

The company is still pursuing development of the Nu.Q™ CRC screening triage test, which is designed to provide a more definitive readout following a positive FIT test and reduce unnecessary colonoscopies. In 2017, the company had to redesign the test to include alternate Nu.Q™ assays, and the logistics and pathway design study for the test has been proceeding more slowly than anticipated (expected completion in Q317) and remains ongoing. Considering these developments, we now expect late 2018 to be the earliest for product sales.

Research kits and CRC in Asia opportunities to watch

VolitionRx recently sold its first Nu.Q™ tests for research purposes to an undisclosed pharmaceutical company partner. Additionally, the company has announced plans to start two trials totaling 7,000 patient samples in Taiwan to support approval in that and other Asian countries. Although we currently do not include these in our estimates, both are opportunities that could provide future revenue streams if they are developed.

Valuation: Decreased to $200m or $7.55/basic share

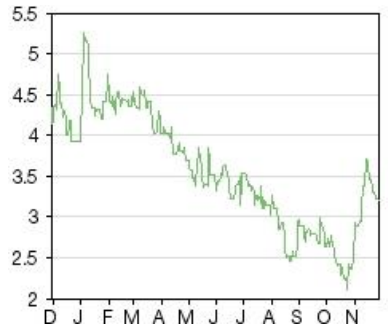
We have decreased our valuation to $200m or $7.55 per basic share, from $236m or $8.89 per basic share. This change is based on a reevaluation of some of our model assumptions, including a decrease in the probability of success for triage, lung, and pancreatic cancer due to the protracted timelines for all programs. We have also delayed expected profitability to 2023 (from 2022), which increased our expected financing to c $82m (from $67m).

28 November 2017

Price	**US$3.20**
Market cap	**US$85m**

Net cash ($m) at September 2017	12.4
Shares in issue	26.5m
Free float	69%
Code	VNRX
Primary exchange	NYSE American
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	35.6	24.5	(27.9)
Rel (local)	34.5	16.9	(38.7)
52-week high/low		US$5.3	US$2.1

Business description

VolitionRx is a diagnostics company focused on developing blood-based cancer diagnostics using its proprietary Nu.Q™ technology. Its lead program is in colorectal cancer, which is being advanced for both triage and frontline testing in Europe and the US.

Next events

4,300 sample EU trial initiation	Q118
10,000 sample EU trial initiation	Q218
Frontline CRC CE mark	Q318

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Investment summary

Company description: Blood-based cancer screening

VolitionRx is developing the Nu.Q™ cell free nucleosome test for the blood-based detection of a series of different cancers. The test detects the fragments of chromosomes that are released on cancer cell death and uses the modifications present on these structures to rule out other diseases. This provides a non-invasive method of detecting cancer, and because the technology is based on the routine ELISA test, it is easily integrated into existing protocols at low cost. The lead program is for the detection of colorectal cancer, a market with approximately 235 million people in the US and Europe. The company in currently in clinical trials to support marketing of the test in Europe and the US, with expected completion in 2018 and 2021, respectively. The program in Europe includes development of a frontline CRC screening test and a triage test to be administered after a positive fecal test. Additionally the company has development programs for the detection of lung, pancreatic, and prostate cancer, each of which is in the early stages.

Valuation: Decreased to $200m or $7.55 per basic share

We have decreased our valuation to $200m or $7.55 per basic share, from $236m or $8.89 per basic share. This adjustment was driven primarily by the continued protracted development timelines and lower probabilities of success, as well as a number of other smaller adjustments, driven by a review of our valuation fundamentals. We have delayed the approval timelines for all programs and do not expect significant revenue in 2018 despite potential approval of the frontline and triage tests late in the year. We have also decreased the probability of success for triage (40% from 50%), lung (20% from 30%), and pancreatic cancer (20% from 30%), due to continued delays in these programs.

Financials: $92m needed before profitability

VolitionRx had operational spending of $4.0m in Q317, which is a slight increase in quarterly spending over the rate for the preceding year ($3.3m-$3.5m), driven by the first payment toward the US clinical trial. We have increased our expected R&D spend for 2018 (to $9.1m from $8.2m) onward to reflect the recently announced European clinical trials. Due to the previously described development delays, we have pushed back expected profitability to 2023 from 2022, and have increased our expected financing requirement to c $82m (modelled as $15m in illustrative debt in 2018 and 2019, $22m in 2020, and $30m in 2021) from $67m.

Sensitivities: Near-term clinical hurdles

The company's greatest risks include conclusively demonstrating the efficacy of its Nu.Q™ tests and communicating this to regulatory and policy-making bodies in the US and Europe. The company has not previously completed a clinical trial for its frontline test using a prospectively defined panel of Nu.Q™ assays. The upcoming 10,000 sample European clinical trial will be the first to use a predefined panel, but it will not prospectively enroll patents, instead relying on banked blood samples. The upcoming US clinical trial will enroll patients prospectively, but the trial will be performed by a third party. VolitionRx also faces unique commercial risks. Adoption in Europe is dependent upon convincing centralized screening programs of the importance of adopting the test, and the Nu.Q™ tests must compete with low-cost alternatives like FIT. We believe that given the potential low cost of the test that it may compete in this market by improving compliance and reducing the need for colonoscopy. Finally, the company will face financial risks typical of a pre-commercial company, and we model that it will require $82m in additional cash before profitability in 2023.

Using nucleosomes to detect cancer

VolitionRx is a clinical-stage diagnostics company focused on the development of blood-based tests for the detection of cancer. The company's Nu.Q™ technology centers on the detection and characterization of circulating nucleosomes. Nucleosomes are complexes of DNA and protein normally found in chromosomes, but in diseased cells, these complexes can be released into the bloodstream. In healthy cells, nucleosomes are modified to control the expression of different genes, but in cancer nucleosomes become hyper-modified as the cell loses the ability to regulate normal gene expression. The company has developed a series of 39 different ELISA based assays to characterize and quantify these nucleosome-based biomarkers in the hopes of identifying signatures indicative of different cancers. Because these tests are based on ELISA technology, they are easily integrated into existing testing infrastructure, do not require any additional capital outlays, and can potentially be sold at low cost, compared to other branded tests which cost multiple hundreds of dollars. The company's lead program is the development of Nu.Q™ based panels for the identification of colorectal cancer (CRC) and it is currently engaged in six ongoing CRC clinical studies. The company has also tested the technology in lung, pancreatic, and prostate cancers, and has an ongoing study examining the technology in 27 common cancers.

Exhibit 1: VolitionRx clinical programs

Indication	Sponsor	Patients	Notes
Colorectal cancer	NCI Early Detection Research Network	13,500	Registration trial, 4,600 retrospective samples, up to 9,000 prospective, 2021 expected completion
Colorectal cancer	VolitionRx	14,300	4,300 sample prospective training set, 10,000 prospective validation set, 2018 estimated completion
Colorectal cancer	Hvidovre Hospital (Denmark)	750	Triage Pathway Design study, near-term completion
Colorectal cancer	Hvidovre Hospital (Denmark)	4800	Biomarker analysis
Colorectal cancer	Hvidovre Hospital (Denmark)	14,000	Population screening following a fecal immunochemical test (FIT). 2,500 patients expected in the first data release
Colorectal cancer	Hvidovre Hospital (Denmark)	30,000	Longitudinal study
27 most prevalent cancers	Bonn University Hospital (Germany)	4,700	Broad screen of 27 most prevalent cancers to identify differences in nucleosome modification
Pancreatic cancer	German Cancer Research Center (DKFZ) (Germany)	750	Pilot study to detect of pancreatic cancer

Source: VolitionRx

Colorectal cancer

CRC is one of the most common cancers worldwide, with approximately 1.36 million cases per year worldwide.[1] Prognosis is highly dependent upon the stage at which the cancer is detected, highlighting the need for improved CRC screening program participation. According to the American Cancer Society the five-year survival rate for patients who have their cancer detected in the localized stage is 90%, compared to just 14% when there are distant metastases.[2]

Therefore, there have been significant efforts to establish screening protocols to identify disease early. The US Preventative Services Task Force (UPSTF) provides guidance on a series of testing strategies for adults between ages 50 and 75:

- an annual fecal occult blood test (FOBT) or fecal immunochemical test (FIT);
- a FIT-DNA test (ie the Cologuard test from Exact Sciences) every three years or less;
- flexible sigmoidoscopy every five years, or every 10 years when combined with yearly FIT;
- CT colonography every five years; and
- colonoscopy every 10 years.

1 International Agency for Research on Cancer

2 American Cancer Society (2017) *Colorectal Cancer Facts & Figures 2017-2019*

Similarly in Europe there are multiple national initiatives to screen the at-risk population, for instance a FIT test distributed to at-risk individuals once every two years, as in Scotland. The problem with these strategies is that compliance for fecal testing is low (in the range of 13-60% depending on the study), and colonoscopy, while highly accurate, is invasive and requires sedation. Combined, the CRC screening market is approximately 235 million people in the US and Europe.

Overview of CRC screening technologies

There are a number of different technologies currently being used or in development for the detection of colorectal cancer and they fall into three categories: invasive, fecal and blood.

Exhibit 2: CRC screening test data comparison

	Company	Type	Cost	CRC sensitivity	AP sensitivity	Specificity
Colonoscopy	Various	Invasive	$1,200	95%	95%	95%
Sigmoidoscopy	Various	Invasive	$600	50%	50%	92%
FIT	Various	Fecal	$23	74%	24%	96%
gFOBT	Various	Fecal	$5	40-70%	12-24%	93-98%
Cologuard	Exact Sciences	Fecal	$428	92%	42%	87%
Epi proColon	Epigenomics	Blood	$339	68-72%	22%	81%
Nu.Q™	VolitionRx	Blood	$100 or less	74-91%	31%*	90%
Colox	Novigenix	Blood	$300	78%	52%	92%

Source: FDA, Exact Sciences, World Gastroenterology Organization, Agency for Healthcare Research and Quality, Imperiale et al., Multitarget Stool DNA Testing for Colorectal-Cancer Screening, *N. Eng. J. Med.* 370, 1287-1297, CMS. Notes: AP=adenomatous polyps. *Improved to 62% with a specificity of 90% with alternate panel, although CRC accuracy on this panel undisclosed.

The guaiac-based FOBT (gFOBT) is a relatively cheap (~$5) test in which stool samples are collected and analyzed for blood. A limitation of the test is that it typically involves collection of up to three different fecal samples on three different days, negatively affecting compliance. In addition, it does not discern between human and not-human blood so an ingestion of meat prior to the test could have a negative impact on results. Antioxidants such as vitamin C may interfere with the chemistry of the test, leading to false negatives. There are a variety of different versions of the test but sensitivity is in the 40-70% range and specificity is 93-98% according to the Agency for Healthcare Research and Quality (AHRQ). Sensitivity for precancerous lesions was pretty low, generally between 12% and 24% depending on the specific test.

The FIT was developed specifically to target human hemoglobin and therefore not be thrown off due to dietary sources. It is more expensive than gFOBT, but at ~$23 is still relatively inexpensive. FIT is considered to be more sensitive than gFOBT with a sensitivity 73.8% and specificity of 96.4%. However, it has limited ability to detect advanced precancerous lesions with a sensitivity of just 23.8%.[3] Like the FOBT, the FIT involves the collection of up to three different fecal samples on three different days.

Cologuard is a test marketed by Exact Sciences that combines a molecular assay, consisting of two DNA methylation markers (NDRG4 and BMP3), seven DNA mutation markers (all related to KRAS) and a DNA normalization marker (Beta Actin), with a FIT test. Unlike the other fecal tests, it only requires one stool sample. In addition, due to the molecular assay component, the test is an order of magnitude more expensive than the standard FIT test. In Q317, average revenue per test was $428 across all providers ($512 from CMS and in the $300 range for private payers). It is also significantly more sensitive than a FIT test with 92.3% sensitivity but is less specific with 86.6% specificity, leading to a greater number of false positives than FIT. Cologuard also has a greater ability to detect advanced precancerous lesions with a sensitivity of 42.4%.

The gold standard for CRC diagnosis is the colonoscopy as it is highly accurate with few false positives or negatives. It is an invasive procedure that requires preparation and anesthesia. The

[3] Imperiale TF, et al. (2014) Multitarget Stool DNA Testing for Colorectal-Cancer Screening, *N. Eng. J. Med.* 370, 1287-1297.

colonoscope is a four-foot long tube the thickness of a finger that is inserted into the rectum. In order to prepare for the procedure a patient is often required to either drink a very large volume of a special cleansing solution or only ingest clear liquids for several days. Large doses of laxatives and enemas are also used. The adverse event rate is relatively high with a hospitalization rate for serious complications of one in 200, usually bleeding, colonic perforation or a negative reaction to anesthesia[4]. This high rate of complications from this diagnostic test is one reason why the FDA is concerned with approving screening methods with high false positive rates as those false positives would be followed up by colonoscopies with their inherent risks. The colonoscopy is also the most expensive of the screening methods for CRC with a cost of $1,200 per procedure according to CMS.

Flexible sigmoidoscopy is an invasive screening method that involves the doctor inserting a 60cm sigmoidoscope into the rectum and permits a thorough examination of the distal portion of the colon but not the proximal portion, which limits its ultimate effectiveness (41% of CRC originates in the proximal colon[5]) and is a major reason why fewer than a percent of eligible individuals get one, according to the CDC. Like a colonoscopy, it requires preparation including a clear liquid diet, laxatives to clean the colon as well as an enema though typically the preparation is less intense than with a colonoscopy. It is, however, a relatively safe procedure with only one in 5,000 screening subjects being hospitalized for a gastrointestinal complication (eg colonic perforation or serious bleeding)[6]. The cost of the procedure is also much less than a colonoscopy, around $600, according to figures from CMS.

Epi proColon is a blood test based on detecting aberrantly methylated DNA of the Septin9 gene. As it is based on just one marker, it is not very accurate, with a significant number of false positives and false negatives. In analyzing its pivotal trial data, the FDA commented that the test yields 37.7 false positives per every true positive compared to 5.4 false positives per every true positive for FIT. Although only approved by the FDA in 2016, Quest, the diagnostics giant, had been selling its version of the Septin9 test, dubbed ColoVantage, since 2009 via a CLIA-waiver (which does not require an FDA approval if certain conditions are met) and sales have been minimal.

Novigenix is developing Colox as a blood-based diagnostic for CRC that examines the activation of immune cells for a profile indicative of cancer. The test measures the expression levels of 29 genes in peripheral blood mononuclear cells. Colox demonstrated a 78.1% sensitivity and 92.2% specificity for CRC in a 782-person clinical trial. Additionally, Colox was able to detect adenomatous polyps (AP) that were greater than 1cm in size with a sensitivity of 52.3% with 92.2% specificity, an improvement over most current technologies. Colox is currently on the market in Switzerland, and the company is developing the next generation Colox Plus targeting EU launch in 2019 and entering US clinical trials in 2019.

The Nu.Q™ advantage

The Nu.Q™ technology has been evaluated in two separate trials for CRC. In a retrospective trial of 4,800 samples from patients presenting with CRC or other bowel diseases, a panel of four Nu.Q™ tests showed 81% sensitivity to detect CRC (at 78% specificity). This trial established the capacity of the test to identify patients with CRC, but had several limitations. Because all the patients included in the screen had a variety of bowel disease, including polyps and adenomas, one would expect a higher degree of false positives than would be observed in the general population: it is a

[4] Rutter CM, et al. (2012) Adverse Events after Screening and Follow-up Colonoscopy. *Cancer Causes Control*.; 23, 289-296.

[5] Siegel RL, et al., (2017) Colorectal Cancer Statistics, 2017. *CA: A Cancer Journal for Clinicians* 67, 177-193.

[6] Levin TR, et al. (2002) Complications of Screening Flexible Sigmoidoscopy. *Gastroenterol*. 123:1786-1792.

reasonable assumption that these patients would also have abnormal DNA expression and higher degrees of cell death. However, the test still performed in this background. A limitation is that the retrospective nature of the test limits the capacity to interpret the statistics of the study. The company followed this study with a performed enrolled trial of 58 patients who were identified in CHU Dinant Godinne – UCL Namur University Hospital in Belgium with symptoms of CRC. In this study, a panel of four Nu.Q™ assays were selected post-hoc, which identified CRC with 74% sensitivity and 90% specificity vs healthy controls. The sensitivity of the test improved to 91% with a post-hoc adjustment for the age of participants. These results, if repeatable, would make Nu.Q™ the best-in-class blood-based CRC diagnostic, but additional studies are needed because the number of CRC cases (23) and healthy subjects (20) was low in the sample. Moreover, although the sample collection protocol was prospectively defined, the assays used to derive the aforementioned accuracy were identified after the fact to match the data. Given that there are over 80,000 different combinations of available Nu.Q™ assays for them to choose, there is the potential that these findings were due to chance, and the company does not provide detailed statistics of how this determination was made.

This same study at CHU-UCL identified a separate panel of four Nu.Q™ tests that was able to identify AP with a sensitivity of 62% (at 90% specificity versus the healthy group). This panel had to be specifically designed to detect AP, as the panel used to identify CRC only had a 31% sensitivity to detect AP. There is potential, however, that the two panels could be combined in future tests, which would position the Nu.Q™ panel favorably compared to other technologies (with the exception of colonoscopy) in its ability to detect AP.

The clinical pathway

VolitionRx is currently in two clinical programs to support the marketing and commercialization of the front-line Nu.Q™ CRC test in the US and Europe, respectively. In July 2017, the company announced that it will be participating a 13,500-person trial in the US investigating biomarkers for colorectal cancer screening. The Nu.Q™ colorectal screening test will be incorporated into the panel, and the company has stated that it believes the data from this study should be sufficient to support US PMA approval, although it has not met with the FDA to delineate the actual approval requirements. 4,677 samples have already been collected for the study and up to an additional 9,000 samples will be prospectively collected from asymptomatic individuals 50 years and over who have not undergone a colonoscopy. The study is being run in collaboration with the National Cancer Institute's (NCI) Early Detection Research Network (EDRN) and the Great Lakes New England (GLNE, of the University of Michigan) Clinical Validation Center and is expected to take two to three years to complete. The precise details of the clinical program have not been announced yet. However, GLNE, which will be performing the trial, is highly experienced at similar large colorectal biomarker screening projects. It previously performed validation testing on Cologuard (along with other biomarkers) in a 6,000-person study. The center has published over 30 papers based on research from its biomarker clinical trials.

A positive aspect of this clinical trial plan is the cost savings to VolitionRx. The company has committed only $3m to the collaboration expenses. This is exceptionally inexpensive considering the size and scope of the trial. This will be one of the largest clinical studies to support the approval of a colorectal cancer screening product. The stool-screening test Cologuard (Exact Sciences) was approved using the data from a 10,000-person prospective trial.

A downside of this plan is that VolitionRx will not have control over the trial protocol. Although experienced, the trial sponsors do not have a vested interest in the approval of Nu.Q™, and there is no guarantee that the protocol will be acceptable to the FDA, which was not consulted by VolitionRx.

In September 2017 the company announced its European development strategy, which will consist of two sequential clinical trials. The first trial targeting initiation in Q118 will consist of approximately 4,300 blood samples, which will be used to identify the optimal panel of Nu.Q™ tests. A finalized panel will be selected and examined in an expanded set of 10,000 blood samples, which will serve as the primary trial to support marketing and adoption of the test by European regulators. This second trial is expected to be initiated in Q218 to support a CE mark application in Q318. Both trials will be performed in Denmark, and both trials will be using constructed sample sets as opposed to naturally presenting patients. The sets will be constructed to include both previously verified CRC patients, FIT positive patients who did not have CRC, and FIT negative patients in ratios that approximate natural screening populations. This protocol was selected because of the logistic hurdles involved in performing the trials in a European setting in the background of a national screening program. Unlike the US, the FIT negative patients will not receive colonoscopies under the screening protocol, and therefore it is not possible to follow these patients in the near term to identify their CRC status. This may limit the interpretation of the sensitivity and specificity for the test because the CRC rate in the FIT negative population is unknown, although the negative predictive value for FIT is high. If there are a high number of Nu.Q™ positive results in the FIT negative population, it will be impossible to tell if these patients truly have CRC or some other condition that is interfering with the test.

Finally, VolitionRx has begun preparations for two clinical trials in Taiwan for approximately 7,000 patients total. It has also initiated the regulatory process to perform a clinical trial in Singapore, which would potentially allow commercialization throughout South-East Asia. Although the markets are large throughout Asia, and incidence of CRC is high, screening is currently very underpenetrated. For instance, compliance in Taiwan is only 21%.

The triage strategy

In September 2016, VolitionRx announced a strategy for commercialization into certain European markets using a specialized Nu.Q™ panel it has termed the Nu.Q™ CRC screening triage test. This simplified test is not designed to diagnose cancer in the frontline setting, but rather be a follow-up diagnostic for patients who have a positive FIT test. The goal in this case would be to further discriminate if the patient should receive a colonoscopy. In theory, this protocol has the capacity to significantly decrease the number of unnecessary colonoscopies, which the company believes would be attractive to certain state-sponsored CRC screening programs. In many European jurisdictions (25 of the 28 EU member states), central health authorities have colorectal cancer screening programs. These generally consist of the distribution of FIT or FOBT tests to the screening population on a regular basis with protocols for follow-up colonoscopy. The new triage test is meant as an intermediary step of this process where the patient will instead be sent to the doctor for a blood test following a positive FIT result. Using an early version of the test, the company reported that the Nu.Q™ test could reduce the number of colonoscopies by 25%, albeit at the cost of missing an estimated 5% of patients with CRC.[7] However, this may be a more attractive option than raising the threshold for FIT positivity: raising the limit from 100ng/mL to 200ng/mL would reduce colonoscopies by 32% but miss 9% of legitimate CRC. Despite these costs, several European countries such as Sweden, Scotland, and the Netherlands have increased their FIT thresholds due to the limited capacity to perform colonoscopies.

VolitionRx initially developed the triage test as a panel of two Nu.Q™ assays, with the goal of securing a position in the Danish national CRC screening protocol and expanding to other territories with national screening programs subsequently. The company initially targeted commercialization in late 2017 or early 2018. The Danish CRC screening board was scheduled to meet in September

[7] Nielsen HJ, et al. (2017) Serological biomarkers in triage of FIT-positive subjects? *Scand. J. Gastroenterol.* 52, 742-744.

2017 to consider the proposal from VolitionRx, and feedback from the committee is still outstanding. However, there are other factors that have delayed the initial launch of the test. In March 2017, the company initiated a "logistics and pathway" study to examine the correct implementation of the triage test into the Danish testing algorithm. The 750-person study was expected to be complete in six months, but is currently still ongoing. In addition, in June 2017 the company announced that it was redesigning the panel because "selected immunoassays individually had a high p-value," and that this process would require new or amended CE marks. It is unclear at this time how much the data from the previous version of the triage test can be used to support the approval of the redesigned test. We expect commercialization of the test at the earliest in late 2018.

The total addressable market for the triage test is smaller compared to the frontline test. There are approximately 136 million patients in Europe eligible for routine colorectal cancer screening. However, many fecal testing programs have historically had low compliance rates. A recent study of fecal testing in France found compliance rates between 47% and 54%[8] over four consecutive two-year periods (24-27% tested per year). A study in Spain identified a FIT positivity rate of 7.2%,[9] similar to rates observed in the US (7.0%).[10] This corresponds to a total market of 2.5 million individuals per year across Europe if all nations adopted FIT screening programs, or a little over 1% of the predicted US and European frontline CRC screening market.

Other cancers

Although CRC is the company's primary focus, it has also tested Nu.Q™ panels for the detection of other cancer types. The three most advanced programs are lung cancer, pancreatic cancer, and prostate cancer.

Lung cancer

VolitionRx is also developing a Nu.Q™ testing panel to identify patients with lung cancer. Lung cancer is another disease that can benefit from early detection, but unlike CRC, widespread screening efforts are currently limited by technology. A majority of lung cancers are identified after metathesis (57%), when the five-year survival rate is only 4.2%.[11] These survival rates are significantly higher (54.8%) if the cancer is detected when still localized.

Despite the significant need for new lung cancer screening methodologies, the market is much smaller than for CRC. Because of its close association with smoking, the population at risk is much lower. The Centers for Medicare and Medicaid Services (CMS) recommend screening for those between age 55-74 with ≥30 pack/year smoking history and cessation less than 15 years ago, which results in 8.6 million people in the US (compared to the 89 million screening population for CRC).

There are a number of different screening methods in general practice (Exhibit 3), but the current standard advocated by the US Preventative Services Task Force (USPSTF) is a yearly low-dose computed tomography (LDCT) scan. LDCT is one of the most effective methods of identifying lung cancer (89% sensitivity, 93% specificity) but it is associated with radiation exposure. The amount of radiation exposures is small on an individual basis (2mSv), but on the scale of the total number of

[8] Denis D, et al. (2015) Participation in four rounds of a French colorectal cancer screening programme with guaiac faecal occult blood test: a population-based open cohort study. *J. Med. Screen.* 22(2), 76-82.

[9] Quintero E, et al. (2012) Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Screening. *New Eng. J. Med.* 366, 697-706.

[10] Imperiale TF, et al. (2014) Multitarget Stool DNA Testing for Colorectal-Cancer Screening. *New Eng. J. Med.* 370, 1287-1297.

[11] SEER database.

screened patients represents a very large level of exposure with potential health effects. So there is still a medical need for new screening regimens.

The company released interim results of 73 patients (as part of a larger 600-person prospective study) that presented at Centre Hospitalier Universitaire de Liege in Belgium with symptoms of lung disease. The study correctly identified 93% of patients with cancer and successfully discriminated them from chronic obstructive pulmonary disease (COPD) patients (with 91% specificity). These results are comparable to LDCT, albeit on a small data set. The release of the full data set has been significantly delayed.

Exhibit 3: Relative efficacy and cost of lung cancer diagnostics

Test name	Company	Sensitivity (%)	False negative rate (%)	Specificity (%)	False positive rate (%)	Cost ($)
Sputum cytology		66	34	99	1	2,500
Needle biopsy		90	10	97	3	9,000
Chest X-ray		54	46	99	1	100
LDCT		89	11	93	7	300
PAULA	Genesys Biolabs	74	26	80	20	95
Lc Detect	Panacea Global	98	2	90	10	200
Percepta	Veracyte	97	3	47	53	4,875
Epi proLung BL Reflex	Epiogenomics	81	19	95	5	
Nu.Q™	VolitionRx	93	7	91	9	40-80

Source: *Chest Journal*[12], ASTRO, *Cancer Journal*, company reports

Pancreatic cancer

Another indication with a desperate need for early screening capabilities is pancreatic cancer. The diagnosis typically is made when symptoms arise as a result of metathesis and a minority of patients (47%) are identified before this point. The five-year survival rate for patients with distant metatheses is also one of the worst in the oncology space at 2.4%, whereas it is 27.1% when localized. The deadly reputation that pancreatic cancer has earned could be significantly reduced with better diagnostics.

There are substantially fewer established technologies used to test for pancreatic cancer. The primary procedure used to screen patients is endoscopic ultrasound, where an ultrasound device is inserted through the esophagus and an ultrasound recording is taken through the wall of the stomach. Needless to say, this is a highly invasive procedure that requires anesthesia and carries the risks of complications. The only other screening method in common use is a blood test called CA19-9. Current ASCO guidelines recommend against the use of CA19-9 as a screening tool for pancreatic cancer due to its inaccuracy. According to a review of CA19-9 studies, it has 79% sensitivity and 82% specificity.[13] Its primary use is to assess the response to the therapy for already established pancreatic cancer patients, but it is frequently used off label for diagnosis, albeit coupled as part of a larger set of diagnostic procedures.

These limitations in screening technology and the relatively low incidence of the cancer (53k new cases per year in the US)[11] are likely the reason why the International Cancer of the Pancreas Screening Consortium does not recommend screening for the general population. Currently, only those individuals with multiple first-degree relatives who have had pancreatic cancer are considered of sufficient risk to warrant screening. We believe that these features severely limit the potential pancreatic screening market, even if VolitionRx can develop an accurate test. Even in the event of substantial clinical success, there is are significant uphill hurdles associated with establishing the market.

12 Rivera et al., (2013) *Chest* 143(s5) e142S-e165S.

13 Duffy et al., (2009) Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report. *Annals of Oncology* 21, 441-447

The Nu.Q™ test for pancreatic cancer has been tested in two retrospective data sets. The first employed 59 samples from Lund University in Sweden, and detected 92% of cancers with 100% specificity with a Nu.Q™ panel of four assays combined with the CA19-9 test. In a follow-up study, the company combined a similar Nu.Q™ panel with a carcino-embryonic antigen (CEA), and identified 95% of cancers with 84% specificity out of the same 4,800 person sample from Hvidovre Hospital in Denmark used in the CRC test development. The company has initiated a 750-person study at the German Cancer Research Center (DKFZ). The results of this study were initially expected by the end of 2016, although the company currently reports it as still ongoing.

Exhibit 4: Pancreatic cancer screening technology comparison

Test name	Company	Sensitivity (%)	False negative rate (%)	Specificity (%)	False positive rate (%)	Cost per test ($)
EUS	Various	89	11	96	4	500
CA19-9	Various	79	21	82	18	20-40
Nu.Q™ + biomarkers	VolitionRx	92-95	3-5	84-100	0-16	40-80

Source: *Annals of Oncology*,[14] VolitionRx, *Pancreatology*

Prostate cancer

VolitionRx recently released its first results on a Nu.Q™ panel for the detection of prostate cancer in April 2016. The test was able to identify 71% of stage 1 cancers and 86% of stage 4 cancers out of a retrospective sample of 537 men with 93% specificity.

Unlike the other indications that the company is targeting, prostate cancer already has a widely used blood-based test: the prostate specific antigen (PSA) test. PSA testing is often combined with digital rectal examination (DRE) to form the standard of detection for the disease. The accuracy of both of these tests varies dramatically in the literature: a meta-analysis in 2003 found sensitivities from 67% to 100% and specificities from 18% to 100% for PSA and from 49% to 69% sensitivity and 18% to 99% specificity for DRE.[15]

Although the number of men screened each year is relatively large (approximately 20 million per year receive a PSA test),[16] the benefits of testing are currently under question. In 2012 the USPSTF recommended against the use of PSA testing for the diagnosis of cancer, not based on the accuracy of the test, but because the benefit to the patient in the event of a diagnosis was small. The number of patients who are affected by early diagnosis is small because the majority either have prostate cancer advanced enough that detection does not alter the prognosis or are more likely to die from other causes before the benefits of early testing can be realized. Future advances in treatment may affect this assessment, but currently the benefits of testing for prostate cancer are limited.

Exhibit 5: Prostate cancer screening technology comparison

Test name	Company	Sensitivity (%)	False negative rate (%)	Specificity (%)	False positive rate (%)	Cost per test ($)
DRE		53	47	84	16	10-20
PSA	Various	72	28	93	7	50
Nu.Q™	VolitionRx	71-86	14-29	93	7	40-80

Source: *J. Am. Board Fam. Med*, VolitionRx

[14] Duffy et al., (2010) Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report *Annals of Oncology* 21, 441-447

[15] Mistry K and Cable G, (2003) Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma. *J. Am. Board Fam. Med.* 16, 95-101

[16] Roswell Park Cancer Institute

Sensitivities

VolitionRx is a development-stage company and as such faces a series of clinical and regulatory risks. The company has initiated a large number of clinical studies, potentially enrolling thousands of patients over the previous years, but only a small amount of data has been produced to support the adoption of a Nu.Q™ test for the detection of CRC. Most of the clinical data to this point employs retrospective analyses, which do not have sufficient statistical rigor to support marketing claims. After many years in development, the company has not conclusively identified the Nu.Q™ panel it intends to use in the commercial setting. The company has two ongoing clinical programs it intends to use for marketing authorization in the US and Europe, although both have significant limitations. The US trial is not being run by VolitionRx and the company has not consulted the FDA regarding whether it can support approval. The European trial will be using banked blood samples like many previous clinical trials, and will be run in a single country, Denmark. It is therefore unclear if this will be adequate to support adoption in screening programs throughout the continent. The triage test development program, once considered a quicker pathway to market, has been delayed significantly, and the test used in the program itself has had to be redesigned.

Moreover, even if VolitionRx is able to reproduce its earlier clinical results, it is unclear if it will satisfy regulatory authorities. Specificity in cancer screening has been cited by the FDA and USPSTF as a very significant factor when evaluating a test, because due to the low incidence rates of these diseases, false positives can outnumber true positives by orders of magnitude. Epi proColon was approved on the basis of improving compliance, despite low specificity, but sales have been very slow (€346,000 Epigenomics total revenue in Q317). However, if the company is able to surmount these hurdles, we believe the test has commercial potential, driven by its low price point and ability to seamlessly integrate into existing infrastructure.

Valuation

We have lowered our valuation to $200m or $7.55 per basic share from $236m or $8.89 per basic share. This adjustment was driven primarily by the continued protracted development timelines and lower probabilities of success, as well as a number of other smaller adjustments, driven by a review of our valuation fundamentals.

We have adjusted our pricing expectations for the frontline CRC test in Europe to be in line with company guidance on pricing for the triage test (which we previously integrated) and now model a $55 price point. This is offset by lower peak penetration (8%) and a delay in our sales ramp-up. We model the product reaching the market in 2018, but now expect sales to be insignificant for that period. We have increased R&D spending to $2m for the program in 2018 to reflect the two planned European trials. We have increased our price point for the US frontline CRC test to $100, although this is similarly offset by a slower sales ramp-up. Due to the prolonged US development timeline, we continue to expect it to enter the US market in 2022. This is in line with the hypothetical reimbursement rate calculated for Epi proColon ($125) determined by CMS, although it is generally not reimbursed by Medicare. We do not include any Asian markets in our valuation at this time, but may include them in the future if the company successfully performs the necessary trials.

We now expect insignificant sales for the triage test in 2018 with increasing revenue in later years to a peak of $42m. We model a price point of $55 in line with the frontline test, as we expect these products to enter different markets. We have reduced our probability of success for the program to 40% from 50% based on the series of development delays that have occurred in 2017.

We continue to include the lung cancer and pancreatic cancer programs in our valuation, although we have reduced our probability of success to 20% from 30% and delayed our expected launch

date to 2020 from 2019 due to the lack of progress in these programs and continued development delays. Otherwise our assumptions remain unchanged. For both programs we model a price of $40 in the US and $20 in Europe.

We currently do not include prostate cancer screening in our valuation, as the company has not demonstrated a benefit over PSA, and current recommendations are against routine screening for prostate cancer, although we may change this in the future following significant clinical results. We also do not include any sales of Nu.Q™ tests for research purposes; although the company recently sold some Nu.Q™ assays to an undisclosed partner, we are currently treating this as a one-off event.

Exhibit 6: Valuation of VolitionRx

Product	Main Indication	Status	Prob. of commercial success	Launch year	Peak sales ($m)	Patent protection	Economics	rNPV ($m)
NuQ™	Colorectal	Development	30%	2018	$404	2034	56% peak margin	$141
	Colorectal triage	Development	40%	2018	$42	2034	50% peak margin	$14
	Lung	Development	20%	2020	$132	2034	61% peak margin	$27
	Pancreatic	Development	20%	2020	$42	2034	58% peak margin	$7
Total								$188
Cash and cash equivalents (Q317) ($m)								$12.4
Total firm value ($m)								$200
Total basic shares (m)								26.5
Value per basic share ($)								$7.55
Warrants and options (m)								4.8
Weighted average exercise price ($)								$3.46
Cash on exercise ($m)								$16.5
Total firm value ($m)								$217
Total number of shares								31.3
Diluted value per share ($)								$6.93

Source: Edison Investment Research, VolitionRx reports

Financials

VolitionRx had operational spending of $4.0m in Q317, which is a slight increase in quarterly spending over the rate for the preceding year ($3.3m-$3.5m). This increase was predominantly driven by the first payment ($250,000) associated with the US clinical trial. We have increased our expected R&D spend for 2018 (to $9.1m from $8.2m) onward to reflect the recently announced European clinical trials. The company ended Q317 with $12.4m in net cash. Due to the previously described development delays, we have pushed back expected profitability to 2023 from 2022, and have increased our expected financing requirement to c $82m (modelled as $15m in illustrative debt in 2018 and 2019, $22m in 2020, and $30m in 2021) from $67m.

Exhibit 7: Financial summary

$'000s	2015	2016	2017e	2018e
Year end 31 December	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS				
Revenue	0	0	0	255
Cost of Sales	0	0	0	(33)
Gross Profit	0	0	0	222
Research & Development	(6,102)	(6,838)	(7,932)	(9,121)
Sales, General & Administrative	(3,904)	(5,429)	(6,111)	(8,673)
EBITDA	(10,006)	(12,267)	(14,043)	(17,571)
Operating Profit (before amort. and except.)	(10,006)	(12,267)	(14,043)	(17,571)
Intangible Amortisation	0	0	0	0
Other	0	0	0	0
Exceptionals	0	0	0	0
Operating Profit	(10,006)	(12,267)	(14,043)	(17,571)
Net Interest	0	0	0	(61)
Other	471	252	197	0
Profit Before Tax (norm)	(9,666)	(12,267)	(14,043)	(17,632)
Profit Before Tax (FRS 3)	(9,535)	(12,014)	(13,846)	(17,632)
Tax	5	0	0	0
Deferred tax	(0)	(0)	(0)	(0)
Profit After Tax (norm)	(9,661)	(12,267)	(14,043)	(17,632)
Profit After Tax (FRS 3)	(9,530)	(12,014)	(13,846)	(17,632)
Average Number of Shares Outstanding (m)	17.7	23.0	26.7	27.7
EPS - normalised (c)	(54.49)	(53.22)	(52.69)	(63.62)
EPS - FRS 3 ($)	(0.54)	(0.52)	(0.52)	(0.64)
Dividend per share (c)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed Assets	1,489	2,721	3,966	3,159
Intangible Assets	705	602	593	593
Tangible Assets	784	2,119	3,373	2,566
Other	(0)	(0)	(0)	(0)
Current Assets	6,070	21,846	11,335	12,470
Stocks	0	0	0	2
Debtors	0	0	0	45
Cash	5,916	21,679	11,164	12,252
Other	154	167	171	171
Current Liabilities	(1,120)	(2,033)	(2,610)	(3,137)
Creditors	(1,120)	(2,003)	(2,202)	(2,728)
Short term borrowings	0	(31)	(408)	(408)
Long Term Liabilities	(548)	(1,524)	(2,134)	(17,134)
Long term borrowings	0	(432)	(1,051)	(16,051)
Other long term liabilities	(548)	(1,092)	(1,083)	(1,083)
Net Assets	5,891	21,009	10,557	(4,641)
CASH FLOW				
Operating Cash Flow	(8,766)	(9,056)	(11,059)	(13,909)
Net Interest	0	0	0	0
Tax	0	0	0	0
Capex	(352)	(415)	(1,340)	(3)
Acquisitions/disposals	0	0	0	0
Financing	12,498	25,302	998	0
Dividends	0	0	0	0
Other	0	(553)	(94)	0
Net Cash Flow	3,379	15,279	(11,495)	(13,912)
Opening net debt/(cash)	(2,139)	(5,916)	(21,216)	(9,705)
HP finance leases initiated	0	0	0	0
Exchange rate movements	13	146	(140)	0
Other	385	-125	124	0
Closing net debt/(cash)	(5,916)	(21,216)	(9,705)	4,207

Source: Edison Investment Research, VolitionRx reports

Contact details	Revenue by geography
22 Rue Phocas Lejeune Parc Scientifique Crealys Isnes, 5032 BE +1-646-650-1351 www.volitionrx.com	N/A

Management team

Chief Executive Officer: Cameron Reynolds MBA	Chief Financial Officer: David Vanston
Mr Reynolds founded the company in Singapore in 2010. From 2004 until 2011, Mr Reynolds founded and served as managing director and director of Mining House, where he was responsible for identifying potential mining projects. From 2005 until present, Mr Reynolds has held several board directorships. Cameron was educated at the University of Western Australia (Bachelor of Commerce and MBA).	Mr Vanston has 20 years of financial management experience. Prior to Volition and Octo Telematics, David held positions as vice president of Excorp Medical, Inc., an early-stage company, chief financial officer for GrowHow Ltd and vice president Europe, finance for Monster Worldwide, Inc. Mr Vanston managed and oversaw the accounting, finance, tax, treasury, financial planning and analysis of the business. Mr Vanston is a certified chartered accountant and holds an MBA from Warwick Business School.
Chief Scientific Officer: Jake Micallef PhD MBA	**Chief Medical Officer: Jason Terrell, MD**
Dr Jake Micallef is an experienced scientific executive with expertise in research and development, and in managing early-stage biotechnical companies. He joined Cronos Therapeutics in 2004. In 2006 Cronos was listed in the UK on AIM, becoming ValiRx. Dr Micallef continued to work as technical officer for ValiRx, where he in-licensed the HyperGenomics and Nucleosomics technologies and co-founded ValiBio, which is now Belgian Volition, a subsidiary of Singapore Volition. Dr Micallef was educated at King's College London (BSc, biology and chemistry; PhD physical chemistry); St Thomas's Hospital Medical School, London (MSc chemical pathology); and Imperial College Management School (MBA).	Dr Terrell has a strong grounding in both medicine and more specifically in diagnostics. He currently owns and operates multiple diagnostic laboratories in Texas. Since 2011, he has been medical director of CDEX, a US-listed company developing drug validation technology, serving on the board since 2013. Dr Terrell was educated at Hardin-Simmons University (biochemistry), where he graduated summa cum laude, receiving the Holland Medal of Honor as the top graduate in the School of Science and Mathematics. He then attended the University of Texas at Houston Medical School and affiliate MD Anderson Cancer Center (Doctor of Medicine).

Principal shareholders	(%)
Lagoda Investment Management, L.P.	12.7%
Martin Faulkes	5.1%
Guy Innes	4.9%
Cameron Reynolds	4.2%
Knoll Capital Management, L.P.	1.7%
Southpoint Capital Advisors LP	1.0%

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