VolitionRx

Company update

Multiple partnerships enable diversification

Healthcare equipment & services

VolitionRx released its Q119 financial results last week and provided an operational update at the capital markets day on 9 April at the NYSE. Among other areas, VolitionRx highlighted the assay upgrade progress, which was one of the main operational goals in 2018. Although this caused delays to original commercial product development timelines, VolitionRx emphasises the current product-grade Nu.Q™ assays excel when it comes reliability and reproducibility. The first batch of proof-of-concept data with the new assays in detection of colorectal and lung cancers was released in March 2019 and larger trials should follow. The other CMD highlights include detailed presentations by the invited KOLs on the newer R&D areas Nu.Q™ Capture and Nu.Q Vet. Our valuation is $215m or $5.46/share.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/17	0.0	(15.1)	(0.57)	0.0	N/A	N/A
12/18	0.0	(18.0)	(0.49)	0.0	N/A	N/A
12/19e	0.1	(18.3)	(0.46)	0.0	N/A	N/A
12/20e	0.1	(19.7)	(0.48)	0.0	N/A	N/A

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

Diversifying beyond human cancer

The KOL presentations at VolitionRx's CMD event showed its determination to explore opportunities beyond its core human cancer programmes. Nu.Q Capture is an R&D project with several goals. One is to use mass spectrometry, which could significantly boost VolitionRx's capability for biomarker discovery (epigenetic modifications in this case). Another opportunity that Nu.Q Capture could open up is the circulating tumour DNA (ctDNA) enrichment, which could be useful for players in liquid biopsy and DNA sequencing. Nu.Q Vet is an attempt to develop Nu.Q assays in animals. Working in partnership with the Texas A&M University, one of the top veterinary schools in the US, VolitionRx sees cancer diagnostics in dogs as potential near-term commercial opportunity.

Near-term plans

According to VolitionRx, the product upgrade resulted in Nu.Q assays that are superior in terms of reliability and reproducibility. Although this caused delays to the development plans, the first batch of proof-of-concept data in colorectal and lung cancer were in line with company expectations. These were still small feasibility studies, but VolitionRx plans to deliver more proof-of-concept data this year and to continue analysing blood samples accumulated in its biobank. In addition, the collaborations with the National Taiwan University and the Chinese IVD company Fosun Long March should deliver newsflow on planned Nu.Q clinical trials in China.

Valuation: $215m or $5.46/share

Our valuation is $215m or $5.46/share versus $233m or $6.60/share previously. The main revision to our R&D projects is the delay of the launch of commercial products by two years in all indications. We believe the assay upgrade was a necessary step to ensure commercially viable products. Our other R&D assumptions remain unchanged, as described in our previous notes.

14 May 2019

Price	**US$3.32**
Market cap	**US$131m**
Net cash ($m) at end Q119 + 5m from warrant exercise post Q119	18.9
Shares in issue	39.5m
Free float	70%
Code	VNRX
Primary exchange	NYSE
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(4.0)	14.1	53.0
Rel (local)	(0.8)	11.7	48.4

52-week high/low	US$3.6	US$1.6

Business description

VolitionRx is a life sciences company developing novel, simple-to-use, blood-based tests to diagnose a range of cancers and conditions by identifying and measuring nucleosomes in the blood stream. The primary focus is to develop the Nu.Q family of blood-based diagnostics tests for cancer.

Next events

Proof-of-concept data in various indications with product-grade assays	2019
Updates on the studies run in partnership with the National Taiwan University	2019
Update on the collaboration progress with the Texas A&M university to develop animal health test	2019
Update on the progress with collaborations with Fosun Long March	2019

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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 can be easily integrated into existing lab protocols at low cost. VolitionRx was established in 2011 as a virtual-style diagnostics start up and has grown into a NYSE-listed company with 20,000 sq ft laboratory facilities in Belgium with more than 30 employees. The lead programmes include cancer screening in several indications in humans, more recent ventures into animal health in partnership with the Texas A&M University and nucleosome-enrichment technology, which could boost the biomarker discovery for the Nu.Q platform and open another unique commercial opportunity for ctDNA enrichment, potentially useful for DNA-sequencing players in the liquid biopsy field.

Valuation: $215m or $5.46/share

Our VolitionRx valuation is $215m or $5.46/share compared to a previous $233m or $6.60/share. This is mainly due to revised launch dates, which were partially offset by a slightly higher net cash position and rolling our model forward. In addition, the warrant exercise had some dilution effect on our value per share. The upcoming multiple data announcements from the proof-of-concept studies should provide interesting catalysts for the share price. While these will be still be small feasibility studies, all of those studies will involve the product-grade assays. The insights from these will likely influence further R&D program and focus areas for VolitionRx, which is when we will revise our valuation accordingly. For the time being we do not include Nu.Q Vet or Nu.Q Capture commercial potential in our valuation due to their early stage.

Financials: Cash reach well into 2020

As expected, VolitionRx reported no income and an operating loss of $4.0m in Q119, compared to $4.6m a year ago; this is largely in line with our expectations. VolitionRx's cash burn is around $4m per quarter. The company had cash of $16.2m at end Q119 after it had raised $6.7m gross in March from warrant exercise. More warrants were exercised after the close of Q119, bringing in an additional $5m for the company. VolitionRx reiterated its guidance that cash burn is likely to be $4m per quarter in the near future, which suggests the cash runway extends well into 2020. According to our estimates the funding gap in 2020 is $7.5m (shown as long-term debt in Exhibit 8). The only significant change to our estimates is that we have postponed the commercial launch of products for clinical use to 2021 or 2022 (more details below).

Sensitivities: Typical diagnostics R&D hurdles

VolitionRx's risks include demonstrating the efficacy of its Nu.Q tests in detecting cancer and communicating this to regulatory and policy-making bodies in the US, Europe and Asia. The company has been upgrading its assays, which means all prospective studies are still to be performed. However, since its establishment the company has accumulated a large blood sample bank, which means that once the assays are ready, the studies could be performed relatively quickly. Presuming successful R&D and regulatory approval, VolitionRx also faces commercial risks. Adoption in Europe depends on convincing centralised screening programmes of the importance of adopting the test and the Nu.Q tests must compete with low-cost alternatives such as the faecal immunochemical test (FIT). The mitigating factor of this is that Nu.Q technology is based on classic ELISA, which is also a low-cost and readily available procedure.

Using nucleosomes to detect cancer

Nu.Q advantages

VolitionRx is a clinical-stage diagnostics company focused on the development of blood-based tests for detecting cancer. The company's Nu.Q technology centres on the detection and characterisation 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 they become hyper-modified as the cell loses the ability to regulate normal gene expression. VolitionRx has developed a series of different ELISA-based assays to characterise and quantify these nucleosome-based biomarkers in the hope of identifying signatures indicative of different cancers. Nu.Q assays have several potential advantages, including:

- Because they are based on ELISA technology, the tests are easily integrated into existing testing infrastructure, so there is no need for additional capital outlays;
- Nu.Q-based tests can potentially be sold at a low cost (compared to other branded tests that cost multiple hundreds of dollars. Currently we have $55-100 per test for colorectal cancer (CRC), $20-40 per test for lung and pancreatic cancers in Europe and the US, respectively, in our model.
- Nu.Q-based tests can be performed quickly and non-invasively (a simple blood draw is sufficient); and
- One unique feature of the Nu.Q platform compared to liquid biopsy tests based on next-generation sequencing technologies is that the latter technology seeks specific mutations, whereas the malignant process caused by these mutations causes epigenetic modifications across the epigenome. This means that a simple, low-cost ELISA-based Nu.Q test can be used to detect those modifications, whereas the detection of specific mutations requires complex DNA sequencing methods.

The journey so far; product upgrade enabled by recombinant nucleosomes

Since establishment in 2011, VolitionRx has accumulated a large blood sample bank by collaborating with various organisations in different regions. Several of the programmes are ongoing (Exhibit 1).

Exhibit 1: VolitionRx blood sample bank

Indication	Sponsor	Patients	Notes
Colorectal cancer	NCI Early Detection Research Network	9,000 prospective 4,600 retrospective	Frontline screening. Main programme in the US; collection ongoing to 2020.
Colorectal cancer	National Taiwan University	5,000 prospective	Frontline screening; collection ongoing to 2021.
Colorectal cancer	National Taiwan University	2,000 prospective	Diagnostic test in symptomatic patients; collection ongoing to 2021.
Colorectal cancer	Hvidovre Hospital (Denmark)	14,000+ prospective	Screening population. Collection complete and analysis ongoing.
Colorectal cancer	Hvidovre Hospital (Denmark)	30,000 prospective	Screening population. Collection complete and analysis ongoing.
Colorectal cancer	Hvidovre Hospital (Denmark)	4,800 retrospective	Diagnostic test in symptomatic patients. Collection complete and analysis ongoing.
Lung cancer	National Taiwan University	1,200 prospective	Collection expected to start in mid-2019 to 2021.
Pancreatic cancer	German Cancer Research Center (DKFZ)	750 retrospective	Collection complete and analysis ongoing.
27 most prevalent cancers	Bonn University Hospital (Germany)	4,500 prospective	Broad, prospective screen of 27 most prevalent cancers to identify differences in nucleosome modification. Collection complete and analysis ongoing.

Source: VolitionRx

VolitionRx's initial focus was CRC, but with the new proof-of-concept data, as described below, this has expanded to other cancers. One of the more notable developments over the last 12–18 months was the upgrade of the assays to product-grade level. Nu.Q assays represent a novel technology

and as such, there was a need to have a reliable control to accurately interpret the measurements. Early in 2018, VolitionRx announced that its partner Active Motif developed recombinant nucleosomes, which allowed this upgrade step. This increased reliability of the measurement interpretation and the company decided to upgrade all of its assays using these recombinant nucleosomes as controls.

With this substantial improvement in technology, VolitionRx reproduced some of the previous studies. Although this caused delays to the original planned timelines for commercial products, the first proof-of-concept data in CRC and lung cancer using these product-grade assays were released in Q119 and did not disappoint; the company is planning larger trials now. We expect VolitionRx will provide more details about the upgrade process and release more proof-of-concept data in various indications over 2019, as guided by the company (Exhibit 2).

Exhibit 2: VolitionRx proof-of-concept studies with product-grade assays

Indication	Sample cohort	Expected	Indication	Sample cohort	Expected
Colorectal cancer	225	Q219	Prostate cancer	120	H119
Colorectal cancer	552	H119	Prostate cancer	100	H219
Colorectal cancer	352	H219	Pancreatic cancer	100	H219
Lung cancer	76	Q119	Head and neck cancer	200	H219
Lung cancer	152	H119	Endometriosis	10 (x 5 collections)	H219
			Endometriosis	300	H219

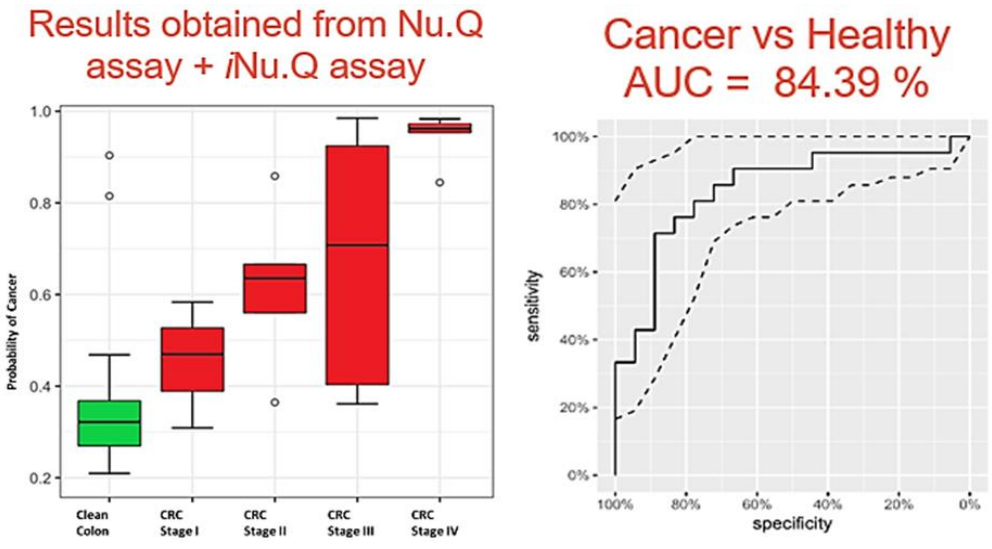
Source: VolitionRx

First proof-of-concept data with product-grade Nu.Q assays

The first proof-of-concept data with the product-grade assay were released with the Q418 financial results. Two studies were done using blood samples from a lung cancer cohort and one from a CRC cohort.

- In a lung cancer cohort (n = 76), a single Nu.Q assay achieved an area under the curve (AUC) of 85% in differentiating cancer versus healthy subjects. The assay was also able to detect stage one cancer.
- In a second confirmatory lung cancer cohort (n = 152), the same single Nu.Q assay also detected lung cancer with an AUC of 79%, cancer versus healthy subjects.
- In a CRC cohort (123 subjects), a single Nu.Q assay detected cancer with an AUC of 72% whereas a two-assay panel had an AUC of 84%, cancer versus healthy subjects.

Exhibit 3: Proof-of-concept results in CRC with product-grade assays



Source: VolitionRx

We note these should be interpreted as proof-of-concept or feasibility studies that provide a rationale to conduct larger trials, rather than actual clinical validity, which is the final step in R&D. Hence, we can draw limited conclusions, that VolitionRx sees the data as sufficient to plan larger studies. One notable insight is that the assays started differentiating cancer as early as stage one. This will have to be repeated in larger trials, but early detection is the ultimate goal in diagnostics. In addition, these studies used only one or two assays, but a commercial product could include a combination of several assays. A single assay measures one epigenetic modification in nucleosomes and there are many potential modification patterns expressed in different cancers. The challenge for VolitionRx is to obtain the best-performing combination of as few of the assays as possible. More assays in the panel than necessary would inflate the cost of the diagnostic test and would increase the risk of data overfitting.

Next steps

VolitionRx's ongoing activities in (human) cancer diagnostics and near-term news flow include:

- Exhibit 2 summarises this year's expected newsflow on generating proof-of-concept data with the updated assays. Although these are mainly small feasibility studies, as explained above, they all are conducted with product-grade assays and will deliver the first performance data, hence are potential catalysts for the share price.
- When it comes to larger programmes, VolitionRx indicated the lung cancer tests were impressive enough to expand the collaboration with the National Taiwan University by opening a prospective study in lung cancer patients, which will collect 1,200 blood samples (the latest announcement was released on 7 May 2019). The aim is to develop either a frontline screening test in lung cancer or a triage test after low-dose computed tomography (LDCT) (gold standard currently) to address the low specificity associated with LDCT. A total cost for VolitionRx is estimated at $320k over the next two years (until 2021). Preliminary data relating to the first 600 patient samples are expected to be released in Q120.
- Once VolitionRx evaluates the data from the ongoing proof-of-concept studies, we believe that it will make a decision how to best proceed and prioritize the analysis of the blood samples in its large biobank (Exhibit 1).
- Fosun Long March is one of the more recently announced partners in Asia. On 28 March 2019, VolitionRx announced a memorandum of understanding with the Asian conglomerate. The goal is to facilitate entrance into China. The final agreement is still to be reached, but the preliminary plan is to conduct three clinical studies in China in CRC, lung cancer and ovarian cancer. Fosun Long March, owned by the Shanghai Fosun Pharmaceutical conglomerate, is an in-vitro diagnostics company active in R&D, manufacturing and marketing of diagnostic and laboratory instruments and reagents. Financial details have not been disclosed yet.

Nu.Q Capture: An R&D project gaining pace

Early in 2018, VolitionRx described its progress with one of its internal R&D projects, which explores Nu.Q technology's potential in enriching nucleosomes of tumour origin for use in ctDNA detection. During its CMD event, for the first time VolitionRx released new details and invited KOL and VolitionRx's scientific advisory board member Professor Axel Imhof to present the progress.

The idea for Nu.Q Capture came from the collaboration of Professor Imhof and VolitionRx seeking to identify how mass spectrometry could be helpful to advance Nu.Q ELISA platform. Dr Imhof is a professor for protein analytics at the Biomedical Center of the Ludwig-Maximilians University of Munich (LMU) and the director of the Proteomics Core Facility of LMU's Biomedical Center. His area of expertise is mass spectrometry for protein analytics, especially characterising histone modifications.

Mass spectrometry is a technique where a test object sample is bombarded with a beam of electrons so the atoms and molecules in it are ionized or become charged. Subsequently, detectors record a spectrum of these ionised particles. This information can then be used to identify the composition of the test sample. Specifically for VolitionRx, this technique could significantly speed up the discovery process of new epigenetic modifications in nucleosomes. The ELISA method allows the targeting of one specific modification at a time. Although this is sufficient for a clinical test, in the discovery of biomarkers (nucleosome epigenetic modifications in this case) mass spectrometry allows the analysis of multiple nucleosome modifications (known and undiscovered) at the same time. The reason such use of mass spectrometry has become available for VolitionRx is the rapid technological advance of the technology. As Professor Imhof explained, only 10 years ago mass spectrometers were still rather cumbersome to work with.

The first challenge was that mass spectrometry would require larger blood sample volumes per run. The solution was to move away from traditional ELISA solid-surface plates and instead use magnetic beads to precipitate nucleosomes from plasma. The first proof-of-concept tests were done using recombinant nucleosomes. These and subsequent tests with blood plasma and serum showed that nucleosome immunoprecipitation can be achieved at required levels for mass spectrometry.

VolitionRx did indicate this is still an early R&D project, but the achieved results potentially have several interesting directions.

- As discussed, the enriched nucleosomes can be analysed with mass spectrometry for epigenetic modification discovery. The specific antibodies could be developed and used in Nu.Q assays.
- Another potential application is DNA sequencing. As discussed above, the arrival of cheap next-generation sequencing technologies prompted a surge in the R&D of so-called liquid biopsy tests. The main hurdle in ctDNA research is the very small amount of tumour DNA. Another layer of complexity is that there can be other types of DNA in the bloodstream, as seen in post-myocardial infarction patients or pregnant women, whose blood contains DNA from the baby (collectively ctDNA and other types are called cell-free DNA). For these reasons the ctDNA-enriching technology could be interesting to other companies in the field.

Nu.Q Vet: Push into animal health taking shape

Another notable highlight in 2018 was VolitionRx's push into animal health, which is a new application area for Nu.Q assays. Early in 2018, the company undertook a pilot veterinary study in collaboration with experts at the Texas A&M College of Veterinary Medicine and Biomedical Sciences. The results showed that using the same assays as in humans, the researchers were able to detect nucleosomes in samples from dogs diagnosed with cancer. Animal health could potentially be a commercially lucrative area due to the combination of a large market, high unmet need and substantially lower regulatory hurdle than in humans. As a result, VolitionRx signed a memorandum of understanding with the Texas A&M University to develop a commercially feasible product. Texas A&M University was chosen for its world-leading reputation in veterinary medicine and the interest from the organisation seems strong as the university could potentially negotiate a shareholding in VolitionRx's US subsidiary, which is being established to run the animal health programme.

The second KOL invited to the recent VolitionRx CMD was Dr Heather Wilson-Robles, who is an Associate Professor at the Texas A&M University. Dr Wilson-Robles presented an overview of the programme, commercial opportunity and the work that has been done so far (a video presentation is available on VolitionRx's website). The key points are:

- Feasibility studies showed that nucleosomes, specifically in dogs, are similar to humans and detectable with the Nu.Q platform. This applied to many other animals that VolitionRx and the Texas A&M university team looked at. Dogs were chosen as the first target population.
- Cancer is relatively more prevalent among dogs due to a combination of negative external factors (many are the same as for humans), but importantly many dog breeds have a much higher than normal risk of developing cancer during their lifetime as a side effect of the breeding process.
- The pet dog market is very large and cancer diagnostics represent a high unmet need. In the US there are c 55 million dogs and approximately 4.2 million cancer diagnoses each year. The increasing size is a combination of increased pet ownership and increased spend per pet.
- There are no reliable non-invasive tests to diagnose cancer in dogs, therefore most animals are diagnosed with an advanced disease. Diagnostics include expensive imaging or invasive operations, which must be done under anaesthesia. This limits the use of these options due to financial costs. A cheap (preliminary price is estimated at $100–200 per test) and simple test could be used for screening dog breeds that have a high risk of cancer.

The Texas A&M University researchers have conducted a study involving blood samples from 112 dogs in three different geographical areas and the Nu.Q platform worked reliably. Another 100 samples have already been collected and will be used to finalise the Nu.Q assay panel. Dr Wilson-Robles described that the first panel can be used to develop a research-use only product. The validation set is expected to be c 200 samples (50:50 diseased and control subjects). If the data are positive, this should be sufficient for the United States Department of Agriculture (USDA) regulatory approval, which is typically less onerous than from the FDA. Detailed timelines or specific cancer indications are not known yet.

Highlights of prioritised cancer indications: CRC

Historically, CRC was the VolitionRx's main focus, partly due to well-defined screening programmes in many countries. CRC is one of the most common cancers, with approximately 1.36 million cases per year worldwide.[1] Prognosis is highly dependent on the stage at which the cancer is detected, highlighting the need for improved CRC screening programme participation. According to the American Cancer Society the five-year survival rate for patients who have their cancer detected in the localised 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 the disease early. The US Preventative Services Task Force (USPSTF) provides guidance on a series of testing strategies for adults between the ages of 50 and 75:

- an annual faecal occult blood test (FOBT) or 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.

The guidance is now under review with the main revision focus on when the screening should be initiated. The American Cancer Society has lowered the recommended age to start screening for CRC from 50 to 45 years old in its updated screening guidelines released in May 2018. In Europe there are multiple national initiatives to screen the at-risk population using similar methods as in the US, but this varies by country.

[1] International Agency for Research on Cancer

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

None of these tests are ideal. The compliance for faecal testing is low (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 (US population likely to increase if new USPSTF guidelines also lower the screening age).

Common CRC screening technologies

There are a number of different technologies being used or in development for detection of CRC and they fall into three categories: invasive, faecal and blood.

Exhibit 4: 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	Faecal	$23	74%	24%	96%
FOBT	Various	Faecal	$5	40–70%	12–24%	93–98%
Cologuard	Exact Sciences	Faecal	$428	92%	42%	87%
Epi proColon	Epigenomics	Blood	$339	68–72%	22%	81%
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.

The FOBT is a relatively cheap (~$5) test in which stool samples are collected and analysed for blood. A limitation of the test is that it typically involves collection of up to three different faecal samples on three different days, negatively affecting compliance. There are a variety of different versions of the test but sensitivity is 40–70% and specificity is 93–98% according to the Agency for Healthcare Research and Quality. Sensitivity for precancerous lesions was rather low, generally between 12% and 24% depending on the specific test.

The FIT was developed specifically to target human haemoglobin and not be affected by dietary sources. It is more expensive than FOBT, but at ~$23 it is still relatively inexpensive. FIT is considered more sensitive than FOBT, 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 faecal 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 normalisation marker (beta-actin), with a FIT test. Unlike the other faecal 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. 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 colonoscopy, as it is highly accurate with few false positives or negatives. It is an invasive procedure that requires extensive bowel preparation and anaesthesia. The adverse event rate is relatively high with a hospitalisation rate for serious complications of one in 200, usually bleeding, colonic perforation or a negative reaction to anaesthesia.[4] The colonoscopy is also the most expensive screening method for CRC at a cost of $1,200 per procedure according to Centers for Medicare and Medicaid Services (CMS).

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

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

Epi proColon is the only blood test based on detecting aberrantly methylated DNA of the Septin9 gene. As the test is based on just one marker it is not very accurate, with a significant number of false positives and false negatives. In analysing its pivotal trial data, the FDA commented the test yields 37.7 false positives per every true positive compared to 5.4 false positives per every true positive for FIT.

The Nu.Q opportunity in CRC screening

VolitionRx has various clinical programmes to support the marketing and commercialisation of the frontline Nu.Q CRC test in the US, Europe and Asia. The programmes (Exhibit 1) have finished collecting blood samples, which are now part of VolitionRx's biobank. Once VolitionRx has identified the right Nu.Q assay panel following the upgrade, it will be able to run the studies relatively quickly, as prospective collection is the time-consuming part. More precise development details are not known yet.

Besides developing a test for frontline CRC screening, VolitionRx has also explored the potential for so-called triage for colonoscopy approach using a separate Nu.Q panel. This simplified test is not designed to diagnose cancer in the frontline setting; rather, it is 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 programmes. The total addressable market for the triage test is smaller compared to the frontline test, but is still substantial if low current compliance could be increased. There are approximately 136 million patients in Europe eligible for routine CRC screening. However, a recent study of faecal testing in France found compliance rates between 47% and 54%[5] over four consecutive two-year periods. A study in Spain identified an FIT positivity rate of 7.2%,[6] similar to rates observed in the US (7.0%).[7] This corresponds to a total market of 2.5 million individuals per year across Europe if all nations adopted FIT screening programmes, or a little over 1% of the predicted US and European frontline CRC screening market.

Previous data

Earlier versions of the Nu.Q assays have been evaluated in several separate trials for CRC. As explained above, because VolitionRx has been upgrading its assays using recombinant nucleosomes as control, we believe little inference can be made from the historical results. Nevertheless, they are indicative at least to some extent of nucleosomics' potential in 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 in detecting CRC (at 78% specificity). Because all the patients included in the screen had a variety of bowel disease, including polyps and adenomas, the hurdle for the test differentiate CRC vs healthy or other bowel disease was higher, although the test performed rather well despite that.
- The company followed this retrospective study with a prospectively 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 was selected post-hoc, which identified CRC with 74% sensitivity and 90% specificity versus healthy controls. The sensitivity

[5] 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.

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

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

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.

Lung cancer

Lung cancer is one of the top indications that VolitionRx is focusing on following the recent positive proof-of-concept results with the upgraded Nu.Q assays. It is another disease that can benefit from early detection, but unlike CRC, widespread screening efforts are limited by technology. The majority of lung cancers are identified late once the cancer has metastasised (57%), when the five-year survival rate is only 4.2%.[8] These survival rates are significantly higher (54.8%) if the cancer is detected when still localised.

Because of its close association with smoking, the population at risk of lung cancer is much lower than CRC. The CMS recommend screening for those aged between 55 and 74 with ≥30 pack per year smoking history and cessation fewer than 15 years ago, which results in 8.6 million people in the US (compared to the 89 million screening population for CRC). Therefore, the theoretical market size is smaller than for CRC, but the unmet need is higher as the screening options used in practice are very limited.

There are a number of possible different screening methods used in practice (Exhibit 5), but the current standard advocated by the USPSTF is a yearly low-dose CT (LDCT) scan. LDCT is an effective method of identifying lung cancer (89% sensitivity, 93% specificity) but it is associated with radiation exposure. The amount of radiation exposure is small on an individual basis (2mSv), but on the scale of the total number of screened patients, it represents a very large level of exposure with potential public health effects. So, there is still a medical need for new screening regimens.

Exhibit 5: Relative efficacy and cost of lung cancer diagnostics

Test name	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

Source: *Chest Journal*[9], ASTRO, *Cancer Journal*, company reports

Pancreatic cancer

Another indication with a desperate need for early screening capabilities is pancreatic cancer. The five-year survival rate for patients with distant metastasis is one of the worst in oncology at 2.4%, whereas it is 27.1% when localised. The deadly reputation that pancreatic cancer has earned could be significantly improved 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, which is a highly invasive procedure that can require sedation. The only other screening method in common use is a blood test called CA19-9. Current ASCO guidelines recommend against using 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.[10] Its primary use is to assess the response to the therapy for already established pancreatic cancer patients, but

8 SEER database.

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

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

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)[8] 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. These features mean that although the unmet need is significant, the screening market is less well developed than CRC and lung cancer. However, the fact that CA19-9 is used in diagnostic work-up in general means that in broader terms, there is a demand for novel diagnostic, especially non-invasive methods in pancreatic cancer.

VolitionRx is yet to announce proof-of-concept data with the upgraded assays, but with the previous versions of the assays, the initial accumulated data seemed supportive. The assays were 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 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.

VolitionRx has also completed blood sample collection, which is part of the 750-person study run in collaboration with the German Cancer Research Center. These samples will be used to test the product-grade Nu.Q assays.

Exhibit 6: 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

Source: *Annals of Oncology*,[11] VolitionRx, *Pancreatology*

Sensitivities

VolitionRx's risks include demonstrating the efficacy of its Nu.Q tests and communicating this to regulatory and policy-making bodies in the US, Europe and Asia. The company has been upgrading its assays, which means all prospective studies are still to be performed. The initial proof-of-concept results from lung cancer and CRC seem encouraging, but much larger studies will be needed to confirm the diagnostic validity. However, since its establishment VolitionRx has accumulated a large blood sample bank, which means that once the assays are ready, the studies could be performed relatively quickly. Presuming successful R&D and regulatory approval, VolitionRx also faces commercial risks. Adoption in Europe depends on convincing centralised screening programmes of the importance of adopting the test and the Nu.Q tests must compete with low-cost alternatives such as FIT. The mitigating factor in this regard is that Nu.Q technology is based on classic ELISA, which is also a low-cost and readily available procedure. Although the company is sufficiently funded for the next 12–18 months, it is likely that further funding rounds will be needed. That said, all past shares issues were carried out by VolitionRx successfully.

Valuation

Our VolitionRx valuation is $215m or $5.46/share compared to previous $233m or $6.60/share. This is mainly due to revised launch dates, which was partially offset by slightly higher net cash

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

position and rolling our model forward. In addition, the warrant exercise had some dilution effect on our valuation per share.

The main revision we have made to our R&D projects was the delay of the launch of commercial products by two years in all indications (to 2021-2022). We believe that the upgrading of the assay was a necessary step to ensure commercial viable products. Our other R&D assumptions remain unchanged as described in our previous notes.

The upcoming multiple data announcements from the proof-of-concept studies should provide interesting catalysts for the share price. While, as described above, these will be still be small feasibility studies, all of those studies will involve the product-grade assays. Of the larger programmes, VolitionRx indicated that the interim readout from the lung cancer trial in Asia is expected in Q120 (n = 600). For the time being we still do not include Nu.Q Vet or Nu.Q Capture commercial potential in our valuation due to early stage of these programmes. However, there is potential for the Nu.Q Vet programme to progress relatively fast compared to cancer diagnostics in humans due to lower R&D hurdles in animal health. Next steps in this programme are the establishment of the assay panel and a subsequent validation study. More details on timelines should be released later in 2019, we believe.

Exhibit 7: 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%	2021	$404	2034	56% peak margin	$152
	Colorectal triage	Development	40%	2021	$42	2034	50% peak margin	$10
	Lung	Development	20%	2022	$132	2034	61% peak margin	$28
	Pancreatic	Development	20%	2022	$42	2034	58% peak margin	$6
Total								$197
Cash and cash equivalents (Q119) + $5m after warrant exercise ($m)								$18.9
Total firm value ($m)								**$215**
Total basic shares (m)								39.5
Value per basic share ($)								**$5.46**
Warrants and options (m)								5.2
Weighted average exercise price ($)								$3.71
Cash on exercise ($m)								$19.4
Total firm value (f. d.) ($m)								$235
Total number of shares (f. d.)								44.7
Value per share (f. d.) ($)								$5.25

Source: Edison Investment Research, VolitionRx reports

Financials

VolitionRx reported no income and an operating loss of $4.0m in Q119, compared to $4.6m a year ago, which is largely in line with our expectations. VolitionRx's cash burn is around $4m per quarter. The company had cash of $16.2m at end-Q119 after it had raised $6.7m gross in March from the warrant exercise. More warrants were exercised after the end of Q119, bringing in an additional $5m for the company.

VolitionRx reiterated its guidance that cash burn is likely to be $4m per quarter for the near future. This suggests the cash runway extends well into 2020. VolitionRx had $1.8m in gross debt at end Q119. According to our estimates, the funding gap in 2020 is $7.5m (shown as long-term debt in Exhibit 8).

The only significant change to our estimates is that we have postponed the commercial launch of products for clinical use to 2021 or 2022, as described above. Other that we only finetuned our operating forecasts following the Q119 results. We include small initial sales of $50k in 2019 and

$100k in 2020 from the research use only (RUO) Nu.Q kits that Active Motif is distributing. Notably, VolitionRx has not recorded sales yet, so there is little visibility of the commercial potential of RUO kits. As we noted before, the primary benefit of selling Nu.Q assays for research should come, in our view, from increasing awareness in the scientific community. This could mean VolitionRx's technology is tested in more projects and ultimately lead to peer-reviewed article publications.

Exhibit 8: Financial summary

$'000s	2016	2017	2018	2019e	2020e
Year end 31 December	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS					
Revenue	0	0	0	50	100
Cost of Sales	0	0	0	0	0
Gross Profit	0	0	0	50	100
Research & Development	(7,905)	(8,906)	(10,907)	(10,561)	(11,195)
Sales, General & Administrative	(4,525)	(6,140)	(6,991)	(7,690)	(8,459)
EBITDA	(12,430)	(15,046)	(17,898)	(18,201)	(19,554)
Operating profit (before amort. and except.)	(12,430)	(15,046)	(17,898)	(18,201)	(19,554)
Intangible Amortisation	0	0	0	0	0
Other	0	0	0	0	0
Exceptionals	0	0	0	0	0
Operating Profit	(12,430)	(15,046)	(17,898)	(18,201)	(19,554)
Net Interest	(20)	(73)	(111)	(125)	(141)
Other	436	414	0	0	0
Profit Before Tax (norm)	(12,450)	(15,119)	(18,009)	(18,326)	(19,695)
Profit Before Tax (FRS 3)	(12,014)	(14,705)	(18,009)	(18,326)	(19,695)
Tax	0	0	0	0	0
Deferred tax	(0)	(0)	(0)	(0)	(0)
Profit After Tax (norm)	(12,450)	(15,119)	(18,009)	(18,326)	(19,695)
Profit After Tax (FRS 3)	(12,014)	(14,705)	(18,009)	(18,326)	(19,695)
Average Number of Shares Outstanding (m)	23.0	26.4	37.0	39.5	41.1
EPS - normalised ($)	(0.54)	(0.57)	(0.49)	(0.46)	(0.48)
EPS - FRS 3 ($)	(0.52)	(0.56)	(0.49)	(0.46)	(0.48)
Dividend per share ($)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	2,721	4,057	3,587	2,838	2,270
Intangible Assets	602	576	467	467	467
Tangible Assets	2,119	3,481	3,120	2,371	1,803
Other	(0)	(0)	0	(0)	(0)
Current Assets	21,846	10,319	13,657	10,259	1,227
Stocks	0	0	0	0	0
Debtors	0	0	0	(91)	18
Cash	21,679	10,116	13,427	10,121	980
Other	167	202	230	230	230
Current Liabilities	(2,033)	(2,290)	(2,333)	(2,283)	(2,308)
Creditors	(2,003)	(1,847)	(1,917)	(1,867)	(1,892)
Short term borrowings	(31)	(444)	(417)	(417)	(417)
Long Term Liabilities	(1,524)	(2,376)	(3,015)	(3,015)	(10,515)
Long term borrowings	(432)	(1,313)	(1,984)	(1,984)	(9,484)
Other long term liabilities	(1,092)	(1,063)	(1,031)	(1,031)	(1,031)
Net Assets	21,009	9,709	11,895	7,799	(9,326)
CASH FLOW					
Operating Cash Flow	(8,865)	(12,193)	(14,733)	(14,966)	(16,640)
Net Interest	0	0	0	0	0
Tax	0	0	0	0	0
Capex	(415)	(1,425)	(302)	(1)	(1)
Acquisitions/disposals	0	0	0	0	0
Financing	25,302	998	17,245	11,661	0
Dividends	0	0	0	0	0
Other	(553)	(136)	(138)	0	0
Net Cash Flow	15,470	(12,756)	2,073	(3,306)	(16,641)
Opening net debt/(cash)	(5,916)	(21,216)	(8,360)	(11,026)	(7,720)
HP finance leases initiated	0	0	0	0	0
Exchange rate movements	146	(89)	(379)	0	0
Other	(316)	(12)	973	0	0
Closing net debt/(cash)	(21,216)	(8,360)	(11,026)	(7,720)	8,921

Source: Company data, Edison Investment Research

Contact details	Revenue by geography
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Management team

Chief Executive Officer: Cameron Reynolds MBA	Chief Financial Officer: David Vanston
Cameron Reynolds founded the company in Singapore in 2010. Mr Reynolds founded Mining House and served as managing director and director from 2004 until 2011; he was responsible for identifying potential mining projects. Since 2005, Mr Reynolds has held several board directorships. Cameron was educated at the University of Western Australia (bachelor of commerce and MBA).	David Vanston has 20 years of financial management experience. Prior to Volition and Octo Telematics, David held positions as vice president of Excorp Medical, an early-stage company, chief financial officer for GrowHow and vice president Europe, finance for Monster Worldwide. Mr Vanston managed and oversaw the accounting, finance, tax, treasury and financial planning. 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 Jason 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).

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Cameron Reynolds	2.9%
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