EDISON

VolitionRx

Initiation of coverage

A PSA-like test for multiple cancers?

Healthcare equipment & services

3 August 2015

Price	**US$3.7**
Market cap	**US$66m**

Net cash ($m) at 31 March 2015	11.0
Shares in issue	17.9m
Free float	67.3%
Code	VNRX
Primary exchange	NYSE MKT
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(6.3)	10.8	94.7
Rel (local)	(8.1)	9.8	78.7
52-week high/low	US$5.24	US$1.68	

Business description

VolitionRx is a Belgium-based diagnostics company focused on developing blood-based cancer diagnostics based on its proprietary NuQ technology. Its lead program is in colorectal cancer, which may enter the European market in 2016.

Next events

Pancreatic data publication	Q315
CE Mark Application	Q315
Additional CRC data	Q415

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VolitionRx develops low-cost blood-based cancer diagnostics based on its proprietary NuQ technology, which detects the level and structure of nucleosomes in the blood using one drop of blood serum. It is currently focused on colorectal cancer (CRC), a very large opportunity with around 225 million people aged 50-75 in the US and EU eligible for screening. Data so far have suggested 84% sensitivity and 78% specificity in detecting CRC. NuQ also has the potential to detect multiple cancers. We value the company at $11.64 per basic share.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/14	0.0	(8.4)	(0.62)	N/A	N/A	N/A
12/15e	0.0	(11.3)	(0.67)	N/A	N/A	N/A
12/16e	0.9	(18.8)	(1.08)	N/A	N/A	N/A
12/17e	2.5	(23.7)	(1.31)	N/A	N/A	N/A

Note: *PBT and EPS are normalized, excluding intangible amortization, exceptional items and share-based payments.

CRC data promising so far

In data from an initial 938-subject tranche of a 4,800-subject CRC trial, the NuQ diagnostic platform had 84% sensitivity and 78% specificity. Importantly, it shows promise in being able to detect pre-cancerous polyps. Additional large tranches of data from this trial should be released in Q415.

Ability to detect multiple cancers

Pilot studies to detect lung and pancreatic cancers have yielded positive results (>70% sensitivity and >90% specificity for both) and the company is currently running a study of 4,200 patients with 27 of the most prevalent cancers to understand which cancers NuQ has the most potential in. Data from the study should start to be released in H116. The potential exists for multiple cancers to be detected through one blood draw.

PSA-like potential in CRC

The PSA blood test is used to screen for prostate cancer as well as to monitor the effectiveness of treatment. It has 71% sensitivity and 91% specificity, which is in the ballpark of VolitionRx's tests and is high enough for 30 million men annually to be tested for PSA. As the costs of the two tests are also similar ($40-80 retail), there is potential for significant adoption of the NuQ platform in multiple cancers.

Valuation: $11.64 per basic share

Using a risk-adjusted NPV model, we value the company at $191m or $11.64 per basic share. On a fully-diluted basis, we value the company at $198m or $9.23 per diluted share. We expect VolitionRx to have c $8.6m in cash at the end of Q2 and to raise additional capital early next year or even earlier ($50m by 2017). Upcoming major catalysts of additional CRC data and a CE mark application in Europe in Q3 as well as the CE mark approval in 2016 could provide upside to our valuation.

Investment summary

Company description: A multi-cancer screening tool

VolitionRx is an emerging life sciences company that was founded as Singapore Volition, a Singapore corporation, in August 2010. In October 2011, the company was publicly listed and changed its name to VolitionRx, and traded on the OTC Bulletin Board. In February 2015, the company up-listed to NYSE MKT.

VolitionRx develops low-cost blood-based cancer diagnostics based on its proprietary NuQ technology, which detect the level and structure of nucleosomes in the blood using one drop of blood serum. It is currently focused on colorectal cancer (CRC), a very large opportunity with at least 125 million people aged 50-75 not currently being screened with colonoscopies or fecal-based tests for CRC in the US and EU. However, it is also conducting a large trial that involves patients with the 27 most prevalent cancers to understand quickly which cancers they have the most promise with, as well as demonstrate an ability to test for multiple cancers through one blood draw. Also, just like the current PSA blood test for prostate cancer, NuQ can be used to monitor the effectiveness of anti-cancer therapy.

Valuation: $11.64 per basic share

Using a risk-adjusted NPV model with a 12.5% discount rate that assumes a 30% chance of commercial success and $404m in peak CRC sales, we value the company at $191m or $11.64 per basic share. On a fully-diluted basis, we value the company at $198m or $9.23 per diluted share. We expect VolitionRx to have c $8.6m in cash at the end of Q2 and to raise additional capital early next year ($50m total by 2017). Upcoming catalysts of additional CRC data and a CE mark application in Europe in Q3 and CE mark approval in 2016 could provide upside to shares.

Financials: Low burn now but that will change

VolitionRx has $11m in cash and equivalents as of the end of Q115. With a burn rate of ~$2m per quarter, it has enough cash to make it through additional data releases. However, that expense rate will need to increase once it obtains CE mark approval as it will need to invest in a commercial organization. Also, it will need to invest in clinical studies to obtain FDA approval through the PMA route in the US. Note that Exact Sciences, which received FDA approval for Cologuard in Q314, had an accumulated deficit of $421m by the end of that year, though NuQ is less expensive to perform and therefore should be less expensive to develop.

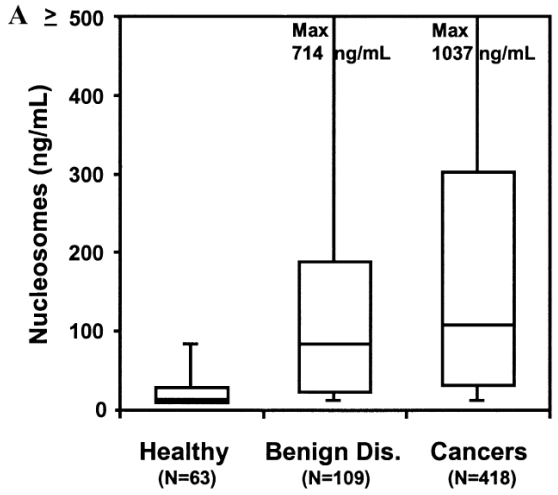
Sensitivities: It is all about accuracy, price and distribution

For a diagnostics company, regulatory approval, especially in the US, is purely a numbers game, namely specificity and sensitivity. Both numbers are important. Too low a specificity and too many people may be receiving unnecessary invasive biopsies, which may have adverse events associated with them. Too low a sensitivity and tumors are missed. Once on the market, it takes quite a bit of time to gain distribution and acceptance. In Europe, the market is very fragmented with unique situations in each country. Finally, health systems are extremely price sensitive with current FIT/FOBT tests for CRC costing $5-23 each. In the US, VolitionRx will likely start with a CLIA-lab strategy prior to official FDA approval; however, that will severely limit its ability to distribute its test beyond the CLIA-certified lab it licenses its technology to and will mean a slow ramp-up in revenues and a lower probability of reimbursement (also, draft guidelines from the FDA suggest that the CLIA-waiver loophole may be closing). True acceptance will likely only come after a full FDA approval and inclusion in various cancer screening guidelines.

One test to diagnose them all

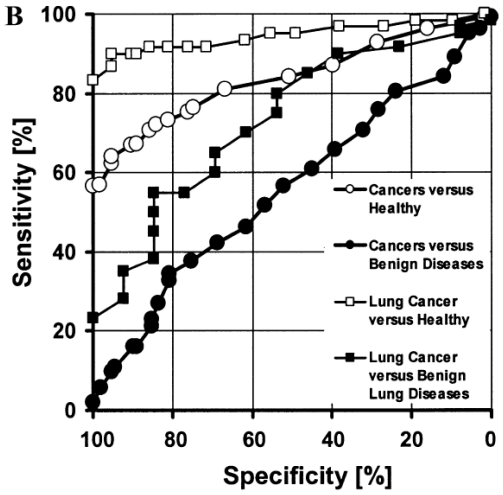
VolitionRx has developed epigenetic NuQ assays that detect the level and structure of nucleosomes in blood. A nucleosome is a unit of DNA packaging and is composed of around two turns of DNA wrapped around a set of proteins called histones. When a cell dies, DNA strings are broken up into individual nucleosomes. As cancer is generally characterized by high levels of cell death, nucleosome levels tend to rise in the blood of cancer patients (see Exhibits 1 and 2).

Exhibit 1: Nucleosome levels in healthy controls, patients with benign disease and cancers



Source: Annals of the New York Academy of Sciences

Exhibit 2: Specificity and sensitivity profile of nucleosomes to detect cancers

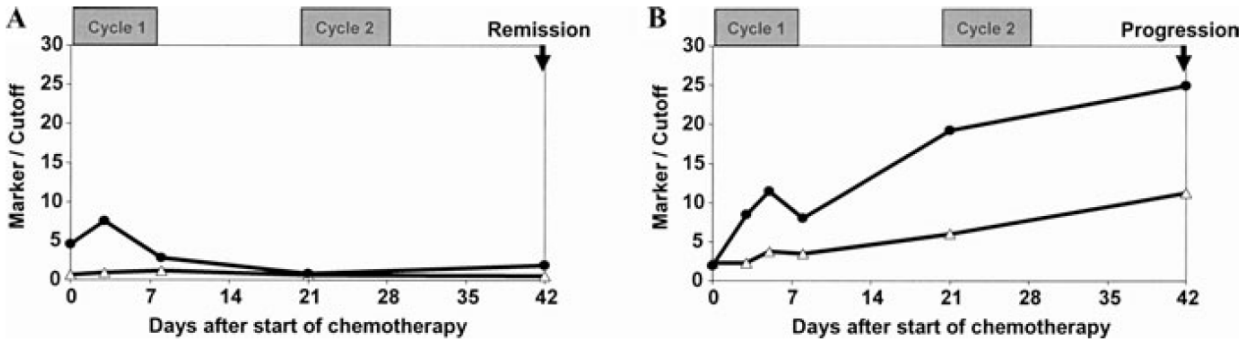


Source: Annals of the New York Academy of Sciences

One issue with nucleosomes in general is that they do increase in situations that are not related to cancer, especially when in the presence of infectious disease or other organ-specific problems (eg Crohn's disease and irritable bowel syndrome). However, all nucleosomes are not created equal and have a very high level of structural variety. That is why VolitionRx's NuQ tests not only for nucleosomes but specific structures of nucleosomes that are associated with cancer.

Another possible benefit of nucleosomes besides detecting cancer is monitoring the efficacy of treatment with a signal potentially coming as early as seven days post treatment (see Exhibit 3).

Exhibit 3: Nucleosome levels (line with black dot points) in two patients, one with remission (A) and one with progression (B) following chemotherapy.



Source: Annals of New York Academy of Sciences

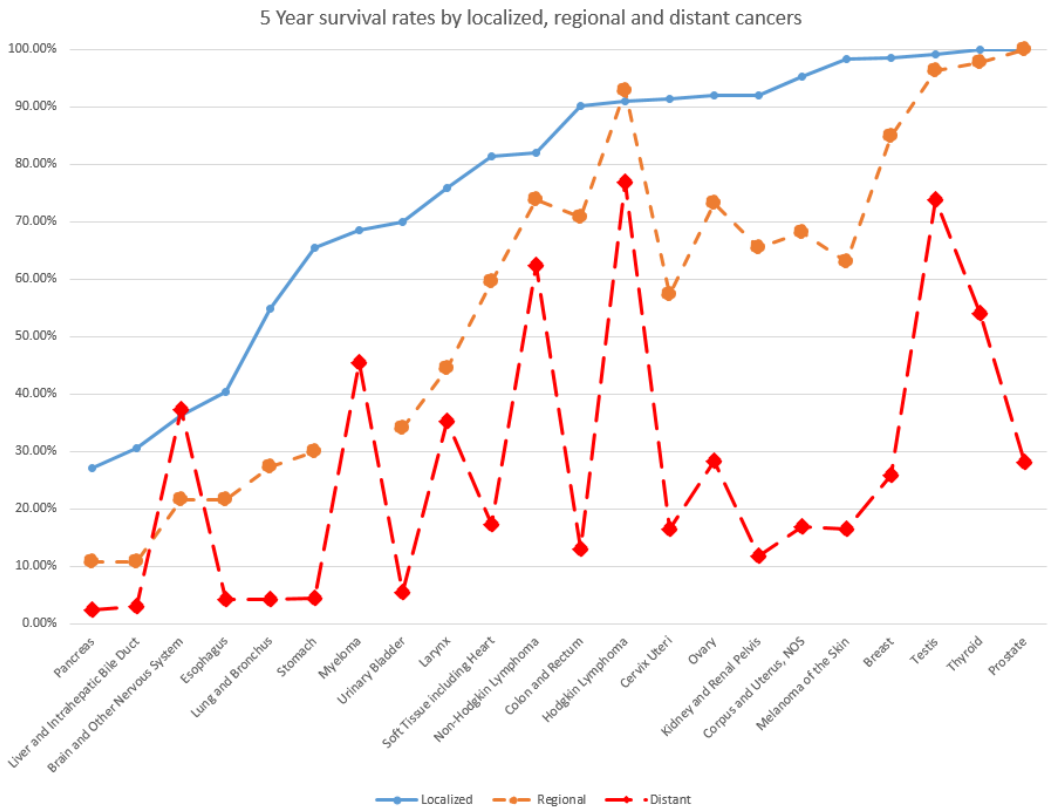
Nucleosomes seem to have a profile very similar to the PSA test, which is a blood test that measures prostate-specific antigen, a protein produced by cells of the prostate gland. It was originally approved in 1986 to monitor the progression of prostate cancer but was approved in 1994 to screen for prostate cancer. Like with nucleosomes, PSA levels also rise in the presence of benign diseases such as prostatitis, benign prostatic hyperplasia (BPH) and urinary tract infections.

With sensitivity of 72.1% and specificity of 93.2% (100% would be perfect precision) for detecting prostate cancer in conjunction with a digital rectal exam[1], the PSA test was able to achieve extremely high market acceptance with around 30 million American men undergoing PSA testing per year at a cost of ~$3bn according to the National Committee for Quality Assurance.

However, one key difference is that there is no reason to believe that testing for nucleosomes needs to be limited to any specific cancer and could potentially be used to screen for multiple cancers. VolitionRx has already announced promising data in colorectal, lung and pancreatic cancer and is currently conducting a 4,200-patient prospective study that involves the 27 most prevalent cancers (95% of the total), which should provide signals of where NuQ testing can be most effective.

The failure of current diagnostic modalities in most cancers is that detection tends to occur at late stages when the cancer tends to be less treatable and mortality is high. For example, according to the National Cancer Institute, 57% of lung cancers are diagnosed when there are already distant metastases, a stage at which the five-year survival rate is only 4.2%. The potential benefit of blood-based screening is clear: the easier it is to screen, the more screening will take place, which will help detect cancer earlier when it is more treatable and survivable (see Exhibit 4).

Exhibit 4: Five-year survival rates by type and stage of cancer



Source: SEER Database

The final benefit of the NuQ platform is that unlike some of the other diagnostic modalities, NuQ tests can be performed on standard ELISA systems and will not require specialized instrumentation. ELISA systems can be found at centralized laboratories as well as all major hospitals in the US and Europe. As NuQ tests will only require one drop of blood serum per test, this means the test can be run alongside other tests as part of a panel without any special training or steps needed. This drastically reduces the costs to perform the test, which is a major hurdle for adoption.

1 Mistry et al., Journal of the American Board of Family Practice 2003;16:95-101.

VolitionRx currently has a variety of clinical trials ongoing (see Exhibit 5), which should enable it to gain a greater understanding of where its platform works best.

Exhibit 5: Ongoing VolitionRx clinical trials

Cancer	Sample size	Population
Colorectal	4,800	Subjects with CRC, polyps or adenomas, benign bowel diseases or other malignancies. All subjects underwent colonoscopy.
Colorectal	14,000	All subjects will have a FIT test and those FIT positive will have a colonoscopy.
Colorectal	800	Subjects with precancerous polyps, no polyps or CRC and those with early-stage CRC.
Colorectal	250	Longitudinal study of subjects with suspected CRC to evaluate NuQ for early detection and prognosis.
Lung	600	Subjects with lung cancer with different subtypes and stages as well as those with benign lung diseases and healthy subjects.
Prostate	Unknown	Subjects with anaplastic prostate cancer and those without, and whether NuQ can differentiate them from castration resistant prostate cancer.
Prostate	120	Subjects with prostate cancer and those without.
Ovarian	40	Subjects with ovarian cancer and those without.
Endometriosis	500	Subjects with endometriosis confirmed by laparoscopy as well as those without.
27 most prevalent cancers	4,800	Subjects with and without various cancers to evaluate NuQ for early detection and differences in nucleosome structures between cancers.

Source: VolitionRx

Shifting the paradigm in the CRC market

VolitionRx is currently focusing its development on CRC, an extremely large market with around 225 million people eligible for screening in the US and EU. CRC is a market where patients would greatly benefit from early screening as 56% of CRC cases are detected after the cancer has spread at least regionally, and the five-year survival rate is 90.1% when the cancer is localized and only 13.1% if it involves distant metastases, according to the National Cancer Institute.

In data from an initial 938-subject tranche of a 4,800-subject CRC trial, the NuQ diagnostic platform had 84% sensitivity and 78% specificity. Importantly, it shows promise in being able to detect pre-cancerous polyps with 60% sensitivity. Additional large tranches of data from this trial should be released in Q415.

In the US the current recommendations are that adults aged 50 and older should be tested with one or more of the following to detect CRC:

- an annual fecal occult blood test (FOBT) or fecal immunochemical test (FIT);
- flexible sigmoidoscopy every five years, with FOBT/FIT every three years; or
- colonoscopy every 10 years.

There are quite a few weaknesses with this system. Firstly, FOBT and FIT tests are very consumer unfriendly as they require handling of feces, severely limiting uptake, and are also associated with high false-negative rates, missing many potential cancers (see Exhibit 6). Secondly, while accurate, colonoscopy is invasive, is associated with adverse events and the standard only requires one performed every 10 years, missing many cancers until it is too late.

Exhibit 6: Current CRC screening technology comparison

	Sensitivity (%)	False negative rate (%)	Specificity (%)	False positive rate (%)	Cost per test ($)	Number of tests in US annually (m)	Negatives
Colonoscopy	95	5	95	5	$1,000-3,000	4.3	Invasive, adverse events, cost
FOBT	50	50	98	2	5	5.6	Fecal-based test, high false negative, accuracy depends on which specific FOBT variant used
FIT	68	32	97.4	2.6	23	4.6	Fecal-based test, high false negative
Cologuard (Exact Sciences)	92	8	87	13	649	~0.1 (launched 10/14)	Fecal-based test, high cost

Source: FDA, World Gastroenterology Organisation, Exact Sciences, VolitionRx

Finally, due to the consumer unfriendly nature of these modalities, the Centers for Disease Control (CDC) estimates that 28% of those in the US who should be tested, are not being tested at all. Data

from the EU are even starker, with major variations across nations and an average CRC screening compliance rate of only 12.7% for the EU as a whole, according to the OECD.

There are quite a few players looking to improve on the CRC screening market. Exact Sciences, which markets the Cologuard test in the US and EU, analyses the DNA that is shed into stool and has markedly improved on the sensitivity of fecal-based tests. However, it is still a fecal-based test and is over an order of magnitude more expensive than FIT and FOBT tests.

There are also a number of small, mostly private companies that are developing blood screening tests to screen for colorectal cancer, using a variety of different markers and at varying cost, many of which have not funded large trials to prove efficacy and gain FDA approval (see Exhibit 7).

Exhibit 7: Blood-based screening tests for CRC

Test Name	Company	CRC sensitivity (%)	False negative rate (%)	Specificity (%)	False positive rate (%)	Cost per test ($)	Method	Availability
Epi proColon	Epigenomics	72.2	27.8	80.8	19.2	141	Septin 9	CE mark in EU
ColonSentry	Gene News	72	28	70	30	350	7 biomarkers	CLIA in US
ColoMarker	EDP Biotech	98	2	84	16	<100	CA11-19	CE mark in EU
Colox	Novigenix	75	25	91	9		29 gene panel	CE mark in EU
EarlyTect Colon Cancer	Genomic Tree	87	13	95.2	4.8		SDC2	
Cologic	Phenomenome Discoveries	86	14	90	10	75-95	GTA-446	Canada
CC Detect	Panacea Global	99	1	91	9	200	HAAH	CLIA in US
ColoVantage	Quest (license from Epigenomics)	70	30	89	11	355	Septin 9	CLIA in US
NuQ	VolitionRx	84	16	78	22	40-80	Nucleosome	

Source: Company reports

The highest-profile company is Epigenomics, which is developing Epi proColon. It has received a CE mark in Europe but failed its original pivotal study for FDA approval. According to the FDA, Epi proColon needed to demonstrate sensitivity of at least 65% and specificity of at least 85%. As the lower bound of the 95% confidence interval was lower than both targets (53.4% on sensitivity and 76.7% on specificity), the FDA rejected the initial application. Epigenomics now believes it can gain approval through the results of the ADMIT study, which shows that CRC screening compliance increases when patients receive a choice of Epi proColon (blood-based) instead of FIT. It will be important to see if this does lead to FDA approval of the test, as, based on the evidence so far, NuQ would likely miss FDA targets for specificity unless the test is improved.

Specificity is especially important to the FDA as too many false positives would lead to unnecessary colonoscopies, which have adverse events associated with them. As an example, if you have a disease that strikes 1% of the population, and you have a screening test for the entire population with 90% specificity, that means 10% of the population will have false positive results, 10 times more than the incidence of the disease. According to an FDA analysis, the standard FIT test has 5.4 false positives per true positive test. The Epi proColon test would have 37.7 false positives per true positive. As NuQ has a similar specificity to Epi proColon, it would likely receive a similar criticism assuming it does not improve on the test prior to seeking FDA approval.

While some of the other competitors in this space appear to have very promising specificity, sensitivity and at an attractive price point, the funding and distribution capabilities of most are limited and without both it is unclear how they would have wide use. Quest, the diagnostics giant, has been marketing its version of the Epi proColon, dubbed ColoVantage, since 2009, but it is generally not reimbursed and costs the consumer $355, which has severely limited sales.

VolitionRx's current strategy is to focus on the EU by applying for a CE mark in Q3 and obtaining it in 2016. This will allow it to market the test in Europe. However, the market is very fragmented with unique situations in each country. Also, governments organize much of the cancer screening so the barriers to entry are quite high, which is why Epigenomics, despite a CE mark, has made little effort

to sell its test in that region. VolitionRx believes that its low price point should appeal to the healthcare systems in cash-strapped Europe and has enlisted two market access consulting agencies, DecideumCogentia and MedPass, to help gain European acceptance The very small amount of blood required may also make the VolitionRx experience different, as the sample required for the NuQ test could be included with the draw taken for other panels (eg LDL, blood sugar). The Epigenomics test needs 10ml of blood, which requires two additional tubes of blood.

In the US, the company plans to launch the NuQ system under a CLIA-waiver (ie selling the test as a laboratory-developed test through a license to a CLIA-certified lab) with FDA approval later and recently enlisted Global Specimen Solutions to support its market entry via this avenue. Launching under a CLIA-waiver would allow the company to reach the market on an accelerated basis; however, it would likely have very limited distribution and reimbursement, limiting sales. Also, based on draft guidelines released by the FDA in October 2014, the CLIA-waiver loophole may be closing for certain tests with clinical trials becoming required for some (though the FDA has not detailed which tests would require clinical testing prior to release into the market). We believe that VolitionRx will initiate FDA approval enabling studies in 2016 and we currently model approval in 2019/20. However, in both the US and EU, the company will also need to seek inclusion of its test in screening guidelines to achieve widespread use.

We are currently modelling peak US/EU sales of $404m in the CRC market for NuQ, which we believe is reasonable given that expectations are for Exact Sciences to achieve $1-2bn in sales with its fecal-based test. Meaningful revenues would likely have to wait until 2020-21, after full FDA approval. We attribute only a 30% chance of commercial success due to the competitive nature of the market and difficulty in diagnostic tests to gain traction. We will increase this probability of success once we have greater visibility on the regulatory path in the US, reimbursement in both the US and EU, see additional trial data and the inclusion of blood-based screening in guidelines.

The lung cancer screening market

VolitionRx has also developed a test on the NuQ platform for detecting lung cancer in blood and sputum (obtained by coughing). Cancer of the lung is also a market where patients would greatly benefit from early screening as 57% of lung cancers are diagnosed after distant metastases have already formed, while the five-year survival rate is 54.8% when the cancer is localized and only 4.2% if it involves distant metastases, according to the National Cancer Institute.

In a pilot study of 46 subjects with non-small cell lung cancer, chronic obstructive pulmonary disease or no disease, NuQ demonstrated 76% sensitivity and 92% specificity in the blood test and 85% sensitivity and 100% specificity in the sputum test. It is conducting a study of 600 subjects with lung cancer with different subtypes and stages of disease, those with benign lung diseases as well as those with no disease.

Lung cancer is the second most commonly diagnosed cancer in the US (following prostate), but due to its link with smoking, the screening guidelines are relatively narrow and hence it is a smaller market than CRC. The guidelines from the Centers for Medicare and Medicaid Services (CMS) recommend screening for those between age 55-74 with ≥30 pack year smoking history with smoking cessation less than 15 years ago (or no cessation). So while CRC has a potential US screening population of 89 million, 8.6 million are eligible for lung cancer screening.[2]

The current screening standard is low-dose computed tomography (LDCT), which has a sensitivity of 88.9% and a specificity of 92.6%. This test is generally covered by insurance and by CMS, and costs $300 out-of-pocket if not reimbursed, though compliance rates are unknown as the lung cancer screening guidelines only came into effect in 2012.

2 Ma et al, *Cancer* 2013; 119:1381-5.

The big issue with LDCT is that there is a dose of radiation involved, which in itself may increase the incidence of lung cancer. The typical dose of radiation is 2 millisieverts (mSv), which is equivalent to 243 days of natural background radiation. Follow-up exams, such as full chest CT, would involve a typical dose of 8mSv or 2.7 years of natural background radiation. According to the results of the National Lung Cancer Screening Trial (NLST), even with the high specificity of LDCT, we see 28 false positives for every true lung cancer positive due to the relatively low incidence of lung cancer. Over time this would lead to unnecessary cumulative radiation exposure greater than that of nuclear industry workers and atomic bomb survivors.[3] Another issue with LDCT is that as an imaging technology, even skilled readers can miss a 3mm nodule. Also, in terms of convenience, a separate trip to an imaging center or a hospital keeps LDCT from being consumer-friendly.

Just as in the CRC screening market, there are also a number of small, mostly private companies that are developing blood screening tests to screen for lung cancer using a variety of different markers and at varying cost (see Exhibit 8). Just as in CRC, Epigenomics is a high-profile competitor in this space, though their current test is somewhat invasive and requires sample from inside the lung. It is working on developing a blood-based test but so far its sensitivity of 62% is likely too low for commercial success. The other players in this area also have many of the same issues as the smaller players in the CRC market – a lack of funding and distribution for their tests.

Exhibit 8: Lung cancer screening technology comparison

Test Name	Company	Mode	Sensitivity (%)	False negative rate (%)	Specificity (%)	False positive rate (%)	Cost per test ($)	Method	Availability
LDCT	Various	Scan	89	11	93	7	300	Scan	Worldwide
Epi ProLung	Epigenomics	Bronchial aspirate	78	22	96	4		SHOX2	CE mark in EU
Epi ProLung	Epigenomics	Blood	62	38	90	10		SHOX2	
EarlyTect Lung	Genomic Tree	Sputum	85	15	82	18		PCDHGA12	
PAULA	Genesys Biolabs	Blood	74	26	80	20	95	4 biomarkers	CLIA waiver in US
Lc Detect	Panacea Global	Blood	98	2	90	10	200	HAAH	Canada
NuQ	VolitionRx	Sputum	85	15	100	0	40-80	Nucleosomes	
NuQ	VolitionRx	Blood	76	24	92	8	40-80	Nucleosomes	

Source: Company reports, National Lung Cancer Screening Trial

We are currently modelling peak sales in the lung cancer market for NuQ of $145m, as based on current screening guidelines it is a much smaller potential market (though this could change if screening guidelines become broader in the future). Also, with screening guidelines only being enacted in 2012, broad-based screening in this market has yet to become widespread. While there is a high chance of the NuQ test reaching the market in one way or another (eg CE mark, CLIA waiver and FDA approval), we attribute only a 30% chance of commercial success. This is because there is an existing reimbursed screening modality, LDCT, which provides accurate results though with a dose of radiation and there will be a lot of education involved to start widespread patient screening in this market.

Pancreatic cancer market

VolitionRx has also developed a test for one of the deadliest cancers, pancreatic cancer. The five-year survival rate for those who catch it when it is localized is 27.1%, a number that falls to 2.4% if distant metastases are involved. Unfortunately, 53% of those diagnosed with pancreatic cancer already have distant metastases.

In a trial of 60 subjects with stage II operable pancreatic cancer, a variety of other pancreatic diseases and no disease, NuQ demonstrated 84% sensitivity and 92% specificity. The company has yet to initiate a further trial to specifically study pancreatic cancer, but it is likely among the cancers being studied in their 4,800-subject study to evaluate NuQ in detecting 27 of the most prevalent cancers.

3 McCunney et al, *Chest*. 2014; 145(3):618-624.

There are no official screening guidelines for pancreatic cancer, but, according to the consensus reached at the International Cancer of the Pancreas Screening Consortium summit, screening is not recommended for the general population, instead focusing on those with first-degree relatives (parents, siblings and offspring) with pancreatic cancer. Those with two first-degree relatives with pancreatic cancer have a 6.4-fold greater risk of pancreatic cancer (8-12% lifetime risk) than the general population. Those with three or more first degree relatives with pancreatic cancer have a 32-fold greater risk (40% lifetime risk)[4]. Gene testing can provide a signal of risk as well but it is thought it is of limited use at the moment as the genetic basis for susceptibility to pancreatic cancer is unclear. The population that is recommended for screening is likely more limited than both CRC and lung cancer as it depends on first-degree family members to have had the disease.

Endoscopic ultrasound (EUS) is generally the procedure performed to screen patients for pancreatic cancer. EUS has sensitivity of 89% and specificity of 96% and costs approximately $500 unless covered by insurance. It is similar to colonoscopy as it does require sedation and sometimes general anesthesia. It involves the insertion of a tube into the mouth, down to the stomach and into the first part of the small intestine. Risks are bleeding and gastrointestinal perforation, and sometimes infection. So, while accurate, it is far from perfect or consumer-friendly, which at least partially explains the fact that such a high percentage of pancreatic patients are detected late.

There is currently a biomarker used in pancreatic cancer and can be measured in the blood. It is called CA19-9 and can be purchased cheaply. However, current ASCO guidelines recommend against 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.[5] It is mainly used in conjunction with imaging to determine the efficacy of therapy as serial levels of CA19-9 correlate with response.

Exhibit 9: 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
NuQ	VolitionRx	84	16	92	8	40-80

Source: Annals of Oncology, VolitionRx, Pancreatology

We are currently modelling peak sales in the pancreatic cancer market for NuQ of $37m as there are currently no screening guidelines and based upon a recent consortium, only those with multiple family members with the disease will likely be recommended for screening. We attribute only a 30% chance of commercial success in this market due to its nascent state and the need for extensive education of the physician community.

Sensitivities

For a diagnostics company, regulatory approval, especially in the US, is purely a numbers game, and the trade-off/balance between specificity and sensitivity is critical. Too low a specificity and too many people may be receiving unnecessary invasive biopsies, which may have adverse events associated with them. Too low a sensitivity and tumors are missed. Once on the market, it takes time to gain distribution and acceptance. In Europe, the market is very fragmented with unique situations in each country. Also, governments organize much of the cancer screening so the barriers to entry are quite high. Finally, health systems are price-sensitive with current FIT/FOBT tests for CRC costing $5-23 each. Note that Epigenomics, which has a blood test for CRC, is three years into its European launch and has only ~$2m in annual revenues in that market. In the US, VolitionRx will likely start with a CLIA-lab strategy prior to official FDA approval; however, that will

4 Canto et al., *Gut* 2012; 0:1-9
5 Duffy et al., *Annals of Oncology* 21: 441-447, 2010

severely limit its ability to distribute its test beyond the CLIA-certified lab it licenses its technology to and will mean a slow ramp-up in revenues, and a lower probability of reimbursement (also, draft guidelines from the FDA suggest that the CLIA-waiver loophole may be closing). True acceptance will likely only come after a full FDA approval and inclusion in various cancer screening guidelines.

Valuation

Using a risk-adjusted NPV model we value the company at $191m or $11.64 per basic share. On a fully-diluted basis, we value the company at $198m or $9.23 per diluted share. While we believe there is a high probability of NuQ reaching the market through CE mark approval and CLIA-waiver, we attribute only a 30% chance of commercial success as it is difficult for a new diagnostic test to gain traction. Our CRC model assumes that the annual screening rate would increase from 11-12% a year to over 20% by 2033 due to a wider availability of blood tests, and that NuQ would have around 21-22% share of that screening market. We also expect that NuQ would be launched with a price of $20 in the EU and $40 in the US. We expect VolitionRx to have c $8.6m in cash at the end of Q2 and to raise additional capital early next year or even earlier. Upcoming major catalysts of additional CRC data and a CE mark application in Europe in Q3 as well as the CE mark approval in 2016 could provide upside to shares.

Exhibit 10: VolitionRx valuation table

Product	Main Indication	Status	Prob. of commercial success	Launch year	Peak sales ($m)	Patent protection	Economics	rNPV
NuQ	Colorectal	Development	30%	2016	$404	2034	56% peak margin	$144
	Lung	Development	30%	2018	$145	2034	61% peak margin	$30
	Pancreatic	Development	30%	2018	$37	2034	58% peak margin	$6
Total								$180
Cash and cash equivalents (Q115) ($m)								$11.0
Total firm value ($m)								$191
Total basic shares (m)								16.4
Value per basic share ($)								$11.64
Warrants (1/2015, m)								3.4
Weighted average exercise price ($)								$1.96
Cash on exercise ($m)								$6.7
Total firm value ($m)								$198
Non-warrant options (1/2015, m)								1.6
Total number of shares								21.4
Diluted value per share ($)								$9.23

Source: Edison Investment Research

Financials

VolitionRx has $11m in cash and cash equivalents as of the end of Q115. With a burn rate of ~$2m per quarter, it has enough cash to make it through additional data releases. However, that expense rate will need to increase once it obtains CE mark approval as it will need to invest in a commercial organization. Also, it will need to invest in clinical studies specifically designed to obtain FDA approval in the US (we forecast $12.5m in R&D in 2016 and $13.7m in 2017). Note that Exact Sciences, which received FDA approval for Cologuard in August 2014, had an accumulated deficit of $421m by the end of that year. If VolitionRx decided to go the self-marketing route of Exact Sciences, we calculate it would need to raise an additional $120m prior to profitability in 2021. Near term, we expect it to raise $25m in 2016 and $25m in 2017 (nominally attributed to debt as per our policy).

Exhibit 11: Financial summary

$000s	2012	2013	2014	2015e	2016e	2017e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue	55	0	15	0	897	2,484
Cost of Sales	0	0	0	0	(90)	(245)
Gross Profit	55	0	15	0	807	2,239
Research & Development	(2,843)	(2,504)	(4,044)	(6,981)	(12,481)	(13,729)
Sales, General & Administrative	(1,295)	(2,072)	(1,908)	(4,648)	(7,148)	(10,248)
EBITDA	(4,083)	(4,576)	(5,937)	(11,629)	(18,822)	(21,738)
Operating Profit (before GW and except.)	(4,083)	(4,576)	(5,937)	(11,629)	(18,822)	(21,738)
Intangible Amortisation	0	0	0	0	0	0
Other	0	0	0	0	0	0
Exceptionals	0	0	0	0	0	0
Operating Profit	(4,083)	(4,576)	(5,937)	(11,629)	(18,822)	(21,738)
Net Interest	0	0	0	32	11	(1,946)
Other	(39)	840	(2,320)	319	0	0
Profit Before Tax (norm)	(4,083)	(4,576)	(8,358)	(11,258)	(18,810)	(23,684)
Profit Before Tax (FRS 3)	(4,122)	(3,736)	(8,258)	(11,279)	(18,810)	(23,684)
Tax	0	0	(0)	0	(8)	0
Deferred tax	0	0	(0)	(0)	(0)	(0)
Profit After Tax (norm)	(4,083)	(4,576)	(8,358)	(11,258)	(18,818)	(23,684)
Profit After Tax (FRS 3)	(4,122)	(3,736)	(8,258)	(11,279)	(18,818)	(23,684)
Average Number of Shares Outstanding (m)	9.4	10.8	13.5	16.7	17.4	18.1
EPS - normalized (c)	(0.44)	(0.42)	(0.62)	(0.67)	(1.08)	(1.31)
EPS - FRS 3 (c)	(0.44)	(0.34)	(0.61)	(0.67)	(1.08)	(1.31)
Dividend per share (c)	0.0	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET						
Fixed Assets	1,522	1,065	1,097	1,031	998	972
Intangible Assets	1,430	1,002	809	766	766	766
Tangible Assets	91	63	289	265	231	206
Other	0	0	(0)	(0)	(0)	(0)
Current Assets	416	941	2,192	2,296	11,088	13,284
Stocks	0	0	0	0	4	12
Debtors	0	0	0	0	160	442
Cash	376	889	2,139	2,229	10,856	12,762
Other	39	53	53	67	67	67
Current Liabilities	(695)	(957)	(2,713)	(997)	(1,005)	(997)
Creditors	(695)	(957)	(2,713)	(997)	(1,005)	(997)
Short term borrowings	0	0	0	0	0	0
Long Term Liabilities	(635)	(433)	(352)	(281)	(25,281)	(50,281)
Long term borrowings	0	0	0	0	(25,000)	(50,000)
Other long term liabilities	(635)	(433)	(352)	(281)	(281)	(281)
Net Assets	607	617	224	2,050	(14,201)	(37,022)
CASH FLOW						
Operating Cash Flow	(2,315)	(3,084)	(4,141)	(11,032)	(18,239)	(21,302)
Net Interest	0	0	0	32	11	(1,946)
Tax	0	0	0	0	0	(8)
Capex	(91)	(1)	(303)	(128)	(30)	(30)
Acquisitions/disposals	0	0	0	0	0	0
Financing	2,576	2,828	5,627	11,203	0	0
Dividends	0	0	0	0	0	0
Other	0	0	0	0	0	0
Net Cash Flow	171	(257)	1,183	75	(18,258)	(23,285)
Opening net debt/(cash)	(348)	(376)	(889)	(2,139)	(2,229)	14,144
HP finance leases initiated	0	0	0	0	0	0
Exchange rate movements	(40)	4	(44)	(32)	0	0
Other	(103)	765	111	47	1886	191
Closing net debt/(cash)	(376)	(889)	(2,139)	(2,229)	14,144	37,238

Source: Edison Investment Research, company accounts

Contact details	Revenue by geography
VolitionRx 1 Scotts Road #25-05 Shaw Centre Singapore 228208 www.volitionrx.com	N/A

Management team

Chief Executive Officer: Cameron Reynolds MBA	Chief Financial Officer: Mike O'Connell
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 O'Connell has held roles as financial director or CFO for a number of private to public companies, including Systems Integrator Pacific Group, and InsightSoftware.com. As founder and CEO of Isosceles, Mr O'Connell provided accounting services to entrepreneurial companies of all sizes. Mr O'Connell was educated at Imperial College London before qualifying as a chartered accountant with Ernst & Young in London.
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	(%)
Guy Innes	8.4%
Cotterford Company	7.9%
Dr Martin Faulkes	7.7%
Cameron Reynolds	7.0%
Rodney Rootsaert	6.1%
Concord International (affiliated with Rodney Rootsaert)	5.6%
Southpoint Capital	4.5%

Companies named in this report

Exact Sciences (EXAS); Epigenomics (EPGNY); Panacea Global (PANG)

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