Zacks Small-Cap Research

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# VolitionRx Ltd (VNRX-OTC)

## VNRX: Clinical Data Looks Promising For Colon Cancer Opportunity

| | |
|---|---|
| **Current Recommendation** | **Outperform** |
| Prior Recommendation | N/A |
| Date of Last Change | 05/07/2013 |
| Current Price (04/08/14) | $2.45 |
| **Target Price** | **$7.00** |

## OUTLOOK

VolitionRx is focused on the development of blood-based cancer detection tests using their NuQ technology which aims to marry high accuracy and reliability typically only achieved with invasive and costly diagnostic methods with the convenience, low-cost and non-invasive nature characteristic of many of the current cancer screening tests. The tests address potentially multi-billion $ markets. Initial clinical data has been very encouraging, showing impressive sensitivity/specificity. Larger studies have since been initiated. Data from ongoing studies is expected to be released on a regular basis. – which should provide further insight into the performance of the technology. Tests are now for sale for RUO. CE Mark for sale to the clinical market in Europe is anticipated in late 2014 or early 2015 which should help fund the U.S. development program. Despite risks such as that VNRX will need to raise significant capital before they reach cash flow positive, we think the shares are very attractive at the current market price. Our DCF model values the stock at about $7/share..

## SUMMARY DATA

| | |
|---|---|
| **52-Week High** | **$3.25** |
| **52-Week Low** | **$0.25** |
| **One-Year Return (%)** | **N/A** |
| **Beta** | **N/A** |
| **Average Daily Volume (sh)** | **4,158** |
| **Shares Outstanding (mil)** | **12** |
| **Market Capitalization ($mil)** | **$29** |
| **Short Interest Ratio (days)** | **N/A** |
| **Institutional Ownership (%)** | **0** |
| **Insider Ownership (%)** | **N/A** |
| **Annual Cash Dividend** | **$0.00** |
| **Dividend Yield (%)** | **0.00** |
| **5-Yr. Historical Growth Rates** | |
| **Sales (%)** | **N/A** |
| **Earnings Per Share (%)** | **N/A** |
| **Dividend (%)** | **N/A** |
| **P/E using TTM EPS** | **N/A** |
| **P/E using 2014 Estimate** | **N/A** |
| **P/E using 2015 Estimate** | **N/A** |
| **Zacks Rank** | **N/A** |

| | |
|---|---|
| **Risk Level** | **N/A,** |
| **Type of Stock** | **N/A** |
| **Industry** | **Med-Biomed/Gene** |

## ZACKS ESTIMATES

**Revenue**
(in '000)

| | Q1 (Mar) | Q2 (Jun) | Q3 (Sep) | Q4 (Dec) | Year (Dec) |
|---|---|---|---|---|---|
| 2013 | $0 A | $0 A | $0 A | $0 A | $0 A |
| 2014 | | | | | $293 E |
| 2015 | | | | | $2004 E |
| 2016 | | | | | $5612 E |

**Earnings per Share**

| | Q1 (Mar) | Q2 (Jun) | Q3 (Sep) | Q4 (Dec) | Year (Dec) |
|---|---|---|---|---|---|
| 2013 | -$0.09 A | -$0.10 A | -$0.08 A | -$0.07 A | -$0.34 E |
| 2014 | -$0.10 E | -$0.09 E | -$0.09 E | -$0.09 E | -$0.37 E |
| 2015 | | | | | -$0.32 E |
| 2016 | | | | | -$0.11 E |

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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## WHAT'S NEW…..

**2013 10-K Filed**
VNRX filed their 10-K for the year ending December 31, 2013. Aside for some slight delays in the timelines for initial commercialization via the RUO channel as well as expectations for CE Mark submission and a non-cash asset impairment in the current period, operating and financial results continue to track our expectations. We have adjusted our model for the delays.

Excluding the $350k impairment charge Q4 operating expenses were $1.3M, compared to our $1.2M estimate. The asset impairment charge relates to a patent licensed by VNRX for their HyperGenomics assay (i.e. – unrelated to the core NuQ tests) – VNRX took the $350k write-down as it was discovered that an unrelated entity had already filed a similar patent. The company hopes to file a new methodology patent related to the HyperGenomics test in the coming months.

Net loss and EPS were $842k and ($0.07), compared to our $1.2M and ($0.09) estimates.

Cash used in operating activities was $709k, down slightly from $828k in Q3 and from $991k in Q2. VNRX exited the quarter with $889k in cash and equivalents, up from $474k at the end of Q3 with Q4 cash bolstered by a $750k cash raise from the issuance of 366k shares ($2.05/share) with 100% warrant coverage (5yrs, $2.40 strike). Subsequent to 2013 year-end, VNRX raised $3M (gross) via the issuance of 1.5M common shares (@ $1.50/share) with 100% warrant coverage (5yrs, $2.20 strike).

We are maintaining our Outperform rating. We recommend accumulating the stock up to our $7/share price target.

**Operational Progress**
On the operational front, 2013 (and into the current) was productive for VNRX – mostly relating to additional positive clinical data and commencing additional clinical studies. Recent positive data from the Bonn University and CHU Dinant Godinne studies, indicating high specificity and sensitivity of the NuQ tests in detection of colorectal cancers complement earlier data which had similar results. In 2013 VNRX also announced the collaboration for two large studies with Hvidovre Hospital at the University of Copenhagen in Denmark. These two studies (one restrospective and one prospective) include ~16k samples and should provide significant insight into how the NuQ tests perform relative the colonoscopy, the latter which is considered the gold-standard for colon cancer screening (but which suffers from serious drawbacks such as being highly invasive and costly. We expect to hear preliminary results from at least one of these studies in the current year – positive results of which would likely be used for support of CE Mark submission.

As we have noted in our ongoing coverage of VNRX the significant drawbacks of colonoscopies could offer the company an enormous opportunity if they can demonstrate their NuQ tests are competitive in terms of accuracy. Drawbacks of colonoscopy include that at about $1,000 per procedure, it's a relatively high cost screening tool (particularly compared to VNRX's relatively inexpensive testing option) and it's very invasive, uncomfortable and time consuming, requiring the patient to be sedated as a fiber optic camera is threaded through the interior walls of the rectum and colon. Approximately 3.1 million colonoscopies are performed in the U.S. every year (and about 4.1 million done in Europe) which indicates that despite the drawbacks, there's a very substantial market for colon cancer screening - which would presumably expand even further with the availability of an accurate, easy to use, inexpensive and non-invasive screening test such as NuQ.

Data to-date from the various studies where NuQ tests have been used for colon cancer indicate reasonably high specificity and sensitivity – although the sample bases have been too small to draw any concrete conclusions. Results from the much larger University of Copenhagen study, if positive, should provide much more definitive evidence into the performance of the tests. We look forward to data from the first 1,000 patients – if positive, we think this could provide a catalyst to the stock price.

***One-Third of Adults Not Meeting Colon Cancer Screening Guidelines…***
And despite several options to screen for colon cancer, a significant portion of the at-risk population is not meeting colon cancer screening guidelines. According to the CDC, as reported in the November 5, 2013 issue of Morbidity and Mortality Weekly Report, one-third of U.S. adults aged 50-75 who should be screened for colon cancer are not being screened. The USPSTF recommends regular screening for colon cancer using fecal occult blood testing, sigmoidoscopy or colonoscopy beginning at age 50 and continuing to age 75.

While the drawbacks of the current screening methods were not cited as a reason for the low compliance rate, we think an easy-to-use and relatively accurate method would likely have significant appeal. Colonoscopy (and sigmoidoscopy) is not the only method that suffers from serious drawbacks. Fecal occult blood tests, while convenient as they can be used at home, suffer from a high rate of false positive. In discussing the recent CDC report, Tom Frieden, CDC Director noted that people are more likely to be screened if they were given more choices. We see this as another indication of demand for another option in colon cancer screening. VNRX's NuQ tests may offer an option that is competitive to colonoscopy in terms of accuracy but with all the convenience and low cost of fecal occult blood tests.

**Hvidore Denmark Prospective Study Expanded From 6,000 To 11,000 Samples**
VolitionRx continues to expand the number of studies as well as the number of patient samples which are using their NuQ technology as a diagnostic for various cancers. Larger trials are expected to build on encouraging results that have come from smaller initial studies which have indicated NuQ can differentiate between healthy and cancerous blood samples with. Larger studies will be key in reducing any potential "noise" in the data sets, to increase the statistical power, and will likely be required as support for applications seeking regulatory approval - we anticipate CE Mark by next year.

At the forefront of the larger studies are two being done in collaboration with Hvidovre Hospital at the University of Copenhagen in Denmark under the direction of Professor Hans Jorgen Nielsen (Professor of Surgical Oncology at the Department of Surgical Gastroenterology). Given that these studies are jointly funded, they are being done at a very low cost to VNRX ($1.85 million).

In May 2013 VNRX announced that they would obtain ~10,800 (subsequently increased to ~15,800) very high quality patient blood samples for analysis with their NuQ tests in two studies, a retrospective study and a prospective study. 4,800 samples come to VNRX at essentially no cost and will be used in a retrospective study, initially for colorectal cancer. Analysis on the first 1,000 of these samples is expected to be completed this year. Data from this study is expected to be used as support for CE Mark submission, also expected in 2014.

When VNRX first announced these two studies in May 2013, the prospective study was expected to collect ~6,000 patient blood samples. However, in mid-November the company announced that the prospective study sample base would be increased to about 11,000. Importantly, the additional samples come at no additional cost to VNRX. The samples will be collected at the University of Copenhagen under the direction of Professor Nielsen.

The additional samples afford the ability to collect additional data points and as well as increase the statistical power - both of which are important for regulatory approval and commercialization purposes. Patients will be screened with a fecal immunological test (FIT) as part of the Danish national screening program. ~8,000 patients with a positive FIT result and ~3,000 patients with a negative FIT result will then be tests using VNRX's NuQ assay panel. These results will then be confirmed by colonoscopy. The samples will be provided to VNRX blinded and randomized.
The prospective study is expected to commence in April 2014 and finish towards the end of 2015.

**Trial Data Remains Highly Encouraging With Results Coming Out On Regular Basis:**

- **Bonn Study Results:** VNRX recently announced results from the Bonn University Study. Dr. Stefan Holdenrieder from Bonn University Hospital in Germany presented the results at the 8th Circulating Nucleic Acids in Plasma and Serum (CNAPS) congress in Baltimore in early November 2013.

  As a reminder, in mid-2012 VNRX entered a collaboration with Bonn University Hospital in Germany (Rheinische Friedrich-Wilhelms-Universitat Bonn) to perform clinical trials in the evaluation of Volition's NuQ assays for cancer diagnosis and in other diseases. Lead investigator of the trials is Dr. Stefan Holdenrieder of the Institute of Clinical Chemistry and Clinical Pharmacology at University Hospital Bonn who is considered a world-renowned expert in the field of circulating nucelosomes and has authored over 70 journal papers. There are currently three studies ongoing at Bonn including an 800-patient retrospective study for various cancer types, a larger (~2,000-patient) prospective study for various cancers as well as non-cancer diseases and a study to validate the tests as a predictor of the performance and therapy monitoring of chemotherapy.

  Data was presented from 90 patients (24 colorectal cancer (CRC), 10 benign colorectal diseased (BCD), and 56 healthy controls (HC)) tested with VolitionRx's NuQ-5m assay for colorectal cancer. Results were encouraging and showed the assay was able to detect 75% of patients with colorectal cancer with a 70%

specificity. These findings were confirmed on a second set of 113 patients (49 CRC, 26 BCD, 38 HC). The assay detected significantly (at 95% CI) lower levels of NuQ-5mc in CRC and BCD compared to HC although no differences were found between CRC and BCD. Relative to differentiation of CRC from HC, sensitivities improved from 33% at a 95% specificity to 75% at a 70% specificity.

These results compare somewhat similarly to results of a small internal study led VolitionRx's own scientists at its Belgium-based lab which were announced in late 2012. The study included 105 patients including 31 healthy patients and those with cancer of the colon(n=25), breast(n=25), and lung(n=24) were included in the initial results which showed. In the colorectal cancer cohort the NuQ assay had a 76% sensitivity (19 of 25 patients detected), 90% specificity (3 of 31 healthy samples false positive).

- **CHU Dinant Godinne / UCL Namur Hospital Study Results:** In early December VNRX announced preliminary results from the study being done at Yvoir, Belgium. As a reminder, in August 2012 VNRX announced an agreement with Biobank of CHU UCL Mont-Godinne, an academic hospital in Yvoir, Belgium for a prospective longitudinal study with ~ 250 patients as they progress through diagnosis and treatment of colorectal cancer. This will be the first trial using VNRX tests focused on a single cancer (colorectal). Enrollment includes patients with a potential digestive pathology such as suspected colorectal cancer, polyps, Crohn's disease and colitis. The goal of the study is for VNRX's NuQ to be able to distinguish between patients with cancer and those with digestive conditions that indicate similar symptoms. Patient sampling will occur at CHU UCL Mont-Godinne and Volition will analyze the samples at their lab in Belgium.

  The preliminary results from 39 patients, announced in December at the Clinical Genomics and Informatics Europe Conference in Portugal, showed that when two of the NuQ tests are combined and used together, they were able to detect 85% of cancers with an 85% specificity. The combination test was also able to detect more than 50% of precancerous polyps.

- **Prostate Cancer Pilot Study Results:** In March 2014 VNRX announced that their NuQ tests were able to detect approximately 80% of prostate cancer cases in a small pilot study. The results from the study, which included 39 patients, were presented at the International Society of Oncology and Biomarkers Congress in Barcelona and also showed the tests were able to distinguish between colon and prostate cancers.

**Beefed Up Distribution**

In September 2013 VNRX announced a distribution agreement with Active Motif for their NuQ product line for the RUO markets. Acitve Motif will have co-exclusive rights, along with VNRX, to market the products in the U.S., Europe and Japan. Active Motif, at the forefront of epigenetics research and a major supplier of reagent products to the research community, should provide significant and targeted distribution reach for VNRX's product line. VNRX more recently signed a similar distribution agreement with Sciencewerke, which will distribute the RUO tests in Singapore, Indonesia and Thailand.

And while, as we have previously noted in our coverage of VNRX, we think the RUO market likely offers only a fraction of the revenue potential compared to the commercial clinical market, it does offer the opportunity to generate some early revenue as well as provides the ability to build awareness about the products and expands the validation experience of their technology. Revenue generated from the RUO channel will help facilitate ongoing and future clinical trials in support of eventual regulatory filings, including for CE Mark and FDA approval. While we had expected initial revenue from the RUO channel to commence in 2014, we have now pushed back this timeline to mid-2014.

**EUREKA Eurostars Grant**

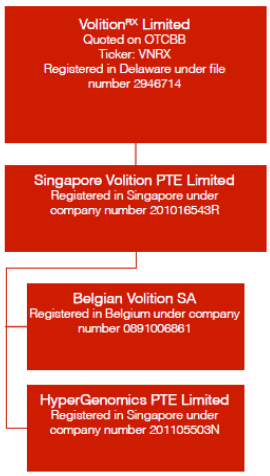
VNRX announced they, along with Alcyomics, were awarded a European grant which is aimed at promoting development of new products from small and medium sized companies. The EUREKA Eurostars grant, worth about $1 million total and about $560k of which is expected to be received by VNRX, will help fund Volition's research for its technology in inflammatory disease. While most of the research to-date of the NuQ technology has focused on cancer applications, the company had talked in the past about expanding research for other conditions that are related to elevated nucleosomes, including inflammatory-related diseases (as well as autoimmune diseases and sepsis). We view this as a small, yet meaningful step towards expanding potential applications outside of cancer, which will remain the company's main focus and where we see the bulk of the near term opportunity for the technology.

## BACKGROUND

VolitionRx Limited (VNRX) is a development-stage company focused on the development of blood-based cancer detection tests aimed at the research, clinical lab, point-of-care, and over-the-counter markets. The suite (currently 15) of tests under development are based on the company's proprietary and patent-protected NuQ technology, which is designed to detect the level and structure of nucleosomes in the blood, a relatively novel approach to cancer detection which may offer the dual benefits of high accuracy and speed. VNRX's platform technology could eventually be expanded to dozens of cancers as well as to other conditions that are related to elevated nucleosomes, such as autoimmune diseases, sepsis, and inflammatory-related diseases.

Characteristic of all cancers is the later the stage, the poorer the patient prognosis. As such, the earlier the diagnosis and initiation of appropriate treatment, the better likelihood of improved patient outcomes. Current cancer diagnosis and screening methods leave a substantial room for improvement in terms of accuracy, cost, patient comfort, and in finding cancers at an earlier, more treatable stage. VNRX's NuQ technology aims to marry high accuracy and reliability typically only achieved with invasive and costly diagnostic methods with the convenience, low-cost and non-invasive nature characteristic of many of the current cancer screening tests - a combination not currently available.

Initial validation of a panel of three of the tests used with blood samples from a small population of patients with cancer of the breast, colon and lung, completed in late 2012, showed sensitivities from 76% to 100% and specificities from 79% to 90%. Large retrospective validation studies and prospective clinical trials are ongoing in Belgium, Germany, and Denmark with additional studies expected to commence in Europe and the U.S. in the near term. Lead investigator of some of these studies, a world-renowned expert in the field of circulating nucleosomes, believes VNRX's tests "hold great promise in oncology diagnostics and monitoring." Current development is focused on cancers which the company believes have the most market potential (initially breast, colon, lung, pancreatic) and assuming these initial tests are successfully commercialized, development will be expanded to include other cancers over the next several years.




The current plan relative to commercialization is to initially promote to the research market which provides the benefits of building awareness of the tests and technology as well as expanding the validation experience without having to first gain regulatory approval. In the meantime, VNRX will pursue CE Mark in order to sell the tests to the clinical market in Europe (which could happen in late-2014 or 2015) and FDA approval for the U.S. market (potentially by 2016). Depending on the success of clinical trials, development and in meeting regulatory requirements, the company hopes to be able to eventually market their tests to the clinical lab, professional point-of-care (POC), and over-the-counter (OTC) markets.

As VNRX is still a development stage company they will require a significant amount of additional capital in order to fund operations and product development.

VolitionRx's principal executive office and laboratory is located in Belgium. The company, formerly named Standard Capital Corporation, went public through a reverse merger with VolitionRx Limited in 2011. VolitionRx's corporate structure encompasses Singapore Volition Pte Limited, its wholly-owned operating subsidiary, which has two subsidiaries; Belgian Volition SA and HyperGenomics Pte Limited.

## INVESTMENT THESIS

VolitionRx is a development stage company and still at the very front-end of initial clinical trials with currently only limited data validating their technology for use as cancer diagnostic. The company will require a significant amount of additional capital to fund ongoing operations including several already planned and future retrospective and prospective clinical studies which will likely encompass several thousand patient samples and potentially cost several (potentially tens of) millions of dollars. Commercialization via a channel supported with broad distribution and attracting meaningful demand could be years away and is, at the very least, dependent on consistently compelling trial data to support use of the technology in the clinical setting. This, of course, also assumes that

requisite regulatory approvals are successfully attained. We provide that paragraph as a run-up disclosure that an investment in the company is not without meaningful risk.

Notwithstanding these risks, we think the risk-reward balance is weighed far greater in favor of an investment in VNRX when considering the following in aggregate…

***Initial Trial Data…***
Initial trial data from small 105-patient study indicated NuQ tests detected between 76% and 100% of cancers with specificities between 79% and 90%. Preliminary results from an 800-patient study, an announcement related to which was made shortly following the 105-patient study data, indicated consistency with the earlier data. While way too early to make any concrete conclusions, the initial data is clearly a positive start and was encouraging enough for management to accelerate the clinical programs and initiate other larger studies. Sensitivities/specificities anywhere near the ranges seen in the early data, if confirmed in larger studies, would be highly encouraging, particularly given that many current cancer diagnostic and screening methods and tests have shown significantly inferior performance relative to this preliminary data and are widely used today.

***~~10,800~~ 15,800 Sample Base Which Should Catalyze CE Mark Submission for CRC…***
In late May 2013 VNRX announced they signed an agreement with Hvidovre Hospital at the University of Copenhagen in Denmark whereby VNRX will obtain ~10,800 (subsequently increased to 15,800) patient blood samples for analysis with VolitionRx's NuQ tests. ~4,800 samples will come to VNRX free of charge. These come with a plethora of patient background, treatment and follow-up data which makes for a very robust set of data for VolitionRx to use in their analysis of the samples with their NuQ tests which will initially use the samples for detection of colorectal cancer. It's anticipated that data from the first 1,000 samples will be used to support a CE Mark application for a colorectal cancer test.

The other ~11,000 (initially was ~6,000 and subsequently increased to 11,000) samples will be collected in a prospective trial which will be jointly funded by VNRX, the University of Copenhagen and a "top ten global diagnostics company." We view this agreement as a significant positive for moving VNRX's development programs forward. This provides the company with a very large, high quality sample and data set for a fraction of the cost that they would have had to spend had they run prospective studies on their own (which could have easily cost $10 million - $25 million) and also now puts a more definitive timeline on when CE Mark application could happen. The data from these studies are also expected to be used to help support an eventual FDA filing.

***Current Cancer Testing Lacking…***
In general, the bar is set fairly low in terms of current cancer diagnostic and screening tests and methods which leave a substantial room for improvement in terms of accuracy, cost, patient comfort, and in finding cancers at an earlier, more treatable stage. This could benefit VNRX as the regulatory (i.e.- accuracy, interpretation, etc.) hurdles and competitive landscape would both favor a relatively high accuracy, easy-to-use, non-invasive and cost effective diagnostic test such as what the NuQ tests potentially offer.

PSA testing (prostate cancer) and mammograms (breast cancer) are two examples of cancer screens that are widely used (annually ~20 million PSA tests and ~40 million mammograms are done in U.S.) yet have such significant reliability issues that they have been cited as potentially causing more harm than good. Fecal occult blood tests, often used as a front-line screen for colon cancer, is another example of a widely used cancer test with questionable reliability. Worldwide there are about 140 million fecal occult blood tests done every year yet they have significant potential for false positives with sensitivities in some studies cited as low as 30%.

In terms of cost competitiveness, VNRX envisions offering their tests in the range of approximately $10 to $40 each (the specific price could be influenced by various factors including the sales/commercialization channel, geographic location, reimbursement policies, etc.). The end-user price would include a mark-up for margin to the distributor but will still be competitive to almost any of the current least expensive, minimally-invasive tests (many of which are fraught with poor performance and reliability issues) and a small fraction compared to the cost of many of the invasive procedures such as colonoscopy/sigmoidoscopy and endoscopic ultrasound.

***Intellectual Property…***
As VNRX is possibly the only (or at least one of very few) company in the world pursuing nuclesomes in the blood for cancer detection, they have been able to rapidly build a patent-moat around their technology and intended applications. Most of the current patents were applied for in 2011, with patent protection afforded through 2031. Even in the event that development stalls or is delayed (which we do not expect), their IP would potentially still have substantial value and should provide a buoy to the market value of the company.

***Scalable, Platform Technology With Enormous Potential Target Markets…***
The NuQ technology is potentially expandable to dozens of cancers as well as other conditions associated with elevated blood nucleosomes. With more than 200 different types of cancer and about 50 major cancer types in existence, the potential market for these tests is enormous. Just the markets of the cancer types that VNRX has indicated may be their initial focus offer significant opportunity. For example, for colon cancer screening there's over 7 million colonoscopies done in the U.S. and Europe (which cost in aggregate about $7 billion) combined every year and for breast cancer there's roughly 100 million (combined U.S. and Europe, which cost in aggregate about $10 billion) mammograms done. As a screening test (or even as an adjunct to current methods) for just these two cancers, this represents a potential market size of over $4 billion (@ $40/patient test). As a screening test for several more cancers (e.g. pancreatic, lung, cervical, kidney, prostate, etc.) the potential aggregate market could be as much as $10 billion or more.

***Industry Standard ELISA Format, Compatible With Standard Instrumentation…***
The tests use the ELISA format which has been in existence for about 40 years and remains the dominant testing format in the clinical lab diagnostics space. As such, the NuQ tests would seamlessly fit with industry standard labs, practices, training, and instrumentation. Initial introduction could be with standard manual multi-well plates with potential to also either partner with an instrument manufacturer (which could include the likes of diagnostic heavyweights such as Siemens, Abbott, Roche, etc.) as a supplier or to sell directly to the installed instrument base.

***Diversifying Risk, Measured and Stepped Roll-Out…***
As opposed to an all-or-nothing, swing-for-the-fences, or all-eggs-in-one basket approach, VNRX has several irons in the clinical trial fires and expects to pursue a measured, stepped roll-out which should both help diversify risk of failure and broaden the potential market opportunities. Relative to current clinical trials, enrollment/patient samples include those of various cancer types, cancer stages and patient backgrounds. This should help them narrow their focus for future larger studies and improve the chances for hitting trial endpoints. Studies will be done through collaborations (i.e. - w/ blood or cancer banks/repositories) where possible to minimize expense and streamline the process.

Relative to the product roll-out, the initial introduction which will be via the RUO channel will provide not only a source of revenue, it will also, perhaps more importantly provide another (inexpensive) mechanism for validation of the technology as well as another conduit for feedback. Assuming requisite regulatory approvals, VNRX would then tap the clinical lab markets - the commercialization game-plan which would likely entail either an agreement with another diagnostic company (instrument manufacturer?) or other third-party distribution (clinical lab?) which could allow VNRX to focus their resources on scaling up production rather than on building a sales force and facing the associated fixed-cost risks of doing so. The European market should afford the opportunity to generate revenue and cash and help fund the U.S. development and regulatory program. And, if and when the POC channel made sense to pursue, VNRX may be in a position to capitalize on that market as well.

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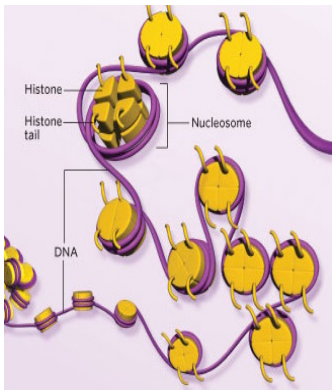
## TECHNOLOGY / PRODUCT CANDIDATES / PIPELINE

***Epigenetics: Relatively New Role In Cancer Detection…***
VNRX's test technology is based on the field of epigenetics. Epigenetics refers to functional changes in the genome, or the switching on and off of genes, which are caused by something other than changes in the underlying DNA sequence (see Appendix for more in-depth explanation of epigenetics). An example is histone (proteins that order DNA into nucleosomes) modification which regulate gene expression but does not change the underlying DNA sequence. Nucleosomes are the basic unit of DNA packaging, which consists of 146 base pairs of DNA wound around a four histone protein core.

Epigenetics' role in detecting cancer is relatively new with the first real discoveries not culminating until around the mid-1990's. Research has accelerated since, facilitated in part by better DNA sequencing technologies. One of the most significant recent discoveries of epigenetic's role in cancer was how certain epigenetic changes in the GSTP1 gene are a marker for prostate cancer.

**Nucleosome: DNA Wound Around Histone**

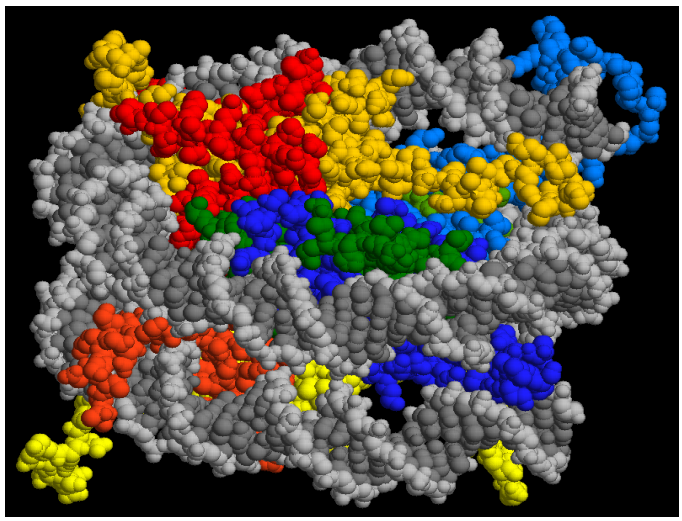



*SOURCE: the-scientist.com / Stefan Kubicek*

The structure of nucleosomes in cancer cells is different than that of healthy cells and it also appears that the structure of nucleosomes is different among types of cancers (e.g. colon vs. breast). VNRX's tests are designed to identify cancer by detecting the level and structure of nucleosomes in the blood. Cancer results in accelerated cell growth and death - when the cells die the nucleosomes are released into the blood and recycled into the body. VNRX's tests have been developed to identify the presence of cancer and also to identify the type of cancer from the levels of nucleosomes in the blood well as the different structure of nucleosomes.

And while VNRX's main focus is on cancer, potential derivative applications include diagnosis of other conditions where elevated blood nucleosomes have also been shown to be present. These include autoimmune diseases (e.g. - rheumatoid arthritis, Crohn's disease, etc), sepsis, and inflammatory-related diseases. Patients with some of these derivative-type conditions (along with healthy and cancer patients) will be included in the planned large (2,000+ patient) clinical trial which is expected to commence enrollment during the current year. And specific to research related to inflammatory disease, in September 2013 VNRX, along with Alcyomics, were awarded a European grant which is aimed at promoting development of new products from small and medium sized companies. The EUREKA Eurostars grant, worth about $1 million total and about $560k of which is expected to be received by VNRX, will help fund Volition's research for its technology in inflammatory disease. We view this as a small, yet meaningful step towards expanding potential applications outside of cancer.

**Structure of Nucleosome**



**Histones - Red/Blue/Orange/Yellow**
**DNA - Grey**

*SOURCE: Protein Data Bank*

***NuQ Cancer Panel…***
VoliotionRX currently has 15 blood tests in development based on its NuQ technology. The tests are being developed and are expected to eventually be commercialized as first-line tests to identify whether cancer is present as well as the type of cancer.

VNRX will initially introduce the tests to the Research Use Only (RUO) market and, supported by data from ongoing and future clinical trials, will seek regulatory approval to sell to the clinical diagnostics markets. VNRX envisions that the tests could be part of routine screenings, when risk factors are present, and even as OTC tests used by patients at home. For the clinical market the tests are designed to be used in combination as a panel to complement each other with an initial test to determine whether cancer is present and the supporting panel of tests to confirm a cancer diagnosis, identify the type of cancer and determine whether other conditions are present. VNRX's tests fall into four categories;

- **NuQ-X**: VNRX is developing two blood tests in the NuQ-X family to detect the presence of cancer by detecting nucleosomes containing specific nucleotides
  - test for quantification of nucleosome associated methylated DNA
  - test for quantification of nucleosome associated hydroxymethylated DNA
- **NuQ-V**: VNRX is developing three blood tests in the NuQ-V family to detect cancer by detecting nucleosomes containing specific histone variants. VNRX's research has found that the pattern of blood levels of the different types of histone variants in nucleosomes is different for different cancer types
  - test for quantification of nucleosome associated histone variant H2AZ
  - test for quantification of nucleosome associated histone variant macro-H2A1.1

- test for quantification of nucleosome associated histone variant macro-H2A2

- **NuQ-M**: VNRX is developing five blood tests in the NuQ-M family to detect cancer by detecting nucleosomes containing modified histones, the proteins that package and order DNA into nucleosomes
  - test for quantification of nucleosome associated H2AX
  - test for quantification of nucleosome associated trimethyl-H3K27
  - test for quantification of nucleosome associated acytel-H4K16
  - test for quantification of nucleosome associated trimethyl-H4K20
  - test for quantification of nucleosome associated ubiquityl H2A
- **NuQ-A**: VNRX is developing five blood tests in the NuQ-A family to detect cancer by detecting nucleosome-protein adducts
  - test for quantification of nucleosome bound Estrogen Receptor
  - test for quantification of nucleosome bound HMGB1
  - test for quantification of nucleosome bound Androgen Receptor
  - test for quantification of nucleosome bound Progesterone Receptor
  - test for quantification of nucleosome bound EZH2

***NuQ Endometriosis Panel…***

In addition to the NuQ-panel tests above, VNRX is developing an endometriosis panel. Endometriosis, usually observed during a woman's reproductive years, is a condition where the uterine cells appear and flourish outside of the uterine cavity. It's estimated that the condition occurs in as much as 10% of women and is the leading cause of infertility in women. No current non-surgical diagnostic method exists to detect endometriosis. The gold-standard for diagnosing the disease is surgical laprascopy, which is generally not covered by most insurance plans unless there are indications of infertility. Unlike the NuQ panel tests, VNRX does not expect to introduce their endometriosis panel to the RUO market. The company completed pilot studies of the test in 2012 and expects to initiate larger trials in the near-term.

***HyperGenomics Test to identify cancer sub-type:***

VNRX's final test currently under development is designed to identify the cancer sub-type after the presence of cancer has already been determined. Their HyperGenomics test, which will be performed on cancer tissue obtained by biopsy or surgery, will help determine the best course of treatment through a personalized medicine approach by providing a detailed epigenetic characterization or signature of the tumor. Discoveries to-date using the test has included a new protocol for analyzing white blood cells, with potential utility with leukemia. VNRX is currently using the HyperGenomics test for contract research purposes (which generated a small amount of revenue in 2012) and expects to continue development of a HyperGenomics research kit, which could potentially be available in the RUO market in 2014. Clinical trials to support approval for the clinical market are still in the planning stage.

**PATENT PROTECTION / INTELLECTUAL PROPERTY**

VNRX product candidates are covered by eight families of patents which the company either authored themselves or licenses from research institutions including from Imperial College, London and the European Molecular Biology Laboratory. As VNRX is possibly the only (or at least one of very few) company in the world pursuing nuclesomes in the blood for cancer detection, they have been able to rapidly build a patent-moat around their technology and intended applications. Most of the current patents were applied for in 2011, with patent protection afforded through 2031. In addition to the current patents (listed below), the company recently (April 2013) filed for two new patent applications (including one using their technology in personalized medicine as a predictor of the efficacy of cancer treatment) and expects to continue to broaden the intellectual property base and further fortify and lengthen the patent protection of their products and pipeline via ongoing patent filings. Current patent protection encompasses (per company public documents);

**Nucleosomics IP**

- Exclusive license from Chroma Therapeutics: Nucleosomics WO2005019826 – Detection of histone modifications in cell-free Nucleosomes. Patent granted in Europe, pending in USA *(Patent that underlies the NuQ-M tests)*
- Worldwide exclusive license in the field of cancer diagnosis and cancer prognosis from the European Molecular Biology Laboratory: EMBL Variant Patent WO2011000573 – Diagnostic method for predicting the risk of cancer recurrence based on macroH2A isoforms. Patent pending worldwide
- Volition-authored application: NuQ Patent UK1115099.2 & US61530300 – Method for Detecting Nucleosomes. Patent pending worldwide *(Patent that underlies the Nucleosomics assay technology)*
- Volition-authored application: NuQ-X Patent UK1115095.0 & US61530295 – Method for Detecting

Nucleosomes Containing Nucleotides. Patent pending worldwide *(Patent that underlies the NuQ-X technology).*

- Volition-authored application: NuQ-V Patent UK1115098.4 & US61530304 – Method For Detecting Nucleosomes Containing Histone Variants. Patent pending worldwide. *(Patent that underlies the NuQ-V technology)*
- Volition-authored application: NuQ-A Patent UK1121040.8 and U.S. 61568090: Method for detecting Nucleosome Adducts. Patent pending worldwide. *(Patent that underlies the NuQ-A technology)*

**HyperGenomics IP**
VNRX had previously licensed a patent from Imperial College, London for HyperGenomics technology. However, in late 2013 it was discovered that an unrelated entity had already filed a similar patent. The company noted in its 2013 10-K that they hope to file a methodology patent for HyperGenomis in the first half of 2014.

**Endometriosis IP**
Volition-authored application: Endometriosis Diagnostic UK1012662.1 – Method for detecting the presence of a gynecological growth. Patent pending worldwide

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## DEVELOPMENT STATUS AND STRATEGY / REGULATORY

VNRX's commercialization strategy involves first promoting to the RUO market which does not require regulatory approval. While we think the RUO market, which consists of selling to research-oriented institutions such as medical universities for uses outside of patient diagnosis, likely offers only a fraction of the revenue opportunity compared to the commercial clinical market, it does potentially provide VNRX with an opportunity to build awareness about their products as well as expands the validation experience of their technology. The only requirement to be allowed to sell to the RUO market is for the tests to complete beta testing (i.e. - general validation by a few labs), which was done on the NuQ cancer panel tests in 2012. VNRX initially started selling these tests through their website (http://www.nucleosomics.com) and has indicated that customers in fields such as stem cell research, inflammatory disease and chromatin structure and function have purchased their tests. In order to beef up distribution of the tests to the RUO channel, in September 2013 VNRX entered into an agreement with Active Motif who will have co-exclusive rights, along with VNRX, to market the products in the U.S., Europe and Japan. We expect Active Motif, which is at the forefront of epigenetics research and a major supplier of reagent products to the research community, will provide significant and targeted distribution reach for VNRX's product line. VNRX followed the Active Motif agreement with a similar distribution agreement with Sciencewerke, who will distribute the RUO tests in Singapore, Indonesia and Thailand.

The next lowest regulatory hurdle relative to a more substantial commercial opportunity is CE Mark for approval to sell the tests to the clinical market in Europe. VNRX is now pursuing additional retrospective studies (namely, the University of Copenhagen collaboration studies) to supplement the initial trial data from 2012 to support a CE Mark submission. Typically, the clinical validation requirement to gain CE Mark is relatively modest compared to FDA approval (either 510(k) or PMA) and can potentially be met with just the already completed and currently planned retrospective studies. In addition to clinical validation of the tests, VNRX is in the process of meeting the other CE Marking requirements, namely manufacturing and standardization compliance and has engaged a regulatory advisor to facilitate this. VNRX's most recent guidance relative to CE Mark submission is that they expect the NuQ-X test and NuQ-panel products will be applied for in 2014. This would indicate that sales to the European clinical market could commence in 2014 or early 2015. The company ballparks CE Marking will cost ~$500k per test.

FDA approval will be required before the tests can be sold for patient diagnosis (i.e. - to the clinical market) in the U.S. Given that there are no tests currently on the market that would likely be considered "predicate devices" and with cancer tests considered Class III medical devices, we think it's probable that FDA approval would need to follow the PMA pathway. This will almost certainly require U.S.-based clinical studies, potentially including several thousands of patients and taking a number of years to complete. VNRX currently ballparks the cost of FDA approval to be ~$825k per product. If, however, U.S. marketing approval can be obtained with the much simpler 510(k) pathway - possibly using the tests as an adjunct to current cancer diagnostic methods - this would likely significantly reduce time to the U.S. market launch.

As it is now, our outlook assumes that VNRX initially focuses on getting the NuQ panel and other products commercialized in Europe to help fund the U.S. regulatory program - which we assume follows a PMA pathway. As such, we don't model the products launching in the U.S. clinical space for at least the next two years.

Key to increase chances of successfully gaining regulatory approvals (Europe and U.S.) will be to demonstrate high enough accuracy (sensitivity = true positive cancer rate, specificity = true negative cancer rate). The lingering question is 'how high is high enough?' - which is very difficult to determine at this point. The hurdle for CE Mark may be lower in that regard than for FDA approval. The current lack of a consistently reliable, low-cost, non-invasive cancer diagnostic means that the bar may be at a very achievable level. Relatively unreliable and low-accuracy cancer-related screens such as PSA and fecal occult blood which are widely used also suggest somewhat liberal standards relative to what's acceptable from a diagnostic utility standpoint. As such, a 70% sensitivity/70% specificity, for example, would potentially be considered relatively strong performance. The other potentially important question that clinical trials should be able to answer is how soon (stage of the cancer) VNRX's tests are able to identify the cancer and to determine the type of cancer. These will both be key to increasing the potential utility of and demand for the tests. Additional trial data should help to start providing more insight into these questions.

**Clinical Trials Initiated in 2012, Larger Trials Started in 2013…**
VNRX initiated clinical testing in 2012 with a small internal study, positive results from which were announced in November of that year. Over the past year the company has announced several more studies including two colorectal cancer studies through collaborations with University of Copenhagen and a "top ten global diagnostics company", a colorectal cancer study at CHU-UCL Mont-Godinne Hospital in Belgium, three studies in collaboration with the University Hospital Bonn in Germany, and a larger (800-patient) internal study being done in collaboration with Wales Cancer Bank. Data continues to be positive, including recent data released from the Bonn University and Mont-Godinne studies. Data from the large Hvidore (Denmark) studies could be available this year. Assuming positive results, the data from these trials may be submitted for publication and used to help support regulatory approval of VNRX's tests in Europe and the U.S.

VNRX has been very active in pursuing additional studies which should aid their efforts in amassing a broad and deep portfolio of clinical data in various cancers. Future studies could include collaborations with partners already well established in the clinical diagnostics space. And while there's only limited clinical data (which has been very positive) that has been released to-date, we expect to see a significantly greater data-flow over the next several quarters. We expect this to not only provide greater insight into the accuracy of the tests in determining whether cancer is present but also in identifying the types of cancers as well how early of a stage that the tests are able to identify the cancers.

Hvidovre Hospital, University of Copenhagen
In late May 2013 VNRX announced they signed an agreement with Hvidovre Hospital at the University of Copenhagen in Denmark whereby VNRX would obtain ~10,800 patient blood samples for analysis with VolitionRx's NuQ tests. This sample base was subsequently increased to ~15,800.

4,800 of the samples were collected by Hvidovre Hospital under the direction of Professor Hans Jorgen Nielsen (Professor of Surgical Oncology at the Department of Surgical Gastroenterology) from 2010 - 2012. These patients had colorectal cancer as well as other diseases. They also underwent colonoscopies, which along with a plethora of patient background, treatment and follow-up data, makes for a very robust set of data for VolitionRx to use in their analysis of the samples with their NuQ tests which will initially use the samples for detection of colorectal cancer. Not only is the sample and data set high quality and comprehensive, it comes at almost no cost to VNRX with Professor Nielsen offering the samples for free in the hopes it will advance VNRX's efforts in bringing an early cancer detection test to market.

Analysis of the first 1,000 samples commenced in June. We expect analysis will be complete in 2014. It's anticipated that this 1,000-patient data will then be used to support a CE Mark application for a colorectal cancer test, which we think could also happen by 2014. We continue to look for CE Mark to be granted in 2014 or early 2015.

The other ~11,000 samples will be collected in a prospective trial which will be jointly funded by VNRX, the University of Copenhagen and a "top ten global diagnostics company." The samples will be collected at the University of Copenhagen under the direction of Professor Nielsen. Collection is anticipated to commence in April 2014 and be completed at the end of 2015. The samples will be provided to VNRX blinded and randomized. VNRX anticipates they will spend only about $1.8 million for collection of these samples.

We view this agreement a significant positive for moving VNRX's development programs forward. This provides the company with a very large, high quality sample and data set for a fraction of the cost that they would have had to spend had they run prospective studies on their own (which could have easily cost $10 million - $25 million)

and also now puts a more definitive timeline on when CE Mark application could happen. The data from these studies are also expected to be used to help support an eventual FDA filing.

Bonn University Hospital

In mid-2012 VNRX entered a collaboration with Bonn University Hospital in Germany (Rheinische Friedrich-Wilhelms-Universitat Bonn) to perform clinical trials in the evaluation of Volition's NuQ assays for cancer diagnosis and in other diseases. Lead investigator of the trials is Dr. Stefan Holdenrieder of the Institute of Clinical Chemistry and Clinical Pharmacology at University Hospital Bonn who is considered a world-renowned expert in the field of circulating nucelosomes and has authored over 70 journal papers.

The collaboration includes a large multi-year prospective study in which blood samples will be collected from patients at U of Bonn Hospital. The study was initially expected to commence in July 2012 but this timeline was pushed back in order for the initial validation studies to complete. With positive results from these initial studies, VNRX is now enrolling for this larger study. Anticipated that blood samples will be taken from at least 2,000 patients including those that are; healthy, those that have cancer (including 20 of the most prevalent cancers at various stages of disease), and those that have conditions other than cancer such as organ-related benign diseases, metabolic diseases (ie - renal failure, autoimmune diseases), acute diseases (ie - sepsis, inflammation, trauma, stroke), and chronic degenerative diseases. The study will evaluate the NuQ tests in diagnosis of cancer as well as derivate application such as with the other diseases and conditions listed above.

In early November 2013 VolitionRx announced data from 90 patients (24 colorectal cancer (CRC), 10 benign colorectal diseased (BCD), and 56 healthy controls (HC)) tested with its NuQ-5m assay for colorectal cancer. Results, which were presented by Dr. Holdenrieder at the 8th Circulating Nucleic Acids in Plasma and Serum (CNAPS) congress in Baltimore, were encouraging and showed the assay was able to detect 75% of patients with colorectal cancer with a 70% specificity. These findings were confirmed on a second set of 113 patients (49 CRC, 26 BCD, 38 HC). The assay detected significantly (95% CI) lower levels of NuQ-5mc in CRC and BCD compared to HC although no differences were found between CRC and BCD. Relative to differentiation of CRC from HC, sensitivities improved from 33% at a 95% specificity to 75% at a 70% specificity.

The Bonn collaboration may also include a study for the validation of the tests as a predictor of the performance and therapy monitoring of chemotherapy. Expected to enroll ~300 patients with a variety of cancers. The samples will be collected before each of the 6 to 8 therapy cycles and will be correlated with the radiological response evaluation. For both clinical scenarios, the NuQ tests will be compared with already established tumor markers to see their specific use in the clinical application.

Colorectal Cancer Study

In August 2012 VNRX announced an agreement with Biobank of CHU UCL Mont-Godinne, an academic hospital in Yvoir, Belgium for a prospective longitudinal study with ~ 250 patients as they progress through diagnosis and treatment of colorectal cancer. This is the first trial using VNRX tests focused on a single cancer (colorectal). Enrollment will include patients with a potential digestive pathology such as suspected colorectal cancer, polyps, Crohn's disease and colitis. The goal of the study is for VNRX's NuQ to be able to distinguish between patients with cancer and those with digestive conditions that indicate similar symptoms. Patient sampling is occuring at CHU UCL Mont-Godinne and Volition will analyze the samples at their lab in Belgium.

Preliminary results from 39 patients, announced in December 2013 at the Clinical Genomics and Informatics Europe Conference in Portugal, showed that when two of the NuQ tests are combined and used together, they were able to detect 85% of cancers with an 85% specificity. The combination test was also able to detect more than 50% of precancerous polyps.

800-Patient Internal Study

Following positive results of the 105-patient internal study (below), in January 2013 VNRX announced that, with patient blood samples supplied by the Wales Cancer Bank, they intend to run a ~800-patient internal study. Samples will include a variety of cancer sub-types and at various stages and are expected to include ~550 with breast cancer, ~230 with colorectal cancer and a smaller number with lung and pancreatic cancers. VNRX views this larger study as the next step towards gaining CE Mark of their tests.

**Initial Results From Internal Study Encouraging, Led To Ongoing Larger Studies…**

In addition to the studies above, VNRX completed a small internal study led by their own scientists at its Belgium-based lab. Preliminary results, which were announced in November 2012, were encouraging with the NuQ tests detecting between 76% and 100% of cancers with specificities between 79% and 90%. While the study was too

small to draw any concrete conclusions relative to accuracy of the tests, the results provide a preliminary indication as to the potential diagnostic utility of the tests - particularly given that current cancer diagnostic and screening tests (some of which are used over 100 million times per yr in the U.S. alone) leave a substantial room for improvement in terms of accuracy and specificity (as well as cost, ease of use and patient comfort). 105 patients including 31 healthy patients and those with cancer of the colon(n=25), breast(n=25), and lung(n=24) were included in the initial results which showed;

> colon cancer: 76% sensitivity (19 of 25 patients detected), 90% specificity (3 of 31 healthy samples false positive)

> breast cancer: 96% sensitivity (24 of 25 patients detected), 90% specificity (3 of 31 healthy samples false positive)

> lung cancer: 100% sensitivity (24 of 25 patients detected), 79% specificity (6 of 28 healthy samples false positive)

Concurrent with the release of these internal study results, VNRX announced that the preliminary results (from 62 healthy, 20 benign colon cancer, and 35 colorectal cancer patients) of the 800-patient retrospective pilot study "are consistent" (specific details were not released) with results of the internal study. Volition's Chief Scientific Officer noted relative to the internal study results that, " Our internal results are extremely promising, and are consistent with independent data from external studies."

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## MARKETS: Commercialization Channels

**96-Well ELISA Kit for RUO Market**

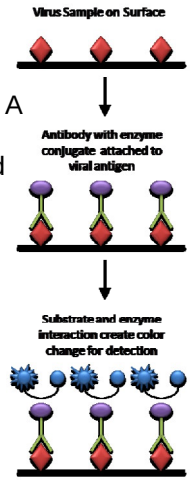



Again reiterating VNRX's commercialization strategy, initially they will sell to the RUO market and, following successfully gaining requisite regulatory approvals, will launch their products to the clinical markets. We view the RUO-related market as somewhat of a testing ground to help gauge interest, build initial awareness and expand the potential future clinical utility of the products - with the additional benefit of being able to generate some early revenue (although clearly not the same commercial opportunity as the clinical market). We also note that although VNRX's tests may have utility in other areas other than cancer (such as autoimmune disorders and acute diseases), oncology is the main focus and the area expected to hold the most promise. As a result, our Markets discussion focuses only on the major commercial channels (clinical laboratories and POC) and diseases (cancer) that are the company's major focus.

All the tests will be blood-based and on the enzyme linked immunosorbent assay (ELISA) format. Fifteen tests are already available for sale to the RUO market as a 96-well kit.

**Backgrounder on ELISA: *Established, Accurate and Trusted***

ELISA diagnostics typically involves multi-well microtiter plates in which the wells of the plate are coated with a specific antigen. The plates are then filled with a patient sample (ie. - blood, plasma, serum, etc) and the antibodies in the sample that are against the antigens will bind to the antigens. A detection antibody is then added which is covalently linked to an enzyme. Finally, an enzymatic substrate is added which interacts with the enzyme and generates visible color (read with the naked eye or an electronic plate reader) and indicates the quantity of antigen in the sample.




*wikipedia.com*

ELISA has been in existence for about 40 years and has had a long reputation for accuracy, performance and reproducibility. Other technologies have recently evolved such as molecular diagnostics that have shown improved sensitivity and potentially great promise in early detection of diseases such as cancer. Nonetheless, ELISA remains the dominant testing format in the clinical lab diagnostics space and is not likely to lose that designation anytime soon. Dozens of companies compete in the ELISA space which includes manufacturers of reagents, kits, and instrumentation.

**Clinical Lab: *Cancer Testing Catalyst to Growth***

The clinical lab market consists of stand-alone or hospital-based professional laboratories which are staffed with well-trained technicians and often equipped with sophisticated, high-throughput instruments used for processing the tests. Assays sold to and processed by these labs are not required to be CLIA-waived, which lowers the regulatory hurdles compared to the POC market.

Instrument manufacturers (which include major corporations such as Siemens, Roche, and Abbott among others) generally supply their installed base with proprietary tests that run on their instruments. VNRX's strategy relative to the clinical lab market is to either license their technology to an instrument manufacturer (or other diagnostic company) or to supply the microtiter plates (i.e.- tests) to the clinical labs directly.

Cancer markers have been one of the fastest growing assay categories in the clinical lab space over the last several years and this trend is expected to continue. According to Kalorama Information, worldwide cancer markers immunoassay sales have increased at a CAGR of 9% from 2007 to 2012. Other market research providers estimate this could accelerate to double-digit growth rates towards the end of the current decade, fueled in part by the aging population and an ever-increasing focus on oncology as a profit center by health care providers and drug companies.

**Worldwide Lab-Based Immunoassay Sales by Analyte Type 2007-2012 (ID, Tumor Markers, Cardiac Markers, Diabetes/HbA1c, Thyroid, Proteins, Autoimmune, Anemia, Therapeutic Drugs, Fertility, Allergy, Drugs of Abuse)**

| | IVD Sales 2007 | % Mkt | IVD Sales 2012 | % Mkt | CAGR |
|---|---|---|---|---|---|
| Infectious Diseases | 2,500 | 37 | 3,325 | 37 | 6 |
| Tumor markers | 740 | 11 | 1125 | 13 | 9 |
| Cardiac markers | 785 | 12 | 1050 | 12 | 6 |
| Diabetes/HbA1c | 370 | 3 | 590 | 7 | 10 |
| Thyroid | 365 | 6 | 465 | 5 | 5 |
| Proteins | 330 | 5 | 420 | 5 | 5 |
| Autoimmune | 250 | 4 | 410 | 5 | 10 |
| Anemia | 305 | 5 | 390 | 4 | 5 |
| Therapeutic Drugs | 310 | 5 | 335 | 4 | 2 |
| Fertility | 280 | 5 | 330 | 4 | 3 |
| Allergy | 260 | 4 | 290 | 3 | 2 |
| Drugs of Abuse | 190 | 3 | 200 | 2 | 1 |
| TOTAL | 6,685 | 100 | 8,930 | 100 | 6 |

*Kalorama Information*

As might be expected, the U.S. and Europe are the two areas of the world with the greatest in-vitro diagnostic testing (including clinical lab, professional POC and OTC) activity. Combined the U.S. and Europe, which are the two geographic markets that VNRX will focus on, account for approximately 75% of the market.

**Worldwide In Vitro Diagnostic Reagent Sales by Country/Region 2007-2012**

| | Sales 2007 | %Mkt | Sales 2012 | % Mkt | CAGR |
|---|---|---|---|---|---|
| N. America | $18,450 | 44 | $23,090 | 41 | 5 |
| EU 15/W. Europe | 12,550 | 31 | 14,895 | 26 | 6 |
| Japan | 4,615 | 11 | 5,065 | 9 | 2 |
| China | 1,015 | 2 | 2,175 | 4 | 16 |
| L. America* | 830 | 2 | 1,695 | 3 | 15 |
| India | 520 | 1 | 1,000 | 2 | 14 |
| E. Europe | 710 | 1 | 950 | 2 | 9 |
| ROW | 4790 | 8 | 7446 | 13 | 9 |
| Total | $41,950 | 100 | $56,316 | 100 | 6 |

*Kalorama Information*

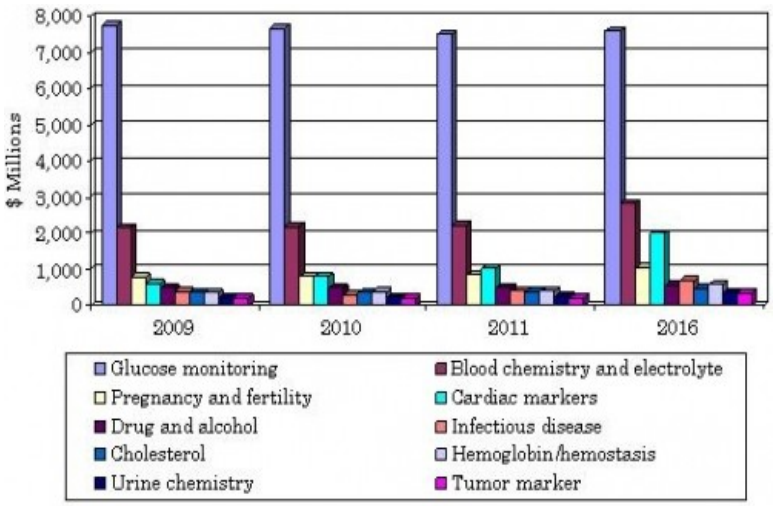
**Professional Point-of Care (POC): *Cancer Testing in Infancy in POC But Accelerating Quickly***

The professional point-of-care market mostly encompasses tests used at physician's offices and health care clinics. POC testing offers the advantage of rapid throughput with results in a matter of minutes, as opposed to days or weeks as is usually the case with clinical lab test processing. This allows the physician to simultaneously report the results to the patient and recommend/start treatment (and counseling if necessary) immediately. VNRX's tests could potentially be used in the POC setting, for example, in oncology clinics or general physician's offices with at-risk (i.e. - symptomatic, remissive, etc.) patients. These tests must be CLIA-waived, which essentially means that they are (per FDA regulations) "so simple and accurate as to render the likelihood of erroneous results negligible…" VNRX envisions that their CLIA-waived tests for the professional POC market will run on a small, portable instrument in an oncology clinic or general physician's office. VNRX's plan would be to contract with an instrument manufacturer to produce an instrument. Similar instruments are manufactured by several companies including Roche, Abbott and Siemens. Another option for the professional POC segment would be to develop a single-use, disposable cartridge-type rapid test (discussed further under "OTC"). The U.S. POC channel is likely to be a longer-term endeavor for VNRX.

By most estimates the POC diagnostics market is expected to experience meaningful growth over the next several years. According to BCC Research the worldwide POC diagnostics market is expected to grow to approximately $16.5 billion by 2016 from $13.8 billion in 2011, representing a CAGR of 3.8%. However, excluding glucose (which accounts for ~90% of OTC POC, ~25% of professional POC, and ~65% of total POC) the global POC market is expected to grow at a CAGR of 7.2% (from $6.3 billion to $8.9 billion) over that same period. While cancer remains a relatively small portion of the overall professional POC testing segment, it has grown faster than other professional POC tests over the last few years (see Kalorama Information chart below) and is one of the three (along with cardiac markers and infectious disease) expected major drivers of growth in POC testing going forward.

| Professional POC | 2008 | % | 2013 | % | CAGR |
|---|---|---|---|---|---|
| Glucose | 1,334 | 28 | 1,400 | 24 | 1 |
| Critical Care | 500 | 10 | 700 | 12 | 7 |
| Cardiac Markers | 490 | 10 | 650 | 11 | 6 |
| Infectious Diseases | 470 | 10 | 550 | 9 | 3 |
| Cholesterol/Lipids | 335 | 7 | 475 | 8 | 7 |
| Coagulation/PT, ACT | 300 | 6 | 475 | 8 | 10 |
| Hematology | 290 | 6 | 310 | 5 | 1 |
| HbA1c | 200 | 4 | 325 | 5 | 10 |
| Chemistry/Immunoassays | 180 | 4 | 210 | 4 | 3 |
| Fecal occult blood | 155 | 3 | 200 | 3 | 5 |
| Drugs of Abuse | 155 | 3 | 185 | 3 | 4 |
| Pregnancy | 146 | 3 | 170 | 3 | 3 |
| Urinalysis | 120 | 3 | 140 | 2 | 3 |
| Oncology | 95 | 2 | 130 | 2 | 6 |
| Other | 10 | 0.2 | 15 | 0 | 8 |
| **Professional Total** | **4,780** | **100** | **5,935** | **100** | **5** |
| Prof w/o glucose | 3,446 | | 4,535 | | 6 |

*Kalorama Information*




*bccResearch*

***U.S. Dominates POC Testing, Although Overseas May Offer Higher Growth…***

According to estimates by Kalorama Information (chart), the U.S. accounts for approximately 55% of the worldwide market for POC diagnostics with Europe next inline at 35%. The majority of growth going forward in POC may come from overseas.

| Region | Sales ($MM) | Percent of Market |
|---|---|---|
| United States | $7,100 | 55% |
| Europe | 4,500 | 35% |
| Asia/Japan | 647 | 5% |
| Rest of World | 647 | 5% |
| **Total** | **12,894** | **100%** |

In Europe, where POC testing had been restricted to some degree as central lab testing dominated in certain countries such as Germany, a shift is underway as a result of a greater emphasis on earlier diagnosis and prevention - which should benefit the POC setting. Similarly, the U.K. recently adopted a more decentralized approach to disease prevention and healthcare delivery, largely driven by an emphasis on controlling healthcare costs - this has resulted in greater use of POC testing. The trends in Europe leading towards growth of POC testing could benefit VNRX, particularly in the early years of commercialization when it's anticipated that they will be selling throughout Europe but still in the process of gaining FDA approval in order to enter the U.S. market.

**OTC: *An Untapped Market For Cancer Testing Yet Likely A Longer-Term Endeavor for VNRX…***
Over-the-counter tests are those that are typically bought at a drug store and used by the patient at home. The most common OTC tests are rapid (cartridge-type) tests such as pregnancy tests and glucose strip tests which use a handheld reader. In 2012 the first HIV test was approved for OTC sale, which could be a precursor to the eventual introduction of OTC for other serious diseases and conditions such as cancer.

**OraSure's OTC HIV Rapid Test**



*cbsnews.com*

**OTC Glucose Test**

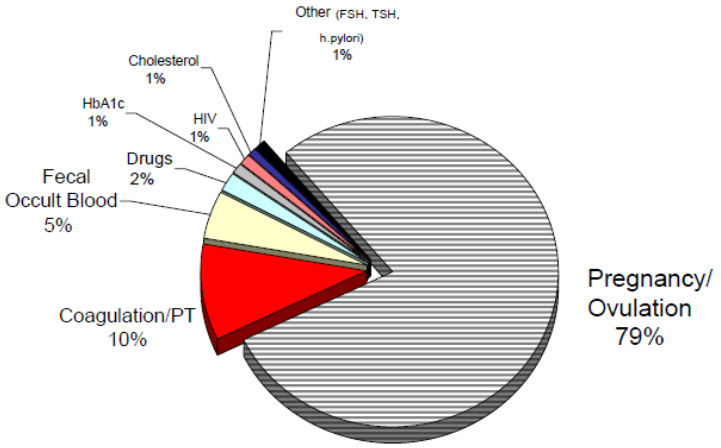


*pre-diabetes.com*

Similar to the professional POC tests, OTC tests must be CLIA-waived. In addition, regulators may require additional validation that the tests can be performed and interpreted by the patient, supplemental instructions and information included in the package insert, and potentially even available telephone call support for patient consultation (particularly for those patients with positive test results) and to answer patient questions. FDA could be particularly stringent relative to requirements for approving OTC tests that are used to diagnose serious and life-threatening diseases (such as HIV, HCV, cancer, etc.). This could mean a longer, potentially drawn-out regulatory process to get any of VNRX's tests on the OTC market. Pursuit of OTC approval is certainly a back-burner endeavor for VNRX and would only be pursued after initially entering the professional POC segment and if the potential opportunity made sense from a risk/return standpoint.

OTC diagnostic testing is mostly dominated by diabetes/glucose and pregnancy tests which, combined, hold about 98% share of the market. Aside from fecal occult blood tests (a positive result from which may indicate risk of colon cancer), which make up less than 1% (or 5% if diabetes/glucose is excluded) of OTC testing, there are no OTC cancer tests on the market. This provides a potentially compelling opportunity and wide open market for VNRX if, when the time comes, it makes sense to pursue OTC approval of their cancer tests.

**OTC Breakout Ex-Glucose**




**Glucose/Diabetes Dominates OTC Testing Market**

| | Sales 2008 | % Mkt | Sales 2013 | % Mkt | % CAGR |
|---|---|---|---|---|---|
| **OTC/Self Tests** | | | | | |
| Glucose | $7,555 | 94 | 9,860 | 94 | 5 |
| Pregnancy/Ovulation | 390 | 5 | 450 | 4 | 3 |
| Coagulation/PT | 50 | 1 | 75 | 1 | 8 |
| Fecal occult blood | 25 | 0.3 | 40 | 0.4 | 10 |
| Drugs of abuse | 10 | 0.1 | 15 | 0.1 | 8 |
| HbA1c | 5 | 0.1 | 25 | 0.2 | 38 |
| HIV | 5 | 0.1 | 6 | 0.1 | 4 |
| Cholesterol | 5 | 0.1 | 6 | 0.1 | 4 |
| Other | 5 | 0.1 | 10 | 0.1 | 15 |
| **OTC/Self Total** | **8,050** | **100** | **10,487** | **100** | **5** |
| OTC w/o glucose | 495 | | 627 | | 5 |

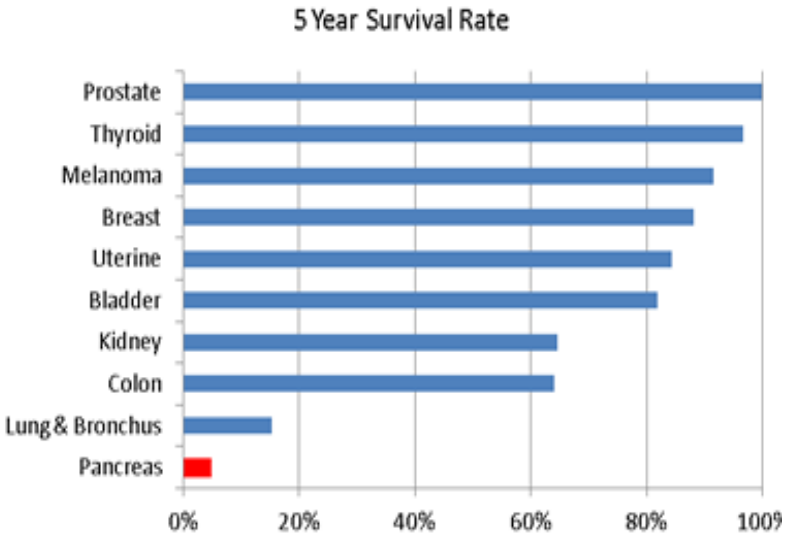
*Kalorama Information*

## MARKETS: Cancers

VNRX has indicated that they expect to initially focus on cancers of the breast, colon, lung, and pancreas as they believe that these offer the most attractive market opportunities. These four cancers account for approximately 650k new cancer cases each year in the U.S. (roughly 1.5 million for the U.S. and Europe combined), or about 40% of all U.S. cancer diagnoses. Characteristic of all cancers is the later the stage, the poorer the patient prognosis. As such, the earlier the diagnosis and initiation of appropriate treatment, the better likelihood of improved patient outcomes. The cancers that VNRX is initially focusing on relative to commercialization are some of the most

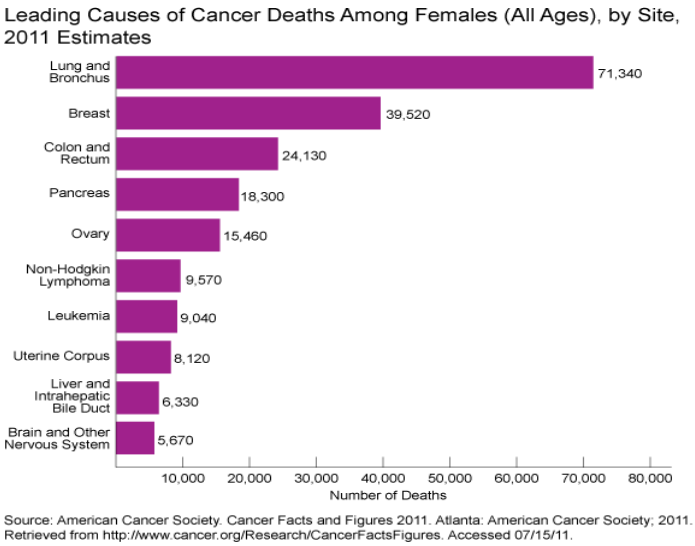
common, causing the most deaths, rapidly progressing/metastasizing and most difficult to treat, particularly if not diagnosed at a relatively early stage. Lung, breast, colon and pancreatic cancer are the top four cancer killers in the U.S. In addition, colon, lung and pancreatic cancers are very aggressive and the three with the lowest average five-year survival rates. Below we provide some general U.S. statistics on these four cancers. Statistics for Europe are less specific and not as readily available but a rough gauge is that cancer incidence and prevalence as well as death rates and total deaths for all of Europe is approximately equal to that of the U.S.

**Lowest 5-Yr. Survival; Colon, Lung, Pancreatic**




*Sanomab Ltd*

**Top Killers; Lung, Breast, Colon, Pancreatic**




*American Cancer Society*

**Breast Cancer**

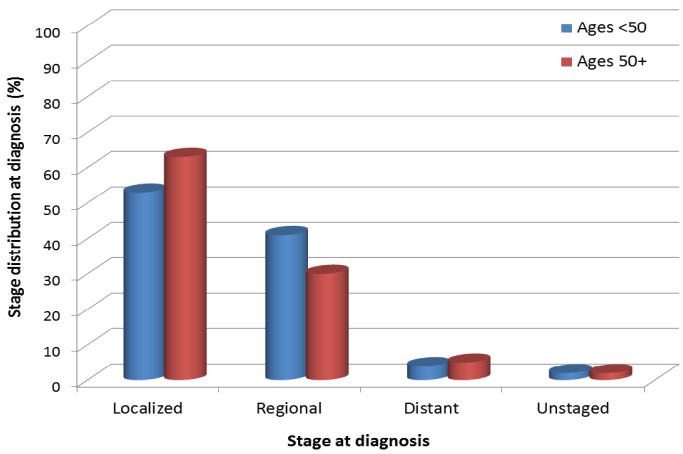
Incidence and Prevalence: ~12% of women will develop invasive breast cancer. Excluding non-melanoma skin cancer, breast cancer is the most common cancer among women. ~230k+ new cases of invasive breast cancer are diagnosed each year. Over 2.7 million American women are living breast cancer

Deaths: ~40k women die from breast cancer each year. Death rate for women from cancer of the breast is highest of all cancers aside from lung cancer

Stage at diagnosis: only about 5% of breast cancers are not found until the advanced stage which has contributed to the relatively high average five-year survival rate

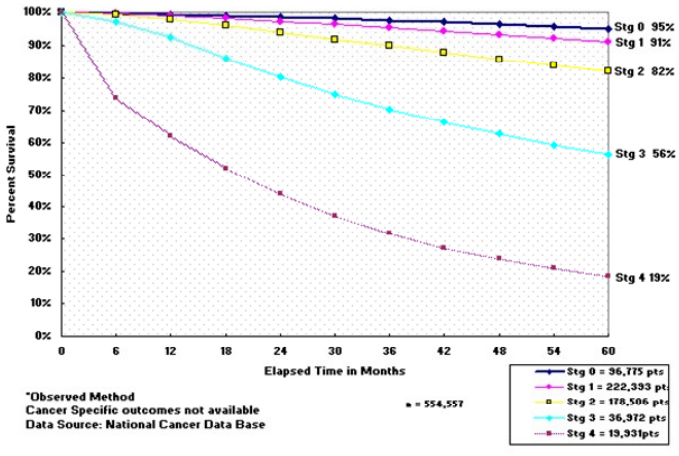
Mortality: five-year survival rate of breast cancer, at about 83%, is one of the highest among all cancers. Like, almost all cancers, however, if left to metastasize, chance of survival decreases significantly

**Breast Cancer Stage At Diagnosis**




*Medinfographics*

**Breast Cancer 5-yr Survival By Stage**




*Gundersen Health*

## Lung Cancer

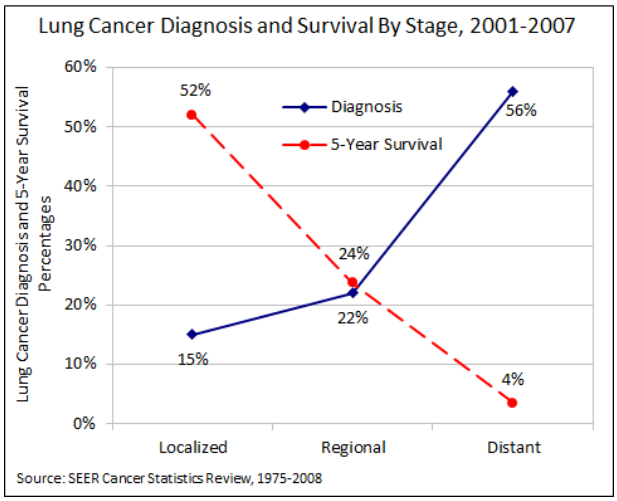
Incidence and Prevalence: Incidence of lung cancer among the entire population is relatively low, at less than one-tenth of one percent. Among smokers the incidence statistics are significantly greater, roughly about 20x that of the general population. Lung cancer is the second most commonly diagnosed cancer in both men and women. ~230k new cases of lung cancer are diagnosed each year. About 400k Americans are living with lung cancer, which is relatively low given the relatively high number of new cases each year - the reason is due to lung cancer's high mortality rate - which is due in part to over 50% of diagnoses not being made until the disease has already spread (see graph below)

Deaths: lung cancer is, by far, the number one cancer killer, causing ~160k deaths per year (colon cancer is second among both men and women, causing ~50k deaths)

Stage at diagnosis: about 56% of lung cancers are diagnosed at the advanced stage

Mortality: lung cancer is relatively aggressive and with an average five-year survival rate of about 18%, prognosis is typically one of the worst of all cancers. If found at an early stage (before spreading to adjacent areas or becoming metastasized), five-year survival is just better than 50%

**Lung Cancer 5-yr Survival and Diagnosis By Stage**




## Colon Cancer

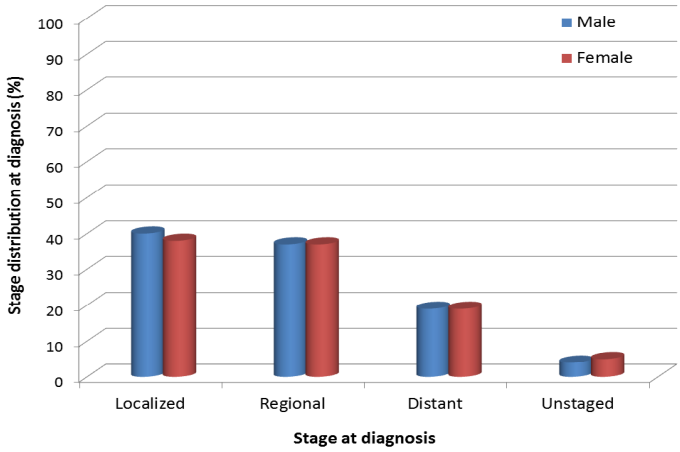
Incidence and Prevalence: About 150k new cases of colon cancer are diagnosed each year which, among women, is the third highest incidence rate (behind breast and lung) and, among men, is the second highest rate (behind lung). There are currently about 1.2 million Americans living with colon cancer

Deaths: about 50k Americans die from colon cancer every year, which is second only to lung cancer in men and third to breast and lung cancer in women

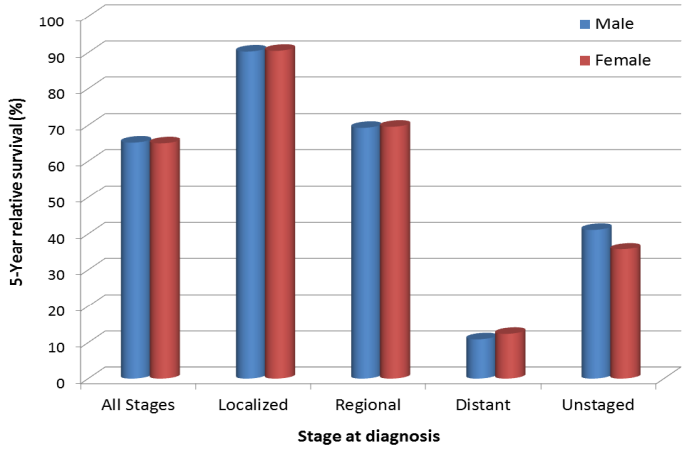
Stage at diagnosis: about 18% of colon cancers are diagnosed at the advanced stage

Mortality: colon cancer has the third most dire five-year survival rate, behind only lung and pancreatic cancers. Average five-year survival of colon cancer is about 50%. While an early stage diagnosis can mean an average expected five-year survival rate of about 90%, a late-stage diagnosis can drop expected five-year survival to about a 10% chance.

**Colon Cancer Stage At Diagnosis**




**Colon Cancer 5-yr Survival By Stage**




*Medinfographics*

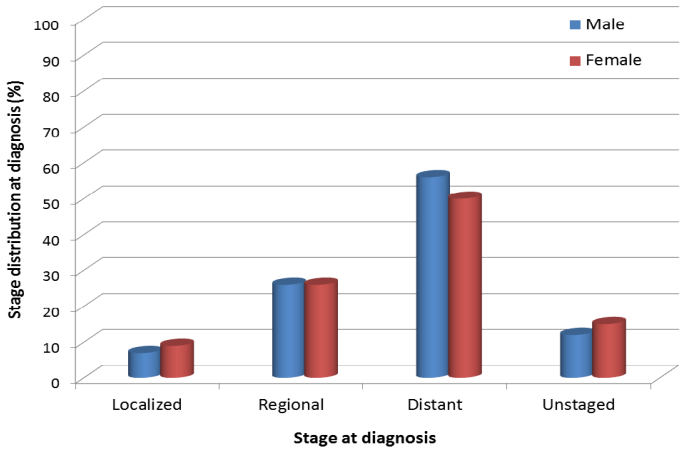
## Pancreatic Cancer

Incidence and Prevalence: about 45k new cases of pancreatic cancer are diagnosed each year (while this makes it one of the less common cancers, it's low survivability means it still ranks as one of the top cancer killers). There are currently about 38k Americans living with pancreatic cancer.

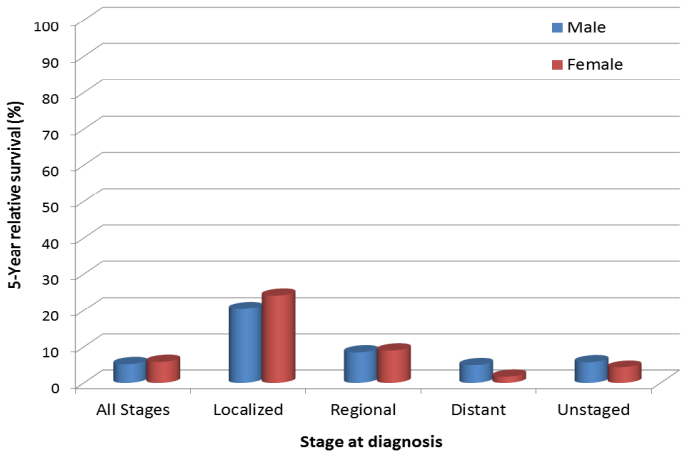
Deaths: about 38k (about the same number living with the disease) will die from pancreatic cancer each year

Stage at diagnosis: there are currently no tests on the market that can reliably diagnose pancreatic cancer at an early stage which has meant that about 50% of pancreatic cancers are not diagnosed until the cancer has already spread to other organs, contributing to the poor five-year prognosis
Mortality: pancreatic cancer has the lowest average five-year survivability rate, about 6%. If found at an early stage, five-year survival averages about 23%, this falls to about 2% with a late-stage diagnosis.

**Pancreatic Cancer Stage At Diagnosis**




**Pancreatic Cancer 5-yr Survival By Stage**




*Medinfographics*

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## CURRENT CANCER DIAGNOSTICS / SCREENING METHODS

Current cancer diagnosis and screening methods leave a substantial room for improvement in terms of accuracy, cost, patient comfort, and in finding cancers at an earlier, more treatable stage. In general, the more definitive diagnostic methods are more invasive, more time consuming and more costly (such as colonoscopy for colon cancer) while the less invasive and less expensive methods, which are often used for screening and more convenient and patient-friendly, can be unreliable and in some cases, cause more harm than good - yet many are still widely used by healthcare practitioners (see Appendix which highlights the issues with PSA testing for prostate cancer). VNRX's NuQ technology aims to marry high accuracy and reliability typically only achieved with invasive and costly diagnostic methods with the convenience, low-cost and non-invasive nature characteristic of many of the current cancer screening tests.

Below we discuss some of the current diagnostic and screening methods and related drawbacks used for the four cancers that VNRX has indicated will be part of their initial focus. While this is not an exhaustive list of cancers that the NuQ technology could be used for, particularly given that VNRX has a platform technology that could be expanded to dozens of cancers (as well as potentially to other conditions that are related to elevated nucleosomes), we think it provides insight into the dearth of reliable, accurate, low-cost and patient-friendly diagnostics and screens for cancer and opens up a significant potential opportunity for a more effective screening test or method - which we think VNRX could potentially exploit with their NuQ panel.

### Colon Cancer

The most effective diagnostic for colon cancer is invasive colonoscopy or flexible sigmoidoscopy. Definitive diagnosis is done with biopsy of suspicious polyps which are removed during colonoscopy/sigmoidoscopy. CT scan is then used to determine the extent of the cancer to determine if and how far it has spread. Colonoscopy screenings are recommended every ten years beginning at the age of 50. Colonoscopy has shown to be an effective diagnostic in finding colon cancer, with published reports indicating a 50% or greater risk reduction in developing early or late stage cancer with recommended screenings. However, there are significant drawbacks of colonoscopies, namely, at about $1,000 per procedure, it's a relatively high cost screening tool (particularly compared to VNRX's relatively inexpensive testing option) and it's very invasive, uncomfortable and time consuming, requiring the patient to be sedated as a fiber optic camera is threaded through the interior walls of the rectum and colon. Approximately 3.1 million colonoscopies are performed in the U.S. every year (and about 4.1 million done in Europe) which indicates that despite the drawbacks, there's a very substantial market for colon

cancer screening - which would presumably expand even further with the availability of an accurate, easy to use, inexpensive and non-invasive screening test such as NuQ.

Other colon cancer diagnostics / screens include;

- Double-contrast barium enema: patient receives an enema with barium sulfate, a contrast agent, followed by x-rays of the colon and rectum. Weakness of double-contrast enemas are that they are moderately invasive, can miss small polyps and false positives can be a serious issue
- Fecal occult blood tests: checks for blood in the feces which may be indicative of cancer. Commonly used as a first-line screen for colon cancer. Drawbacks include stool handling, significant potential for false positives, results can be influenced by diet, and lower sensitivity (as low as 30% in some studies). Despite these drawbacks fecal occult blood tests are widely used with approximately 140 million of these tests performed worldwide every year

**Lung Cancer**

There's been some debate about the merits of screening for lung cancer given the lack of consistently reliable evidence that lung cancer screening programs provide a definitive benefit relative to improving earlier detection of the disease. Unlike colon and breast cancer, which have their respective gold-standard (albeit not necessarily very effective 'gold-standards', particularly with mammography) screening tests/methods, lung cancer does not have a leading screening test or method. While some medical organizations such as the American College of Chest Physicians recommend against routine lung cancer screening, others such as the National Comprehensive Cancer Network, which issued its guidelines in 2012, are in favor of a process for screening higher-risk individuals. The U.S. Preventative Services Task Force (USPSTF), recommendations from which often influence public and private insurance reimbursement policy and decisions, recommends annual screening with CT for those 55 – 85 years old with a 30 pack/yr smoking history or those who have quit within the last 15 years (i.e. – high risk individuals). Most recommendations that are in favor of lung cancer screening are aimed at symptomatic and high-risk individuals such as smokers as smoking causes about 90% of lung cancers.

Lung cancer diagnostics / screens include;

- Chest radiographs (with or w/o sputum cytology): advantages of a chest x-ray is it's non-invasive, relatively fast and has been shown to be at least somewhat effective in finding lung cancer, even at early-stages. Drawbacks are that some studies have shown a low sensitivity and not effective in reducing mortality of lung cancer
- Low-dose computed tomography (LDCT): advantages are CT may be more effective in finding lung cancer than chest x-rays. CT scans have shown some promise in detecting even early-stage lung cancers in some studies but its effectiveness has not been consistently confirmed in other studies. Disadvantages are CT scans are relatively expensive and have shown a high false positive rate in studies with high-risk patients, which have ranged from 5% to 50%

**Breast Cancer**

Mammography remains the number one screening tool for breast cancer with about 40 million mammograms done every year in the U.S. In Europe the use of mammograms is even higher than that in the U.S. Advantages are that it's relatively fast and is non-invasive. Disadvantages are that it's arguably (depending on the study cited) ineffective at reducing breast cancer mortality, has a substantial false positive rate (7% - 15%), is even less effective in women with dense breasts and has even been implicated as causing more harm than good. For a variety of these reasons, mammography is not recommended for asymptomatic women under 50. For women over 50 the USPSTF recommends a mammography every two years.

Other breast cancer diagnostics / screens include;

- MRI: advantages are its non-invasive and has demonstrated higher sensitivity than mammography, can check multiple tumor locations, and analyze tumor growth in dense tissue. MRI suffers some significant weaknesses, however, including low specificity (~30% rate in some studies) which, along with a higher cost than mammography, has confined its use mostly to high-risk patients. Unlike mammography which is used both as a screening and diagnostic tool, breast MRI is largely only used for diagnosis.
- BRCA1 / BRCA2 gene mutations: these gene mutations may indicate an individual is at higher risk of developing breast and ovarian cancer. Advantages are ease and low cost of testing (done using a blood sample). Weakness is that this does not detect cancer, it only indicates a higher risk of developing it, and only about 5% - 10% are linked to these genes

**Pancreatic Cancer**

There are currently no tests on the market than can reliably diagnose early-stage pancreatic cancer. The USPSTF has a grade D recommendation on pancreatic cancer screening, recommending "against routine screening for

pancreatic cancer in asymptomatic adults using abdominal palpitation, ultrasonography, or serological markers." The USPSTF notes that they "found no evidence that screening for pancreatic cancer is effective in reducing mortality. There is a potential for significant harm due to the very low prevalence of pancreatic cancer, limited accuracy of available screening tests, the invasive nature of diagnostic tests, and the poor outcomes of treatment. As a result, the USPSTF concluded that the harms of screening for pancreatic cancer exceed any potential benefits."

Pancreatic cancer diagnostics / screens include;

- CA19-9 Marker test: cancer antigen 19-9 is considered the best tumor marker test in identifying pancreatic cancer. The advantages are it's an easy to perform blood test. The weaknesses are many, however, and include a high rate of both false negatives and false positives and it is generally not reliable in detecting early stage cancer (which is particularly important with pancreatic cancer)
- Endoscopic Ultrasound: involves the insertion of an endoscopy combined with ultrasound. Advantages are that it's been found to have a relatively high sensitivity in detecting pancreatic cancer in symptomatic patients. Disadvantages are it's invasive and may not be very effective in finding early stage cancer
- Imaging (CT/MRI/PET): mostly used to determine staging (i.e. - how far it's spread) of the disease. Generally ineffective as a screening tool or for early diagnosis

## FINANCIAL CONDITION / CAPITAL STRUCTURE

**Balance Sheet / Cash Flow**
As of the most recent reporting period (ending 12/31/2013) the company had $889k in cash and equivalents. Subsequent to 2013 year-end, VNRX raised $3M (gross) through the sale of 1.5M common shares (@ $2.00/share) with 100% warrant coverage (5yrs, $2.20 strike).

Cash used in operating activities was $3.1M in 2013, up from $2.31M in 2012. CapEx has been relatively insignificant.

VNRX raised about $2.8M and $2.6M through the issuance of common stock in 2013 and 2012, respectively. The company will need to continue to raise a significant amount of capital in order to fund ongoing operations including their various clinical studies. Based on our projections, VNRX will not reach a level of self-sustainable cash flow for at least the next three years.

**Debt / Contingencies**
Aside from the $433k repayable grant (related to the Walloon Region grant) listed as a long-term liability on the balance sheet, VNRX is debt/contingency-free.

Relative to the Walloon Grant, in 2010 the Walloon Region government in Belgium agreed to pay VNRX up to approximately $1.4 million to fund a certain research project. Specifics of the project have not been publicly disclosed. To-date VNRX has been paid about $1.3 million under the grant. The company will be obligated to repay at least $433k if the project is deemed a failure and, if the project is a success, will be obligated to repay a minimum of $433k plus a 6% royalty on related sales. The maximum amount repayable is twice the amount of total funding received. In Q4 2013 VNRX booked $866k of the $1.3M as income. In the 2013 10-K, VNRX notes that they are required to repay the $433k (the difference between received amount and amount book as income) – implying that the project was a failure – this does not affect our modeled projections as we had yet to incorporate a related contribution. VNRX is required to repay the $433k over the period 6/30/14 through 6/30/23.

**Capital Structure**
No preferreds or convertibles in the capital structure. Equity at the most recent quarter end consisted of approximately 11.4 million common basic shares outstanding. In addition, there were approximately 1.9 million warrants and options outstanding.

## OUTLOOK / VALUATION / RECOMMENDATION

***Outlook Could End Up Being Conservative…***
VNRX's current plan relative to commercialization is to initially promote to the research market which potentially provides the company with an opportunity to build awareness about the products as well as expands the validation experience of their technology. The company recently brought on a director of sales and marketing to lead the RUO sales effort and also signed distribution agreements for RUO products for the U.S., Europe, Japan, Thailand, Indonesia and Singapore. The RUO market, which consists of selling to research-oriented institutions such as medical universities for uses outside of patient diagnosis, likely offers only a fraction of the revenue opportunity compared to the commercial clinical market, however.

In the meantime, VNRX will pursue CE Mark in order to sell the tests to the clinical market in Europe (which could happen in 2014 or early 2015) and FDA approval for the U.S. market (potentially by 2016). Key to increase chances of successfully gaining regulatory approvals (Europe and U.S.) will be to demonstrate high enough accuracy (sensitivity = true positive cancer rate, specificity = true negative cancer rate). The lingering question is 'how high is high enough?' - which is very difficult to determine at this point. The hurdle for CE Mark may be lower in that regard than for FDA approval. The current lack of a consistently reliable, low-cost, non-invasive cancer diagnostic means that the bar may be at a very achievable level.

VNRX's most recent guidance relative to CE Mark submission is that they expect the NuQ-X test and NuQ-panel products will be applied for in 2014. The recent agreement with University of Copenhagen with VNRX obtaining a large patient sample set for analysis of colon cancer should help to catalyze progress towards a CE Mark submission. Our model assumes launch to the clinical lab market in Europe in early 2015 (pushed back from prior expectations of mid-to-late 2014).

Relative to FDA approval, given that there are no tests currently on the market that would likely be considered "predicate devices" and with cancer tests considered Class III medical devices, we think it's probable that FDA approval would need to follow the PMA pathway. This will almost certainly require U.S.-based clinical studies, potentially including several thousands of patients and taking a number of years to complete. If, however, U.S. marketing approval can be obtained with the much simpler 510(k) pathway - possibly using the tests as an adjunct to current cancer diagnostic methods - this would likely significantly reduce time to the U.S. market launch. As it is now, we model a launch to the clinical lab market in the U.S. in mid-to-late 2016 - which could end up being conservative, particularly if 510(k) clearance is deemed sufficient to sell to the clinical market.

Assuming requisite regulatory approvals, VNRX's commercialization game-plan to tap the clinical lab markets will likely entail either an agreement with another diagnostic company (instrument manufacturer?) or other third-party distribution (clinical lab?) which could allow the company to focus their resources on scaling up production rather than on building a sales force and facing the associated fixed-cost risks of doing so. The European market should afford the opportunity to generate revenue and cash and help fund the U.S. development and regulatory program. The POC and OTC channels, particularly as it relates to the U.S., are likely longer-term endeavors.

Over the next ten years our model assumes very incremental (low single-digit by 2023) penetration of the clinical lab IVD cancer markets, which we estimate at approximately $300 million in Europe and $460 million in the U.S., with projected growth rates of 5% - 6% annually. We also model a much smaller contribution (and lower penetration rate) from the POC channels, our assumptions which incorporate the added uncertainty of entering the U.S. POC market.

Data from ongoing and future clinical trials should not only provide more insight into the chances of regulatory approval, it should also help determine the potential diagnostic utility of the tests. There may be more insight into this with results from the studies using the samples from the University of Copenhagen for colon cancer - the first glimpse of which could be available before the current year-end. Depending on how strongly healthcare practitioners, third party payers (public and private), and influential medical organizations (such as USPSTF, American Cancer Society, etc.) view the utility of the tests, it's conceivable that VNRX's tests could take share of not only the current IVD cancer market, but also penetrate the markets of other cancer screening and testing methods (e.g. - colonoscopy, mammogram, advanced imaging, etc). These markets are enormous (as we discussed earlier in this report) and many times the size of the current IVD cancer segments. We note that we currently do not incorporate any assumption of penetration into these other diagnostic markets in our model - which, could provide significant upside to our estimates - which will be updated if and when appropriate. As cancer is VNRX's main focus we also do not include commercial contribution from potential future ancillary

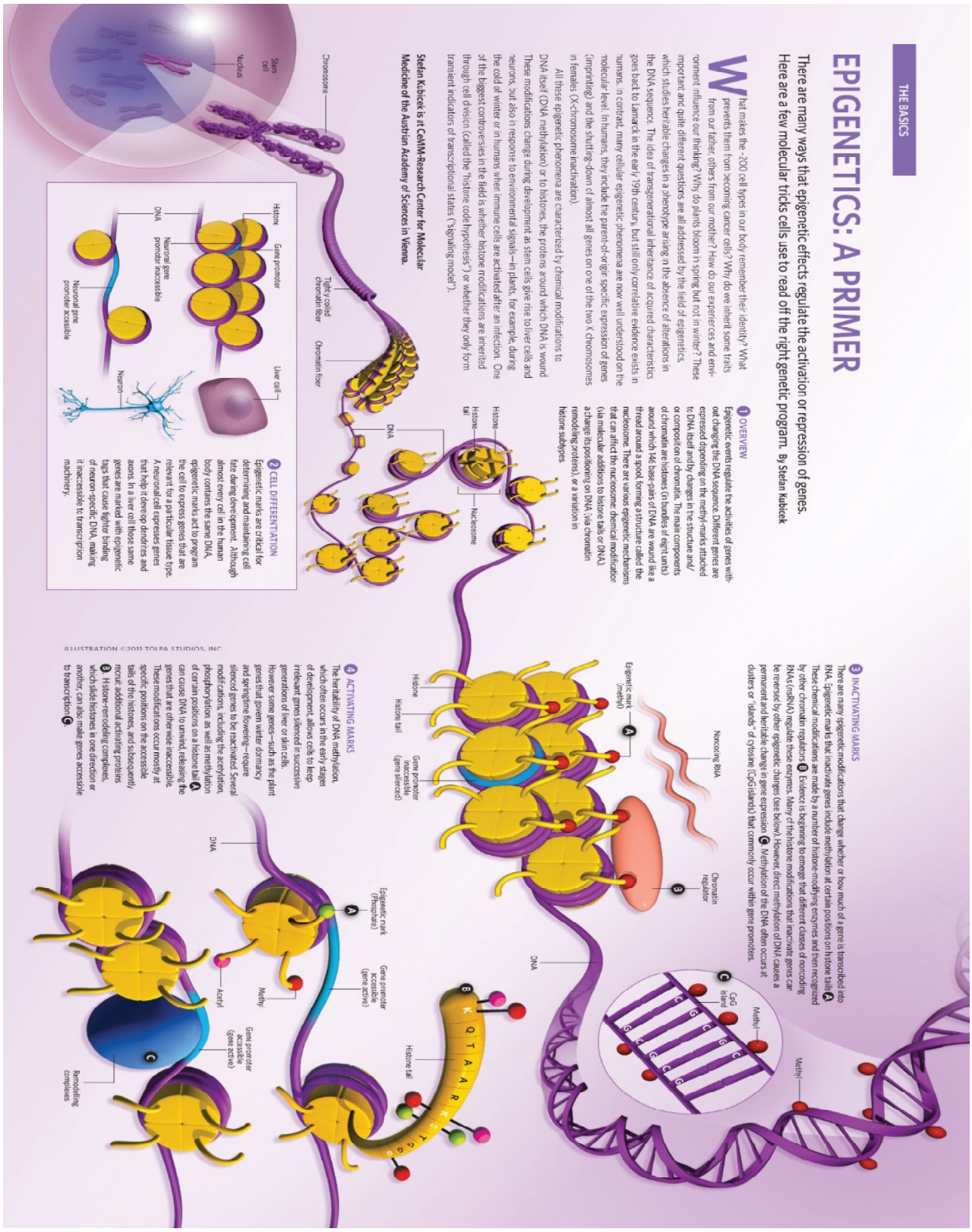
applications (i.e. - autoimmune diseases, sepsis, inflammatory-related diseases, chemotherapy efficacy, etc) - which also could provide some upside.

***Valuation Very Attractive…***

Based on our DCF model which goes out to year 2024 and uses an 11% discount rate (based on CAPM) and 2% terminal growth rate, VNRX is valued at $6.93/share (which we round to $7.00). Our model and assumptions will be updated if appropriate based on news flow which could also influence valuation. As it is now, we value VNRX at $7.00/share. We feel the current market price ($2.45) substantially undervalues the company and recommend accumulating the stock up towards our $7.00 price target. We are maintaining our Outperform rating.

## APPENDIX

## A.) Epigenetics




*SOURCE: the-scientist.com / Stefan Kubicek*

## B.) PSA Testing: Widely Used Despite Serious Reliability Issues

According to the National Cancer Institute, it is estimated that ~ 241k men will be diagnosed with and ~34k men will die of prostate cancer in the U.S. The key to improving prostate cancer diagnosis and patient outcomes is being able to accurately (i.e. minimize false-positives/false-negatives and determine the extent of progression) diagnose the disease at an early stage which in-turn will allow physicians to better determine the most appropriate course of treatment (if any) and reduce patient anxiety related to false-positive diagnoses. The current standard screening method for prostate cancer is a digital rectal exam (DRE) along with the prostate-specific antigen (PSA) test, which measures a protein released by prostate cells to determine the presence of cancer.

Despite its widespread use (~20MM PSA tests done every year in North America and ~45MM worldwide, representing markets worth ~$200MM U.S. and ~$500MM worldwide), PSA's accuracy in detecting prostate cancer as well as its effectiveness in reducing mortality (the ultimate goal) is highly controversial and has recently come under increasing scrutiny. Among the evidence that detractors cite as support against the use of PSA is the results of a meta-analysis of clinical trial data on over 400k patients which were published in the British Medical Journal in 2010. The study found that while PSA increases cancer detection, it is not associated with a "significant effect of screening on death from prostate cancer or overall mortality." The authors concluded that, "The existing evidence from randomized controlled trials does not support the routine use of screening for prostate cancer with PSA with or without digital rectal exam."

In a well publicized announcement, based on the results of several large clinical trials in the U.S. and Europe, in late 2011 the U.S. Preventative Services Task Force recommended that healthy men without any symptoms of prostate cancer not receive a PSA test. The recommendation, which was finalized in May 2012, carries significant weight and can determine whether public (including Medicare) and private health insurers will reimburse for the test. Per the chairwoman of the task force relative to the recommendation, "Unfortunately, the evidence now shows that this test does not save men s lives. This test cannot tell the difference between cancers that will and will not affect a man during his natural lifetime. We need to find one that does." The Task Force gave the PSA test its lowest rating, D, noting that it does more harm than good.

Studies have shown that PSA testing has a sensitivity and specificity of approximately 85% and 30%, respectively - indicating that while it is fairly good at detecting cancer (detects 85% of cases) it is very poor at differentiating between what is, and what is not cancer (i.e. - very low specificity, resulting in high false-positive rate). The heart of the accuracy problem with PSA testing is that levels of the PSA protein can be elevated (and result in the test indicating positive for cancer) under fairly common circumstances when cancer may not actually be present which could result in a false-positive diagnosis. The most common of these is when there is an enlargement of the prostate (called benign prostate hyperplasia or BPH). While the majority of men will experience some enlargement of the prostate as they age, only a very small percentage of them will develop prostate cancer. The correlation between BPH and increased levels of PSA results in only about 30% of positive PSA tests (i.e. PSA elevated beyond what is considered normal, >4ng/ml) actually turning out to be cancer. And of those accurately diagnosed as having cancer (as confirmed by biopsy) with PSA, most have slow-growing cancers that would never become life-threatening. There is also no definitive evidence that the presence of BPH increases the chances of eventually developing prostate cancer.

In the event of a positive PSA test showing, a biopsy will be done to confirm the diagnosis. If cancer cells are found in the tissue a Gleason score is assigned which is a measure of the severity or aggressiveness of the cancer. Prostate cancer biopsy involves the insertion of needles into different regions of the prostate gland to extract tissue which are then examined under a microscope. As a result of the low specificity of the PSA test, almost 75% of biopsies for prostate cancer turn out to be negative for the disease. Consequences of this include unnecessary mental anxiety associated with the thought of having a potentially deadly disease (this mental stress, especially with the elderly, can also result in physical health risks such as heart stress) and the risks inherent with biopsy such as infection. And even if the biopsy comes back negative, there still can be lingering mental anxiety from wondering if the biopsy was wrong and cancer is actually present. Instead of what might be a more appropriate course of action such as watchful-waiting (i.e. monitoring including future follow-up testing), this anxiety can prompt the patient to undergo unnecessary treatments such as surgery, radiation, and hormone-blocking medication which can expose them to further negative side effects such as persistent blood in the semen, impotence, erectile dysfunction, urinary incontinence, bowel dysfunction, and even death (the latter, a result of complications from surgery). The unnecessary mental anxiety and over-treatment associated with PSA testing was a major reason for the recommendation by the U.S. Preventative Services Task Force against use of the test.

## FINANCIAL MODEL

VolitionRx Ltd.

| | 2013 A | Q1E | Q2E | Q3E | Q4E | 2014 E | 2015 E | 2016 E | 2017 E |
|---|---|---|---|---|---|---|---|---|---|
| Revenue | $0.0 | $0.0 | $63.1 | $89.4 | $140.6 | $293.1 | $2,003.6 | $5,612.1 | $9,490.4 |
| *YOY Growth* | *-100.0%* | - | - | - | - | - | *583.5%* | *180.1%* | |
| Cost of Goods Sold | $0.0 | $0.0 | $13.1 | $39.4 | $65.6 | $118.1 | $199.6 | $668.6 | $1,130.2 |
| Gross Income | $0.0 | $0.0 | $50.0 | $50.0 | $75.0 | $175.0 | $1,804.0 | $4,943.4 | $8,360.2 |
| *Gross Margin* | *#DIV/0!* | - | *79.2%* | *55.9%* | *53.3%* | *59.7%* | *90.0%* | *88.1%* | *88.1%* |
| SG&A | $1,722.2 | $445.0 | $495.0 | $470.0 | $530.0 | $1,940.0 | $2,450.0 | $3,200.0 | $3,800.0 |
| *%SG&A* | - | - | - | - | - | *661.8%* | *122.3%* | *57.0%* | *40.0%* |
| R&D | $2,503.7 | $725.0 | $730.0 | $755.0 | $855.0 | $3,065.0 | $4,885.0 | $3,850.0 | $3,850.0 |
| *% R&D* | - | - | - | - | - | *1045.6%* | *243.8%* | *68.6%* | *40.6%* |
| Asset Impairment | $350.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 |
| Operating Income | ($4,575.9) | ($1,170.0) | ($1,175.0) | ($1,175.0) | ($1,310.0) | ($4,830.0) | ($5,531.0) | ($2,106.6) | $710.2 |
| *Operating Margin* | - | - | - | - | - | - | - | - | *7.5%* |
| Total Other Expense (Income) | ($865.6) | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 |
| Pre-Tax Income | ($3,710.3) | ($1,170.0) | ($1,175.0) | ($1,175.0) | ($1,310.0) | ($4,830.0) | ($5,531.0) | ($2,106.6) | $710.2 |
| Taxes (benefit) | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 |
| *Tax Rate* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* |
| FX translation | $25.5 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 |
| Net Income | ($3,735.8) | ($1,170.0) | ($1,175.0) | ($1,175.0) | ($1,310.0) | ($4,830.0) | ($5,531.0) | ($2,106.6) | $710.2 |
| *Net Margin* | - | - | - | - | - | - | *-276.0%* | *-37.5%* | *7.5%* |
| EPS | ($0.34) | ($0.10) | ($0.09) | ($0.09) | ($0.09) | ($0.37) | ($0.32) | ($0.11) | $0.03 |
| *YOY Growth* | - | - | - | - | - | - | - | | |
| Diluted Shares O/S | 10,832 | 12,000 | 13,000 | 13,500 | 14,200 | 13,175 | 17,500 | 19,500 | 21,500 |

*Brian Marckx, CFA*

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## MANAGEMENT *per company filings*

### Cameron Reynolds
***President & Chief Executive Officer***
Cameron Reynolds has over 17 years' entrepreneurial executive expertise in mining and biotechnology companies. He has strong experience in the management, structuring and strategic planning of start-up companies.
Cameron has returned to his life sciences and biotechnology roots where in 1996 he began working for Integrated Coffee Technologies, a genetically modified coffee company, in a junior management position, where he was responsible for business plan creation, office management, recruitment, and business development. After working for Integrated Coffee Technologies, Mr Reynolds served as the commercialization director for Probio, Inc., a company that commercialized intellectual property in the animal biotechnology fields including transgenisis and cloning research from the University of Hawaii. Mr. Reynolds held that role from 1998 until 2001, and his main responsibilities were managing all legal and contract issues with the University of Hawaii; implementing patenting strategy; managing all shareholder issues including the merger and its legal and contractual documentation; head office management; budgetary control; team building and recruitment.
From 2004 until 2011, Mr. Reynolds founded and served as Managing Director and Director of Mining House Limited, where he was responsible for identifying potential mining projects, coordinating the preliminary evaluations and securing the financing with a view to listing the companies on AIM, TSX and US OTC. From 2005 until present, Mr. Reynolds has held a number of board Directorships including Atlantic Mining PLC; Carbon Mining PLC, Magellan Copper and Gold (Carbon Mining and MCG were both became part of Solfotara Mining and Copper Development Corp on AIM, CDC.L after a vend); KAL Energy Inc. (KALG, OTC), Iofina Natural Gas PLC (IOF, AIM); Canyon Copper Corp. (TSX.V: CNC, OTCBB: CNYC), and Hunter Bay Resources (HBY, TSX-V). Cameron was educated at the University of Western Australia (B.Comm, 1993; and MBA, 2003).

### Malcolm Lewin
***Chief Financial Officer & Treasurer***
Malcolm Lewin has a strong background in finance and accounting both for public and private companies alike.
Mr. Lewin qualified as a chartered accountant with Coopers & Lybrand in 1976.
From 1989 to 2000, Mr. Lewin was a partner of Mercer Lewin, a chartered accounting firm. From 2000 until present, Mr. Lewin has acted for various companies listed on AIM and the TSX-V. In particular, Mr. Lewin acted as the finance director of OMG plc (AIM: OMG), a supplier of motion capture and visual geometry systems, from April 2000 to June 2003.
In June 2004, Mr. Lewin was appointed as the finance director of Real Estate Investors Plc (AIM: REI), a property investment company with interests in quality commercial and industrial properties throughout the United Kingdom, and held this position until August 2006. In September 2006, Mr. Lewin was appointed a Director and Chief Financial Officer of Hunter Bay Minerals Plc (TSX-V:HBY), a junior mining company with interests in South America and Canada, and held this position until June 2011.

### Jason Terrell
***Head of US Operations***
Dr. Terrell has a strong grounding in both medicine and more specifically in diagnostics. He currently owns and operates a number of diagnostic laboratories in Texas within the Any Lab Test Now franchise, a direct access lab testing company, and has also served as a National Franchise Corporate Medical Director for Any Lab Test Now, giving him oversight of over 70 franchises in 14 states.
Since 2011, he has been Medical Director of CDEX Inc, 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). He undertook his General Medicine Internship, and Anatomic and Clinical Pathology Residency at Texas Tech University Health Sciences Center.
Dr Terrell holds medical licences in 14 states across the USA.

### Rod Rootsaert
***Secretary***
Rodney Rootsaert has over six years of experience in providing corporate, legal and administrative services to start-up companies through Mining House Ltd., of which Mr. Rootsaert has been a director since 2007.
From 2007 until 2011, Mr. Rootsaert has served as corporate secretary for several junior mining companies. He was the corporate secretary for Magellan Copper and Gold Plc., from 2007 until 2011, where his duties included maintaining and preparing company documents, accounts and contracts. He also served as corporate secretary for Delta Pacific Mining Plc., from 2007 until present, where he was responsible for ensuring compliance with all relevant statutory and regulatory requirements. Mr. Rootsaert was educated at the University of Western Australia (Bachelor of Laws, 1993).

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**Thomas Bygott**

***Sales & Marketing Director***

Tom Bygott has over 12 years' experience in sales and marketing for technology companies.

Mr Bygott started his career with the Australian electronics company AWA as a business analyst conducting reviews of their Traffic division and electronics factory, later becoming a Marketing Executive for their Aerospace division.

Moving to the UK, he joined Geneva Technology, a Cambridge start-up developing what became the world's leading billing software for telecommunications providers. Geneva Technology was awarded the Queen's Award for Enterprise in 1999 and was acquired by Convergys, a US telecoms billing and customer care vendor for $700M in 2001. Mr Bygott was Product Marketing Manager for Europe at Convergys.

Mr Bygott moved into biotechnology in 2004, studying at Corpus Christi College in Cambridge before joining the Wellcome Trust Sanger Institute, first as a bioinformatician specialising in genome assembly and then as Project Manager for a resequencing project for malaria parasites.

At Active Motif, a leading supplier of epigenetics research kits, he was Sales and Marketing Manager, Europe for their TimeLogic division, selling specialised hardware to accelerate bioinformatics algorithms at research institutes, biotech companies and universities throughout Europe. • Mr Bygott is also currently a member of the Board of Governors of Cambridge University Hospitals NHS Trust, which operates Addenbrooke's Hospital in Cambridge.

Mr Bygott holds a BSc with First Class Honours in Pure Mathematics from the University of Sydney, an MPhil in Computational Biology from the University of Cambridge and an MBA from Cranfield University.

**Jake Micallef**

***Chief Scientific Officer, Belgian Volition***

Dr. Jacob Micallef has 20 years of experience in research and development and in the management of early stage biotechnical companies, including the manufacture of biotechnology products and the establishment of manufacturing operations.

Dr. Micallef gained this experience while working for the World Health Organization ("WHO") over a 10-year period from 1985. While working for the WHO, Dr. Micallef developed new diagnostic products in the areas of reproductive health and cancer. In 1990 he commenced development of a new diagnostic technology platform for WHO which was launched in 1992 and supported 13 tests. Dr. Micallef also initiated and implemented in-house manufacture (previously outsourced to Abbott Diagnostics Inc) and world-wide distribution of these products for WHO. In 1990, he started a "not-for-profit" WHO company, Immunometrics Ltd., which marketed and distributed those diagnostic products worldwide.

In 1999 Dr. Micallef studied for an MBA and went on to co-found Gene Expression Technologies in 2001 where he successfully lead the development of the chemistry of the GeneICE technology and implemented the manufacture of GeneICE molecules. He also played a major role in business development and procured a GeneICE contract with Bayer Pharmaceuticals. From 2004 to 2007, he taught "science and enterprise" to science research workers from four universities at CASS Business School before joining 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 SA., which is now Belgian Volition SA, a subsidiary of Singapore Volition. Dr. Micallef was educated at King's College London (BSc, Biology and Chemistry, 1977; PhD Physical Chemistry, 1981); St Thomas' Hospital Medical School, London (MSc Chemical Pathology, 1985); and Imperial College Management School (MBA, 2000.

**Mark Eccleston**

***Chief Scientific Officer, HyperGenomics***

Dr. Mark Eccleston is a biotechnology entrepreneur with over 18 years of experience in the sector, both in academia and in industry. From 2008 to 2009, Dr. Eccleston held a program management position at ValiRx Plc., where he ran multiple epigenetics-based diagnostic and therapeutics programs.

Dr. Eccleston has also held various other roles in business and industry including: CEO of Vivamer Ltd. in 2002, a company spun out from Cambridge University where he was responsible for commercialization of drug delivery and imaging technologies based on extensive work in this area during his academic career; and Chief Scientific Officer then consultant to Cambridge Applied Polymers from 2005 to 2008, where he devised and managed multiple high value consultancy projects for clients including Cadburys, Kellogg's, Reckitt Benckiser, Proctor and Gamble, and Umbro as well as a Spanish company specializing in non woven (polymeric) fabric, Tesalca.

In 2010, Dr. Eccleston founded OncoLytika, which focuses on opportunity recognition and product/process innovation within start-ups as well as established companies, where his main responsibilities are advising companies on business development and preclinical project management.

Dr. Eccleston was educated at University of Aston in Birmingham, UK (Chemistry, 1992; PhD in Polymer Chemistry (for biomedical applications), 1998); and Dundee University (MBA, Entrepreneurship, 2008; through the Royal Society of Edinburgh's Enterprise Fellowship Scheme).

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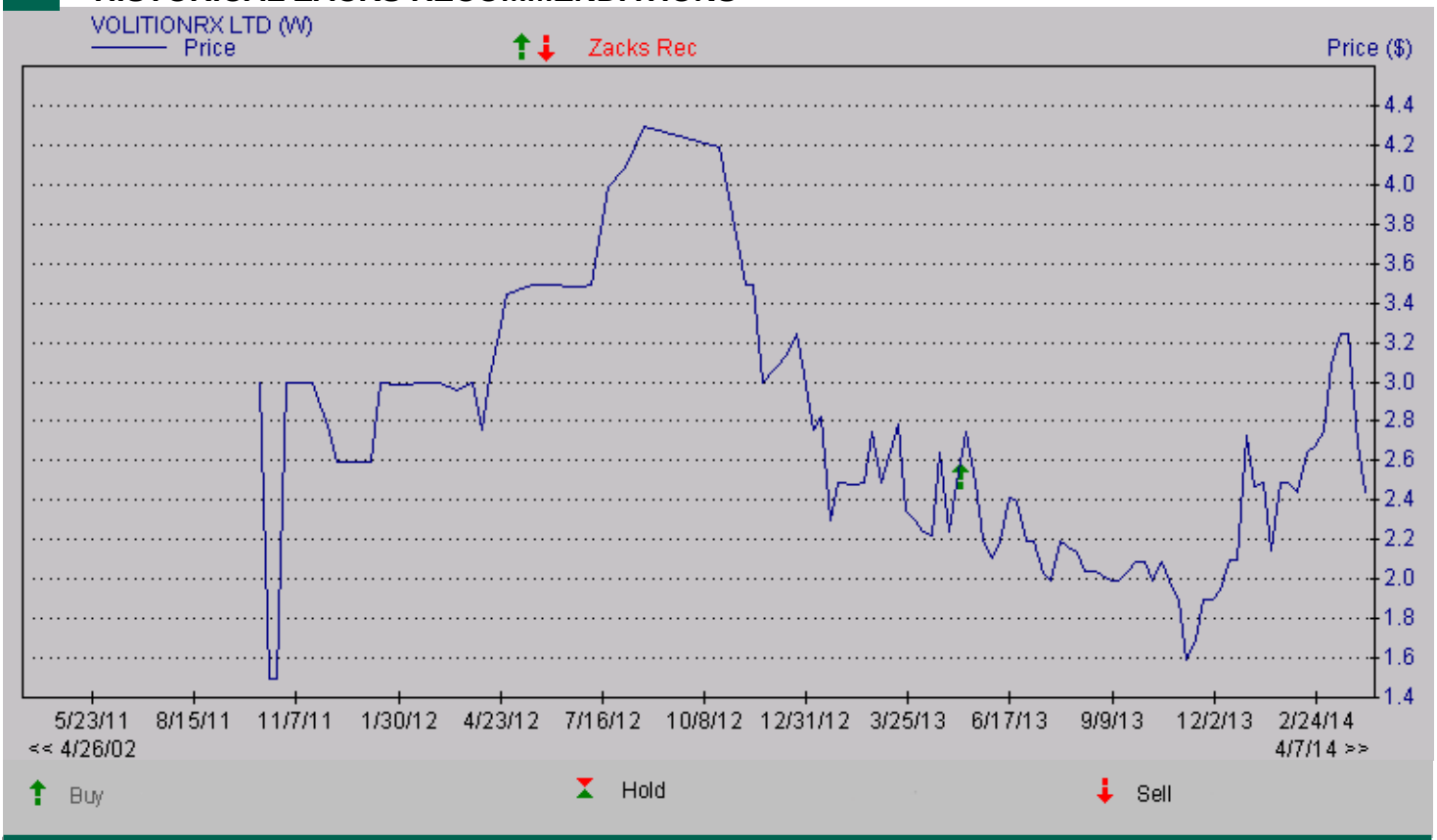


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