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VolitionRx Ltd (VNRX-NYSE)

VNRX: Pathway Design Study Progressing. Continue To Look For European Launch in 2018

Based on our DCF model which goes out to year 2026 and uses a 9.5% discount rate (based on CAPM) and 2% terminal growth rate, VNRX is valued at $7.50/share. Our model and assumptions will be updated if appropriate based on news flow which could also influence valuation

Current Price (08/29/17)	$2.56
Valuation	**$7.50**

OUTLOOK

Pathway design study for Triage is "progressing very well" and management hopes to have the data from that soon. VNRX is also in-process of replacing the Triage assay, following which the CE Mark will need to be updated. We model initial launch of Triage in Europe in 2H 2018. VNRX also appears quite committed to bringing a frontline CRC screen to Europe and Asia, development updates on which will be of particular interest given the relatively enormous size of asymptomatic populations, low CRC testing compliance, cost and risk related headwinds of colonoscopy, and dearth of cost-effective and accurate non-invasive testing options.

Relative to the U.S., the newly announced 13.5k sample NCI study is expected to serve as support for an eventual FDA (PMA) filing for a NuQ frontline CRC screen. But, in the meantime, VNRX plans to pursue initial U.S. commercialization with a symptomatic CRC test - the strategy for which seems to be firming up, although still needs to be finalized.

SUMMARY DATA

52-Week High	**$5.86**
52-Week Low	**$2.45**
One-Year Return (%)	**-33.51**
Beta	**-1.58**
Average Daily Volume (sh)	**37,106**
Shares Outstanding (mil)	**27**
Market Capitalization ($mil)	**$68**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**19**
Insider Ownership (%)	**28**
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 2017 Estimate	**N/A**
P/E using 2018 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(in '000)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	$0 A	$0 A	$0 A	$0 A	$0 A
2017	$0 A	$0 A	$0 E	$0 E	$0 E
2018					$659 E
2019					$3990 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$0.13 A	-$0.13 A	-$0.15 A	-$0.12 A	-$0.52 A
2017	-$0.13 A	-$0.13 A	-$0.14 E	-$0.15 E	-$0.55 E
2018					-$0.49 E
2019					-$0.38 E

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

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Q2 Results / Operational and Business Update:

VNRX reported Q2 results and provided an operational update. Relative to the financials, the $3.5M in operating expenses were inline with our $3.6M estimate. We continue to model only incremental growth in operating expenses through the remainder of 2017, despite expectations of additional development and pre-commercialization activities including those related to the Triage reconfiguration and CE Mark updating as well as completion of the pathway design study in Denmark. We continue to model no revenue until 2018.

Cash used in operating activities was $2.8M and $5.5M ($2.7M and $5.3M, ex-changes in working capital) in Q2 and 1H 2017, respectively. Another $875k and $1.2M was used in investing activities - primarily for upfitting the new R&D facility, over the same periods. Cash balance was $16.5M at quarter-end, which represents ~16 months of operating capital at the current burn rate. VNRX will continue to look to obtain additional grant funding from the Walloon Region of Belgium.

Relative to the operational update, the newly-announced large U.S.-based asymptomatic-sample clinical trial was the most recent major highlight, discussion surrounding which was largely covered during a July 20th conference call. But, management did have some updates on other operational items on the Q2 call including clinical programs and related activities aimed at Europe and Asia. The also talked about updated plans related to bringing a symptomatic CRC test to the U.S. market.

- Europe: management noted that the pathway design study for Triage is "progressing very well" and hope to have the data from that soon. VNRX is also in-process of replacing the Triage assay (see our Appendix for additional background), following which the CE Mark will need to be updated. We model initial launch of Triage in Europe in 2H 2018. VNRX also appears quite committed to bringing a frontline CRC screen to Europe (as well as to Asia) - and while we have much less clarity relative to potential development and commercialization timelines for an asymptomatic test launch, management has recently indicated that they believe that could also be a 2018 event.

Development updates on the Europe/Asia frontline screen will be of particular interest given the relatively enormous size of asymptomatic populations, cost and risk related headwinds of colonoscopy, and dearth of cost-effective and accurate non-invasive testing options. Timing of data read-outs may be one gating factor related to timelines of eventual commercialization. As a reminder, VNRX has two very large CRC screening trials ongoing in collaboration with Hvidore Hospital in Denmark; a 14k sample prospective study as well as a more recently initiated 30k-subject prospective longitudinal study of individuals that tested negative for CRC in a national fecal-test screening program.

- Asia: VNRX's first significant discussion that Asia was a near-term target was only a few months ago. Since then they noted that their first clinical evaluation of Triage is underway in Taiwan and the regulatory process has started in both Taiwan and Singapore - approval in Singapore would also open up sale of the test to nine other S.E. Asian countries. VNRX also recently hired a V.P. to lead efforts in that region of the world. The company also mentions in their Q2 10-Q that they are preparing "the submission of our tests to numerous Asian authorities" and that they "aim to announce several trials in Asia for our various potential CRC products in the coming quarters." Clearly management's message on recent conference calls was that they believe Asia, which in aggregate has very low compliance to CRC testing, represents a highly attractive market. Cost and risks associated with colonoscopies as well as cultural barriers to handling feces (i.e. with fecal tests) appear to be hindrances to CRC testing adherence in many Asian countries.

We ballpark the market opportunity in Taiwan and Singapore at approximately $7.2M and $1.7M, respectively – but, perhaps more important could be that these might represent just the initial foray into Asia which could be a harbinger for eventual introductions into countries with larger populations, including India and China.

The game plan for Asia is similar to that of Europe - that is, to bring both Triage as well as a CRC screen to market. In terms of the regulatory pathway - management noted that most Asian countries (ex-China) will register the tests using the CE Mark but may also require clinical evaluation with Asian populations to support registration. These studies commenced in Q2. VNRX estimates an approximate 8 - 12 month timeline from submission to obtain approval in most Asian countries. So while VNRX hopes to have a CRC test (Triage, CRC screen or both) in Asia sometime in 2018, we think initial launch may be more likely to happen in 2019.

China's regulatory process is more involved and will likely require a pivotal clinical trial to support a CFDA (i.e. China FDA) filing. Management estimates approximately 30 months from clinical trial commencement to approval in China.

Relative to the U.S….., the recently announced 13.5k-sample U.S.-based clinical trial is expected to serve as support for an eventual FDA (PMA) filing for a NuQ frontline CRC screen (see Appendix for background and discussion). But, in the meantime, VNRX plans to pursue initial U.S. commercialization with a symptomatic CRC test. The symptomatic-related regulatory strategy seems to be firming up, although still needs to be finalized. Current thoughts are to pursue a 510(k) pathway. Management believes a symptomatic study can be relatively small (600 - 700 patients, given the much higher positives CRC rates vs. asymptomatic) and ballparks cost at about $1.2M. The U.S. symptomatic program is not expected to begin until after launch of an asymptomatic test in Europe and Asia - as such, we do not expect any related U.S. revenue until at least 2019 and quite possibly, not until 2020.

Outlook / Valuation:

Danish Market Is Small But Could Serve As Litmus Test As VNRX Prepares For Follow-On Launches…
The population of Denmark is roughly 5M people – about 1.5M of which we estimate are of CRC screening age. We estimate that approximately 6% of FIT tests are positive and reasonably think that approximately 65% of the screening-age population will actually be screened. Screening guidelines typically recommend CRC testing once every two years. Further assuming revenue to VNRX of ~$50/test, this means Denmark represents a total annual market of approximately $1.5M (or ~30k tests). While not overly substantial, it can still be meaningful to VNRX given that it should require relatively little in the way of sales-spend to capture and gross margins are expected to be significant (we think as high as 90% or more). Additionally, if Triage is accepted into the Danish screening program, it could mean VNRX gets the entire annual market (i.e. not a slow ramp over time) – which means VNRX's initial order, as management indicated on a recent earnings call, could be in the tens-of-thousands in volume.

And maybe more importantly, Denmark could serve as the initial litmus test for other countries which could potentially come onboard in the near-term. In addition to certain parts of Asia (including Taiwan and Singapore), the other initial four EU countries that VNRX has mentioned are on the short-list represent an additional ~$30+ million in potential annual revenue (~600k annual tests). So while Denmark is expected to be the first launch territory, follow-on launches in other countries could follow. The other countries in Europe that the company has previously indicated are on their initial list (along with our estimated annual potential revenue of each) include Ireland ($1.5M), Scotland ($1.5M), the Netherlands ($5M) and France ($19M). Other countries may require logistics studies similar to that being done in Denmark in order to be granted access to their respective national screening programs.

Asia Represents Relative Enormous Market
While Europe has been considered to be where the bulk of the near-term opportunity lies, parts of Asia, most notably Taiwan and Singapore, now seem to also be on the short-list of possible initial launch territories. Approval in Singapore would also open up sale of the test to nine other S.E. Asian countries. Studies, which commenced in Q2, are simply to confirm Triage has acceptable performance among these populations. Pursuit of regulatory clearance in other Asian countries including China, India and Japan could follow - granting of which would open up sale of the test to relatively enormous populations. And while much of these parts of the world remain economically emergent, that may actually play in VNRX's favor given what they have indicated is expected to be a relatively low cost of production and processing of their tests (and related ability to keep pricing highly competitive).

While management is aiming to launch in Asia in 2018, we think it may be more likely to slip to 2019. While we have yet to model any revenue from Asia, this is subject to updating based on development, validation and regulatory-related progress. We ballpark the market opportunity in Taiwan and Singapore at approximately $7.2M and $1.7M, respectively – but, perhaps more important could be that these might represent just the initial foray into Asia which could be a harbinger for eventual introductions into countries with larger populations, including India and China.

Valuation
Prior to the announcement of the large 13.5k-sample NCI/EDRN study, our DCF-derived valuation calculated fair value of the company at $6.75/share.

We estimate VNRX will save approximately $30M over a period of three years by being part of this NCI study, versus what they would have spent had they solely sponsored a U.S. PMA-supporting pivotal study. We discount

this $30M back to present at (our DCF discount rate of) 9.5% and apply a 25% haircut to reflect what we think fairly represents risk that the study is not sufficient to act as a pivotal study for U.S. regulatory purposes. The result is incremental value of approximately $18M, or $0.70/share. **Our updated valuation is $7.50/share.**

Additional clinical data should help to handicap U.S. regulatory success of a NuQ-based asymptomatic CRC screen, help to compare the potential competitiveness against what is already on the market and aid in modeling related U.S. revenue.

Appendix

Large U.S. Prospective Trial Could Support Eventual Asymptomatic FDA Filing

In July VNRX announced that it will participate in a large U.S. study that could potentially serve as primary support for an eventual FDA filing seeking U.S. regulatory approval for a NuQ technology-based blood test in the primary diagnosis of colorectal cancer. Such a test would be aimed at the asymptomatic U.S. population - a market size estimated at approximately 90M individuals and, per our estimate, valued at over $4B. Given the relative enormous and valuable market, coupled with drawbacks of currently available non-invasive CRC testing options - including low accuracy, required fecal-handling, dietary restrictions and high cost, eventual FDA approval would likely be a highly substantial value driver.

VNRX is required to contribute just $3M (paid in equal quarterly installments over 3 years), with most of the funding borne by the study's main sponsor, the U.S. National Cancer Institute's (NCI) Early Detection Network (EDRN), which is the leading cancer research organization in the U.S. The Great Lakes New England Clinical Validation Center and the University of Michigan are also major participants and, along with EDRN, focused on the pursuit of technologies for the early detection of cancer.

While complete details of the study have yet to be made public (although we think the study design may be publicly available later this year), we do know the following:

- will include ~13.5k asymptomatic screening samples from subjects $\geq$ 50 years of age who have not previously undergone colonoscopy or CRC screening. This "non-adherent" (to CRC screening guidelines) population is at particular risk and a focus for organizations such as EDRN in improving screening compliance
- 4,677 samples have already been collected (retrospective collection). The remainder (~8.8k) will be prospectively collected at multiple sites prior to participants undergoing colonoscopy
- 2 to 3 years is the expected timeframe for collection to be completed
- samples will be tested with a panel of NuQ colorectal cancer assays
- samples will also be tested with other (non-VNRX) diagnostics - while specifics were not provided, this could presumably include traditional FIT/gFOB (i.e. fecal) tests as well as potentially more recently commercialized diagnostics such as Exact Sciences' ColoGuard stool DNA test. This could provide a unique opportunity for a true head-to-head comparison of results against (potential) competing products from the same study and samples

Given that this is a third-party study in which VNRX is a participant but not the main sponsor, they did not have the benefit of direct consultation with and feedback from FDA relative to the study design. But, management stressed that the study was developed by NCI for the purpose of acting as a pivotal study which could be used as primary support by VNRX for an eventual FDA PMA filing seeking U.S. regulatory clearance for a NuQ-based blood test as a first line CRC screen (i.e. for asymptomatic patients). Whether this study will be 'sufficient' in the eyes of FDA as a pivotal study is something that we may not know for quite some time - VNRX expects their first significant interaction with FDA to be a pre-submission meeting which likely would not be scheduled until after this study is largely completed and initial results are compiled.

But, we think that there are certain aspects that should play in VNRX's favor in that regard. Most notably is the large size of the study - 13.5k samples, including ~9k collected prospectively. This compares to ~10k total (prospective) samples for Exact Sciences' ColoGuard pivotal FDA study. And as it relates to the inclusion criteria of non-compliant subjects - we think that is another (positive) key point as the goal for VNRX will be to demonstrate that their test can improve screening compliance (National Colorectal Cancer Roundtable is leading an initiative to improve compliance to 80% by 2018). The lack of an appropriate study population (i.e. enrollment was not confined to only non-compliant subjects) ultimately created an issue for Epigenomics in their FDA studies with Epi proColon - this resulted in FDA requesting an additional clinical study and delayed U.S. approval by ~2 years. Another aspect that we think bodes well for VNRX is the reputation and expertise of NCI, EDRN and Great Lakes and their focus on facilitating the development (and eventual commercialization) of cancer detection technologies - clearly the most efficient way to do that would be to design their studies to meet anticipated FDA requirements and protocol.

The most significant benefit of participating in this study versus designing their own study (in which case they would have pre-study interaction with FDA) is cost. VNRX contributes just $3M over three years and will have access to over 13k blood samples for validation - that compares to management's estimates of $30M to $40M

(cost of Exact's pivotal study as a proxy) that it would cost to design and conduct their own study. The valuable data and ~$30M or more that they will save by participating in this NCI study, in our opinion, is more than worth the risk that they will need to conduct additional clinical work to support an eventual FDA filing.

Additional Salient Points…

Below we discuss what we think are some of the most salient points relative to VNRX's potential opportunity in the U.S. in the context of the current environment of screening and diagnosis of CRC including available non-invasive methods/modalities and the opportunity to address unmet needs.

- **Non-Compliance Provides Opportunity**: The United States Preventive Services Task Force (USPSTF) recommends screening for CRC beginning at age 50 and until age 75. Currently, only about 65% of screening-age Americans adhere to recommended CRC screening guidelines. A consortium of healthcare and other organizations have a goal of increasing that to 80% by the year 2018, which they estimate will prevent 277k new cases of CRC and 203k deaths within 20 years. With approximately 90M Americans of screening age, that means over 30M are non-compliant. While organizations such as USPSTF and FDA are not part of this consortium, they are undoubtedly aware of the benefits of improving compliance.

  The reasons for lack of adherence to screening guidelines vary and include a lack of access to care, concerns specific to the testing modality such as risks associated with invasive screening methods (such as risk of bowel perforation during colonoscopy) or handling feces with gFOB/FIT tests, cultural barriers, lack of insurance or financial resources and general lack of awareness of the benefits of screening. Additional screening options, such as what VNRX hopes to bring market, have the potential to address some of these barriers, particularly as they relate to concerns of other modalities such as colonoscopy and FIT/gFOB but also, possibly, as they relate to other factors such as cost.

  Noteworthy is evidence which has indicated that screening by any available means is more important than the specific screening modality in reducing rates of CRC. To this point, USPSTF mentions in their CRC guidelines that screening with Hemoccult II, compared with no screening, consistently resulted in a 9% to 22% reduction in CRC-specific mortality. This is despite the fact that Hemoccult II, a guaiac-based FOBT test, is relatively very inaccurate (sensitivity between 13% and 50%) - in fact it is no longer recommended as a CRC screening test. We think this may also provide some context for how motivated (and potentially lenient) U.S. regulators may be in improving CRC screening compliance.

- **Refine Panel**: the 2+ year collection time and large ongoing (and upcoming) OUS clinical trials provides VNRX with the ability to further refine the accuracy of their technology (actual testing, once the specific biomarkers have been chosen and the panel developed, can be done in only a matter of months). All else equal, the higher the sensitivity/specificity, the greater the chance of eventual FDA approval, inclusion as a recommended CRC screening option, reimbursement and for uptake of the test. And while we have not included colonoscopy in our review of alternative screening methods as it is (today) considered as a definitive diagnosis, level of sensitivity/specificity (across all cancer stages) could also determine how potentially competitive VNRX's test could be against invasive modalities.

  In May 2017 VNRX announced results of a small (n = 58) study which showed a panel of four NuQ assays detected 74% of all stages of CRC cancer at a 90% specificity. When incorporating an age-adjusted scoring system, 91% of CRC's were detected at a 90% specificity. Detection of early-stage cancers was also high, with 62% of pre-cancer polyps detected at 90% specificity. While the study was too small to presume replicability of detection at these levels, VNRX will be working to bring the highest performing test into this large NCI study.

- **Sensitivity / Specificity Threshold**: the threshold that may be required for FDA approval can be gleaned from Epigenomics' pivotal trial data. The FDA PMA filing for Epigenomics' Epi proColon blood-based (Septin 9) DNA test was supported by two clinical studies (n = ~2k in aggregate) which demonstrated sensitivity / specificity in detection (across all levels) of CRC of 68.2% / 78.8% in one study and 72.2% / 80.8% (versus FIT sensitivity of 68.0% at 97.4% specificity) in the other. The data was less then overwhelming, resulting in an adverse vote (5 in favor, 6 against) by an FDA advisory panel relative to the question of effectiveness of the test which ultimately required Epigenomics to conduct another clinical trial - this one aimed at assessing how their test would be received in a real-world situation (i.e. could the test improve adherence to CRC testing). Epi proColon finally received FDA approval in April 2016 but as a result of the less than compelling clinical data, it came with a relatively narrow label (discussed below). So while we think the Epi proColon pivotal trial data provides a goal for FDA approval purposes, meaningful adoption, competitiveness and ability to increase compliance of CRC screening may require VNRX to demonstrate a level of sensitivity / specificity that is more in-line with that of FIT and Exact's ColoGuard (FIT-DNA).

- **Target Market**: we think certain characteristics of VNRX's test may appeal differently to two somewhat distinct U.S. target markets; the non-compliant population (~30M people) and the compliant population (~60M people). Assuming $50 per test and recommended annual testing, this values the non-compliant and compliant U.S. markets at approximately $1.5B and $3B per year, respectively. We suspect that the non-compliant market may be less concerned with superior accuracy than aspects such as cost or concerns over exposure to feces handling or risks of invasive screening methods. And while these potential benefits (i.e. lower cost, lack of exposure to feces and invasive risks) may also appeal to a certain portion of the compliant population, relative sensitivity/specificity will undoubtedly be a significant determinant in choice of screening modality for these people and their physicians. The design of this NCI study clearly focuses on improving non-adherence, although should also provide insight into competitiveness versus current, non-invasive screening methods, which we discuss below.
    - **Epi proColon**: labeling was ultimately restricted to a relatively narrow indication - that is, for only those individuals (average risk, age 50 years and older) who are first offered, and decline, a USPSTF-recommended screening test (such as FIT/gFOB or colonoscopy). It is contraindicated as a replacement for (guideline-recommended) CRC screening tests. While Epi proColon was not included in the updated (2016) USPSTF recommended CRC screening guidelines, that may have to do with (inferior) data from a prior version of the test being used in the determination. Updated clinical and longitudinal data as well as evidence supporting an increase in screening compliance could be favorable for inclusion in future USPSTF updates. Nonetheless, as Epi proColon is not currently covered by Medicare (although legislation has been introduced in the U.S. House for Medicare coverage of FDA-approved blood-based CRC screening tests) and its label essentially relegates it to a second-line option to FIT/FOB (which are covered by Medicare and included as recommended CRC screens), we think its competitiveness and ability to meaningfully address the non-compliant population are compromised. Epigenomics was taken private earlier in 2017 and information relative to the market performance of Epi proColon since its launch is largely unavailable.

    - **ColoGuard**: ColoGuard was the first technology approved through the FDA-CMS parallel review program - resulting in FDA approval and Medicare coverage coming on the same day in August 2014. It is indicated for the screening of individuals 50 years and older at average risk of CRC. Pivotal study (n = 10k) demonstrated 92.3% sensitivity and 86.6% specificity in CRC. ColoGuard was included in USPSTF's updated (2016) CRC screening guidelines although does note that while single-test sensitivity of ColoGuard is higher than that of FIT, specificity is lower, resulting in more false positives. Medicare reimburses ColoGuard at a rate of approximately $500 every 3 years for those 50 - 85 years old who do not have symptoms and are not at increased risk of CRC. ColoGuard sales have ramped quite rapidly since its launch in late 2014. Approximately 10k tests were sold during the first full quarter (Q1 2015) on the market and this has grown at an average quarterly rate of almost 34%. In the most recent quarter (Q2 2017) 135k tests were completed. We think the relatively strong market performance of ColoGuard may be the product of a number of factors including; reimbursement at time of launch, relatively high accuracy, inclusion in USPSTF guidelines and a robust direct-to-consumer marketing campaign. And while fecal handling is a widely cited headwind to FIT adoption, that may be somewhat offset by the convenience of at-home sample collection (which is then shipped directly to the lab). In addition to (USPSTF's citing of) risk of false positives, the high cost is a drawback, particularly for the uninsured or under-insured.

    - **FIT:** USPSTF recommends fecal immunochemical testing every year. Medicare reimburses FIT at a rate of approximately $25 every 12 months. Given the various FIT test choices available by different manufacturers there is a lot of heterogeneity among performance. In evaluating FIT for their guidelines, USPSTF focused on those tests that had available data from at least two clinical studies. Among three clinical studies (encompassing ~26k samples) of OC-Light, a qualitative test, and five studies (encompassing ~13k samples) of OC FIT-CHEK, a quantitative test, the lowest sensitivity was 73% at 96% specificity while the highest sensitivity was 88% with 92% specificity. In the largest study (n = 9,989), sensitivity was 74% at 93% specificity – this was also the FIT (OC FIT-CHEK) comparator arm of ColoGuard's pivotal study.

      One of the drawbacks of stool-based testing is fecal handling which can affect compliance – although evidence of rates of compliance varies widely depending on the source. Two separate studies[1,2] indicated

[1] van Rossum LG, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology. 2008 Jul;135(1):82-90. doi: 10.1053/j.gastro.2008.03.040. Epub 2008 Mar 25.
[2] Hol L, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut. 2010 Jan;59(1):62-8. doi: 10.1136/gut.2009.177089.

FIT compliance between 60% and 62%, while (3 stool-sample) gFOB compliance was between 47% and 50% . Those rates are much higher than results from a retrospective study sponsored by Exact Sciences which used claims data from over 150k patients and found a compliance rate of just 0.3% (i.e. compliance in 3 of 1,000) using either FIT or FOB.[3]

- **gFOB**: similar to FIT, USPSTF recommends guaiac-based fecal occult blood testing annually. While legacy gFOB tests suffered from low sensitivity, this has improved with the next generation (such as Hemoccult SENSA) which have demonstrated in clinical studies to have a sensitivity of between 62% and 79% and specificity of 87% to 96%. In addition to fecal handling, other drawbacks of gFOB testing is it require sample collection of three consecutive stools (which can result in low compliance), generally considered to be less accurate than FIT and may require dietary restrictions.

USPSTF List of CRC Screening Strategies: 2016 Final Update

Table. Characteristics of Colorectal Cancer Screening Strategies[a]

Screening Method	Frequency[b]	Evidence of Efficacy	Other Considerations
Stool-Based Tests			
gFOBT	Every year	RCTs with mortality end points: High-sensitivity versions (eg, Hemoccult SENSA) have superior test performance characteristics than older tests (eg, Hemoccult II)	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT[c]	Every year	Test characteristic studies: Improved accuracy compared with gFOBT Can be done with a single specimen	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT-DNA	Every 1 or 3 y[d]	Test characteristic studies: Specificity is lower than for FIT, resulting in more false-positive results, more diagnostic colonoscopies, and more associated adverse events per screening test Improved sensitivity compared with FIT per single screening test	There is insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative diagnostic colonoscopy; may potentially lead to overly intensive surveillance due to provider and patient concerns over the genetic component of the test
Direct Visualization Tests			
Colonoscopy[c]	Every 10 y	Prospective cohort study with mortality end point	Requires less frequent screening Screening and diagnostic follow-up of positive findings can be performed during the same examination
CT colonography[e]	Every 5 y	Test characteristic studies	There is insufficient evidence about the potential harms of associated extracolonic findings, which are common
Flexible sigmoidoscopy	Every 5 y	RCTs with mortality end points: Modeling suggests it provides less benefit than when combined with FIT or compared with other strategies	Test availability has declined in the United States
Flexible sigmoidoscopy with FIT[c]	Flexible sigmoidoscopy every 10 y plus FIT every year	RCT with mortality end point (subgroup analysis)	Test availability has declined in the United States Potentially attractive option for patients who want endoscopic screening but want to limit exposure to colonoscopy

Abbreviations: FIT, fecal immunochemical test; FIT-DNA, multitargeted stool DNA test; gFOBT, guaiac-based fecal occult blood test; RCT, randomized clinical trial.

[a] Although a serology test to detect methylated *SEPT9* DNA was included in the systematic evidence review, this screening method currently has limited evidence evaluating its use (a single published test characteristic study met inclusion criteria, which found it had a sensitivity to detect colorectal cancer of <50%).[1] It is therefore not included in this table.

[b] Applies to persons with negative findings (including hyperplastic polyps) and is not intended for persons in surveillance programs. Evidence of efficacy is not informative of screening frequency, with the exception of gFOBT and

[c] Strategy yields comparable life-years gained (ie, the life-years gained with the noncolonoscopy strategies were within 90% of those gained with the colonoscopy strategy) and an efficient balance of benefits and harms in CISNET modeling.[2]

[d] Suggested by manufacturer.

[e] Strategy yields comparable life-years gained (ie, the life-years gained with the noncolonoscopy strategies were within 90% of those gained with the colonoscopy strategy) and an efficient balance of benefits and harms in CISNET modeling when lifetime number of colonoscopies is used as the proxy measure for the burden of screening, but not if lifetime number of cathartic bowel preparations is used as the proxy measure.[2]

Replacing Triage Assays

In a brief June 27th press release VolitionRx (VNRX) noted that the company's proprietary blood assays incorporated into Triage would be replaced. Both assays, as indicated in the release, were found to have high p-

[3] Anissa Cyhaniuk, MA, and Megan E. Coombes, MSc. Longitudinal Adherence to Colorectal Cancer Screening Guidelines. AJMC Feb 2016

values during an additional analysis of the validation data that showed Triage has the potential to prevent 24.5% of colonoscopies and detect almost 95% of colorectal cancers and 88% of (high-risk) adenomas. Given the brevity and seemingly serious potential implications of the announcement, we talked to management for additional clarity on exactly what this might mean in terms of development timelines as well as the overall feasibility of actually bringing Triage to market.

These are the key takeaways from our conversation with management (some of which are based on interpretation given that management could not provide specific answers to all of our questions):

- Triage validation, that is: able to prevent 24.5% of colonoscopies and detect 95% of colorectal cancers and 88% of high-risk adenomas, remains valid. Although this may actually improve with the new assays
- Bullet-proof the data. We suspect the decision to re-develop the two assays was to bullet-proof the data and avoid risk of claims of "correlation does not imply causation", particularly as additional manuscripts are expected to be submitted to peer-reviewed journals
- Short delay? Our interpretation is that validation with the two new assays is expected to be accomplished in relatively short-order and done using a portion of the 8k samples utilized for the initial assays. Given the higher throughput and capacity, we think VNRX should be able to run the samples relatively very quickly. Timelines for CE Marking of the assays and the panel may require a little more guesswork although experience gleaned from the first time around and that fact that CE Marking, in general, is a relatively short process, could mean that all of this might be accomplished as soon as current year-end or shortly thereafter. We hope to know more relative to potential timelines as VNRX provides future updates.
- Improved performance? Again, based on our interpretation from management's comments, we think the re-development may result in assays that outperform those they are replacing. Clearly the goal is to get the p-value down which, all else equal (the other components of Triage, age adjustment and FIT score remain unchanged), should result in a higher performing panel. As such, the 24.5% (colonoscopy reduction), 95% (CRC detection) and 88% (high-risk adenoma detection) cited above may be improved upon. If that is the case, demand for and utility of the test in national CRC European screening programs would likely be further enhanced.
- Pathway design studies continue in Denmark. These should be completed by the time the new assays are CE Marked.

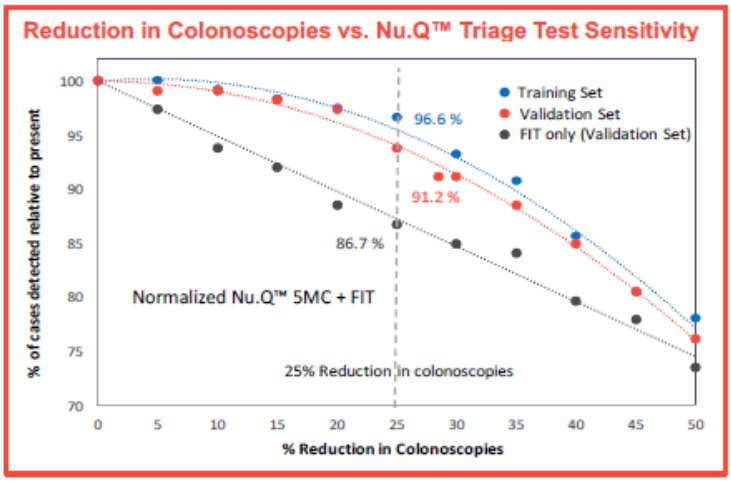
Our comments:
The delay is a disappointment but if that (i.e. a short-term delay) is the only meaningful consequence of having to redevelop these assays, it is effectively a non-event - or possibly even a positive event given the possibility that Triage performance is further bolstered. We had previously modeled initial revenue contribution beginning in early 2018 - subsequent to news of the redevelopment we incorporated a six-month delay. Although given that we had previously expected relatively insignificant revenue for the full year 2018 and model the delay to have virtually no long-term related impact, it had a largely immaterial effect on our DCF-generated price target.

Triage Validation

As a reminder, Triage will be positioned for use following a positive result from a fecal immunochemical test (FIT). As envisioned by VNRX, Triage will be used following positive FIT results which would reduce the number of colonoscopy referrals for people that do not have CRC - this in-turn will reduce bottlenecks and increase throughput of colonoscopy screening for those people that are most likely to have cancer.

Importantly, management believes they have sufficient supporting clinical data. Data is from their ongoing 14k sample prospective CRC study being conducted in collaboration with Hvidovre Hospital (Denmark). Approximately 8k of the 14k samples are of positive FIT tests (the other 6k are negative FIT tests) of subjects aged 50 to 75 years with average risk and no prior colonoscopy. FIT cut-off was set at 100ng/mL (i.e. level consistent with Danish FIT screening) The 8k positive samples were divided into a ‘training’ set (1,907) and two ‘validation’ sets (1,961 and ~4,000). The training set was optimized for a 25% reduction in colonoscopies which, per data announced at ESMO in October 2016, the test demonstrated while maintaining a 97% sensitivity (i.e. detection rate) for CRC.

Then at ENDO 2017 in February, data from the 1,961-sample validation set was presented – which largely confirmed the prior results, although with a slight reduction in sensitivity (showing 29% reduction in colonoscopies with 91% sensitivity). Results are in the chart below.



SOURCE: ENDO Poster Presentation March 2017

Validation Confirmed in Larger Sample-Sets, Presented at DDW…

Data from the remaining 4,076 samples as well as for the full ~8k FIT-positive sample set was then presented at DDW 2017 in May which also confirmed earlier results. Specifically, colonoscopies were reduced by 22.3% at a 96% sensitivity (i.e. 4% miss rate) in the 4k samples while colonoscopy reduction was 24.5% at 95% sensitivity for colorectal cancers and 88% for (high-risk) adenomas in the full 8k sample set. The data was published May 2017 in a manuscript titled "Circulating nucleosomes as new blood-based biomarkers for detection of colorectal cancer" in Clinical Epigenetics.

Performance of Triage was also compared to FIT at a higher threshold – that is, 200ng/mL (up from 100ng/mL), which is consistent with the protocol in some other European countries. The higher threshold has the benefit of reducing FIT-positive results (i.e. reducing colonoscopy referrals) but at the expense of increasing the number of false-negatives (i.e. increasing the CRC miss rate). At the higher 200ng/mL threshold, colonoscopies were reduced by 36% but at a sensitivity of 91% for all cancers and 75% for high-risk adenomas – the higher miss rates substantially underperformed those of Triage for all cancers as well as for adenomas.

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FINANCIAL MODEL

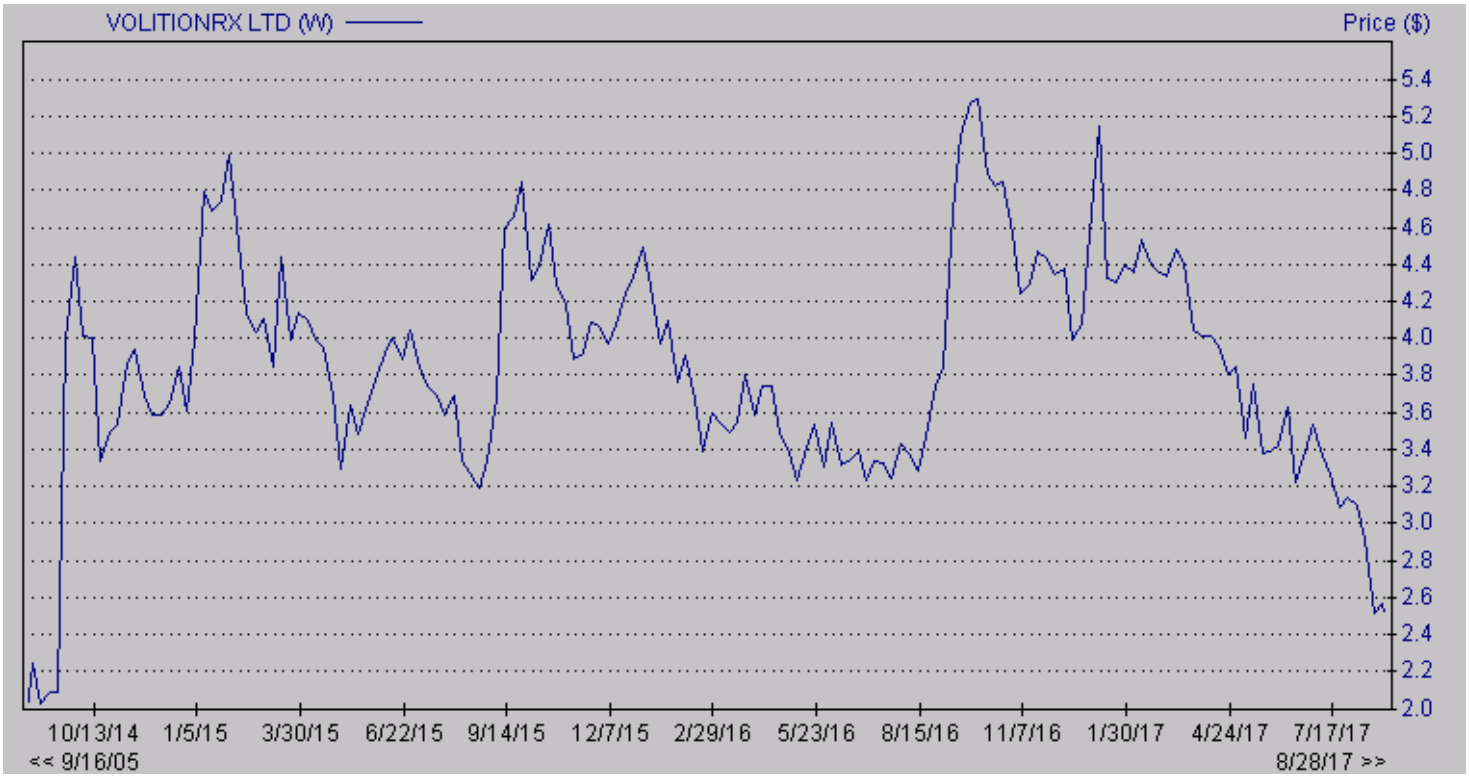
VolitionRx Ltd.

	2016 A	Q1 A	Q2 A	Q3 E	Q4 E	2017 E	2018 E	2019 E
Revenue	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$658.9	$3,989.9
YOY Growth	-	-	-	-	-	-	-	*505.5%*
Cost of Goods Sold	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$171.3	$798.0
Gross Income	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$487.6	$3,191.9
Gross Margin	-	-	-	-	-	-	*74.0%*	*80.0%*
SG&A	$5,429.1	$1,509.1	$1,734.5	$1,792.0	$1,888.0	$6,923.7	$7,820.0	$8,660.0
%SG&A	-	-	-	-	-	-	*1186.8%*	*217.0%*
R&D	$6,837.6	$1,841.6	$1,728.5	$1,921.0	$2,214.0	$7,705.0	$9,688.0	$9,512.0
% R&D	-	-	-	-	-	-	*1470.3%*	*238.4%*
Asset Impairment	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($12,266.6)	($3,350.7)	($3,463.0)	($3,713.0)	($4,102.0)	($14,628.7)	($17,020.4)	($14,980.1)
Operating Margin	-	-	-	-	-	-	*-2583.1%*	*-375.4%*
Total Other Expense (Income)	($361.3)	$0.0	$0.0	$8.0	$8.0	$16.0	$27.0	$27.0
Pre-Tax Income	($11,905.3)	($3,350.7)	($3,463.0)	($3,721.0)	($4,110.0)	($14,644.7)	($17,047.4)	($15,007.1)
Taxes (benefit)	$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%*
FX translation	$109.1	($31.5)	($61.3)	$0.0	$0.0	($92.8)	$0.0	$0.0
Net Income	($12,014.4)	($3,319.2)	($3,401.7)	($3,721.0)	($4,110.0)	($14,551.9)	($17,047.4)	($15,007.1)
Net Margin	*#DIV/0!*	-	-	-	-	*#DIV/0!*	*-2587.2%*	*-376.1%*
EPS	($0.52)	($0.13)	($0.13)	($0.14)	($0.15)	($0.55)	($0.49)	($0.38)
YOY Growth	-	-	-	-	-	-	-	
Diluted Shares O/S	23,049	26,129	26,383	26,500	26,700	26,428	35,000	39,000

Brian Marckx, CFA

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