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VolitionRx Ltd (VNRX-NYSE)

VNRX: Frontline CRC Studies Read-Out ~1H 2018, Could Be Value-Inflection Event

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 (11/22/17)	$3.35
Valuation	**$7.50**

OUTLOOK

Pathway design study in Denmark for Triage is in "final stages" and expected to conclude by the end of November – the company will announce the findings when completed. VNRX also continues to work to update Triage, following which the CE Mark will need to be updated. The goal is to have Triage completed by around the time that the pathway design study finishes. Management indicated that the commercialization game-plan for Triage may be somewhat fluid and influenced by that of the frontline test – this is definitely a "stay tuned" situation.

In terms of a frontline CRC screen for Europe, VNRX noted on the Q3 call that they made significant headway during the quarter and they now hope to have the panel chosen by current year-end. That panel will then be validated against 4.3k samples (expected in Q1 2018) and followed by 10k samples (expected in Q2 2018). We think read-out from these two studies may be 'edge-of-seat" anticipation events and may offer much greater competitiveness and utility-type insight and depending on the strength of the data, could offer significant value-inflection opportunity in our opinion.

SUMMARY DATA

52-Week High	**$5.45**
52-Week Low	**$2.08**
One-Year Return (%)	**-21.61**
Beta	**-1.57**
Average Daily Volume (sh)	**41,514**
Shares Outstanding (mil)	**27**
Market Capitalization ($mil)	**$88**
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	**High,**
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 A	$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	-$0.15 A	-$0.16 E	-$0.56 E
2018					-$0.51 E
2019					-$0.41 E

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

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Q3 Results / Operational and Business Update:

VolitionRx (VNRX) reported Q3 results and provided a business update. Relative to the financials, results were very much inline with our estimates (we note that R&D expense was $283k higher than what we modeled, although $250k of this relates to the initial payment related to the U.S. colorectal cancer EDRN study). EPS was ($0.15) vs. our ($0.14) estimate. We model roughly flat OpEx from Q3 to Q4 and continue to expect no revenue until 2018.

Cash used in operating activities was $2.8M and $8.3M ($3.1M and $8.5M, ex-changes in working capital) in the three and nine months ending 9/30/2017, respectively. Another $105k and $1.3M was used in investing activities - primarily for upfitting the new R&D facility, over the same periods. Cash balance was $13.8M at quarter-end, which represents ~14 months' worth of operating capital. Additional capital is available from a recently secured (yet currently-untapped) $1.2M loan and ~$300k non-repayable grant from SOFINEX (a Belgian public organization) and the Walloon Region (Belgium), respectively. VNRX expects to continue to seek non-dilutive sources of funds such as this.

Relative to the operational update, there were no big surprises either in the earnings release or on the call and most of the main-focused development programs appear to be largely tracking earlier anticipated timelines. The one exception may be the forecasted timeline for launch of Triage in Europe, which we feel may have become a bit ambiguous given that the pathway design study has dragged on longer than expected and development of the frontline screen has progressed. But, given that we consider Triage as somewhat of a tire-kicking, test-run at the European colorectal cancer market as VNRX completes development of a front-line screen, the ongoing delays to the symptomatic test are not overly concerning.

While no major revelations, the call was informative. Management laid out timelines and plans for development of a frontline screen for Europe, including planned validation studies. They also offered a little bit more insight into nuances of the different countries that they hope to target with both CRC tests. That included some general thoughts and information related to accuracy thresholds and regulatory requirements.

- Europe: Pathway design study in Denmark for Triage is in "final stages" and expected to conclude by the end of November – the company will announce the findings when completed. VNRX also continues to work to update Triage, following which the CE Mark will need to be updated. The goal is to have Triage completed by around the time that the pathway design study finishes. While we continue to model launch of Triage in 2H 2018, we also think buttoning-up remaining development and CE Marking of Triage may take a backseat to the frontline test, the market for which is significantly larger. Management indicated that the commercialization game-plan for Triage may be somewhat fluid and influenced by that of the frontline test – this is definitely a "stay tuned" situation.

In terms of a frontline CRC screen for Europe, VNRX noted on the Q3 call that they made significant headway during the quarter and they now hope to have the panel chosen by current year-end. That panel will then be validated against 4.3k samples (expected in Q1 2018) and followed by 10k samples (expected in Q2 2018). If all goes smoothly they think they can get the test CE Marked by Q3 2018.

We note that while VNRX's new R&D facility and additional resources should facilitate validation and regulatory activities, we suspect that this timeline may prove somewhat aggressive and would not be surprised to eventually see final pieces of this move by ~6 months. But, there should one or more incremental-value milestones related to the EU CRC screen over the next few quarters – including completion of the panel and, certainly, data read-outs (interim read-outs may not be feasible given this is an asymptomatic test, therefore initial data may also be final data). If sensitivity/specificity is competitive with FIT, expect that could be a significant value-inflection event. As such, we will be highly interested to hear updates on the panel selection and then, on results of the validation studies.

Management also provided some insight relative to accuracy thresholds, noting that many countries in Europe are more concerned with specificity, although some others may lean more on sensitivity. While some countries still utilize relatively antiquated and inaccurate FOBT tests, many others use FIT in national screening programs. The general theme seems to be that VNRX hopes to be competitive with FIT, which is considered relatively accurate (depending on the study cited accuracy can vary) – management cited FIT sensitivity/specificity of ~70%/90% - so we think that provides some general guidance on the level that VNRX will be shooting for with their EU CRC frontline screen.

We think VNRX may also refine a CRC frontline screen over time (to further increase accuracy) and in the event that sensitivity/specificity of initial NuQ frontline panels are not competitive with that of FIT, the non-compliant population (i.e. those of CRC screening age that do not get tested) may represent an initial market opportunity, particularly among those with concerns over fecal handling.

Importantly, we do not view certain recently commercialized novel technologies, including Exact Sciences' ColoGuard and EpiGenomics' Epi proColon, as significant potential competitive threats to VNRX in most European markets. National screening programs are highly budget sensitive, which largely excludes the relatively expensive ($300 - $500 per test) ColoGuard while relatively poor accuracy of Epi proColon means it is unlikely to unseat FIT as the non-invasive testing standard. See our Appendix for a detailed discussion about Exact and Epi proColon. Meanwhile, VNRX expects to develop a frontline screen that is competitive with FIT in accuracy and manufacture it at a cost that will qualify it for national screening programs. The added benefit of NuQ versus that of FIT is ease of use and the fact that fecal handling is completely avoided.

- 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 Q3 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 has been 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. But, as with Europe, plans for Triage may be somewhat dynamic and largely driven by the pace of a CRC frontline screen. 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 additional deliverables, potentially including clinical evaluation with Asian populations to support registration. They indicated on the Q3 call that they are in-process of nailing down exactly what to expect in terms of regulatory requirements for each of the Asian countries that they may initially target – so we may hear more on that subject on future calls.

But, in the meantime, they are wasting no time with preparing to validate their technology with Asian populations. Earlier this month VNRX signed an MOU with National Taiwan University (binding contract expected to be signed in Q1 2018) to conduct two studies encompassing a total of 7k blood samples related to CRC. The first study will include 5k samples from asymptomatic individuals while the second is 2k samples from symptomatic CRC patients. These studies are only for marketing/commercialization purposes and not regulatory-related.

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). Study design has now been approved and is expected to be on clinicaltrials.org in the near-term.

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.

Research Use Only Kits: In September VNRX announced the introduction and first sale of Nu.Q-based RUO kits. The first sale was made to a (unnamed) "large multinational pharmaceutical company". The company noted that the customer requested a customized kit, which is how the initial sale materialized. From our experience, it is almost impossible to judge potential demand for RUO products (at least at initial launch). So while it is possible significant and consistent demand could materialize, (particularly if, for example, they were used as a companion diagnostic for a new popular drug), we currently do not model any related potential contribution. We will update this if appropriate.

Outlook / Valuation:

Asymptomatic Screen, If "Successfully" Developed, Offers Potentially Significant Value-Inflection Opportunity
VNRX estimates that there are approximately 150M people of CRC screening age (i.e. 50 – 74) in Europe and ~200M in Asia, which dwarfs the estimated symptomatic populations (~9M and 12M, respectively). Assuming $50 per test, Europe and Asia represent total potential markets for a CRC frontline screen of ~$7.5B and $10B. We estimate the U.S. market is valued at around $4B.

We have not previously and, at this time, still do not model contribution from a NuQ frontline CRC test given that we believe it is too early to judge the likelihood of successful development and regulatory approval(s). In addition, in the event of "successful" development, commercial potential may largely depend on relative utility (including accuracy) versus current non-invasive CRC screens – and at this time have no basis to guess potentially critical aspects such as sensitivity/specificity.

Our assumptions and model will be updated as appropriate which will consider potential milestones such as finalization of the frontline (European) CRC panel and results from large clinical studies. As such we will be eager to hear ongoing developments and updates. Read-out from the 4.3k and 10k sample studies may be 'edge-of-seat" anticipation events - the first (or possibly both) of which could happen in 1H 2018, and may offer much greater competitiveness and utility-type insight and depending on the strength of the data, could offer significant value-inflection opportunity in our opinion.

Clinical data may be the most significant factor that influences commercialization strategy. Clearly data that indicates competitive accuracy to FIT (fecal immunochemical test) is the most desirable, although we think there may be optionality even with less robust results. Non-compliance to CRC screening guidelines is cited as one of the most significant reasons why this disease kills as many people as it does and one of the main reasons for non-compliance is concern over fecal handling. Evidence has indicated that screening by any available means is more important than the specific screening modality in reducing rates of CRC. So, almost any non-invasive CRC test that can improve compliance (and can be manufactured at a low enough cost to fit within national screening program budgets), as VNRX's blood test may do among the fecal-concerned, may be considered as having utility, even if it is not competitively-accurate with FIT.

So, while we do not know what to expect from results of these two frontline validation studies, depending on the data, we do believe that VNRX is likely to have commercialization optionality. We think VNRX may also refine a CRC frontline screen over time (to further increase accuracy) and in the event that sensitivity/specificity of initial NuQ frontline panels are not competitive with that of FIT, the non-compliant population (i.e. those of CRC screening age that do not get tested) may represent an initial market opportunity, particularly among those with concerns over fecal handling.

Danish Market Is Small But Could Serve As Litmus Test For Triage…
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 for Triage, 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. 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).

Valuation
While we think the strategy for Triage could change based on development progress with the frontline screen, we continue to only model revenue contribution from the former given that it is further along in development as well as in commercialization strategy.

We model initial revenue contribution in 2018 as a result of inclusion of Triage on Denmark s national CRC screening program. We also model some incremental revenue from stocking orders later than same year related to inclusion in follow-on countries among the initial targeted five EU countries. While all of our assumptions will be updated with relevant news flow, our confidence of inclusion in Denmark was recently bolstered by the additional clinical validation. Further support to our confidence would come if the pathway studies prove successful.

Initial introduction in Denmark as an adjunct may provide foot-in-the-door opportunity as well as the chance to build early awareness, follow-on launches in additional countries, particularly those with larger populations (such as France and The Netherlands) would significantly increase VNRX s initial revenue opportunity. We have yet to model any potential contribution from Asia although given VNRX's moves in that direction, including the recent hiring of an executive to lead their strategy in that part of the world and pursuit of validation studies in Taiwan and Singapore, those assumptions are also subject to a near-term change.

Relative to the U.S. market, given management's non-commitment up to this point, our model reflects no related revenue nor significant development-related expense. Our assumptions will be updated as appropriate.

Our DCF model was recently updated for inclusion of VNRX in the large 13.5k-sample NCI/EDRN study. 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.

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]

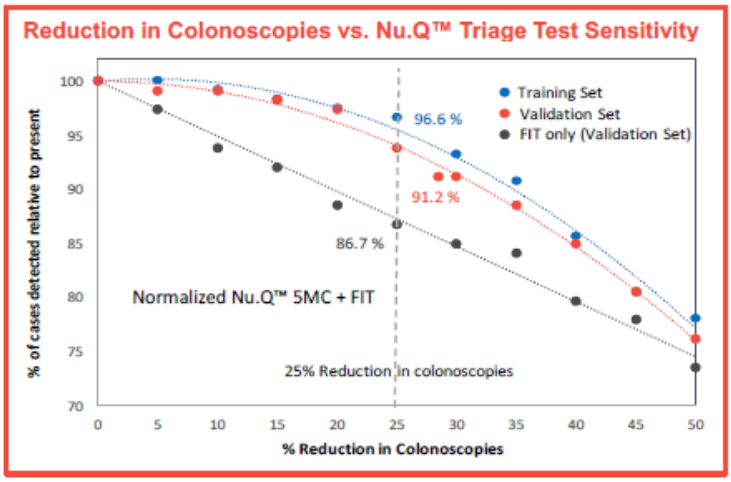
Triage Validation

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.

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

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 A	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	$1,825.2	$1,941.0	$7,009.9	$7,820.0	$8,660.0
%SG&A	-	-	-	-	-	-	1186.8%	217.0%
R&D	$6,837.6	$1,841.6	$1,728.5	$2,204.0	$2,214.0	$7,988.0	$10,577.0	$10,455.0
% R&D	-	-	-	-	-	-	1605.2%	262.0%
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)	($4,029.2)	($4,155.0)	($14,997.9)	($17,909.4)	($15,923.1)
Operating Margin	-	-	-	-	-	-	-2718.0%	-399.1%
Total Other Expense (Income)	($361.3)	$0.0	$0.0	($136.6)	$8.0	($128.6)	$27.0	$27.0
Pre-Tax Income	($11,905.3)	($3,350.7)	($3,463.0)	($3,892.7)	($4,163.0)	($14,869.3)	($17,936.4)	($15,950.1)
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)	$32.4	$0.0	($60.4)	$0.0	$0.0
Net Income	($12,014.4)	($3,319.2)	($3,401.7)	($3,925.1)	($4,163.0)	($14,808.9)	($17,936.4)	($15,950.1)
Net Margin	#DIV/0!	-	-	-	-	#DIV/0!	-2722.1%	-399.8%
EPS	($0.52)	($0.13)	($0.13)	($0.15)	($0.16)	($0.56)	($0.51)	($0.41)
YOY Growth	-	-	-	-	-	-	-	
Diluted Shares O/S	23,049	26,129	26,383	26,512	26,515	26,385	35,000	39,000

Brian Marckx, CFA

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