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VolitionRx Ltd (VNRX-NYSE)

VNRX: More Compelling Prostate Cancer Data, Opportunities Remain for Near-Term Data-Driven Value Inflection

Based on our DCF model which goes out to year 2027 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 (08/28/18)	$1.99
Valuation	**$7.50**

OUTLOOK

Relative to the operational update, one of the most exciting recent announcements relates to compelling prostate cancer data – while from a small, proof-of-concept(esque), single-arm trial, the results suggest NuQ could substantially improve on the (proven) poor performance of PSA testing. It also builds on earlier data, which also showed encouraging accuracy of NuQ in prostate cancer.
While certain delays have slowed timelines in Europe, progress does continue – including in Asia. Given the large populations of the Asia Pacific region and other characteristics favorable to blood-based CRC testing in that part of the world, we continue to believe that Asia represents a highly attractive market for VNRX. In Europe, the large validation CRC validation studies and regulatory activities of the initial commercial CRC tests have been somewhat slower-going than anticipated due to the time-consuming work necessary to ensure their 'discovery assays' can be validated for practical commercial use. While time consuming, it appears this is moving along and making substantive progress. Despite the ongoing delays, we continue to see opportunities for near-term data-driven value inflection.

SUMMARY DATA

52-Week High	**$4.00**
52-Week Low	**$1.44**
One-Year Return (%)	**-20.24**
Beta	**-0.64**
Average Daily Volume (sh)	**190,130**
Shares Outstanding (mil)	**30**
Market Capitalization ($mil)	**$60**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**15**
Insider Ownership (%)	**27**
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 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(in millions)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	$0 A	$0 A	$0 A	$0 A	$0 A
2018	$0.0 A	$0.0 A	$0.0 E	$0.1 E	$0.1 E
2019					$3.8 E
2020					$18.8 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$0.13 A	-$0.13 A	-$0.15 A	-$0.16 A	-$0.56 A
2018	-$0.17 A	-$0.15 A	-$0.16 E	-$0.16 E	-$0.64 E
2019					-$0.48 E
2020					-$0.33 E

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

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Q2 Results / Operational and Business Update:

VolitionRx reported Q2 financial results and provided a business update. Relative to the financials, operating expenses were right on the nose with our $4.57M estimate and flat from Q1 of this year. Despite the significant operational progress, including that related to their numerous (and growing number of) trials in various cancers, operating spend through the first six months of 2018 was up just $2.4M (+35%) from the prior year period, to $9.2M.

R&D expenses increased by just $1.5M (+43%) to $5.1M in 1H '18. For some context of the efficiency of VNRX's product development, we estimate their average cost per sample (of all ongoing trials) is approximately $100 – a small fraction of the estimated ~$3.5k per sample cost of pivotal studies of other non-invasive CRC diagnostics. And while later stage, larger, prospective registration studies may cost significantly more than $100/sample, we find it impressive how much progress has been made with relatively minimal spend to-date.

The efficiency of product development is even more obvious in the relatively light cash-burn. Cash used in operating activities was $2.9M and $6.5M ($3.9M and $7.5M, ex-changes in working capital) in the three and six months ending 6/30/18, compared to $2.8M and $5.5M ($2.7M and $5.3M, ex-changes in working capital) in the prior year periods.

The balance sheet is solid. Cash balance was $11.9M at Q2 quarter-end, subsequent to which VNRX received $700k of non-dilutive funding from the Walloon Regional Government and $9M in gross proceeds from the sale of 5M common shares (@$1.80/share).

Relative to the operational update, one of the most exciting recent announcements relates to compelling prostate cancer data – while from a small, proof-of-concept(esque), single-arm trial, the results suggest NuQ could substantially improve upon the (proven) poor performance of PSA biomarker testing. It also builds on earlier data, which also showed encouraging accuracy of NuQ in prostate cancer.

Prostate cancer data

With the mid-August announcement of new and compelling prostate cancer data, we think VNRX could be moving much closer to the real possibility of large, prostate cancer validation studies – success of which could be a tremendous value driver. Results of the n=84 proof of concept study showed a panel of five assays (two NuQ, PSA and two unidentified inflammatory biomarkers) identified 94% of 'high-grade' prostate cancers at 88% specificity. This compares to PSA-alone, which identified just 33% of high-grade cancers. 'High-grade', as defined by the Gleason score, are prostate cancers that are likely to grow and spread rapidly and, therefore, require aggressive treatment.

Unlike most cancers, prostate cancer is usually too slow-growing to be lethal and, therefore, the potential benefits of treatment are often outweighed by the possible risks (such as impotence and urinary incontinence). The exception are high-grade cancers, which often require aggressive treatment. VNRX hopes to confirm results in larger follow-on studies – which may also provide more insight into per-stage performance. Given the poor performance of PSA and lack of alternatives, we think an accurate and reliable test which could differentiate between low and high-grade prostate cancers (and which would guide treatment vs. watchful-waiting decision-making) could see immediate widespread adoption. We continue to view prostate cancer as one of the most attractive targets and will be eager to hear updates on VNRX's validation studies.

As a reminder, this is not the first indication that NuQ could have utility in prostate cancer. The first real evidence of NuQ's potential in prostate cancer was the April 2016 announcement of results from a retrospective study of 537 blood samples. The data, which were presented at AACR that year, showed a single NuQ assay detected 71% of early stage I (and 86% of late stage IV) prostate cancer cases at 93% specificity. This is significantly more accurate than that of the widely used PSA test. PSA tests are the most widely used front-line diagnostic with ~20 million tests performed each year in U.S. and ~45 million worldwide. But PSA is fraught with accuracy issues as 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).

Prostate Cancer 537-Sample Date Presented at AACR-2016

Cancer Stage	Sensitivity (@ 93% specificity)	N=
Stage I	71%	93 / 131
Stage II	63%	22 / 35
Stage III	79%	11 / 14
Stage IV	86%	12 / 14

Colorectal cancer
While certain delays have slowed timelines in Europe, progress does continue – including in Asia. Most recently that included finalizing agreements (that had previously been under MOUs) with National Taiwan University to conduct two large, CRC studies; a 5k-sample asymptomatic CRC screening study and a 2k-sample symptomatic CRC study. As previously noted, these are marketing-oriented (as opposed to regulatory) studies. Given the large populations of the Asia Pacific region and other characteristics favorable to blood-based CRC testing in that part of the world, we continue to believe that Asia represents a highly attractive market (and potentially even more so than Europe) for VNRX. So, continued development progress, even incremental progress such as turning the MUOs into formal agreements, should be viewed as meaningfully positive steps forward. If all goes to plan, initial commercial introduction in Asia could happen sometime next year.

Europe: Triage and Frontline CRC
As it relates to the larger validation CRC validation studies and regulatory activities of the initial commercial CRC tests, management noted that progress has been somewhat slower-going than anticipated due to the time-consuming work necessary to ensure their 'discovery assays' (i.e. those used to determine final assays in trials) can be validated for practical commercial use (and used in any lab).

This has pushed back timelines of Triage and the frontline CRC screen. While CE Marking of Triage was previously anticipated to happen by late-2018, that is now pushed back to Q1 '19. Read-out of the 4.3k-sample (i.e. pre-validation study) and 12k-sample screening studies is now expected in Q1 and Q2 '19, respectively. CE Marking of the frontline screen is now expected in Q2 '19 – pushed back from Q1. As our modeled timelines were already about 3 – 6 months behind those of management's, these recent delays only have a moderate impact on our forecasts. However, we still think that even the revised timelines, particularly as related to CE Marking of the frontline screen, are likely to prove optimistic.

Relative to commercialization strategies – the frontline should evolve as data becomes available. The strategy for Triage appears to continue to evolve - the initial gameplan for which had revolved around national CRC screening programs in certain European countries. This may now be more of a stay-tuned for updates situation and something we could hear more about with the upcoming data release.

And despite the ongoing delays, there should be opportunity for near-term data-driven value inflections. In addition to these large CRC validation studies, initial data from the ongoing Bonn27 (27 most prevalent cancers) cancer study could be upcoming (early 2019) as could data from an endometriosis proof-of-concept study (late 2018), which completed sample collection (from 350 patients over three years) in August.

RUO Kits
In the meantime, initial revenue from sale of RUO kits is expected in 2H 2018. As a reminder, last September VNRX announced the introduction of Nu.Q-based RUO kits. In May VNRX signed a licensing agreement with Activ Motif which (per their website) "is the industry leader in developing and delivering innovative tools to enable epigenetics and gene regulation research." Activ brings a vast distribution network that includes large research institutions and commercial life sciences customers. Under this arrangement, VNRX licenses their technology to Activ and Activ does all of the work – from manufacturing to sales and to distribution. VNRX will receive a royalty on sales. On August 1st VNRX announced that the initial RUO kit was available for purchase through Activ Motif.

Summary of development programs…

NuQ Compelling Asymptomatic Detection of Pre/Early Cancers:
In early 2018 VNRX announced results of a 680-subject study, which included ~100 with cancer. A panel of three NuQ assays detected 80% of stage 1 cancers and 66% of high-risk pre-cancer adenomas at 78% specificity. Data of the later-stage cases and detection across all cancers was not released, although we expect that more comprehensive data will be included in future announcements.

For context of the performance of some of the leading non-invasive CRC screening diagnostics in detecting pre-cancers; Exact Sciences (stool-based) ColoGuard showed 42% sensitivity in detection of advanced precancerous adenomas at 87% specificity, FIT showed 24% sensitivity in detection of advanced precancerous adenomas at 94% specificity and Septin9 showed 18% sensitivity in detection of advanced precancerous adenomas at 80% specificity. While the differences in specificity of all of the studies makes head-to-head performance comparison difficult, we think this at least provides some insight into the relatively poor pre-cancer detection abilities of currently available non-invasive diagnostics and helps illustrate the unmet need for a more accurate test.

As it relates to performance in detecting CRC (of any stage) published studies showed sensitivity / specificity of these tests at; ColoGuard 92% / 87%, FIT 79% / 94% and Septin9 68% / 80%. Again, we provide this only for some context and also note that, as we have discussed in detail in prior reports, all non-invasive CRC diagnostics suffer from one or more meaningful drawbacks – some of which include low accuracy, high cost and requisite fecal handling. As such, sensitivity / specificity, while important, is not the only criteria in gauging the potential utility of a CRC screen – instead as long NuQ can increase compliance of CRC screening at an acceptable cost, it should have commercial appeal.

And while Exact Science's ColoGuard has had solid uptake since its launch in early 2015, compliance of it is also lacking to some extent. Approximately 10k ColoGuard tests were sold during the first full quarter (Q1 2015) on the market and this has grown at an average quarterly rate of almost 28%. In the most recent quarter (Q1 2018) 186k tests were completed. But, EXAS reports that (as of their most recent reporting) their compliance was 68%. 'Compliance' in their context relates to the percentage of test kits that were used and sent to EXAS' lab for processing as compared to the total number prescribed (insurers are charged once a ColoGuard kit is ordered). So, despite relative ease-of-use and in the privacy of the home, ColoGuard also appears to have a certain level of compliance issues (despite EXAS' dedicated efforts to improve compliance rates). We think that this further highlights the potential opportunity for VNRX's frontline screen.

VNRX will look to further improve upon the performance of their asymptomatic screen. Additional assays and panels will be evaluated in the 680-patient training study. A larger 4.3k subject training study will then afford powering the evaluation of a larger panel – the final panel is expected to include 5 or 6 assays. It may also include legacy genericized CRC markers, such as CEA. The next step will then be to validate that panel in a 12k subject study. In the meantime, VNRX will put as many pieces as possible in place towards applying for CE Mark so as to facilitate launch ASAP.

Assuming no significant delays to management's updated anticipated timelines (below), we think there could be at least two value-inflection opportunities (including data read-outs of the panel in the 4.3k and 12k studies) related to this EU CRC asymptomatic screen development program over the next 6 to 9 months. Performance updates, including relative sensitivity/specificity compared to FIT and the other CRC screens (particularly for pre and early-stage cancer), will be of obvious particular interest but as noted above, it is not the only criteria that dictate potential commercial appeal. Management's current anticipated timelines are;

- Q1 2019: report results of 4.3k training study
- Q2 2019: commence 12k subject study
- 1H 2019: launch asymptomatic CRC screen in EU

VNRX has yet to provide specifics regarding thoughts on launch and initial commercialization strategy of a CRC frontline screen, although did mention that they have already done some legwork in assessing opportunities. Some of the 'where, when and hows may be dictated by performance in these larger validation studies – so hopefully we will get some more details with upcoming data announcements, if not sooner.

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. If VNRX can 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, that could be a true game-changer for CRC screening. The added benefit of NuQ versus that of FIT is ease of use and the fact that fecal handling is completely avoided.

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.

- Europe (Triage): Successful completion of the logistics and pathway design study happened in early February. VNRX also continues to work to update Triage, following which the CE Mark will need to be updated. Initial introduction may now not happen until next year. Also, unclear what the commercialization strategy might be. This remains a "stay tuned" situation.

- Asia: VNRX's first significant discussion that Asia was a near-term target was only 12 months ago. Since then progress has been made in clinical evaluation of Triage in Taiwan. Regulatory steps 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. 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 remains fluid and may be modeled somewhat after 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. Some of the initial legwork includes nailing down 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. In August the (previous MUO) agreement was finalized with National Taiwan University 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.gov in the near-term.

But, in the meantime, VNRX has indicated that they plan to pursue initial U.S. commercialization with a symptomatic CRC test. Current thoughts on a symptomatic-related regulatory strategy include pursuit of a 510(k) pathway. Management has previously mentioned that they believe a symptomatic study can be relatively small (600 - 700 patients, given the much higher positives CRC rates vs. asymptomatic) and cost 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 2020 and quite possibly, not until 2021.

Outlook / Valuation:

Frontline 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.

Given management's (arguably very aggressive) timelines for launch and the potential to refine performance over time, we interpret their initial goal as one to (at least) address the non-compliant subset of CRC screening populations. As such, we assume the initial NuQ screen is positioned not as a replacement for FIT or any other frontline screen but more as a complement aimed at increasing overall CRC screening compliance. Non-compliance varies by country and geography although, for ease, we assume 40% non-compliance in all targeted markets and model low single-digit penetration in the first full-year of launch and not exceeding 5% penetration by year-3. We model initial launch occurring in mid-to-late 2019 with introduction in several European countries with aggregate total populations of approximately 100M within the first 12 months. We incorporate a 75% haircut, which represents risk of failure to reach commercialization – subject to change based on developments.

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 12k sample studies may be 'edge-of-seat" anticipation events – which 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.

ColoGuard and Compliance, Further Highlights Opportunity for NuQ CRC Screen…
And while Exact Science's ColoGuard has had solid uptake since its launch in early 2015, compliance of it is also lacking to some extent. Approximately 10k ColoGuard tests were sold during the first full quarter (Q1 2015) on the market and this has grown at an average quarterly rate of almost 27%. In the most recent quarter (Q2 2018) 215k tests were completed. But, EXAS reports that (as of their most recent reporting) their compliance was 68%. 'Compliance' in their context relates to the percentage of test kits that were used and sent to EXAS' lab for processing as compared to the total number prescribed (insurers are charged once a ColoGuard kit is ordered). So, despite relative ease-of-use and in the privacy of the home, ColoGuard also appears to have a certain level of compliance issues. This further highlights the potential opportunity for VNRX's frontline screen.

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. VNRX should also have the option to 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 still represent a very valuable and long-term market opportunity, particularly among those with concerns over fecal handling. VNRX may also be able to tweak the algorithm based on the country/continent of use (U.S. more concerned with sensitivity, while Europe more concerned with specificity).

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 early/mid-2019 with launch of Triage. Initial introduction of NuQ CRC tests via Triage as an adjunct in national healthcare programs may provide foot-in-the-door opportunity in Europe and an opportunity 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.

Our assumptions relative to the frontline screen are highly susceptible to change and influenced by results from the two larger studies, although we think the compelling data from the 680-sample training study warranted initial modeling of that market. We also 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.

While we think the prostate cancer data to-date is compelling, we think it is prudent to forego modeling in that potential indication until after successful validation, including from larger studies, is completed. However, as we have noted in the past, given the poor performance of PSA testing and lack of alternatives, view prostate cancer as one of the most attractive targets and one which a validated (and approved) NuQ test could potentially see immediate and robust uptake.

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.

Based on our DCF model which goes out to year 2027 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 $510 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 28%. In the most recent quarter (Q1 2018) 186k 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. But, EXAS reports that (as of their most recent reporting) their compliance was 68%. 'Compliance' in their context relates to the percentage of test kits that were used and sent to EXAS' lab for processing as compared to the total number prescribed (insurers are charged once a ColoGuard kit is ordered). So, despite relative ease-of-use and in the privacy of the home, ColoGuard also appears to have a certain level of compliance issues. This further highlights the potential opportunity for VNRX's frontline screen.

    - **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 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]

[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.

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

FINANCIAL MODEL

VolitionRx Ltd.

	2017 A	Q1 A	Q2 A	Q3 E	Q4 E	2018 E	2019 E	2020 E
Revenue	$0.0	$0.0	$0.0	$25.0	$50.0	$75.0	$3,056.9	$15,591.8
YOY Growth	-	-	-	-	-	-	*3975.8%*	*410.1%*
Cost of Goods Sold	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$611.4	$3,508.2
Gross Income	$0.0	$0.0	$0.0	$25.0	$50.0	$75.0	$2,445.5	$12,083.6
Gross Margin	-	-	-	*100.0%*	*100.0%*	*100.0%*	*80.0%*	*77.5%*
SG&A	$6,139.9	$2,206.2	$1,879.0	$2,028.0	$2,089.0	$8,202.3	$8,724.0	$10,009.9
%SG&A	-	-	-	-	-	*10936.4%*	*285.4%*	*64.2%*
R&D	$8,906.0	$2,423.2	$2,686.5	$2,774.0	$3,027.0	$10,910.7	$12,411.0	$16,551.0
% R&D	-	-	-	-	-	*14547.6%*	*406.0%*	*106.2%*
Operating Income	($15,045.9)	($4,629.4)	($4,565.5)	($4,777.0)	($5,066.0)	($19,038.0)	($18,689.5)	($14,477.3)
Operating Margin	-	-	-	-	-	*-25383.9%*	*-611.4%*	*-92.9%*
Total Other Expense (Income)	($276.7)	$23.0	$26.6	$35.0	$41.0	$125.5	$155.0	$185.0
Pre-Tax Income	($14,769.2)	($4,652.4)	($4,592.1)	($4,812.0)	($5,107.0)	($19,163.5)	($18,844.5)	($14,662.3)
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%*
FXtranslation	($64.0)	($14.9)	($132.2)	$0.0	$0.0	($147.1)	$0.0	$0.0
Net Income	($14,705.2)	($4,637.5)	($4,459.9)	($4,812.0)	($5,107.0)	($19,016.4)	($18,844.5)	($14,662.3)
Net Margin	*#DIV/0!*	-	-	-	-	*-25355.2%*	*-616.5%*	*-94.0%*
EPS	($0.56)	($0.17)	($0.15)	($0.16)	($0.16)	($0.64)	($0.48)	($0.33)
YOY Growth	-	-	-	-	-	-	-	-
Diluted Shares O/S	26,390	27,265	30,027	30,031	32,000	29,831	39,000	45,000

Brian Marckx, CFA

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HISTORICAL STOCK PRICE



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