VolitionRx

Pharma and biotech

15 August 2022

Price	$2.05
Market cap	$110m

Share price graph

Share details

Code	VNRX
Listing	NYSE
Shares in issue	53.8m
Gross cash ($m) at 31 March 2022	23.7

Business description

VolitionRx is a clinical diagnostics company developing easy-to-use and cost-effective blood tests to diagnose a range of diseases in humans and animals including sepsis and cancer. Diagnostic Nu.Q® tests are based on the science of Nucleosomics™, which is the practice of identifying and measuring nucleosomes in the bloodstream or other bodily fluid.

Bull

- Sepsis diagnostic market has clear unmet need, which represents an opportunity.
- Broad portfolio with entry into diverse markets.
- First company to develop a standardised assay to measure nucleosomes.

Bear

- Oncology liquid biopsy technologies require significant capital to fund development.
- Slower route to market if BDD not granted for sepsis.
- Clear clinical benefit will need to be demonstrated to disrupt existing diagnostic methods.

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Unravelling the web of NETs in sepsis

VolitionRx is a clinical diagnostics company with a different perspective on immunoassay technology for the detection and monitoring of severe diseases in both humans and companion animals. Unlike sequential organ failure assessment (SOFA), which requires multiple physiological measurements, VolitionRx's proprietary Nu.Q neutrophil extracellular traps (NETs) immunoassay technology takes a more direct route in a largely stale and fragmented market. This ability to rapidly diagnose and monitor patients supports numerous clinical use cases across specialties and most immediately addresses sepsis, which has a c 25% mortality rate. VolitionRx aims to leverage its CE marking and demonstrate further proof of concept (PoC) in both preclinical and clinical settings to increase commercial activities in Europe in H222 and generate further clinical evidence to help support the application for FDA breakthrough device designation (BDD).

Multiple shots on goal

VolitionRx has developed a new type of blood-based assay (Nu.Q H3.1 assay) that detects biomarkers (NETs) in inflammatory disease. It has the potential to serve as a more direct path in educated clinical decision making in complex situations for better outcomes. The company has demonstrated PoC in both preclinical and clinical settings with CE markings that serve as a strong foundation, and we believe there are notable potential crossover applications that could support a long runway for growth. Additionally, VolitionRx has built a strong patent portfolio around the Nu.Q assay with c 90 approved patents and a further c 115 patent applications pending, providing significant market protection.

Sepsis, the low-hanging fruit

VolitionRx has been working towards fully defining the clinical utility and intended use of the assay in humans and, most recently, in companion animals. In the near term, a practical application would be sepsis in high-risk environments, including severe conditions noted in Exhibit 1 where recent studies correlated the massive release of NETs into the bloodstream as a pivotal consideration in acute and chronic debilitating and fatal conditions. Globally, the mortality rate of sepsis cases is estimated at c 25% so early diagnosis is critical to patient outcomes. Incrementally, management continues to run clinical trials and educate key opinion leaders (KOLs) in efforts to bolster its current position and expand outside sepsis.

In this note we focus on VolitionRx's human assay business. We will provide an overview of the company's veterinary business (which recently attracted a $10m milestone payment from Heska Corporation) in a separate note.

New thinking in detection of inflammation and toxicity

VolitionRx's offering (Nu.Q NETs technology) is centred around the quantification and detection of nucleosomes, strands of DNA wrapped around proteins called histones, Exhibit 2. These structures may serve as effective biomarkers for the early detection of serious conditions such as endothelial damage, microthrombi, organ injury/failure (sepsis) and cancer. Unlike other diagnostics, this quantitative measure has potential to quickly provide clinically relevant information and help guide decision making in point-of-care settings. The platform is the first analytically validated, standardised clinical assay for the detection of nucleosomes in blood, which is a different approach from traditional diagnostics and has broader applications across specialties. Preliminary studies have shown a correlation between nucleosome levels and patient outcomes, providing supporting evidence for the assay's use in a clinical setting. Additionally, the test aims to produce results within one hour, compared to around five hours for manual sepsis assays, a critical feature when assessing and triaging in high-risk situations.

Although VolitionRx anticipates that its Nu.Q NETs immunoassay (antibody-based assay) technology has different applications outside of diagnosing sepsis, it is currently an area where there are commercially comparable diagnostics. In the longer term, VolitionRx anticipates a broader use of Nu.Q NETs immunoassay technology with expanded clinical utility outside sepsis but, since it is the most relevant area of potential use, we have focused most of this note on sepsis.

Exhibit 1: NETs-related indications – global annual incidence and mortalities

Condition	Cases	Deaths
Sepsis	42 million	11 million
Severe trauma	40 million	8 million
Metastatic cancer	20 million	10 million
Alzheimer's disease	44 million	2.4 million

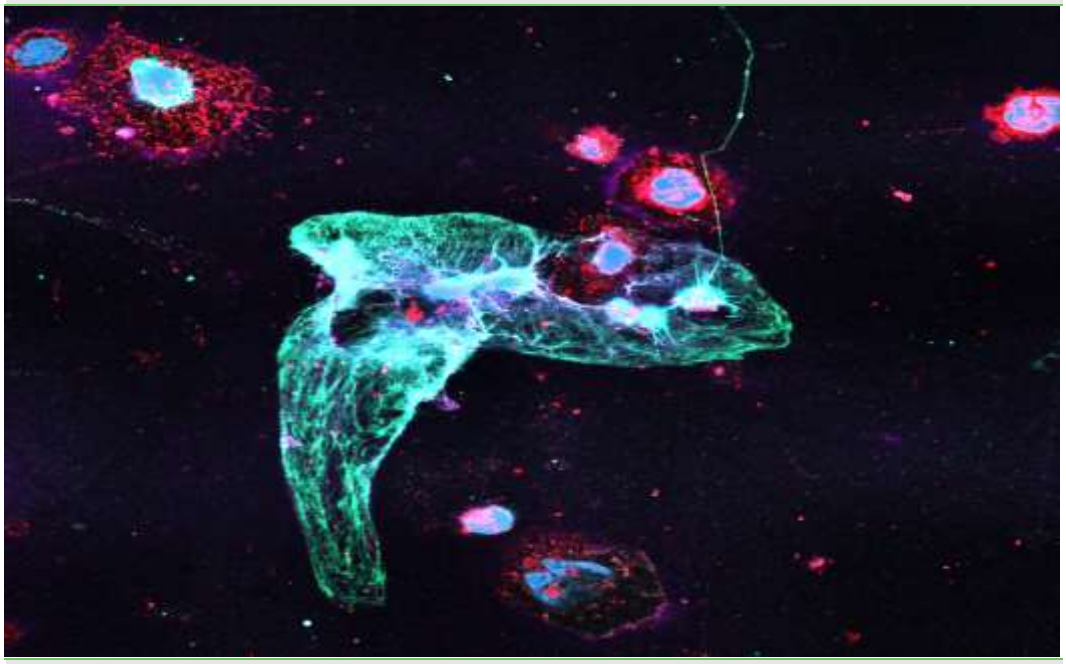
Source: VolitionRx Deck, Capital Markets Day, May 2022

The most common method used to evaluate patients in intensive care units (ICUs) is a SOFA score. A SOFA score is a validated ICU mortality prediction used to determine the extent of a person's organ function or rate of failure in patients with severe sepsis. Higher scores indicate an increased probability of patient mortality. However, SOFA measurements are involved processes and require the collection of six physiological parameters from patients. In contrast, the Nu.Q assay only analyses one biomarker (nucleosomes) to assess disease severity. During infection, these nucleosomes are released into the blood through a process called NETosis.

What is NETosis?

During infection, white blood cells called neutrophils target bacteria and viruses and eject strings of nucleosomes, via a process called NETosis, to form NETs (Exhibit 2). Aptly named, NETs are net-like structures composed of DNA-histone complexes (nucleosomes), fragmented DNA and antimicrobial proteins. NETs are an important part of the body's immune system, forming one of the front lines of defence against invading pathogens (viruses and bacteria). NETs can trap the invading pathogens, which are then destroyed by cytotoxic proteins. However, if the immune system over-responds to the threat, it may lead to the overproduction of NETs, excessive levels of which can lead to damage to healthy parts of the body. More commonly, this abnormal autoimmune response to an infection is known as sepsis, which can be caused by any type of infection – viral (eg COVID-19), fungal or bacterial – and can lead to tissue damage, multiple organ failure and death.

Exhibit 2: Formation of NETs via NETosis



Source: VolitionRx

The pivotal role NETs play as a trigger for chronic inflammatory conditions is well documented. However, unlike most diagnostic companies, VolitionRx is using its assay to target and measure the source of the autoinflammatory problem. The most common diagnostic tool for sepsis is a C-reactive protein (CRP) test, which measures the levels of CRP in the body; CRP concentrations increase during infection or inflammation. While the CRP test is a good indicator of inflammation, CRP production is only triggered in response to inflammatory cytokines, which means measurement of CRP levels does not correlate directly to the patient's condition. Procalcitonin (PCT) is another biomarker that is released in large amounts in the body in response to an infection and PCT tests are used as a sepsis diagnostic technique. However, as with CRP, PCT is not the direct cause of the damaging internal autoimmune response. Overall, the measurement of NETs provides a more clinically relevant result, correlating more to the outcome of the patient and providing a further useful addition to healthcare professionals' decision-making toolkit.

Key milestones

Management will continue to educate the market on NETs and prioritize clinical use cases while pursuing FDA regulatory approval. Although VolitionRx is in the early stages of development, its initial regulatory success provides a strong foundation.

In May 2022, VolitionRx announced that its Nu.Q NETs test had been awarded a CE mark in Europe for the detection and evaluation of NETosis, enabling clinical use in more than 27 countries. This represents a critical regulatory milestone for VolitionRx as it means the technology is registered for use in Europe in both enzyme-linked immunosorbent assay (ELISA) and automated chemiluminescent immunoassay (ChLIA) formats.

VolitionRx's focus in H222 will be to execute on its US clinical strategy as it looks to apply for BDD from the FDA by end CY22. To support the application, additional quantitative, clinically relevant data will be collated to define the Nu.Q NETs assay's primary intended use and clinical utility for which it can receive designation.

The announcement in May 2022 that Santersus's NucleoCapture apheresis technology had been awarded BDD as an adjunctive treatment to antibiotics in patients provides further support for

VolitionRx's Nu.Q assay's BDD bid. VolitionRx partnered with Santersus, a Swiss biotech focusing on the removal of excess levels of NETs from the blood, providing the Nu.Q assay as part of its preclinical study. The test was found to be the best proxy measurement tool for monitoring levels of circulating NETs and Santersus plans to use the test in its first in-human trial.

Receiving BDD would provide significant advantages, including greater engagement and communication with the FDA to design and run efficacy studies, generating investor interest and, overall, expediting access to market. VolitionRx intends to align with existing biomarker technologies (CRP test) and register Nu.Q NETs as a class II FDA medical device. Subject to approval, this would allow it to prepare a 510(K) premarket application. However, as there is currently no evidence-based clinical precedent on measuring NETs to deliver clinical benefit, the FDA may class the Nu.Q assay as a category III device, requiring a more extensive premarket approval submission.

Additionally, VolitionRx has partnered with Diagnostic Oncology CRO (DXOCRO) to support its in vitro diagnostics (IVD) study designs and regulatory strategy.

Building support from a reputable base

VolitionRx is currently a member of the International Sepsis Forum (ISF), a non-profit organization committed to improving understanding of the clinical biology around sepsis, improving patient management and promoting global physicians and lay education in sepsis. This educational initiative will be critical in raising awareness in the clinical community of the benefits and intended application of VolitionRx's Nu.Q assay. The assay is not intended to compete directly with existing diagnostics such as CRP tests, but has an advantage in that it quickly produces additional key information. The insight that the Nu.Q assay provides on NETs levels in sepsis patients generates a unique view of the patient's condition and a new tool for effective sepsis management.

Membership of the ISF provides VolitionRx with a significant platform to promote Nu.Q NETs to recognised KOLs in the sepsis community and to input its technology in key clinical studies. NETs studies are now generating considerable interest due to their suggested roles in a wide variety of disease settings. As well as VolitionRx's expanding international network and presence, we believe this increased level of research activity positions it well within the market.

Competitive landscape

The IVD market is dominated by six key players: Roche Diagnostics, Abbott Diagnostics, Siemens Healthineers, Johnson & Johnson MedTech, Beckman Coulter and bioMérieux. In the broader IVD market, a lack of product differentiation means economies of scale are critical, with smaller companies tending to be more specialised. This fragmented market represents significant opportunities for new, innovative diagnostic technologies. Deals of note include Illumina's $8bn takeover of GRAIL in 2021 to acquire the latter's pan-cancer blood test, currently in large-scale clinical studies. In sepsis, precision diagnostics company Prenosis announced that it had entered into a $6m partnership with Roche Diagnostics. The partnership combines Prenosis's ImmunoScore machine learning platform with Roche's Elecsys IL-6 immunoassay for early sepsis detection, prediction and risk stratification.

VolitionRx intends to begin executing its commercial strategy by launching the Nu.Q assay as part of an integrated automated system. In July 2022, VolitionRx announced that it had entered into a partnership with Immunodiagnostic Systems to integrate the Nu.Q assay into its automated assay platforms. By partnering with Immunodiagnostic Systems, VolitionRx's assay will be marketed with the IDS-10 system aiming to target hospitals in Europe as early adopters.

Beach head: Sepsis across specialties

Detection and treatment of early inflammation is critical

Globally, it is estimated that c 50 million people develop sepsis each year with a c 25% mortality rate. In the US, approximately 1.7 million adults develop sepsis annually with more than a quarter of a million deaths, representing a major financial burden on US healthcare systems. According to the Centers for Medicare & Medicaid Services (CMS), Medicare spent more than $41.5bn on sepsis inpatient submissions and subsequent skilled nursing facility care.

Sepsis is a clinical condition that occurs when the body's immune system overreacts to a bacterial infection and begins to damage its own tissues and organs. If not diagnosed and treated quickly, it can lead to severe, often life-threatening health complications. In the United States, CMS has implemented the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1), establishing sepsis as a national priority. The initiative requires hospitals to report sepsis management as part of the CMS Inpatient Quality Reporting Program. Participation and compliance can allow hospitals to receive additional funding, incentivising them to improve outcomes in sepsis patients. In many cases, readmissions result in financial and rating penalties.

The ideal sepsis diagnostic should have rapid detection, minimal invasiveness and high sensitivity and help guide effective clinical decision making. Since there is a high level of correlation between NETs and sepsis, VolitionRx's automated Nu.Q assay can reduce overall time to test results (TTRs) to c 45 minutes. Currently, the standard CRP ELISA tests can take up to five hours to process. Additionally, along with the correlations, the ease of use in administering Nu.Q is an improvement on current very involved legacy diagnostic testing, SOFA. When considering the time criticality for sepsis diagnosis and treatment this difference is of statistical clinical significance.

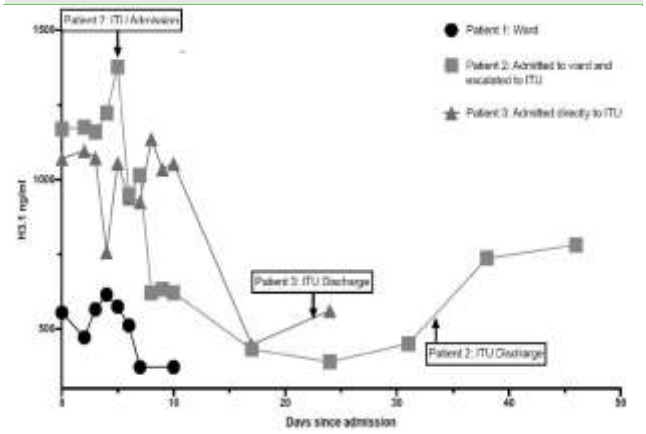
Land and expand: NETs triggered by COVID-19 and cancer

As an early mover in rapid early-stage NETosis diagnosis and monitoring, VolitionRx provides ease of use and a rapid response to current legacy systems to track sepsis. It has completed several small-scale hospital studies that have started to demonstrate clinical PoC in the use of its assay as a toxicity management tool with sepsis as a subsegment. Sepsis appears across many specialties and the company has had initial success in detecting NETs in COVID-19 patients during the pandemic and in cancer patients.

NETosis in COVID-19 (viral infection)

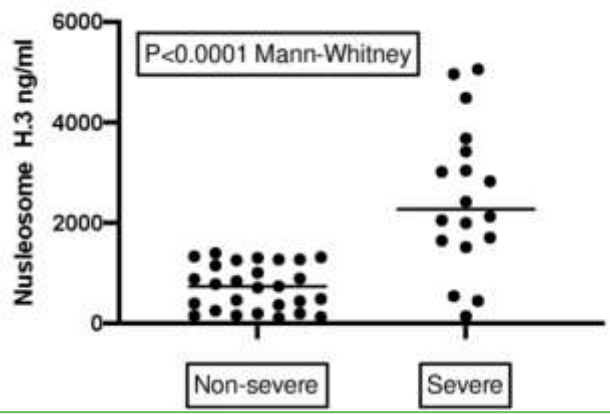
A UK-based study with King's College Hospital London evaluated NETs levels in three patients admitted to hospital, triggered by varying severity of COVID-19 infection. The aim was to assess correlations between disease severity and NETs levels throughout the clinical progression of each patient, Exhibit 3. The study suggests that nucleosome findings may support risk stratification and clinically relevant information to guide decision making.

Exhibit 3: Nucleosome measurement in three COVID-19 patient groups



Source: ISTH 2021 Congress

Exhibit 4: Nucleosome levels in non-severe versus severe COVID-19 patients



Source: ISTH 2021 Congress

Two of the patients who were admitted had heightened levels of NETs. However, one was admitted to the intensive therapy unit (ITU) and one was initially admitted to a lower severity ward before being transferred to the ITU. The latter patient received treatment in hospital for c 45 days, considerably longer than the patient admitted directly to the ITU (c 25 days). It may therefore be possible to risk stratify patients to treatments on hospital admission and track the clinical course before escalation in disease severity, reducing hospital admission time and health service expense.

A larger study, which assessed nucleosome concentrations in both mild and severe COVID-19 patients admitted to hospital, has also helped further demonstrate proof of concept in correlating NETs levels with disease severity. Plasma samples were evaluated and compared between 20 patients with severe COVID-19, requiring organ support, and 28 patients with non-severe COVID-19. Nucleosome levels measured by the Nu.Q assay were significantly higher in the severe patient cohort, Exhibit 4. Additionally, it was observed that there was a correlation between heightened nucleosome concentrations with 28-day mortality in severe patients.

In a separate study presented at the International Society on Thrombosis and Haemostasis (ISTH) congress in 2022, Nu.Q NETs was used to assess the relationship between NETs concentration and SOFA scores. Blood samples from a cohort of 48 patients diagnosed with septic shock were assessed using the Nu.Q NETs assay. The results demonstrated a direct correlation between NETs concentration and SOFA score; patients with lower NETs levels had lower scores and those with higher NETs levels had higher scores. While trials involving larger patient populations will need to be undertaken, these positive preliminary results provide initial indications for the clinical utility of the Nu.Q assay. The ability to use the Nu.Q assay as a replacement for traditional SOFA scores also brings cost and resource benefits.

NETosis in oncology

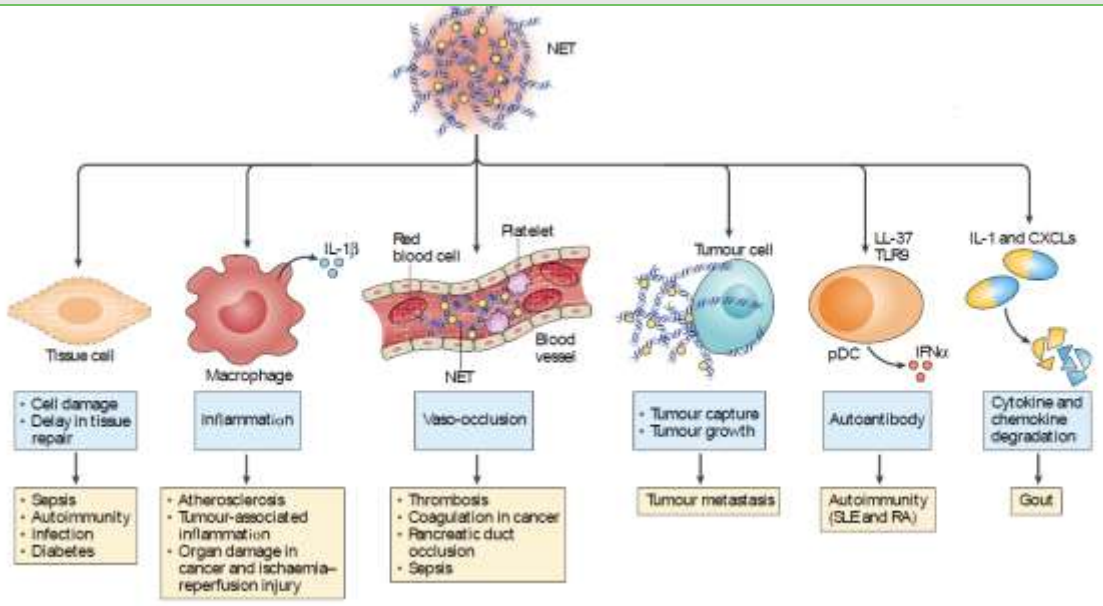
In many oncology cases, sepsis is extremely harmful and can be a factor in the cause of death due to impaired immune responses. Recently, VolitionRx announced the initiation of a clinical study with MD Anderson for the early detection of sepsis in cancer patients, as cancer patients are 10 times more likely to develop sepsis and account for c 20% of all sepsis cases. The cost of care for these patients is up to 90% higher than patients without sepsis. The study will span two years and aims to detect nucleosome levels and susceptibility of sepsis in this highly vulnerable patient population.

Clinical long game: Oncology

NETs are known to contribute to a myriad of different disease indications and, as such, the development of diagnostic tools to measure NETs could provide significant clinical benefit (Exhibit

5). Additionally, it provides future opportunities to target further areas in which there is an unmet need for early diagnostic tools.

Exhibit 5: NETs contribution to various diseases



Source: Neutrophil extracellular traps in immunity and disease

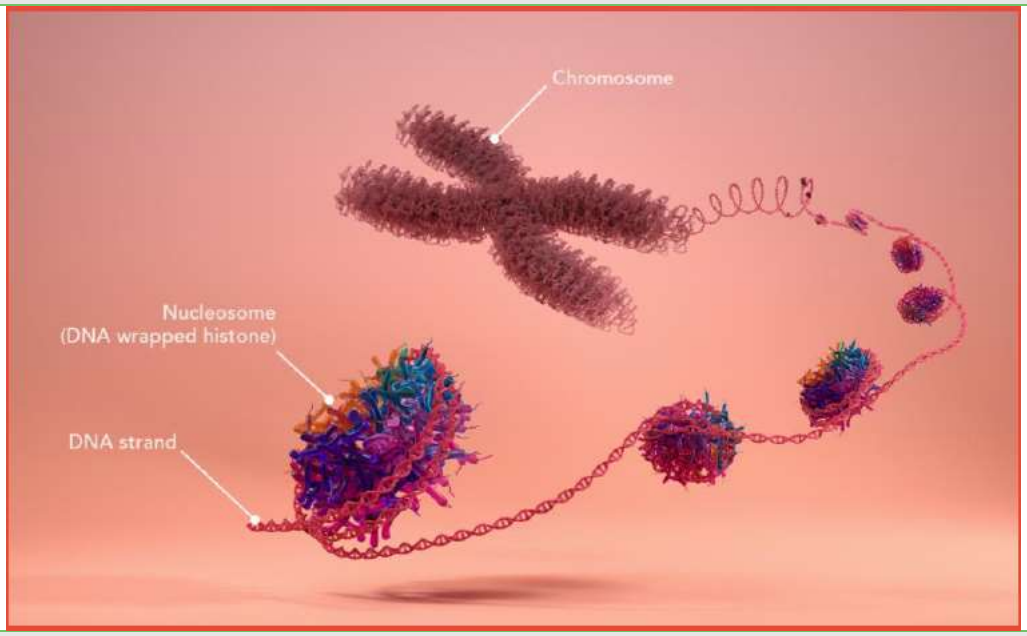
In sepsis, VolitionRx's technology is advancing and if BDD is achieved it would be a significant milestone towards accessing the US market. However, its use as a liquid biopsy cancer diagnostic tool will take more time. Clinical development is still in the early stages and success is predicated on the initiation of further, larger patient studies. Many of these pivotal trials will require significant capital to fund and extended study durations, and they must achieve high specificities and sensitivities, something that remains extremely challenging for cancer liquid biopsy diagnostics. As an example, GRAIL announced in June 2022 that the UK trial for its epigenetic Galleri blood test (which achieved FDA BDD in 2019) for detecting multiple cancers will recruit up to 140,000 patients spanning two years. So far, GRAIL has had to raise c $2bn in venture capital to fund its overall development programme.

However, VolitionRx's preliminary cancer diagnostic data have demonstrated promising results and, although a longer journey to market than the sepsis pathway, there is significant opportunity in this developing area.

Potential new cancer diagnostic

Cancer and severe infections are very different disease areas. However, nucleosomes play an important role in both and it is this common feature that VolitionRx's Nu.Q assay aims to exploit. In cancerous cells, nucleosomes can undergo different structural changes that distinguish them from those found in healthy cells (Exhibit 6). These changes have been found to be associated with the pathogenesis of various cancers, making them unique biomarkers for diagnosis.

Exhibit 6: The structure of nucleosomes



Source: VolitionRx corporate presentation deck, May 2022

When cancer cells die, they release their nucleosomes into the blood stream. VolitionRx's technology aims to be the first blood-based biomarker assay to quantify levels of circulating nucleosomes for the early detection of cancer.

Interim results in lung cancer

VolitionRx has collaborated with the National Taiwan University Hospital (NTUH) to conduct a study to evaluate the Nu.Q assay for the diagnosis of early-stage lung cancer. The study has recruited 1,200 patients who have undergone low-dose computed tomography (LDCT) scans with known outcomes for cancer. Interim results from a subset of 220 patients were presented in January 2021 at the World Conference on Lung Cancer. Results suggest that nucleosomes may discriminate well between non-cancerous versus early-stage lung cancer (stages 0, I and II) in patients. It was found that the assay could help reduce unnecessary biopsies by up to 32%. We believe the ability to reduce unnecessary biopsies and the frequency of radiation exposure from repeated LDCT scanning through a non-invasive blood test has clear cost and patient benefits.

More recently, at the 2022 American Society of Clinical Oncology (ASCO) symposium results were presented from two studies to measure lung cancer-related nucleosome biomarkers in non-smoker and smoker patients for early diagnosis. Across both studies, nucleosome measurements could detect c 34% of patients with lung cancer at 95% sensitivity.

Non-Hodgkin lymphoma supporting BDD designation

With limited diagnostic methods, VolitionRx has also targeted non-Hodgkin lymphoma (NHL) as an indication of interest. A smaller-scale clinical study undertaken by VolitionRx in collaboration with Austin Dell Medical School aimed at investigating circulating nucleosome levels in patients with haematological malignancies. The data, presented at ASCO 2020, highlighted that a cohort of patients (n=25) diagnosed with NHL had median blood nucleosome concentrations of 276ng/ml compared to 40ng/ml for healthy subjects. VolitionRx has continued to focus on NHL and has signed an agreement with DXOCRO to initiate an early cancer study in H222 to further investigate this indication. The data readouts from this will not only contribute to clinical validation of the Nu.Q assay as a cancer diagnostic but also support the BDD application that will be submitted for sepsis.

A clear forward strategy

In this note we have discussed VolitionRx's human assay business, more particularly the studies and progress in sepsis diagnostics, which represent its nearest-term opportunity. We have also briefly touched on the preliminary work that VolitionRx has conducted in cancer diagnosis, a market that will be a longer-term strategic objective.

VolitionRx has a foundation for growth in the positive results observed to date from its sepsis studies. H222 and H123 will be a critical time as it aims to make inroads into the US market by applying for a BDD designation and to begin executing its European commercial strategy following the CE designation. While the clinical studies that it has performed so far may be small, they have provided evidence to start setting out the clinical utility of the assay and the benefits of measuring NETs in patients. The studies that VolitionRx has started and intends to initiate in collaboration with DXOCRO will further support the BDD application. Collaborations with major institutions such as MD Anderson and membership of the ISF will also help VolitionRx generate global publicity. In parallel, it will continue to work on early-stage cancer diagnostics, although we believe the route to market in this indication will require further larger-scale studies.

We will provide an overview of VolitionRx's veterinary business in a separate report.

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