VolitionRx

Snaring sepsis, with early NETs detection

VolitionRx continues to make headway in growing a body of clinical evidence to build Nu.Q® NETs as a potential breakthrough tool in sepsis. These efforts, coupled with its CE mark in Europe, are a strong foundation in rapid and simplified sepsis detection that seeks to address the limitations and complexities of the current standard of care. Sepsis (immune-system triggered organ dysfunction) has a worrisome prevalence, affecting c 50 million per year with a mortality rate of c 20–25%, exceeding the combination of many leading cancers. Further, every hour of delayed treatment increases the chances of mortality of this preventable condition by c 8%. In this note we recap VolitionRx's recent clinical updates, as we look forward to near-term improvements in early sepsis detection.

Casting a wide NET

The Nu.Q technology platform is designed for the rapid detection and quantification of nucleosomes (DNA-wrapped histones, the building blocks of chromatin), which serve as an effective biomarker for severe diseases. Nu.Q NETs utilizes the process of NETosis, which is associated with cell death and characterized by the release of NETs (consisting of modified chromatin and bactericidal proteins) from neutrophils (a type of white blood cell) in the bloodstream. Although essential in fighting infections, elevated levels of NETs can be early predictors of a range of diseases, including cancer and COVID-19, with the most immediate application in sepsis, based on clinical progress to date. Supported by its global centers of excellence program, VolitionRx is building an impressive data package across a number of settings (ICU and emergency department A/E), with the most recently published data showcasing the utility of nucleosomes as a biomarker to evaluate disease severity in septic shock patients.

510(k) application in sepsis on the cards

VolitionRx's Nu.Q NETs test already holds a CE mark in Europe (enabling clinical use in over 27 countries), and the company has recently completed the Q-Sub process with the FDA, which has recommended the 510(k) regulatory pathway for Nu.Q NETs in the US. While the timing for the regulatory filing is expected to be announced this year, we believe the company is seeking to strengthen its data submission package with larger studies prior to 510(k) submission. For example, VolitionRx has recently initiated a 500-patient prospective study in collaboration with Guy's and St Thomas' NHS Foundation Trust in the UK and expects the results from several other large-scale studies (1,000+ patients) to be published at the European Society of Intensive Medicine (ESICM) Congress in October 2024.

Utility beyond diagnosis and monitoring?

We believe that the ability to provide quick and clinically relevant information will help guide decision making in clinical settings, potentially improving disease prognoses. This rapid turnaround time is a critical feature when assessing and triaging in high-risk situations. Overall, we believe that the measurement of NETs could provide more clinically relevant results, translating to better outcomes and providing a useful addition to healthcare professionals' decision-making toolkit.

Pharma and biotech

8 February 2024

Price	**$1.07**
Market cap	**$84m**

Share price graph

Share details

Code	VNRX
Listing	NYSE
Shares in issue	78.7m
Net cash at end-June 2023	$16.1m

Business description

VolitionRx is a clinical diagnostics company developing easy-to-use and cost-effective blood tests for early diagnosis and monitoring of a range of diseases in humans and animals including cancer and sepsis. Its flagship Nu.Q® tests are based on the science of Nucleosomics™, which identifies and measures nucleosomes in the bloodstream or other bodily fluids, as an indicator of disease. VolitionRx has also developed a novel cancer detection method CTCF-ChIP/qPCR for early-stage cancer screening.

Bull

- Management continues to leverage its rapid Nu.Q technology platform and its CE mark to advance its regulatory application in sepsis.
- VolitionRx continues to develop and commercialize products across its Nu.Q platform, which is highly scalable and agnostic to legacy venues, technologies and populations.
- First company to develop a standardized assay to measure nucleosome concentrations.

Bear

- Challenges in gaining acceptance for Nu.Q will require advocacy of KOLs to support education and integration into established protocols.
- Potential commercialization challenges may require winning incremental partnering deals.
- Potentially slower route to market with 510(k) device application pathway.

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Edison profile page

Tackling the sepsis challenge…

Sepsis is caused by the body's improper immune response to an infection, which may lead to organ failure, tissue damage and even death (further details below). Bacterial infections are the most common origin of sepsis, but the condition can also be caused by viral infections (such as COVID-19) and fungal infections. According to the Centers for Disease Control and Prevention, 80% of sepsis cases originate outside of the hospital. The condition is more of a threat to the elderly, people with weakened immune systems, hospitalized patients and those with chronic medical conditions. Under the Sepsis-3 definition (revised in 2021), sepsis can be broken down into two levels of progressive severity: sepsis and septic shock (under Sepsis-2 there was a third category, severe sepsis, situated between the two above classifications). Septic shock (c 16% of hospitalized sepsis patients) is associated with a significantly increased risk of mortality (40–80%).

Globally, it is estimated that c 50 million people develop sepsis each year (42% of which are children under five years of age), the condition is associated with a c 20–25% mortality rate and survivors are typically left with one or more long-term consequences. In the US, it is estimated that approximately 1.7 million adults develop sepsis annually, corresponding to c 350,000 deaths. A direct consequence of this is the major financial burden on US healthcare systems. According to the Centers for Medicare & Medicaid Services, Medicare spends more than $41.5bn annually on sepsis inpatient admissions, as well as subsequent skilled nursing facility care.

Despite sepsis being a serious condition affecting a sizable number of people (it has a similar prevalence to cancer and cardiovascular diseases and causes more deaths per annum than breast, bowel and prostate cancer combined), widespread understanding of sepsis remains limited, with clinical development lagging behind that of cancer and heart conditions. Exhibit 1 contrasts the number of patients affected by sepsis and other major disease areas versus the R&D spend in each.

Exhibit 1: Patient population by condition versus related R&D spend

Source: VolitionRx company documents, courtesy of Professor Djillali Annane

The accurate diagnosis of sepsis (particularly at the early stage of disease presentation) can be challenging, due to the non-specific clinical signs and symptoms in the early stages. Blood culture-based tests take upwards of 24–48 hours to return results, and the utility of physiological tests is only reliable 24–72 hours post admission, due to typical delays in symptom presentation, and may lack accuracy if performed in the first 24 hours. Given that the risk of mortality grows by c 8% for every hour that passes without treatment for sepsis, patients often progress to more serious stages before a definitive diagnosis can be made. The need for a quick and effective solution is therefore acutely felt in this space, in our opinion.

Currently, the most widely used sepsis diagnostic approach (to quantify the severity of sickness in sepsis) that has been validated for intensive care unit (ICU) settings is the use of Sequential Organ Failure Assessment (SOFA) scores. This test aims to assess performance on six physiological parameters, based on the patient's respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems, and assigns a score (0 to 4) based on the data obtained in each category. A higher score indicates an increased probability of patient mortality (the highest possible score is

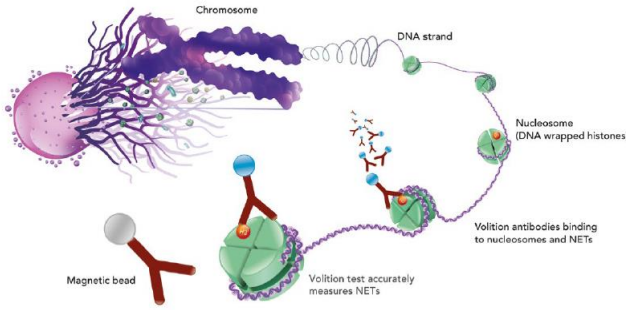
24). However, the scoring has been observed to be a better predictor of risk of mortality only when conducted 72 hours after hospital admission, and as it is a highly involved process, this poses a greater risk for patients in a more critical condition. Alternatively, ICUs may also employ Acute Physiology and Chronic Health Evaluation (APACHE II) scores, as well as Simplified Acute Physiology Score (SAPS II), to detect and monitor severe disease and risk of death in critical care scenarios. However, these assessments are also typically applied only 24 hours after a patient is admitted to the ICU. For reference, APACHE II is a 71-point scale (score of 0 to 71 with higher scores corresponding to more severe disease and a higher probability of mortality) based on 12 physiological criteria with additional points assigned based on age (higher ages equate to higher scores) and medical history. The SAPS II score is made up of 12 physiological and disease-related variables (scores range from 0 to 163 points; higher scores correspond to higher disease severity).

…Harnessing the properties of NETs

NETs: First line of defense, but can be a double-edged sword

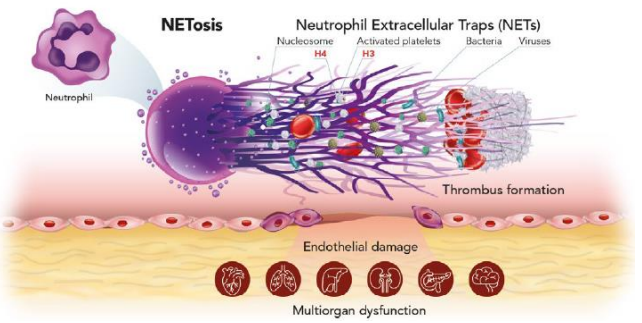
When the body becomes infected, white blood cells (called neutrophils, believed to be the first line of defense) target the invading pathogens (such as bacteria and viruses), and eject strings of nucleosomes (strands of DNA wrapped around proteins called histones) (Exhibit 2). These strings of nucleosomes form NETs (neutrophil extracellular traps), in a process called NETosis. As the name suggests, NETs are net-like structures, made up of nucleosomes, fragmented DNA and antimicrobial proteins. NETs are an important part of the body's immune system, as they catch bacteria and viruses, and destroy them using cytotoxic proteins (Exhibit 3). However, in extreme cases, the body's immune system can over-respond to threats, leading to the overproduction of NETs; excessive levels of which can cause damage to healthy parts of the body. The aberrant autoimmune response to infection is known as sepsis, and can lead to tissue damage, multiple organ failure and even death.

Exhibit 2: The structure of nucleosomes (and VolitionRx's approach for detection)



Source: VolitionRx company documents

Exhibit 3: NET targeting pathogens (and risk of multiorgan dysfunction)



Source: VolitionRx company documents

The VolitionRx solution: Nu.Q NETs technology platform

VolitionRx's Nu.Q NETs technology aims to identify and stratify disease risk in sepsis by early identification of elevated levels of NETs in hospitalized patients. This technology is centered around the detection and quantification of nucleosomes, which are released into the bloodstream in the form of NETs, which can then be detected using the company's proprietary Nu.Q NETs test, as an early indicator of high-risk patients. More specifically, VolitionRx's assay identifies H3.1-nucleosomes (nucleosomes associated with a variant of histone H3, which features distinct modifications), which serves as a dependable proxy for measuring NETs. Unlike other biomarker-based tests, which are more complex and have longer lead times, the Nu.Q NETs test is designed to be a simple, low-cost, quick-turnaround and accessible solution, to provide better ease-of-use and a rapid response compared to current legacy systems.

From an analytical perspective, a commonly used 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, the change in CRP levels typically takes 10–12 hours, meaning the test is only sensitive after this time. Procalcitonin (PCT) is another biomarker that is released in large amounts in the body in response to an infection, and PCT tests are also used as a sepsis diagnostic technique. However, as with CRP, PCT is not the direct cause of the damaging internal autoimmune response. Exhibit 4 presents a list of selected diagnostic biomarkers for sepsis, although we note that they each come with limitations, including long turnaround times for test results.

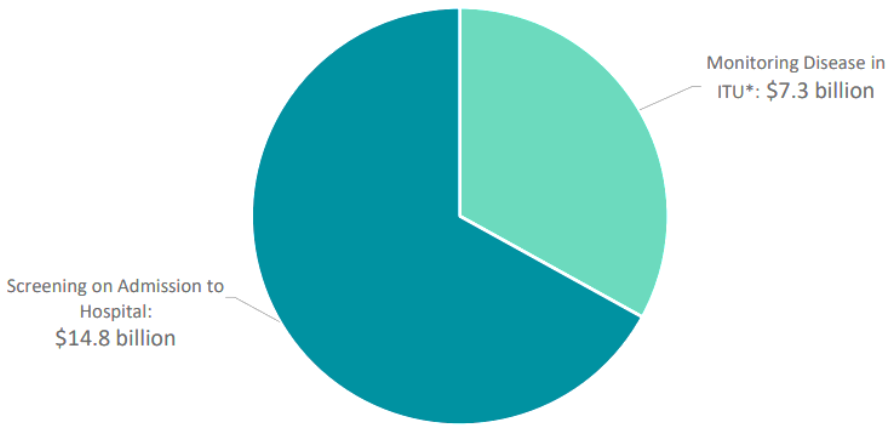
Exhibit 4: Selected biomarkers for sepsis diagnosis

Biomarker	Description	Limitation
C-reactive protein (CRP)	Protein secreted by hepatocytes (liver cells) in response to inflammation in the body related to pathogens or tissue damage.	Only triggered in response to inflammatory cytokines. Low sensitivity during the early phases of sepsis (CRP levels take 10–12 hours to significantly change after the onset of infection).
Procalcitonin (PCT)	Precursor of hormone calcitonin secreted by C cells of thyroid gland. PCT levels rise more rapidly than CRP levels.	PCT levels only tend to rise in response to bacterial infections. Not an effective biomarker for viral infections.
Presepsin (P-SEP)	sCD14 is cleaved by proteases during inflammation, to form an N terminal fragment – the sCD14 subtype. P-SEP levels tend to rise even faster than PCT (<30 mins), while sensitivity and specificity values are comparable.	P-SEP levels may be elevated in newborns and elderly individuals even in the absence of disease. It may not be applicable for patients with renal failure as P-SEP levels are already elevated in patients with kidney dysfunction.
Interleukin 6 (IL6)	A cytokine, mainly produced by macrophages and lymphocytes in response to infection, and it can affect the activation of B and T lymphocytes.	Long lead time to receive test results (one day to several days).

Source: Edison Investment Research

We believe that the ability to provide quick and clinically relevant information will help guide decision making in clinical settings, potentially improving disease prognoses. VolitionRx management states that Nu.Q tests can potentially reduce the overall time to test results to c 45 minutes, which, considering the time criticality of sepsis or septic shock diagnosis, is of clinical significance, in our opinion. This rapid turnaround time is a critical feature when assessing and triaging in high-risk situations. Overall, we believe that the measurement of NETs can provide more clinically relevant results, translating to better outcomes for the patient, and providing a useful addition to healthcare professionals' decision-making toolkit, with sepsis as the most immediate application. Given the current unmet medical need, the potential commercial opportunity remains sizeable, as estimated by VolitionRx (Exhibit 5).

Exhibit 5: Total addressable market for sepsis



Source: VolitionRx corporate presentation, August 2023. Note: *Based on two tests per patient.

VolitionRx has completed several small-scale hospital studies in septic shock and COVID-19 patients that demonstrate clinical proof-of-concept in the use of its assay as an organ toxicity management tool within the sepsis subsegment, as highlighted below. These studies have shown a correlation between elevated nucleosome levels and poor patient outcomes, providing support for the assay's use in a clinical setting for the rapid diagnosis of sepsis, where timely treatment is

essential. It is this physiological characteristic that VolitionRx aims to leverage with its Nu.Q NETs test, using nucleosomes as a single biomarker to rapidly measure and assess disease severity. We note that this unique approach may have the potential to expand into broader applications across indications (Exhibit 6).

Exhibit 6: Conditions with elevated NETs (million per year)

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

Source: VolitionRx capital markets day, May 2022

Nu.Q potential backed by growing clinical data

Latest study data showcase utility in septic shock patients

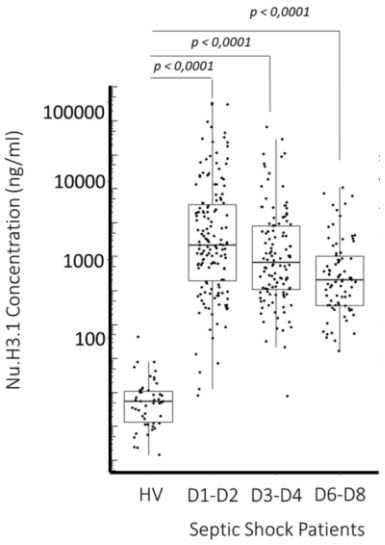
The latest research is the first published data from VolitionRx's global centers of excellence program (details below). It involved a detailed investigation into the association between the elevated formation of NETs and concentration of nucleosome biomarkers, with mortality in septic shock patients. The trends observed were highly supportive, in our view, that increased levels of the measured nucleosomes were associated with higher risk of mortality. We believe, therefore, that VolitionRx's Nu.Q NETs test could serve as a rapid and reliable assay to help clinicians assess and triage patients in such high-risk settings, by efficiently identifying those at higher risk of a poor outcome, and prioritizing treatments.

This study included septic shock patients admitted to the ICU (Hôpital Edouard Herriot, Hospices Civils de Lyon), and blood samples were taken at days (D): D1–2, D3–4 and D5–6 (one sample per day). Nucleosome levels were measured using VolitionRx's Nu.Q H3.1 assay, and mortality up to day 28 was taken as a clinical measure, alongside other routine ICU assessments. A total of 345 samples were taken from 151 septic shock patients, and 50 blood samples from healthy volunteers (HVs) were also analyzed as a control measure. We present key observations from the study below.

Nucleosome levels correlate with SOFA and SAPS II scores

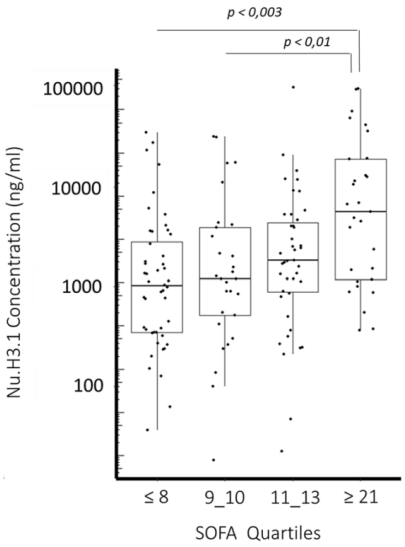
Across the full cohort of septic shock patients, there was a sizeable elevation in the concentration of the measured nucleosomes when compared to the HVs (Exhibit 7). This was the most pronounced at D1–2, but even at D6–8 these nucleosome levels were notably higher than the control, and to a high degree of statistical significance. SOFA and SAPS II scores were taken from the patients as part of their ICU assessments, and compared to the measured nucleosome levels across the day periods, showing a correlation with both (Exhibit 8). Given that these assessments are currently the mainstay in tracking sepsis, we believe these initial observations capture the potential of the Nu.Q NETs test as an efficient complementary tool to aid doctors in ICUs.

Exhibit 7: Nucleosome levels in HVs and septic shock patients at D1–2, D3–4 and D6–8



Source: VolitionRx company documents

Exhibit 8: Correlation between nucleosome levels and SOFA scores



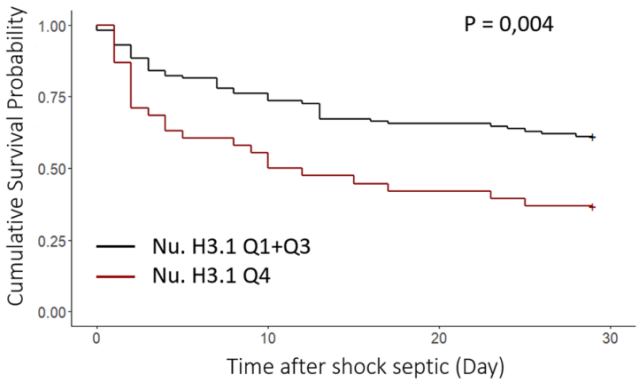
Source: VolitionRx company documents

A potential biomarker to predict mortality in sepsis

The association between the measured nucleosome levels and mortality rates was also assessed at day 28. For the non-survivor patients, concentrations of these nucleosomes were notably higher at D1–2, suggesting that such measures could be used as a mortality predictor, even early into such testing. The highest values (ie above the third quartile) were found to be independently associated with mortality, as assessed using a multivariate analysis. A Kaplan-Meier analysis was also conducted, which confirmed that elevated levels of the measured nucleosomes were linked to a lower likelihood of survival (Exhibit 9).

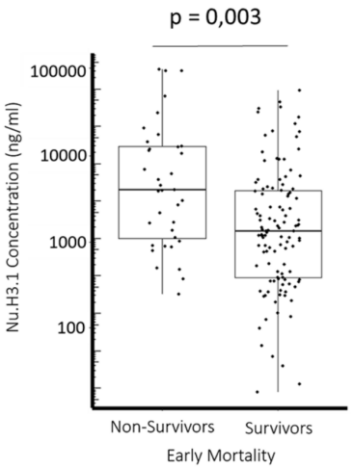
The results show that, of the 151 patients evaluated, there were 68 non-survivors, and 83 survivors, at day 28 (45% mortality rate). Considering this outcome, mortality over time was also assessed. A notable portion of the patient deaths occurred up to the day 5 timepoint (53% or 36/68 of all deaths), highlighting the critical condition of septic shock patients. Inspection of the D1–2 nucleosome concentration data revealed a statistically significant correlation with day 5 mortality (Exhibit 10). As with the day 28 data, the highest values (ie above the third quartile) were found to be independently associated with mortality, determined by a multivariate analysis.

Exhibit 9: Kaplan-Meier analysis showing a lower probability of survival in the upper quartile



Source: VolitionRx company documents

Exhibit 10: Nucleosome levels measured at D1–D2 in non-survivors compared to survivors at day 5

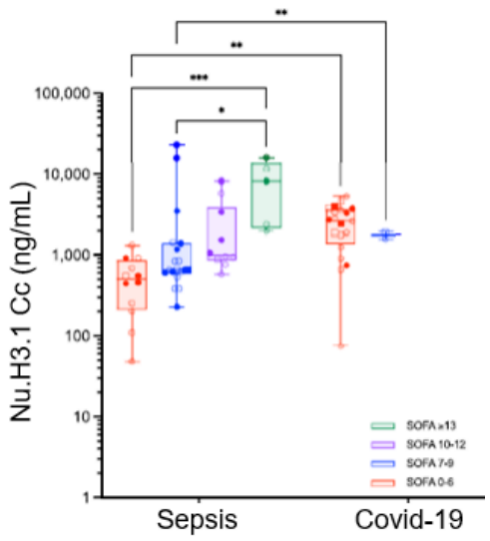


Source: VolitionRx company documents

Supported by prior studies in sepsis and COVID-19

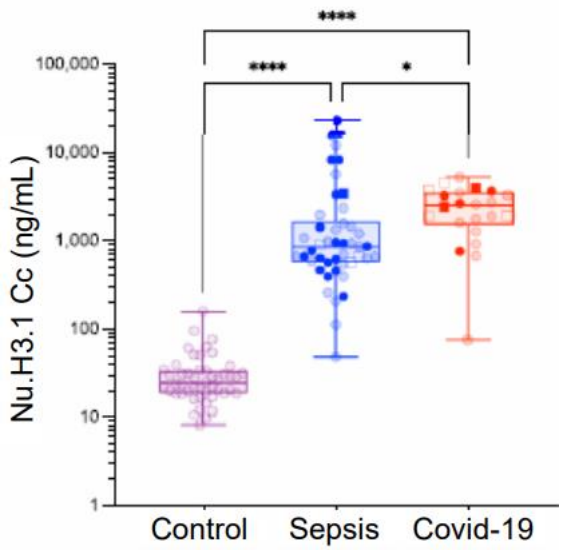
In October 2022, VolitionRx presented encouraging results from a sepsis study at the 26th International Symposium on Infections in the Critically Ill Patient. The study (n=48) was based on data from patients diagnosed with septic shock, where blood samples from the cohort were assessed using the Nu.Q NETs test to determine the relationship between nucleosome levels and SOFA scores. The results demonstrated a direct correlation (Exhibit 11). Additionally, the Nu.Q NETs test was proficient in detecting elevated levels of these nucleosomes triggered by COVID-19 (n=22), demonstrating the potential application of the technology across multiple disease areas (Exhibit 12).

Exhibit 11: Nucleosome concentrations in septic shock patients as measured by Nu.Q NETs



Source: International Symposium on Infections in the Critically Ill Patient

Exhibit 12: Nucleosome measurements in septic shock (n=46) and COVID-19 patients (n=22)



Source: International Symposium on Infections in the Critically Ill Patient

Research outlook

Collectively, we believe that these results capture the application of the Nu.Q NETs test as a standardized and efficient approach to evaluating septic shock patients, offering the potential to establish its position as a diagnostic tool within a medical setting. The assay can identify elevated levels of nucleosomes in patients in critical conditions, following the trend of measured SOFA scores, highlighting how the assay may serve as a practical approach to complement legacy systems for tracking patients in the ICU, rapidly identifying those in more critical conditions or situations, and prioritizing treatments. However, we specify that the test does not necessarily identify the direct cause of the condition (eg sepsis), for which additional work may be required by the clinician.

While we acknowledge that much of the research conducted to date has focused on septic shock patients, and does not consider milder forms of the condition, it is our opinion that NETs could be a promising biomarker for the assessment of all stages of the condition, with the potential to support prognosis assessments. VolitionRx's test could therefore be used to guide clinicians in managing sepsis patients, regardless of condition severity, and accurately identify those with a higher risk of mortality. We believe additional research into broader sepsis populations could further corroborate the application of Nu.Q NETs for both screening patients on admission to hospitals, as well as for monitoring the condition.

VolitionRx is now focusing on testing Nu.Q NETs in larger cohorts and varied clinical settings (detailed below) to help establish utility across a spectrum of patients and strengthen its data package. We reiterate that sepsis, as a whole (including both sepsis and septic shock sub-

populations), is likely to be a more favorable overall market opportunity for Nu.Q technology than targeting septic shock alone. Overall, we believe Nu.Q NETs has the potential to provide significant cost, resource and patient benefits in contrast to alternatives, such as SOFA assessments.

Focus on strengthening data package in the near term

Collaborating with industry KOLs and centers of excellence…

VolitionRx is a member of the International Sepsis Forum (ISF), a non-profit organization committed to improving the healthcare community's understanding of the clinical biology of sepsis, improving patient management, as well as promoting global physicians and lay education in sepsis. Membership of the ISF provides VolitionRx with a significant platform to promote Nu.Q NETs to recognized KOLs in sepsis, and to input its technology in key clinical studies. VolitionRx's studies in NETs are generating considerable interest due to their suggested roles in a wide variety of disease settings. The company organized its first sepsis KOL roundtable in September 2023 in Athens, Greece, which provided an opportunity to engage with subject experts. The discussion was chaired by Djillali Annane, professor of medicine at University Paris Saclay-UVSQ and a specialist in sepsis. The discussion included a panel of 10 KOLs and focused on challenges in sepsis, the connection between NETs and sepsis, as well as the potential of VolitionRx's Nu.Q NETs in sepsis diagnosis and monitoring. The panel acknowledged the potential of the Nu.Q NETs test as a promising option for the early diagnosis of sepsis, but also noted that further clinical work is required to fully support the utility of this technology.

In an effort to build a strong body of clinical data, VolitionRx has been focused on conducting studies collaboratively with several centers of excellence. As per our understanding, the company has studies and projects ongoing with several leading EU hospitals (seven as of August 2023). In December 2023, VolitionRx launched a 500-patient (sepsis and septic shock) observational study (EPICTETUS) to assess the applicability and efficacy of the Nu.Q NETs assay as a diagnostic tool for sepsis. The study is being undertaken in collaboration with the Guy's and St Thomas' NHS Foundation Trust, and will be funded by VolitionRx. The study will take approximately 12–18 months to complete and the results will be benchmarked against the current standard blood tests used by clinicians to evaluate sepsis patients. In addition to this prospective study, the company is also collaborating on two larger-scale studies with the German Sepsis Group and UMC Amsterdam, both of which will be based on retrospective analysis of prospectively collected samples (from 1,000 and 522 intensive care patients, respectively). The company expects to publish data from these studies at the ESICM Congress in October 2024. Details on these studies, as well as some other collaborative studies, are presented in Exhibit 13.

Exhibit 13: Selected ongoing studies for Nu.Q NETs with centers of excellence

Study	Description	Cohort size	Outcome measures	Comparator	Principal investigator	Guided completion date
EPICTETUS (Guy's and St Thomas' NHS Foundation Trust, London)	Prospective, blinded, longitudinal cohort study	■ Sepsis n=450 ■ Control (cardiac surgery pts) n=50 ■ Daily samples up to 14 days ■ Intensive care patients	■ Sepsis-3 ■ ICU mortality ■ 28-day mortality ■ Duration of organ support	■ Standard blood tests for sepsis	Dr Andrew Retter	April 2025
The German Sepsis Group	Retrospective analysis of prospectively collected cohort	■ 1,000 intensive care patients ■ Multiple timepoints	■ Discrimination of development of acute kidney injury in patients with sepsis ■ Prognostic value for: 28-day mortality, 90-day mortality ■ Duration of ICU stay ■ Hospital mortality	■ Severity of organ dysfunction as defined by the SOFA score ■ Requirement for mechanical ventilation ■ Duration of mechanical ventilation ■ Prediction of dependence on renal replacement therapy at discharge	Prof M Bauer	Sample processing and data analysis – Q124; publication of data – ESICM (Oct 2024)
UMC Amsterdam	Retrospective analysis of prospectively collected cohort	■ 522 intensive care patients ■ Multiple timepoints	■ Length of stay ■ ICU mortality ■ Hospital mortality ■ 28-day mortality ■ 90-day mortality ■ 1-year mortality	■ Severity of organ dysfunction as defined by the SOFA score ■ Requirement for mechanical ventilation ■ Duration of mechanical ventilation	Dr Lieuwe Bos	Sample processing and data analysis – Q1/Q224; publication of data – ESICM (Oct 2024)
Extended DXOCRO pilot study	Prospective, blinded, longitudinal cohort study. Patients recruited in the emergency department (ED) study and followed into ICU/CCU	■ Total 250 patients, extended study to include 40 patients who proceed to intensive care	■ Length of stay ■ ICU mortality ■ Hospital mortality	■ Severity of organ dysfunction as defined by the SOFA score ■ Requirement for mechanical ventilation ■ Duration of mechanical ventilation		Enrolment ongoing, data to be added to FDA filing
RECORDS (Rapid rEcognition of COrticosteRoiD resistant or sensitive Sepsis)	Prospective multicenter, placebo-controlled, biomarker-guided, adaptive Bayesian design basket trial	■ 1,500 intensive care patients ■ Multiple timepoints	■ Number of vasopressor-free days at day 28 ■ Occurrence of severe adverse events ■ 28-day mortality ■ 90-day mortality		Prof Djillali Annane	April 2025

Source: VolitionRx company documents

We remind readers that VolitionRx had signed deals in August 2022 with DXOCRO, a specialist diagnostic biomarker contract research organization, to conduct larger-scale patient studies and with MD Anderson, for a clinical study for the early detection of sepsis in cancer patients, as cancer patients are four times more likely to develop sepsis and account for c 15–20% of all sepsis ICU admission cases. Notably, the cost of care for these patients is up to 90% higher than patients without sepsis, marking the ongoing medical need, in our view. The study has a duration of approximately two years and aims to assess nucleosome levels and susceptibility to sepsis in this highly vulnerable patient population. As per our understanding, VolitionRx is also working on another clinical review article, and plans to publish this work in Q124, adding to its growing data package in sepsis.

…To support market access efforts

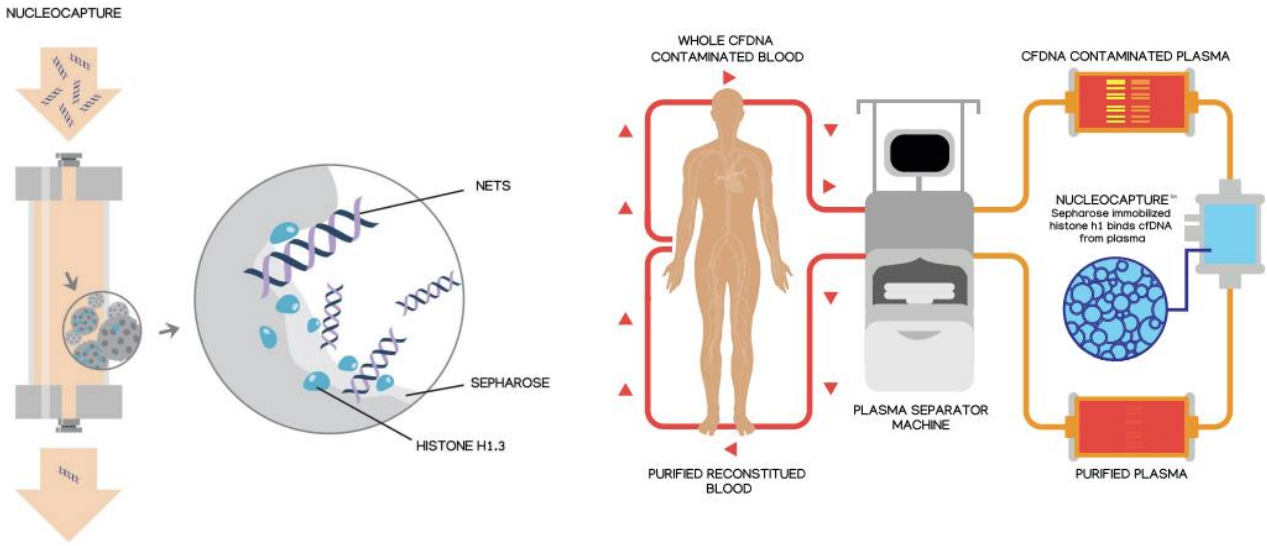
VolitionRx recently announced that it has completed the Q-Sub process (an optional pre-submission process that companies can use to get feedback from the FDA before submitting their devices for regulatory clearance), which has recommended the 510(k) regulatory pathway (also

referred to as the premarket notification) for Nu.Q NETs in the US. The 510(k) pathway is applicable for bringing a medical device to the market that shows substantial equivalence to a device already on the market (predicate device). This submission process aims to determine if Nu.Q NETs is at least as safe and effective as the predicate device through adjudication. The 510(k) pathway is considered an expedited review, typically processed within 90 days. While the expected timing for the regulatory filing is unclear, we believe the company is seeking to strengthen its data submission package throughout 2024 with larger studies prior to the 510(k) submission. We remind readers that the test is already CE marked in Europe, enabling clinical use in 27 countries within this region.

Beyond diagnostics

Beyond diagnostics and monitoring, VolitionRx is working with Santersus, which is focused on the development of NucleoCapture apheresis technology, which could be used to complement treatment in sepsis. A fundamental question in current sepsis research is whether NETs play a 'main actor' role in sepsis, or if they are a bystander. In other words, if the presence of NETs is a direct cause of the dysregulated immune response observed in sepsis patients, whether they could be a valuable treatment target, and whether approaches that clear them from the blood provide better patient outcomes. NucleoCapture is being developed as a blood-cleansing device (Exhibit 14) and has thus far been investigated in various animal models, where it has demonstrated the ability to remove over 95% of NETs with a single pass.

Exhibit 14: Selective capture of NETs with NucleoCapture



Source: VolitionRx poster presentation

A prior study demonstrated that treatment with NucleoCapture apheresis technology resulted in improved organ function and survival in a seven-hour porcine model of sepsis. The latest published research followed this work, by investigating the use of NucleoCapture in combination with antibiotic treatment (compared to a sham treatment control) in an extended 24-hour clinically relevant porcine intensive care model of sepsis. As expected, the results showed elevated levels of NETs following infection. However, the sham-treated subject saw these nucleosome levels continue to rise through to the end of the treatment duration, whereas the NucleoCapture-treated subject saw a marked reduction. Encouragingly, this was associated with an attenuation in septic shock. In our view, while we acknowledge that this is early-stage animal-based research, these results support the hypothesis that NETs may play a central role in septic responses. Therefore, we believe that blood-cleansing by NucleoCapture apheresis technology could serve as an effective companion for the treatment of sepsis, and, in our view, warrants further clinical investigation.

On the regulatory front, Breakthrough Device designation was awarded to Santersus's NucleoCapture technology in May 2022, as an adjuvant treatment to antibiotics in patients with sepsis. An initial study has suggested that NucleoCapture apheresis for humans with sepsis is feasible and safe, and could improve patient outcomes. Currently, Santersus management is gearing up for further clinical studies to build a data package, with the aim of directing this research focus toward personalized sepsis care for humans. We speculate this may involve measuring the concentration of NETs in a patient with sepsis, using the Nu.Q NETs assay, and prioritizing treatment with NucleoCapture apheresis for those with elevated NETs levels, regardless of condition severity.

Summary

Sepsis may not capture as much public attention as more commonly discussed conditions (such as cancer) but is nevertheless still a preventable and serious medical threat. With a comparable number of recorded cases to cancer, heart disease and strokes, and with a mortality risk that increases highly for each hour without treatment, the need for a rapid and effective diagnosis approach is paramount, as it would help guide optimal treatment and facilitate the development of novel treatment options to improve patient outcomes. Current standard-of-care diagnostic tools (such as SOFA and APACHE II) rely on cumbersome and complex physiological assessments. Other biomarker-based tests (such as CRP and PCT) either have long turnaround times or are limited in their applicability. It is therefore our opinion that a simple, non-invasive blood test, with a turnaround of less than an hour and applicability as a sepsis diagnosis tool, is intriguing and warrants attention.

VolitionRx continues to build a growing body of clinical evidence on Nu.Q NETs, a CE-marked diagnostic solution, as a potential breakthrough tool in sepsis. The test utilizes the concept of NETs and NETosis to identify patients at high risk of sepsis, by analyzing and quantifying circulating nucleosomes in the blood. Nu.Q NETs has demonstrated clinical proof-of-concept across multiple small-scale hospital studies in patients with septic shock; the company is now focusing on validating this data in larger patient cohorts. With the FDA go-ahead to file for regulatory clearance under the 510(k) pathway, we expect the 2024 focus for VolitionRx will be on growing and securing a strong data package to support regulatory submission. With several new developments expected this year and beyond, we recommend readers watch this space for more updates on this exciting technology.

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