VolitionRx

Building real-world Nu.Q NETs sepsis data

Volition continues to build data demonstrating that the Nu.Q® NETs H3.1 diagnostic platform is a potential breakthrough tool in sepsis management. These efforts underpin Volition's aim to advance Nu.Q NETs as a rapid, accessible and accurate diagnostic test to manage this potentially devastating condition. Sepsis (immune system triggered organ dysfunction) affects c 50 million people a year worldwide, and results in c 11 million deaths. Further, every hour of delayed treatment raises the mortality risk by c 8%. In this note we review Volition's recent updates from the ESICM Annual Congress, where it provided evidence across data comprising more than 3,000 patients that its technology can quickly and reliably detect the patients most at risk of mortality, septic shock and organ failure. Improving the identification and tracking of at-risk patients should help improve treatment paradigms.

Nu.Q NETs H3.1 reliably detects H3.1 nucleosomes

The Nu.Q platform is designed to rapidly and accurately identify and quantify nucleosomes (DNA-wrapped histones, the building blocks of chromatin), which serve as an effective biomarker for NETosis, a mechanism the body uses to fight infections. When uncontrolled, NETosis can lead to complex immunothrombotic reactions, potentially resulting in sepsis and/or other severe diseases. Nu.Q NETs H3.1 identifies H3.1 nucleosomes, which serve as a valid proxy for NETosis.

Strong predictive capability of Nu.Q NETs H3.1

At the ESICM conference, Volition reported data from three independent studies at three centers of excellence (total n>3,000). The new data show high correlations between H3.1 nucleosomes and disease severity in sepsis and related diseases. The Nu.Q assay, which can deliver results within 15 minutes, consistently showed that individuals with elevated H3.1 levels had a higher risk of mortality, septic shock and (multi-) organ failure. The Nu.Q NETs test could serve as an effective assay to help clinicians assess patients in high-risk settings by efficiently identifying those at higher risk and prioritizing those most in need. It already has a CE mark in Europe and the company is in discussions with potential partners for commercialization.

Potential to inform new treatment approaches?

We expect that Nu.Q NETs' ability to provide crucial information will assist treatment decision-making in critical care settings, potentially improving disease outcomes. As NETosis is believed to play a key role in the pathophysiology of sepsis and related conditions, the ability to quickly identify a verifiable proxy should also aid in the development of new and potentially personalized therapies, which may further improve prognoses and treatment success rates in the longer term.

Historical financials

Year end	Revenue ($m)	PBT ($m)	EPS ($)	DPS ($)	P/E (x)	Yield (%)
12/22	0.3	(30.6)	(0.55)	0.00	N/A	N/A
12/23	0.8	(35.7)	(0.50)	0.00	N/A	N/A

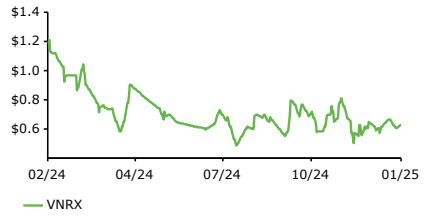
Source: LSEG Data & Analytics

Healthcare

28 January 2025

Price	**$0.62**
Market cap	**$57m**

Share price performance



Share details

Code	VNRX
Listing	NYSE
Shares in issue	92.7m
Net cash at end-June 2024	$1.1m

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 as an indicator of disease. VolitionRx has also developed a novel cancer detection method, Capture-PCR, for early-stage cancer screening.

Bull points

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

Bear points

- 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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Nu.Q NETs shows promise in sepsis management

Sepsis is one of the most critical areas of unmet need in acute medicine and infectious diseases. The condition is caused by the body's exaggerated and extreme immune response to an infection, which may lead to organ failure, tissue damage and even death.

Sepsis is the most expensive condition involving US hospital inpatient care, with the aggregate cost of total sepsis hospital care in the US estimated at over $57.5bn in 2019, excluding subsequent outpatient skilled nursing facility care. Volition's Nu.Q NETs aims to be an accessible, accurate and rapid key diagnostic test to help facilitate the management of this potentially devastating condition.

A brief review of sepsis incidence and pathophysiology

Bacterial infections (particularly from gram-positive sources) are the most common origin of sepsis, but the condition can also be caused by viral and fungal infections. According to the Centers for Disease Control and Prevention, 80% of sepsis cases originate outside 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.

It was estimated that 1.7 million people in the United States developed sepsis in 2014, resulting in c 270,000 deaths. Sepsis is believed to contribute to one in every three deaths among hospitalized patients. Globally, it is estimated that c 50 million people develop sepsis each year, resulting in c 11 million deaths. Those who survive are often left with lasting physical (bodily organ) damage and/or neurological or mental effects.

The underlying mechanisms by which sepsis develops and evolves are complex. As a brief overview, the systemic immune response to a bacterial infection causes the activation of various immune cells and production of inflammatory agents including cytokines due to pathogen-associated molecular patterns, damage-associated molecular patterns and lipopolysaccharides produced by the bacteria. In a normal infection, the immune stimulation is fairly quickly resolved. However, in sepsis, the stimulus is far greater and can lead to an excessive and dysregulated immune response.

While timely diagnosis is critical, limitations exist

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 physiological tests are 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 (often antimicrobial) treatment for sepsis, patients often progress to more serious stages before a definitive diagnosis can be made. A quicker and effective quantifiable solution is therefore acutely necessary, in our view.

To assess disease states and severity, the most widely used diagnostic approach that has been validated for sepsis in 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. Alternatively, ICUs may also employ Acute Physiology and Chronic Health Evaluation (APACHE II) scores, as well as the Simplified Acute Physiology Score (SAPS II), to detect and monitor severe disease and risk of death in critical care scenarios. However, these are all highly involved and time-consuming processes, thus there is a significant need for a more rapid and objective means to quantify disease progression, given the speed with which sepsis can progress and worsen in critically ill patients.

Nu.Q NETs shows diagnostic promise for sepsis monitoring

Volition has been studying nucleosomes and neutrophil extracellular traps (NETs) and ways to detect these structures using its proprietary diagnostic technologies and antibodies. At the European Society of Intensive Care Medicine (ESICM) Annual Congress on 5–9 October 2024, the company reported new data from three studies including more than 3,000 patients (comprising more than 14,000 patient samples), which showed how its nucleosome quantification technology could be used to enhance sepsis management in clinical practice. Nucleosomes are strands of DNA

wrapped around proteins surrounding DNA called histones.

NETs: Key defensive pathway, but can be a double-edged sword

When infections occur, certain white blood cells (neutrophils) target the invading pathogens (such as bacteria, viruses and fungi) and eject strings of nucleosomes (Exhibit 1) towards them. These nucleosomes combine to form NETs to trap the targeted entities in a process called NETosis.

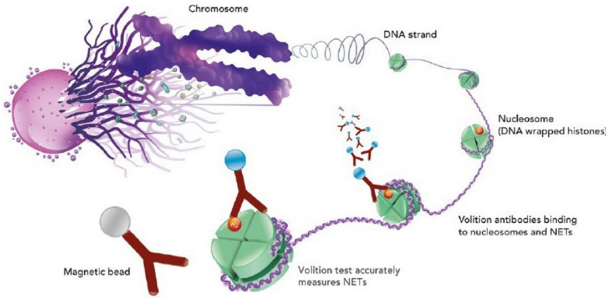
First reported in 2004, NETs are net-like structures, made up of nucleosomes, fragmented DNA and antimicrobial proteins, which can catch and kill or inactivate bacteria and viruses, and sterilize blood within minutes. NETs can catch bacteria and viruses and destroy them using cytotoxic proteins (Exhibit 2).

NETosis involves the formation of NETs through a rapid decondensation of chromatin (within the cell's nucleus), followed by the release of web-like NETs containing long strands of chromatin and associated antimicrobial enzymes.

While NETs can be a crucial defense mechanism, in extreme cases the body's immune system can over-respond to threats, resulting in the overproduction of NETs (such as when NETs are produced faster than they can be removed) whereby they can migrate beyond the initial site of infection or injury. Excessive NETs levels can damage healthy bodily tissues by blocking blood vessels and causing micro blood clots. This process is called thromboinflammation and Volition argues that extracellular damage and pathology is due to the indiscriminate binding of anionic (negatively charged) components of the histones with elements of the circulation and vasculature.

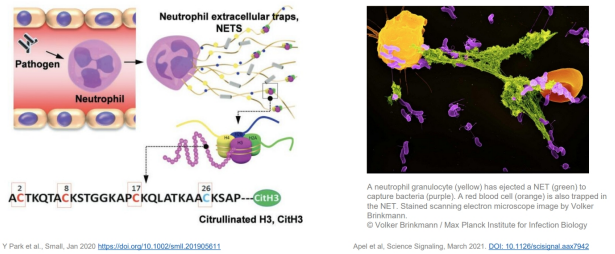
Altogether, dysregulation and excessive NETs formation can contribute to or lead to sepsis and other immunothrombotic disorders by creating a hyperinflammatory feedback loop, leading to disseminated intravascular coagulation. These pathways can result in tissue damage, multiple organ failure and eventually lead to death.

Exhibit 1: The structure of nucleosomes (and Volition's approach for detection)



Source: Volition documents

Exhibit 2: Neutrophil extracellular traps (NETs) contain proteins and trap pathogens



Source: Volition documents

Volition's Nu.Q NETs technology platform

Volition's Nu.Q NETs technology aims to identify and categorize disease risk in sepsis by rapidly identifying and quantifying the levels of NETs in hospitalized patients. In particular, the Nu.Q NETs H3.1 assay is being developed as a low-cost, novel, easy-to-use, rapid diagnostic blood test to detect and quantify a specific nucleosome, H3.1 (which is associated with a variant of histone H3), which is a validated proxy for the measurement of NETs and NETosis.

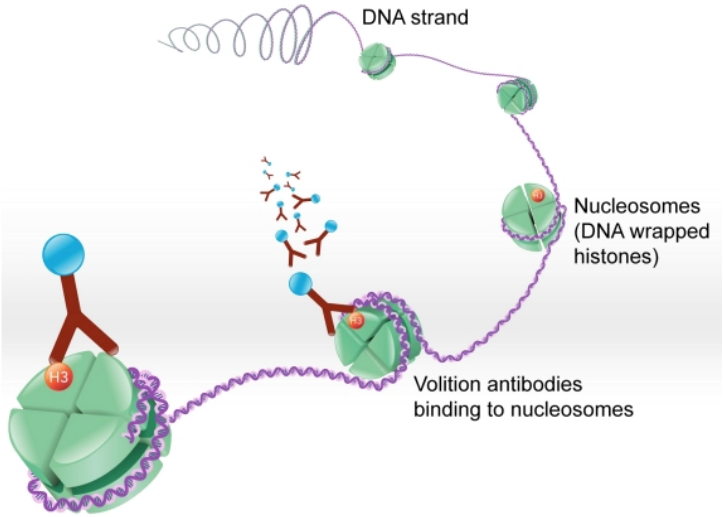
Exhibit 3: Nucleosomes and histones schematic

Key message:

The H3.1 assay can detect nucleosomes using chemiluminescence technology and provide a result within 15 minutes

The lower limit of quantification is 20ng/ml

The upper limit of quantification is 20,000ng/ml

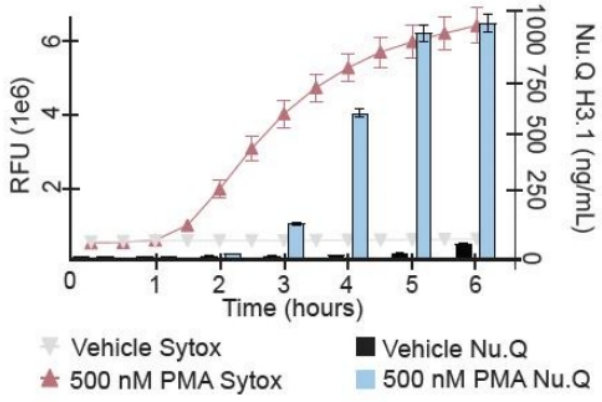


Source: Volition documents

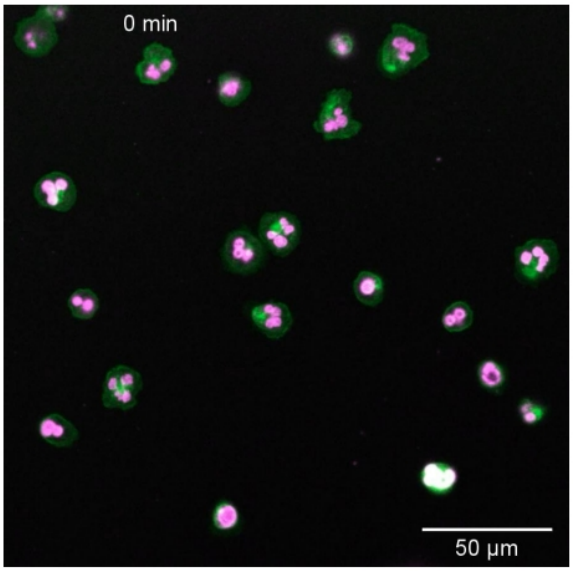
Nu.Q NETs H3.1 applies chemiluminescence technology and is designed to deliver quantitative data in as little as 15 minutes that can guide clinicians in the management of patients with sepsis, which may potentially help improve outcomes. The technology can detect H3.1 at levels as little as 20ng/mL and at quantities up to 20,000ng/mL.

As shown below, H3.1 nucleosome levels were found to increase with NETosis in preclinical models, validating the measurement as a proxy for the assessment of NETosis.

Exhibit 4: H3.1 nucleosome levels increase with NETosis



Zukas et al, Journal of Thrombosis & Hematology, 2024



Source: Volition documents

New data show strong predictive capability of Nu.Q NETs H3.1

At the ESICM conference, Volition provided newly reported data from three independently run studies at three centers of excellence (SISPCT study in Germany, Amsterdam UMC in the Netherlands and RHU Records in France), which in total included more than 3,000 patients. Volition's new data show high correlations between H3.1 nucleosomes and disease severity in sepsis and other related diseases.

Exhibit 5: Studies covering Nu.Q NETs H3.1 nucleosome levels in sepsis

Study	Country	Description	Cohort Size
SISPCT	Germany	Retrospective analysis of prospectively collected cohort	971 intensive care patients Multiple timepoints
Amsterdam UMC	Netherlands	Retrospective analysis of prospectively collected cohort	1,713 intensive care patients Multiple timepoints
RHU RECORDS	France	Prospective, multi-center, placebo controlled, bio-marker-guided, adaptive Bayesian design basket trial	1,500 intensive care patients Interim analysis of 416 patients

Source: Volition documents

In these studies, Volition's Nu.Q NETs H3.1 diagnostic system was retrospectively analysed in patients with sepsis in intensive care, as well as in several patients who also developed acute kidney injury and acute respiratory failure. The studies consistently showed that elevated H3.1 levels demonstrate a dysregulated immune response and are associated with increased risks of mortality, septic shock, (multi-) organ failure, renal failure and acute respiratory distress syndrome (ARDS).

Importantly, these correlations were consistent across populations. The measurement of H3.1 was not affected by the gender, height, weight or age of the patient. In addition, the H3.1 level was found to be only minimally correlated with the neutrophil blood count, which means it provides additional information to full blood count alone. Effectively, the H3.1 quantitative level (measured by Nu.Q NETs diagnostics test) by itself correlates directly and predictably with the severity of the dysregulated ongoing immuno-inflammatory condition affecting the patient (such as sepsis).

Strong predictive ability shown for near-term mortality in sepsis

In the SISPCT study in Germany (n=971) in ICU patients with severe sepsis, patients underwent the NETs H3.1 diagnostic test at the outset (hospital admission). Data accumulated on 869 patients showed a strong predictive capability in terms of mortality within 14 days, with mortality inversely correlated with H3.1 measures. Patients with >20,000ng/mL (n=5) had a 100% mortality rate, those with 10,000–20,000ng/mL (n=16) had a 25% mortality rate and those with the lowest H3.1 levels (<1,000 ng/mL) had the lowest 14-day mortality rates (7%). This strong association should enable clinicians to prioritize resources accordingly and may, through further research, lead to the discovery of therapeutic modalities that can help lessen this high mortality rate among the highest risk group (those with high H3.1 levels).

Exhibit 6: Mortality risk shown in SISPCT study based on H3.1 levels at admission

14 day mortality	**Survivor**			
Initial H3.1 (ng/mL)	**Yes**	**No**	**Total**	**Risk**
>20,000	0	5	5	100%
10,000-20,000	12	4	16	25%
1,000-10,000	264	36	300	12%
<1,000	508	40	548	7%
Total	**784**	**85**	**869**	**10%**

Source: Company documents

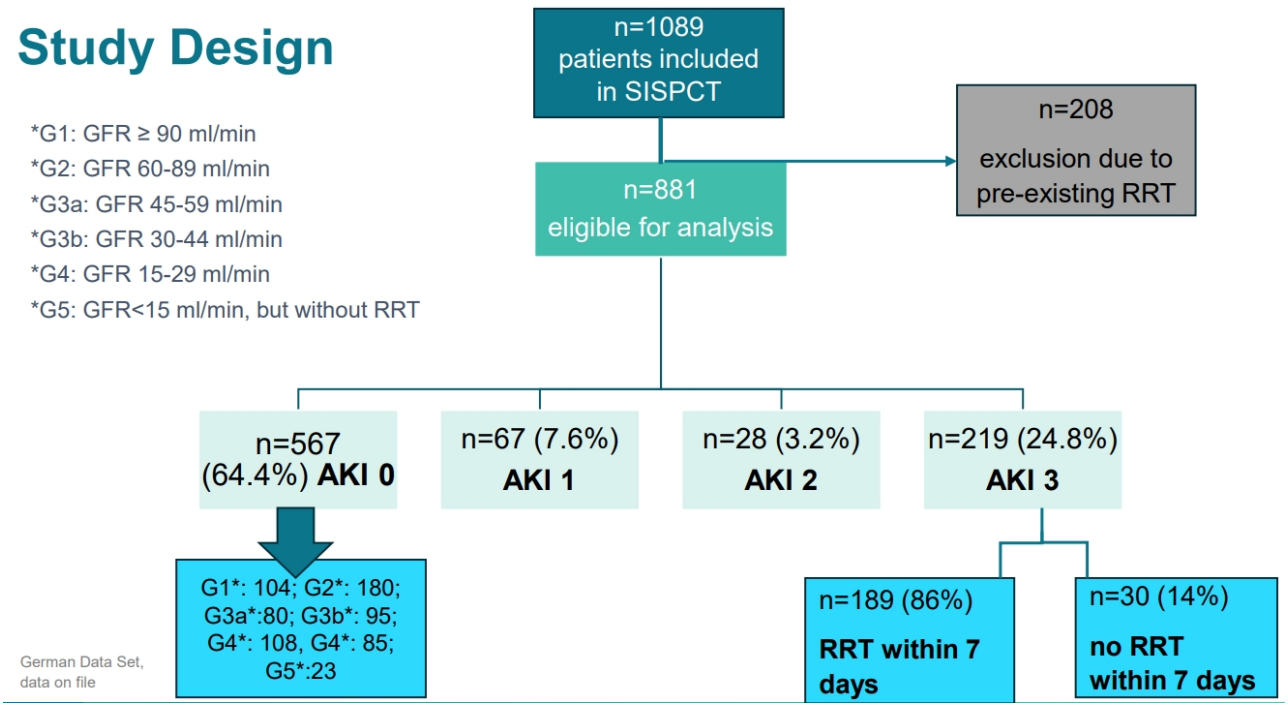
Predictive capability also shown for Sepsis-induced AKI

The kidneys and renal system are the most common organs affected by sepsis, leading to sepsis-associated acute kidney injury (SA-AKI). SA-AKI is a strong contributor to the high mortality and poor prognosis in patients with sepsis, but can be clinically nonspecific, making it difficult to identify quickly which sepsis patients have SA-AKI. While some more recently identified biomarkers of kidney injury such as urinary neutrophil gelatinase-associated lipocalin and urinary exosomal activating transcriptional factor 3 have been studied to identify high-risk patients, their clinical application has been found to be limited. Hence there is a relevant need to quickly identify sepsis patients at risk of SA-AKI and/or those who may require renal replacement therapy (RRT). RRT is a treatment intended to replace the normal blood-filtering function of the kidneys and can include dialysis, hemofiltration and hemodiafiltration and, ultimately, renal transplantation.

A secondary analysis of patients recruited for the SISPCT study was conducted to determine whether H3.1 nucleosomes measures (as a surrogate of NETosis) at admission to intensive care and/or any changes over time would show predictive utility to determine which patients would develop AKI or kidney failure and/or could guide in the management of such conditions.

Of the 881 SISPCT patients eligible for analysis, 64% did not develop AKI and 25% progressed to Stage 3 AKI, among which more than 86% required RRT within seven days, and the remainder (c 10%) developed lower-grade AKI.

Exhibit 7: SISPCT study design for AKI sub-analysis

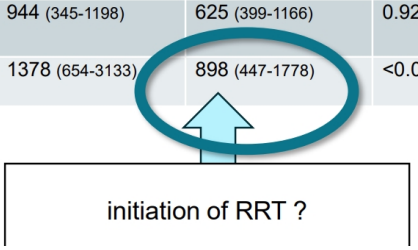


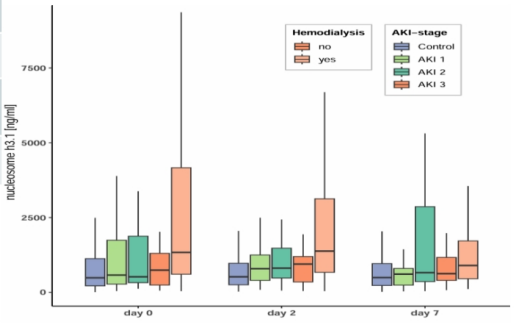
Source: Company documents

The study analysis covered the H3.1 measurements taken throughout the seven-day period. The analysis found that at day 7, the patients who developed Stage 3 AKI and who required RRT had higher levels of H3.1 (at baseline) than the other subgroups. Hence, the likelihood that sepsis patients would eventually require RRT was correlated with H3.1 levels on admission.

Exhibit 8: H3.1 nucleosome levels over time correlate with AKI and RRT need

AKI stage	D0 (Nu.Q® Level)	D2 (Nu.Q® Level)	D7 (Nu.Q® Level)	p-value
0	484 (216-1127)	518 (249-974)	492 (229-969)	0.785
1	577 (266-1881)	790 (393-1319)	608 (234-820)	0.084
2	518 (319-1917)	809 (477-1477)	658 (356-2864)	0.574
3	1151 (509-3797)	1169 (611-2881)	885 (438-1641)	0.001
3 without RRT	741 (242-1362)	944 (345-1198)	625 (399-1166)	0.924
3 with RRT	1335 (604-4165)	1378 (654-3133)	898 (447-1778)	<0.001





Source: Company documents

Statistical analysis also found that H3.1 levels at admission were superior to creatinine measures in predicting which patients would eventually require RRT. Volition and its collaborators studied the massive data set and developed a highly predictive clinical model that combined three variables:

- an H3.1 level of more than 2,600ng/mL at baseline;
- a low platelet count; and
- a low urine output rate at baseline.

They found that this model of three parameters, which could be readily obtained when a patient is admitted to intensive care (ie assuming commercialisation of the Nu.Q NETs diagnostic test) was capable of identifying 84% of the patients who would go on to require RRT at seven days (SISPCT data set, on file). Altogether, this 84% identification rate compares very favourably with a recently studied prediction model for AKI in patients with sepsis, which combined 10 risk factors at onset (including presence/absence of diabetes mellitus, chronic kidney disease, congestive heart failure, chronic liver disease, hyperbicarbonemia, hyperglycemia, low blood pH, prolonged clotting time, hypotension and hyperlactatemia) and was found to have a c 72% positive predictive value. The ability to quickly identify which patients may require RRT at onset or at hospitalisation has the potential to improve clinical care outcomes given how quickly sepsis can lead to morbidity and organ failure when not treated optimally.

Volition also reported that data from the Amsterdam UMC and RHU Records studies found a similar association between H3.1 levels and AKI risk. The RHU Records study also found that higher H3.1 levels correlated with an increased likelihood of requiring RRT. The Amsterdam UMC study also found that the higher a patient's H3.1 level, the higher their risk of multiple organ failure.

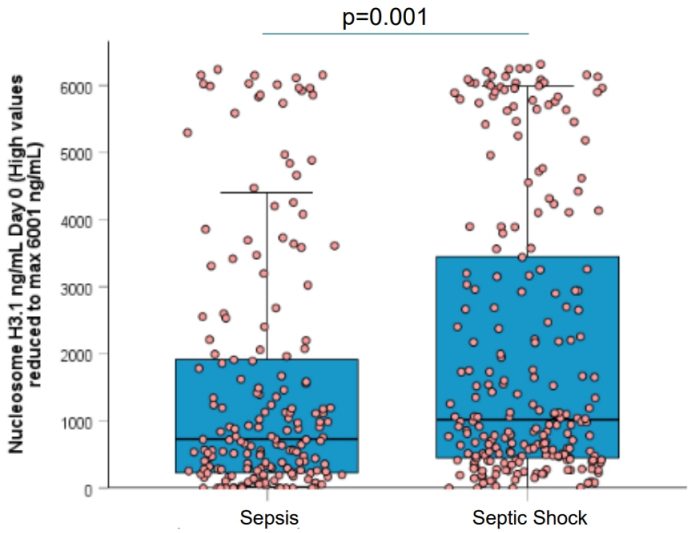
Further, ongoing data from the RHU Records study show that H3.1 levels can identify which sepsis patients are more likely to develop septic shock (the most severe form of sepsis, whereby the infection causes low blood pressure, resulting in damage to multiple organs, associated with c 50% mortality). Data from the study showed that septic shock patients had a median H3.1 level of just over 1,000ng/mL versus a median level of around 700ng/mL in those sepsis patients without septic shock. This study also showed a strong positive correlation between patients who develop ARDS and H3.1 levels.

Exhibit 9: RHU Records study showing correlation of H3.1 and ARDS severity and septic shock

				Nu.Q® H3.1 levels Sepsis	Nu.Q® H3.1 levels Septic Shock	Statistical
No ARDs	138 (14.2%)	70 (15.8%)	63 (12.1%)	285.7	647.8	0.0017
Mild ARDs	201 (20.7%)	102 (23%)	96 (18.5%)	396.3	646.7	0.0044
Moderate ARDs	436 (44.9%)	193 (43.6%)	243 (46.7%)	465.5	921.6	***
Severe ARDs	196 (20.2%)	78 (17.6%)	118 (22.7%	540.1	1,306	***

Source: Company documents

Exhibit 10: RHU Records study data showing correlation of high H3.1 and septic shock



RECORDS

	Sepsis	Septic Shock
n=	183	233
Median (ng/ml)	727	1029

Source: Company documents

Altogether, the reported data from more than 3,000 patients (two of the studies being prospectively defined retrospective analyses) demonstrate robust evidence of the potential diagnostic utility of Volition's H3.1 measurement system in identifying patients with sepsis and those at a higher risk of progression. We therefore believe that its 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.

Can treating H3.1 itself be a viable therapeutic strategy?

The above studies show robust evidence, in our view, that H3.1 levels can offer positive predictive benefits in clinical settings and can potentially direct clinical resources when needed. What is less immediately clear is whether H3.1 nucleosomes represent a 'treatable trait' in sepsis or immunothrombotic disorders, and whether therapeutic strategies aimed at lowering H3.1 nucleosome levels can improve therapeutic outcomes and reduce organ failure or the need for RRT.

Volition believes that recent preclinical evidence shows that treating or removing H3.1 nucleosomes or NETs can indeed improve outcomes. A recent (2024) study in a porcine model of ARDS shows that removing NETs during ex vivo lung perfusion improved lung function and morphology in aspiration-damaged donor lungs. The study authors suggest that the ability to remove NETs could represent a new therapeutic approach.

Santersus has developed NucleoCapture technology that is designed to selectively remove NETs from blood after it passes through a proprietary apheresis device. Santersus states that a single pass of NET-contaminated blood through

its NucleoCapture device would remove more than 95% of NETs. In 2022, Santersus's NucleoCapture technology was awarded Breakthrough Device designation as an adjuvant treatment to antibiotics in patients with sepsis. Earlier work has suggested that NucleoCapture apheresis for humans with sepsis is feasible and safe and could improve patient outcomes. Santersus management is planning to conduct clinical studies to generate relevant data, with the aim of advancing a potential treatment of sepsis. We speculate that this may involve applying the Nu.Q NETs H3.1 assay to measuring the concentration of H3.1 nucleosomes in patients with sepsis, and then applying treatment with NucleoCapture apheresis for those with elevated readings. We note that beyond the NucleoCapture approach, other small molecule inhibitors of NETs are being assessed in preclinical sepsis models to determine whether blocking NETs can protect against renal failure or other organ damage. Further research in this area is required.

The data reported at ESICM show, in our view, that elevated H3.1 can assist in the early diagnosis and management of sepsis and the identification of patients more likely to deteriorate. This could help better allocate scarce hospital resources with appropriate monitoring and potential treatment plans for the highest-risk patients. For instance, while there is no proven specific treatment yet for elevated NETs, a high score could potentially guide personalized therapies (eg as high H3.1 may be a sign of a hyperinflammatory immune response, corticosteroids or other anti-inflammatory or immunosuppressive/immunomodulatory treatments could be considered).

Other biomarkers may lack the speed and specificity of H3.1

From an analytical perspective, one of the most commonly used diagnostic biomarker tools 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 blood test is a good indicator of inflammation or infection, the change in CRP levels typically takes 10–12 hours, potentially hampering its applicability for early-stage diagnosis. Further, CRP has low specificity for the detection of sepsis, and the plasma level of CRP is not necessarily viewed as a very reliable indicator of the level of systemic inflammation.

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.

Interleukin-6 (IL-6) is a cytokine that is produced by white blood cells in response to infection and, while it has been found to be accurate in the detection of sepsis, IL-6 levels and their progression do not always correlate clearly with a risk of mortality. PCT may be potentially more responsive and increase more rapidly (in the first 24 hours following infection) and decrease more rapidly following resolution, but other studies have suggested that CRP may be superior to PCT and IL-6 in assessing the prognosis or evolution of patients with sepsis and that PCT score trends had only weak correlations with patient outcomes.

We believe that the ability to provide quick and clinically relevant information will help guide decision making in clinical settings, potentially improving disease prognoses. Volition's management states that Nu.Q tests can potentially reduce the overall time to H3.1 nucleosome test results to approximately 15 minutes, which, considering the time criticality of sepsis or septic shock diagnosis and progression, is highly advantageous, in our view. A rapid turnaround time is a critical feature when assessing and triaging in high-risk situations.

Overall, we believe that the measurement of NETs has the potential to provide more clinically relevant results, which should eventually translate to better outcomes for the patient, by providing timely, relevant data to the decision-making toolkit of healthcare professionals, particularly if new treatments targeting NETs are developed, with sepsis as the most immediate application.

The aforementioned three 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 and management of sepsis, where timely treatment is essential. Given the current unmet medical need, the potential commercial opportunity remains sizeable.

Nu.Q NETs H3.1: Next development steps

Volition is looking to monetize the intellectual property behind its H3.1 nucleosome diagnostics technology and seek partners for non-exclusive licensing deals. It is seeking potential partners to commercialize the Nu.Q NETs H3.1 diagnostic test in hospital ICU settings as a quick triage tool for sepsis. The company is seeking potential collaborators with broad geographic and established customer bases and experience in tech transfer, regulatory and clinical affairs.

In terms of potential market size, Volition estimates that the Nu.Q NETs could be used as part of routine blood testing

and sample collection in ICU settings. Sepsis is very common in ICU settings, with a global study estimating that 29.5% of patients admitted to an ICU either have sepsis or will develop sepsis during their stay. Hence, the company's position that Nu.Q NETs H3.1 could be applied as part of the regular test battery for all or most patients admitted to an ICU setting is defensible.

Volition estimates that ICU visits in the US amount to approximately 14.7m per year and US government data from 2006 estimated about 5.7m US ICU visits per year. Given the 14% US population growth rate since then, we estimate that each year approximately 6.5 million to 7.0 million people would visit US ICUs, a somewhat more conservative assumption than the company's estimates. We calculate that in Europe (including non-EU countries) up to 15–16 million individuals may visit an ICU each year. The mean length of stay in the ICU varies between approximately five to 10 days across various studies in North America and Europe.

As Volition expects to sell the H3.1 diagnostic test at $20.00/iteration in Europe and $27.50/iteration in the US and assuming that 100% of patients have a test on a daily basis, this would place the potential addressable market sizes at c $2.3bn and c $1.5bn, respectively, providing substantial commercial opportunities if fully tapped. We note of course that real-world utilization rates would likely differ as other diagnostic tests and clinical considerations are undertaken on an individual basis.

Exhibit 11: Total addressable market for sepsis diagnostics as assessed by Volition

Country	Intensive Care Population	Average Length of Stay (tested daily)	Price	Total Addressable Market
Europe (incl UK)	18m	10 days	$20	3.6 Billion
U.S.	14.7	10 days	$27.5	4 Billion
TOTAL				7.6 Billion

Source: Volition documents

Altogether, we believe that Volition's Nu.Q NETs test could serve as a rapid and reliable assay to help clinicians assess and triage patients in high-risk settings by efficiently identifying those at higher risk of a poor outcome and prioritizing treatments. While there are emerging competitors also looking at alternative rapid test approaches for the detection of sepsis, to our knowledge Volition is the most advanced-stage diagnostic platform looking specifically at nucleosomes, and H3.1 nucleosomes in particular, for the detection and management of sepsis and related conditions.

Summary

Sepsis remains a serious medical threat. With a comparable number of recorded cases to cancer, heart disease and strokes, and with a mortality risk that increases greatly in each hour without treatment, a rapid, reliable and effective diagnosis approach is crucial, as it would help guide optimal treatment and facilitate the development and evaluation 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. We believe that a simple, non-invasive blood Nu.Q NETs H3.1 nucleosome test, with a turnaround of c 15 minutes and applicability as a sepsis diagnosis tool, warrants serious consideration.

Volition continues to build clinical evidence on Nu.Q NETs, a CE-marked diagnostic solution, as a novel and potentially compelling tool in sepsis detection and management. The H3.1 diagnostic test utilizes the concept of NETs and NETosis to identify patients at high risk of sepsis, by quantifying circulating H3.1 nucleosomes in the blood. With several new commercial and clinical developments anticipated over the coming year, we recommend that readers watch this space for more updates on this technology.

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