EDISON

NetScientific

Portfolio overview

Transatlantic healthcare technologies

Healthcare equipment & services

NetScientific has a focused portfolio of potentially disruptive biomedical and healthcare technology investments. 2015 saw significant strategic changes, including senior management restructuring, bringing a new highly experienced CEO on board, rationalisation of the portfolio and new funding (£18.2m gross from the issue of 15.2m new shares at 120p). 2016 will be a year for execution and delivery for the portfolio companies on their path to commercialisation, ahead of potential exits from 2017 onwards.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
12/14	0.0	(5.5)	(13.4)	0.0	N/A	N/A
12/15	0.1	(10.2)	(21.8)	0.0	N/A	N/A
12/16e	0.7	(14.6)	(25.0)	0.0	N/A	N/A
12/17e	3.4	(13.7)	(22.9)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items and share-based payments.

Digital health, diagnostics, therapeutics

NetScientific has evolved its strategy and rationalised its portfolio into three clear investment themes: digital health, diagnostics and therapeutics. The current portfolio consists of five core investments in which it has controlling stakes (Vortex, Wanda, ProAxsis, Glycotest and Glucosense) and one material investment (PDS). The aim is to bring these to commercialisation over the next two years, with the ultimate goal of an exit, realising value for investors. Timing of the potential exit will be determined by development progress and opportunity.

Proactive strategy; external validation to come

NetScientific's approach involves proactive management of the core portfolio of majority-owned investments. As these companies mature, dedicated CEOs are recruited to navigate the next growth phase and attract external growth capital though Series A funding rounds and potentially follow-on rounds. External investment will provide important third-party validation. Series A rounds are in process or planned for Wanda, ProAxsis and Glycotest. Vortex is sufficiently funded from the November 2015 capital raise.

Commercial traction to unlock value

Efforts by NetScientific to raise both its profile and that of its portfolio companies with UK and US investors should increase the visibility of forthcoming value inflection points. Achieving a number of near-term commercial milestones should drive share price appreciation as value creation becomes more apparent. These include Vortex commercial VTX-1 launch in 2017, Wanda launch of OncoVerse in 2016, ProAxsis CE mark approval around end-2016, Glycotest HCC Panel launch end-2017, Glucosense CE mark end-2018 and PDS's Phase II initiations in 2016. These milestones may also enable exits through IPO or trade sale.

13 June 2016

Price	**80.5p**
Market cap	**£41m**

Net cash (£m) at end-March 2016	19.5
Shares in issue	51.1m
Free float	16.2%
Code	NSCI
Primary exchange	AIM
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	0.6	(9.6)	(54.0)
Rel (local)	1.0	(11.1)	(49.1)

52-week high/low	201.0p 72.0p

Business description

NetScientific is a transatlantic biomedical and healthcare technology group. Its portfolio of five core investments and one material investment is focused on three main sectors: digital heath (Wanda, Glucosense), diagnostics (Vortex, ProAxsis, Glycotest) and therapeutics (PDS Biotech).

Next events

Capital Markets Day	14 June 2016
Interim results	October 2016
Series A closure (Wanda, ProAxsis, Glycotest)	2016+

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Advancing a focused portfolio to commercialisation

NetScientific completed a strategic review in 2015, which has refined its focus onto building a transatlantic biomedical and healthcare technology group concentrated on chronic diseases through three main sectors: **digital heath**, **diagnostics** and **therapeutics**. The current portfolio of opportunities has been identified from a range of sources across the company's network, including strategic partnerships, global institutions and leading technology incubators. Since mid-2015, a number of significant changes to transform the business and enable strategic execution have been implemented, including:

- **Senior management restructuring:** most notably, François Martelet MD, a highly experienced biopharma professional, was appointed CEO in June 2015. Additionally, so far in 2016, the appointments of a new non-executive director, Professor Stephen Smith, and a new CFO, Ian Postlethwaite (formerly of Allergy Therapeutics), have been announced.
- **Portfolio rationalisation:** divestment of non-core assets created a streamlined portfolio of predominantly majority-owned, healthcare-focused companies. The current portfolio (Exhibit 1) consists of five core companies, two of which (Vortex and Wanda) have been prioritised for accelerated growth, one (PDS) represents a material investment (albeit not majority owned) and five seed-stage investments (Exhibit 2). NetScientific's investment in its portfolio has typically been leveraged by major grant funding or less visible prior academic support funding.
- **New capital issued:** 15.2m new shares were issued at 120p in November 2015 raising £18.2m (gross) from new and existing shareholders. Proceeds will principally be used in accelerating the development of Vortex and Wanda through important milestones ahead of commercialisation. Cash resources at end-December 2015 stood at £23.2m (vs £16.9m at 31 December 2014).

We provide a brief strategic overview of the company below. In the next section, we profile the core portfolio and material investments presented in Exhibit 1, outlining progress to date, the underlying technologies, market opportunity and forthcoming milestones.

Exhibit 1: Core portfolio and material investment

Investment	Technology	% held	Founded	Status	Business advantage	Targets
Vortex	"Centrifuge-on-chip" cancer diagnostic using liquid biopsy from circulating tumour cells	95.0%	2012	VTX-1 instrument beta units prepared	Faster separation of viable cancer cells with high purity.	VTX-1 launch Q216 into US research labs for beta testing; clinical validation to complete during FY16. CE mark in EU and FDA Class I exemption filing in H216. First commercial sales in FY17.
Wanda	Clinical decision support software to reduce hospitalisation risk. Initially focused on CHF	71.3%	2011	CHF and oncology deals signed Q116	Patient friendly interface. Highly scalable, predictive analytics.	Expand platform to cover additional chronic conditions. Planned DTC campaign to target consumers. Economic validation: raised marketing profile 4k sponsored and unsponsored users Q416; 15k Q417.
ProAxsis	Protease-Tag diagnostic products for monitoring disease biomarkers; focus on CF and COPD	56.5%	2013	Lab tests launched; NEATstik in R&D	NEATstik home test detects neutrophil elastase with high reliability and specificity. Potential to reduce hospitalisation risk.	PoC test in clinical trials from Q217. CE mark approval Q416/Q117; EU launch 2017 of in clinic and self-test NEATstik devices.
Glycotest	Liver cancer diagnostic test based on proprietary biomarkers and algorithms	87.5%	2012	HCC panel developed, 208pt clinical study completed	Outperforms current biomarker AFP test.	Clinical validation by Q317, CLIA registration Q317, HCC test launch Q417.
Glucosense	Non-invasive glucose monitoring device	60.7%	2011	Prototype, limited data	Supplement/replace finger-stick testing. Possible wearable device.	Testing of benchtop device by end 2016; clinical studies in 2017; EU launch possible 2019.
PDS*	Therapeutic vaccine, clinical trials against HPV	14.85%	2006	Clinical	Low production cost; deals with Merck-Serono and MedImmune	Phase II initiations; further licensing deals.

Source: NetScientific. Note: *Material investment. PoC = point-of-care; CHF = congestive heart failure; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease.

Exhibit 2: Seed-stage investments

Investment	Technology	% held	Founded	Status	Business advantage	Targets
G-Tech	Electrical monitoring of GI function via wearable disposable patch	ND	2014	Early-stage	Real-time diagnosis and monitoring of GI disease	Innovation needs to be linked to clinical outcomes
Longevity Biotech	Uses β amino acids scaffold to resist degradation in blood	ND	2014	Early-stage	Longer half-life biosimilar therapeutics	Needs clinical equivalence and toxicology and safety
CytoVale	Microfluidics to measure >10 biophysical cell markers	2.15	2014	Concept validation	Detects early stages of sepsis in white cells	Clinical validation and commercial test development
Epibone	Customised bone grafts	ND	2015	Research	Grown from own stem cells	Clinical, economics
Neumitra	Real-time stress level measurement	ND	2015	Retail market	Neuma biowatch (embedded biomodules in jewellery)	Validation and marketing

Source: NetScientific. Note: Seed-stage investments sourced from Breakout Labs. ND = not disclosed.

Infrastructure to support growth

NetScientific remains focused on sourcing, funding and building early- to mid-stage US and UK companies that are developing potentially breakthrough technologies in growing markets with unmet needs. Following the strategic review, the company is evolving away from a classic healthcare/tech seed-stage investment approach (the strategy at IPO in 2013) towards being an active investor involved in all phases of development, management and growth of a focused group of largely majority-owned subsidiary companies. The goal is to provide management expertise to support the core portfolio companies as they transition from development stage and approach commercialisation. This initially involves direct senior management input and technical, financial and administrative support from NetScientific; however, as the companies mature, dedicated management teams with experienced CEOs are recruited to navigate the next growth phase.

Significant milestones and potential validation ahead

CEOs are now in place at four of the five priority companies; Glucosense is the exception being led by an experienced project manager until such time as it achieves key milestones. In addition to executing on strategy and taking their respective companies through commercial milestones, these individuals have been tasked with attracting external growth capital though Series A and potentially follow-on rounds. Proceeds from the recent NetScientific equity issue have been largely earmarked for investment into Wanda and Vortex; Series A rounds are in process or planned for Wanda, ProAxsis and Glycotest.

In addition to providing the funds necessary for growth and further development, securing external investment is critical from other perspectives. Importantly, it signifies third-party validation for the various technological approaches/market opportunities, and secondly it will allow for an explicit company valuation (carrying value) within NetScientific's future accounts. The evolution of the carrying value of NetScientific's portfolio as these assets gain commercial traction should drive share price appreciation as value creation becomes more apparent. Efforts by NetScientific, such as the forthcoming Capital Markets Day, to raise both its profile and that of its portfolio companies with investors in the UK and US should also increase the visibility of potential forthcoming inflection points. These may also result in an uplift to the current share price and, at the portfolio level, may also enable exits (value realisation) through IPO or trade sale.

Longer-term value creation

Achievement of NetScientific's long-term strategy of maximising shareholder value and generating capital for pipeline reinvestment into new opportunities rests on the potential for significant value realisation through exits. The timing of exits is not determined as progress of portfolio company development and availability of funding will govern how long any investment might be held. Nevertheless, under NetScientific's refined strategy, 2016 will be a year for execution and delivery of the next steps on the path to commercialising investments ahead of potential exits, at a premium from 2017 onwards.

Swirling into the Vortex

Vortex BioSciences is a California-based spin-out focused on cancer diagnostics. It has developed a novel 'liquid biopsy' system to capture rare circulating tumour cells (CTCs) from whole blood based on technology developed at the Department of Bioengineering at UCLA. The system includes a novel liquid biopsy automated instrument (VTX-1) and integrated microfluidic cartridge. CTCs are an area of intense clinical research interest and technical development (see review) as they provide information about an individual's cancer, which can be used for prognostic, diagnostic and treatment stratification purposes. Rising CTC numbers are a known risk marker for cancer reoccurrence in diagnosed patients, therefore a combination of effective CTC isolation with sophisticated analysis could enable much better and earlier cancer diagnosis, monitoring and personalised cancer therapy. The initial focus is on the research market, The VTX-1 system was introduced at the American Association for Cancer Research (AACR) conference in April 2016. The system is currently in the late stages of development, with the official launch into the US research market planned for Q117.

Investment and management

NetScientific's shareholding in Vortex is 95%. Vortex was founded in 2012 and, as at 31 December 2015, NetScientific had invested £5.6m. Grant funding received to develop the underlying technology prior to Vorex's formation was £1.6m.

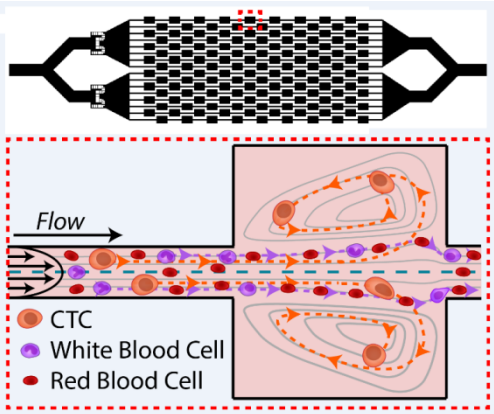
A new CEO, Gene Walther was appointed in January. He has over 20 years' experience in diagnostics, having previously held roles as deputy director of diagnostics at the Bill & Melinda Gates Foundation, executive chairman at GenturaDx (from foundation, through product development, to acquisition by Luminex), and president and global head of diagnostics at Novartis. Other notable management additions in Q116 include a chief commercial officer, VP of manufacturing and director of quality.

Technology overview

The Vortex technology, using microfluidics, isolates larger cells from whole blood. As CTCs tend to be much bigger than red blood cells and larger than most white immune cells, they are preferentially captured (Exhibit 3). Note that the method is not specifically selective for cancer. Key advantages include the rapid processing time (taking as little as one hour), collection efficiency (sensitivity) and purity of captured CTCs with limited white blood cell contamination (specificity). Most importantly, the captured CTCs are intact and undamaged and can be identified, analysed and enumerated using different methods. The Vortex technology is label-free, requiring no pre-treatment; hence it can be used in a variety of applications including cancer diagnosis and monitoring, personalised medicine, drug development and cancer research. The current FDA-approved system uses antibodies to capture CTCs, but misses many.

During 2015, Vortex has made significant progress in optimising the VTX-1 instrument and the microfluidic cartridge, and strengthening its IP portfolio. IP consists of 12 patents, including three issued company-developed patents and six licensed patents. These include the devices (instrument and cartridges) and various applications; Vortex also benefits from significant know-how. It has selected contract manufacturing partners for VTX-1 (Gener8) and the microfluidic cartridge (Symbient/Z-Microsystems) ahead of commercialisation. Transition to scale manufacturing will happen in early 2017 to support commercial supply.

Exhibit 3: Vortex technology

Vortex feature	Comment
Physical principle	Cancer cells are typically larger that both red blood cells and leukocytes. To separate out the larger cells, blood samples are pushed down parallel microchannels, with each channel having successive collection chambers. Cells flowing down the microchannels are pushed outwards by a 'shear-lift' force, which increases as cell size rises. Stable fluid vortices form in the chambers. As larger cells pass into the chambers, the wall lift drops and the shear lift pushes larger cells into the vortices where they are trapped. Small cells, like red blood cells and leukocytes, do not experience enough shear lift to be pushed into the vortices so they continue down the channel.
Trapped in the vortex	Once in a vortex, the large cells are trapped and cannot re-enter the channel while the flow is maintained. To release the cells, the flow is reduced, vortices vanish and the cells flow out for collection. Smaller cells that enter the vortex are expelled as they are too small to be retained.
Chip structure and function	 Blood samples travel down the channel with larger cells including CTC captured by the vortex as they pass a chamber.
Product	The Vortex system is designed as a benchtop instrument with a disposable microfluidic cartridge for CTC enrichment.
How many CTCs?	The level of CTCs, even in metastatic cancer patients, is extremely low. In one millilitre of whole blood, a patient may have one CTC per 5 billion red blood cells and 5-10 million white immune cells. CellSearch has a clinical level of significance of five or more CTCs per 7.5ml blood sample.
Analysing the cells	Once isolated, the identity of the captured cells must be confirmed. CTCs can be identified by looking at the nucleus of the cells and staining for markers of epithelial cells like epithelial cell adhesion molecule (EpCAM) and cytokeratin 19 *(CK-19). It is possible to carry out DNA sequencing on isolated CTCs to find mutations and select optimal therapies. Other techniques and markers can also be used to analyse the cells.
Effect of cancer cell type	Different cancer cell lines have different densities and sizes. Cells around 13µm (1µm = one millionth of a metre) diameter and larger stay in the vortex and are captured by the Vortex system.
Efficiency	Up to 9mls of blood can be processed in one run. CTC recovery can be as high as 80%.
Purity	The Vortex system is able to capture CTCs with high purity, minimising the CTCs captured. White blood cell (WBC) contamination varies by patient sample, but WBCs can be as low as 30 WBC/ml of blood processed.
Adding value	Vortex has been actively working with collaborators to demonstrate the use of the Vortex system for clinical applications. Recent posters presented at the 2016 AACR conference demonstrate the ability of Vortex's technology to rapidly collect highly enriched populations of CTCs, undamaged by labels or reagents, for colorectal and prostate cancer research.

Source: Edison Investment Research, King (2012), Che (2016), graphic from NetScientific

Market opportunity

The current 'gold standard' procedure for obtaining tumour information is a solid biopsy; however, this has limitations. The primary tumour is not always easily accessible, nor are metastatic disease sites, and single-site biopsy may not provide a complete genomic landscape of the tumour due to intra-tumour heterogeneity. Liquid biopsy (CTC or ctDNA, Exhibit 4) is minimally invasive and may allow better assessment of prognosis and optimised therapy and be easily repeated.

Exhibit 4: Liquid biopsy approaches – circulating tumour DNA (ctDNA) and cells (CTC)

Aspect	Comment	Competitive landscape
ctDNA area	Tumour DNA fragments are rare, possibly 0.01% of plasma DNA. If mutations can be detected, this is an indication of a cancer and the mutation type can suggest the tumour type and possible treatment. However, ideally tumour cells are available to confirm this. We view ctDNA as a potential initial screening system that complements CTC analysis.	Competition focuses on defining and validating unique marker sets with high detection sensitivity. Companies include Agena, Boreal, Chronix, Genomic Health, Guardant Health, Inivata, Molecular MD, Myriad Genetics, Natera, Personal Genome Diagnostics, Sysmex Inostics and Trovagene. FDA approval has proved hard so most suppliers, like Boreal, offer a CLIA service. CLIA labs do not need FDA test approval since the tests are run by experts and this route allows companies to sell service tests. However, healthcare providers are not always willing pay for tests without clinical verification.
CTC	There are various physical and antibody capture systems, mostly in development. Not all systems are well described; many are academic. Single cell sequencing is possible and can help in understanding the heterogeneity of disease.	Life Technologies (Thermo Fisher), sells the Ion Torrent integrated system "from blood to gene sequence in two days" using the Cynvenio CTC system. Cynvenio also offers sequencing and mutation analysis via a lab service. CytoTrack and DEPArray both use computer image analysis to count cells as part of their tests (CTCs have to be stained with a marker). BioFluidica uses electrical conductance to count CTC and aims to add sequencing.

Source: Edison Investment Research based on literature sources

Vortex is one of several companies with CTC detection systems in development (Exhibit 5). A number are currently marketed for clinical use in Europe or for research use. CellSearch is the sole CTC system that is FDA approved, but its use is limited to enumeration in certain cancer types. This month, the FDA approved the first ctDNA blood-based genetic test: Roche's cobas EGFR Mutation Test v2 as a blood-based companion diagnostic for Tarceva (erlotinib).

Exhibit 5: Selected CTC detection technologies

Product (company)	Status	Notes
Antibody-based systems		
CellSearch (Veridex/Janssen Diagnostics)	FDA approved, CE marked for clinical use	FDA approved for enumeration of CTCs for prognostic purposes in metastatic breast, colorectal and prostate cancer. Isolates CTCs using magnetic particles coated with anti-EpCAM antibodies. Limited to epithelial CTCs. Captured CTCs typically have low yield and purity, and are not viable.
IsoFlux (Fluxion Biosciences)	Lab-run test	Antibody-coated magnetic beads combined with microfluidic processing, not limited to epithelial markers. High-sensitivity (>80%), tumour DNA purity >10%. CTCs can be analysed using a number of analysis platforms.
GILUPI CellCollector (GILUPI)	CE marked for clinical use	In vivo diagnostic. Anti-EpCAM antibody-coated functionalised medical wire, which is placed directly into the antecubital vein for 30 min to sample a large blood volume. High CTC sensitivity of c 70%. Captured CTCs can be used for enumeration and analysis. Limited to epithelial CTCs.
AdnaTest (Qiagen)	CE marked for clinical use	Immunomagnetic beads with MUC1-coupled and EpCAM-coupled antibodies. Specificity of >90% and a sensitivity of two CTCs per 5ml of blood at a recovery rate of >90%. Cell lysis means that enumeration is not possible. Obtained mRNA can be analysed by PCR.
LiquidBiopsy (Cynvenio)	Lab-run test	Immunomagnetic capture of CTCs and cfDNA within a microfluidic chip. Reports capture sensitivity of one CTC per ml of blood with high purity. Automated platform means cell populations can be directly analysed by NGS and other platforms.
Epic AR-V7 Test (Epic Sciences)	Lab-run test	Protein immunofluorescence to characterize AR-V7+ CTCs as biomarker for mCRPC treatment decisions (identification of potential resistance to androgen directed therapies).
RosetteSep (Stem Cell Technologies)	Marketed for research use only	Density-based whole blood cell separation for isolation of purified cells. Antibody cocktail crosslinks unwanted cells to red blood cells forming rosettes, which pellet with free RBCs when centrifuged.
AccuCyte CyteFinder (Rarecyte)	Lab-run test	System combining density-based collection of nucleated blood cells with automated staining, high-resolution digital microscopic imaging, image analysis and single-cell retrieval. Specificity of >90% using various cell lines. Targeting applications in oncology, prenatal health and infectious disease.
Membrane-based systems		
ScreenCell (ScreenCell)	CE marked for clinical use	Filtration based on cell size through a microporous membrane filter. Capture sensitivity reported to be two CTCs per ml of blood. CTCs can then be analysed in situ, or harvested for analysis and/or culture. Not limited to epithelial CTCs.
ISET (Rarecells Diagnostics)	CE marked for clinical use	Filtration based on cell size. Capture sensitivity reported to be one CTC per ml of blood. Captured CTCs can then be analysed by FISH and PCR. WBC contamination due to membrane becoming clogged. Not limited to epithelial CTCs.
Microfluidic, centrifugation and Vortex flows		
ClearCell FX System (Clearbridge Biomedics)	Marketed for research use only	Automated machine using the CTChip FR1 microfluidic chip to isolate CTCs on the basis of their size and inertia. Recovery >40% with spiked samples. Reports ultra-high purity and high throughput. Harvested CTCs are intact and viable. The system can be integrated with a number of downstream analysis technologies and culture of CTCs.
VTX-1 (Vortex Biosciences)	Validation	Microfluidic chip to isolate CTCs on the basis of their size and other physical properties. Preliminary testing suggests >80% purity and high throughput. CTCs are viable and can be harvested for downstream analysis and culture.
Parsortix (Angle)	CE marked for clinical use	Microfluidic disposable cassette captures CTCs on the basis of their size and morphology. CTCs can be fixed and stained in situ or harvested for analysis or culture.

Source: Edison Investment Research. Note: Published data are limited on many systems. EpCAM: epithelial cell adhesion molecule; WBC: white blood cell; FISH: fluorescence in situ hybridisation; NGS: next-generation sequencing; PCR: polymerase chain reaction.

CTC detection technologies can be used in various applications (research, drug development, diagnosis, monitoring and treatment); some of these are explored in more detail in Exhibit 6.

Exhibit 6: CTC applications

Application	Description	Vortex	Other
Risk for metastatic relapse or progression	This is the current FDA-approved use. The current clinical risk threshold is >5 cells/7.5ml determined on CellSearch.	Vortex separates on size so is not applicable to all cancers. Vortex needs its own validation studies. Vortex is fast to run, a big advantage in routine diagnostics, but then needs analysis.	Systems that capture most CTC irrespective of size or markers may be best at monitoring, possibly iChip. These then need accurate staining and image analysis.
Use of CTC to gain information about optimal therapies	This still seems to be a research application. Viable cells can be used for cell cultures, testing for mutations and sequencing.	CTC isolation systems could be bought by many research groups with their own analysis capabilities. The systems with high yields of viable CTC might do best in the market. CTC purity is also important.	Many companies use captured CTCs for genetic analysis. This can be as a service (Fluxion, Biocept) or as system sale like LiquidBiopsy.
Monitoring	CTC at this stage does not seem to be a screening method, but might be used for monitoring to identify patients whose cancer is progressing. The CytoTrack system appears to be being targeted at screening and monitoring.		

Source: Edison Investment Research

Vortex flags that liquid biopsy could represent a $22bn market opportunity (according to JP Morgan), excluding the research segment. This represents a significant growth opportunity for the

company as its product pipeline expands from initial research use to downstream clinical applications, which will be addressed by next-generation instruments. Three different generations are in the pipeline, but the timelines to commercialisation will depend on development progress and funding. Vortex has sufficient current funds to take it through the launch of VTX-1; on existing visibility, the second-generation technology may be on the market in the next two to three years.

Vortex's business model is akin to a razor/razor blade model whereby the instrument is sold at a small mark-up to cost, with profits made through the supply of the disposable microfluidic cartridges. Vortex's pricing strategy is in development, but current indications are that each instrument will cost $125-150k with a per-cartridge price of $250-350.

Timeline/future steps

The key milestone for the company will be direct commercial launch into the US and European clinical research market in 2017.

An algorithm called Wanda

Wanda is a digital health company that has developed a software platform for the management of patients with chronic disease. The Wanda application is an integrated solution to improve patient monitoring and provide behavioural modification and ultimately reduce hospitalisations. The company has developed applications to monitor patients for congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) and is currently developing an oncology monitoring application.

Wanda initially began commercialisation in 2015 with Triventis Health, a joint venture between NetScientific and the hospital operator Meridian Health, which was responsible for developing dedicated devices to use the platform. Sales expectations for the Triventis devices were not met, so a strategic decision was made to dissolve the collaboration, enabling Wanda to partner with multiple healthcare providers and device makers. The company has subsequently partnered with the home care company Health Resource Solutions to provide its CHF and COPD application and has a collaboration agreement with the hospital operator Dignity Health for the development and launch of the oncology application. Another commercial agreement has been recently signed, with additional new customers expected in 2016.

Investment and management

NetScientific has a 71.3% equity stake and as of 31 December 2015 it has invested £5.1m. Grant funding received to develop the underlying technology, prior to Wanda's formation, was £7.7m.

In September 2015, Steve Curd joined as CEO. He has over 20 years of operational experience in the digital health sector, most recently as the COO of NantHealth and previously as the CEO of CareInSync (merger with Zynx Health in 2014), CIO of UnitedHealth Group, COO of WebMD and CEO of VantageMed ($13m merger with Nightingale Informatix in 2007).

Technology overview

The Wanda application collects data from remote monitoring systems (RMS) and patient self-assessments on mobile devices to monitor disease progression and uses the company's proprietary analytics to predict disease risk. The project resulted from 12 years of clinical research into chronic disease management at UCLA. The information gathered is automatically leveraged by the application to provide behavioural modifications to the patient, as well as to inform the patient's physician care team should intervention be necessary. The ultimate goal of the application is to

reduce the number of hospitalizations by providing more timely feedback based on the patient's status.

The Wanda platform is versatile and, hypothetically, can be employed to monitor a wide variety of chronic diseases. The first module developed for the platform was for the monitoring of patients with CHF. The software integrates the patients' medical record information with regular blood pressure and weight measurements gathered wirelessly from Bluetooth-enabled devices, as well as self-reported symptom assessments. The system was previously tested utilizing a 1,500-person trial performed at UCLA. Wanda is currently developing a module for the prediction of complications associated with COPD. The company will provide the CHF and COPD modules as a combined application because of the comorbidity of these two diseases.

Market opportunity

The vast majority of medical expenses in the US are associated with the management of chronic disease. For heart failure alone, the annual costs to the healthcare system exceed $60bn.[1] Approximately 60% of these costs are associated with hospital visits, and preventing a single trip to the hospital can save the healthcare system $10,000 on average. Wanda's primary customers will be businesses interested in reducing the cost of care, namely healthcare providers and payers.

The deal to provide the CHF/COPD application to Health Resource Solutions is a useful model for understanding the potential structure of future agreements. Health Resource Solutions is a home nursing and support system providing services to approximately 1,000 patients per month in the Chicago area. The agreement would provide the application to patients at an upfront cost of $225 and $60 per month, with a target of 50 patients per month from this pool. Wanda will launch its second product, OncoVerse, for the monitoring of cancer patients in 2016. The company has already entered into an agreement with Dignity Health to launch the programme in more than 40 of Dignity's facilities.

The digital health market as a whole is poorly developed, with few to no market leaders, and highly fragmented due to low barriers to entry. There are a large number of companies in the immediate space of Wanda developing similar solutions for chronic disease management. These can be roughly subclassified into different groups based on their approach (Exhibit 7).

Exhibit 7: Selection of digital chronic disease management companies

Company	Approach
AMC Health	RPM, remote care
CloudMedX	Data, analytics
Flatiron Health	Data, analytics
Health Catalyst	Data
MD Revolution	Analytics, remote care, behaviour modification
MedeAnalytics	Data, analytics
Ornada	RPM, behaviour modification
SyTrue	Analytics, population health
Tactio	RPM, behaviour modification
Vital Connect	RPM, data
Viterion	RPM, population health
Vivify Health	RPM, population health, remote care
Wanda	Analytics, RPM, behaviour modification

Source: Various

Timeline/future steps

The company's current focus is expanding the number of patients using the Wanda system, because data gathered on these patients can subsequently be used to validate and improve the

[1] Voigt J, et al. (2014) A Reevaluation of the Costs of Heart Failure and Its Implications for Allocation of Health Resources in the United States. *Clin Cardiol.* 37(5), 312-321.

algorithm. The roll-out of the CHF/COPD application to Health Resource Solutions is ongoing, and the launch of OncoVerse is expected to initiate later in 2016. The current number of patients using Wanda is small due to the recent launches and revenue from the agreements has not been reported yet, but is expected to increase throughout 2016. The company has stated that it expects revenue from these two licences to be c $600,000.

Wanda's goal is to have 4,000 people using the system by end-2016. It intends to address this primarily through business-to-business deals with hospital systems and care providers by leveraging the cost-saving potential of the system. However, the company is also planning to initiate a direct-to-consumer campaign targeting early adopters, which we expect to raise the company's profile. The company will be expanding its offering with the introduction of new disease modules and the 2016 target is to enrol at least two new business clients using existing and new systems. The company hopes to have 15,000 registered users by the end of 2017.

ProAxsis: Advancing respiratory patient care

ProAxsis was founded in 2013 as a medical diagnostics spin-out of Queen's University Belfast in Northern Ireland. ProAxsis has developed proprietary molecules, called ProteaseTags, which selectively bind active proteases and can be used in a range of diagnostic and disease monitoring tools. The company produces a commercially available immunoassay for research use and is currently developing a PoC test called NEATstik for routine monitoring of neutrophil elastase. Neutrophil elastase is involved in chronic respiratory diseases such as cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) and is an established biomarker of infection and inflammation. Significant progress with the development of NEATstik was made in 2015 and, contingent on raising further funds in 2016, the company expects to be ready for EU commercialisation by mid-2017.

Investment and management

NetScientific's shareholding in ProAxsis is 56.5% and as at 31 December 2015 it had invested £0.1m. Grant funding received to develop the underlying technology, the majority of which was received prior to the formation of ProAxsis was £1.0m. ProAxsis has initiated a Series A fund-raising round seeking £7m, with closure anticipated H216. The cash will be used to complete NEATstik development and CE marking, to build a small commercial sales team in key EU markets and to fund a COPD clinical trial.

Recent management changes have included the appointment of Dr David Ribeiro as CEO in October 2015. He has previously held senior management roles at Solvay Healthcare, Encysive Pharmaceuticals, Pfizer and Pharmaxis Pharmaceuticals. In addition, Professor Brian Walker, one of the company co-founders has been confirmed as Chief Scientific Officer.

Technology overview

Active proteases ('molecular scissors') play a key role in many physiological processes and are considered important therapeutic targets, as well as being biomarkers of many diseases. They may be unregulated in diseases including cancer, heart disease, stroke, Alzheimer's disease, rheumatoid arthritis, multiple sclerosis, CF and COPD. Current assay systems for proteases utilise chromogenic or fluorogenic substrates, are often complex and may not be sufficiently specific to detect the active form of the enzyme. ProAxsis has developed novel and patented ProteaseTags to irreversibly inhibit/trap active proteases. Because they are designed to form a bridge to a solid support via covalent binding they can be combined with established diagnostic technology platforms such as ELISA, lateral flow or multi-analyte biochips.

ProAxsis's first ProteaseTag immunoassay kit was launched in August 2015 and is commercially available for research-only use, including academic labs and clinical research organisations involved in clinical trials. The kit measures active neutrophil elastase (NE), which is produced by white blood cells (neutrophils) in response to lung infections and is also a potential therapeutic target. Elastase destroys the elastic connective tissue that keeps the lungs supple, which results in permanent scarring. Clinical studies have shown that high neutrophil elastase levels are linked to deteriorating lung function (eg Sagel *et al* 2012). Sales in 2015 were modest, although the company expects them to grow as further pharma company customers are secured (following completion of internal validation testing). Beyond the NE kit, three further specific immunoassays are in development against different proteases targets, including those involved in pulmonary fibrosis, CF/COPD and Acute Respiratory Distress Syndrome.

ProAxsis is also developing a lateral flow device (NEATstik, Neutrophil Elastase Airways Test) for rapid, easy monitoring of NE levels in the clinic or home from sputum samples. It aims to be the first-to-market, PoC NE test. NE activity in respiratory diseases is responsible for significant airway damage and is a strong predictor of lung function decline. The goal is to detect increased NE levels earlier to reduce exacerbations and hospitalisation risk in patients with CF and COPD, and improve health outcomes.

Market opportunity

The chronic respiratory diseases CF and COPD are associated with frequent lung infections, irreversible tissue damage and lung function decline. There are 70,000 patients diagnosed with CF worldwide (30,000 patients in the US and Canada and c 40,000 elsewhere, mainly in Northern Europe) and 35.7 million patients with COPD in the US and EU. The treatment of lung diseases is estimated to cost the UK NHS £4.7bn a year and, according to NICE, "a reduction of 5% in COPD exacerbations would be expected to save the NHS £16 million per annum".

The target population for home testing is adult CF patients and moderate-severe COPD patients, 65% and 25% of whom respectively are 'natural sputum producers'. Even at a conservative price, assuming a 40% share of CF patients (testing weekly) and a 20% share of COPD patients (testing monthly), ProAxsis estimates the European CF/COPD home test market could be around £16.5m. The US market would probably be twice this, giving an estimated US/EU market of c $70m.

Timeline/future steps

Newsflow in 2016 should include an announcement of customers for the NE immunoassay, although the key triggers will be CE mark approval (Q416/Q117) and launch of the NEATstik device in Europe during 2017. Full development and commercialisation of the NEATstik PoC device requires additional funding, and ProAxsis is seeking an initial £7m through a Series A fund-raising.

Technical development of NEATstik is well advanced, with clinical validation ongoing and transfer to manufacture targeted for Q316. Focusing initially on Europe, the company is aiming for CE mark approval for general diagnostic use in clinics by healthcare professionals by the end of 2016, followed by separate CE marking of the commercially more valuable self-test home device in Q217. EU launch of the in-clinic device is anticipated Q117, with self-testing launch Q217.

New funds with enable ProAxsis to run a multi-centre, blinded, two-arm, prospective pan-European trial in 100-120 COPD patients, which will start in 2017. The trial will measure exacerbations over 12 months, with patients enrolled in the trial using the NEATstik to measure their NE levels. In one arm of the study, clinicians monitoring the patients will be able to use the NEATstik readings to inform their treatment interventions, while in the other arm clinicians will not have access to the NE readings, instead basing treatment decisions on only standard symptomatology.

Readout of the trial results in 2020 will provide clinical validation and, crucially, data to support potential healthcare utility claims relating to the reduction of exacerbations. This will be key for both marketing and reimbursement discussions.

In the US the NEATstik is classed as a medical device rather than in vitro diagnostic. The US commercialisation pathway is less clear. The COPD trial will also form part of the US regulatory application for NEATstik, although formal discussions with the FDA are yet to take place. However, the immunoassays could be sold in the US via accredited CLIA labs as a service without FDA approval. ProAxsis is seeking collaborators to assist in raising awareness in the US market and contributing to the KOL publication strategy.

Glycotest: Screening for liver disease

Glycotest is a US-based company developing a non-invasive diagnostic and monitoring test for early-stage liver disease based on proprietary blood-based biomarker panels and algorithms. Its lead product (HCC Panel) is a biomarker panel for curable early-stage hepatocellular carcinoma (HCC), the most common form of primary liver cancer. Liver disease is a large and growing market and current surveillance tests underdetect early-stage HCC. Glycotest's HCC Panel outperformed the alpha-fetoprotein (AFP) blood test, a commonly used screening test, in a 208-patient study. Using other biomarkers, Glycotest's approach could be extended to other liver diseases. Glycotest's commercialisation strategy in the US is to market HCC Panel as a laboratory service through a CLIA-accredited laboratory. Glycotest is seeking $10m Series A funding to complete clinical validation of the test, obtain CLIA lab status and launch HCC Panel by Q417.

Investment and management

Innovator grant funding received to develop Glycotest's underlying technology prior to Glycotest's formation was £5.9m ($8.9m). NetScientific has invested £1.2m and its current holding is 87.5%.

Larry Cohen was appointed CEO in December 2015. Larry has over 30 years' experience in the medical device and diagnostics industry and most recently was CEO of Exalenz Bioscience, a medical device start-up company for the diagnosis and management of gut and liver diseases. Before this he held executive positions at large diagnostic companies such as OrthoClinical Diagnostics (J&J), International Technidyne Corporation (Thoratec) and Beckman Instruments.

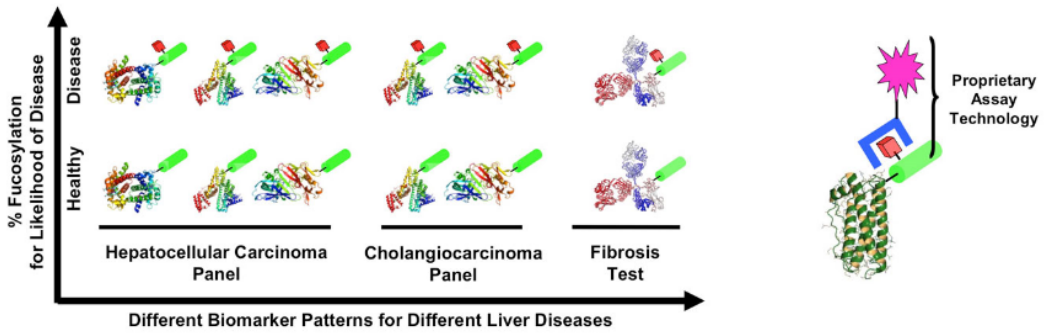
Technology overview

Glycotest was founded on technology developed at the Baruch S Blumberg Institute and Drexel University College of Medicine in Philadelphia. Diseased livers secrete a range of glycoproteins with fucose sugar modifications at abnormally high levels, and different diseases may have characteristically abnormal fucosylation patterns. Glycotest has licensed exclusive worldwide rights, with low royalties, to over 50 patented serum glycoprotein biomarkers that exhibit increased fucosylation in liver cancers. Glycotest also owns the rights to assay technology to quantify fucosylated glycoproteins using engineered lectins (sugar-binding molecules). The lectins can be conjugated to an immunoassay detection system for a convenient readout method. Glycotest's platform uses biomarkers, either singly or in panels, to measure both quantitative and qualitative disease signals. Its current patent portfolio consists of four families covering the use of novel fucosylated biomarkers, lectin assay technology, and biomarker panels. Three patents have been issued in the US, two in Australia and others are pending in commercially important regions, including China.

Glycotest has developed its proprietary HCC Panel test for six biomarkers that are elevated in HCC. The individual biomarkers have been evaluated in >800 patients and the HCC algorithm has been developed in thousands of patients. The technology can be extended to other liver diseases,

using a different array of validated biomarkers. Glycotest is also developing tests for cholangiocarcinoma and intermediate-stage liver fibrosis-cirrhosis (Exhibit 8).

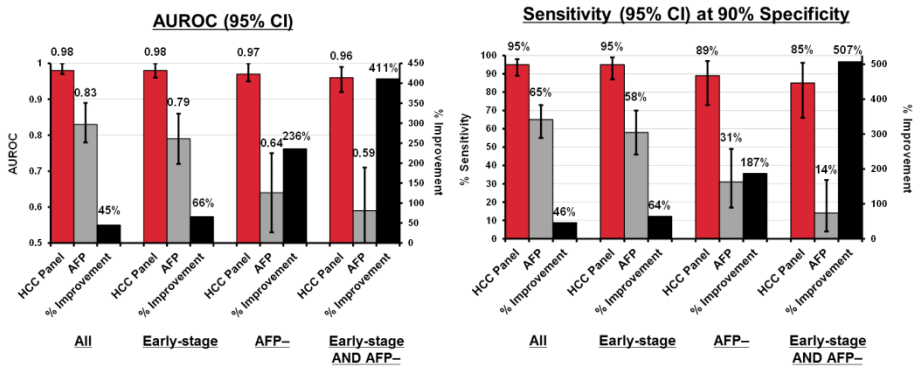
Exhibit 8: Glycotest biomarker panels



Source: Glycotest

Initial validation of HCC Panel is promising. In 2015, a preliminary head-to-head clinical study of the HCC Panel vs the standard blood test AFP was performed in 208 HCC and cirrhosis patients (Exhibit 9). HCC Panel significantly outperformed the AFP test (with an AUROC score, a measure of diagnostic performance, of 0.98 HCC vs 0.84 for AFP). Furthermore, HCC Panel was more effective than AFP in identifying patients with early-stage HCC (AUROC 0.98 vs 0.80) and much more effective at identifying AFP-negative patients (AUROC 0.97 vs. 0.64).

Exhibit 9: Performance superior to AFP for discrimination of early-stage and AFP-negative HCC from cirrhosis



Source: Glycotest

Market opportunity

HCC is the third leading cause of cancer-related death worldwide and the ninth leading cause in the US, with an increasing incidence. Globally, there are c 500k deaths due to HCC per year. Cirrhosis is a scarring of the liver resulting from liver disease and 5-30% of patients with cirrhosis go on to develop HCC. The predominant risk factors for cirrhosis (and therefore HCC) are chronic hepatitis C infection (26% of cirrhosis), hepatitis B infection (15%), as well as non-viral factors such as alcohol consumption (21%) and non-alcoholic fatty liver disease – NAFLD (18%), see Exhibit 10. NAFLD is linked to obesity (BMI >30) and is a growing problem affecting 30% of the US population. It can progress to nonalcoholic steatohepatitis (NASH), which has a 15-25% risk of cirrhosis. The prevalence of alcoholic steatohepatitis (ASH) is unknown, although it may be estimated from the prevalence of alcoholism (8% of the US population, one-third with ASH), which is still a major cause of liver disease in western countries.

Exhibit 10: Liver disease prevalence statistics

	US	Worldwide
Chronic hepatitis B	0.7-1.4m	c 350m (75% Asian)
Chronic hepatitis C	2.7-3.9m	c 180m
Fatty liver disease and NASH/ASH	>100m	>1.5bn
	(NAFLD occurs in c 30%, NASH in c 3%, ASH c 3% of population)	c 20% of population
Total at risk	**105m**	**2bn**
(included with above, population with cirrhosis)	633,000	50m (4.5-9.5% of adult population)

Source: American Liver Foundation, CDC, WHO

There is a clear medical need for an effective surveillance test to detect HCC at an early stage when it is potentially curable by surgery. The American Association for the Study of Liver Diseases (AASLD) recommends that high-risk patients undergo surveillance for HCC with ultrasound every 6 months. Current blood tests for HCC are cheap but insufficiently sensitive/specific. The commonly used AFP test is inadequate when used alone as AFP is secreted by less than 50% of tumours; so many high-risk patients are referred for abdominal ultrasound (AUS). However, AUS sensitivity (detection of true positives) is highly dependent on operator experience and is reportedly less accurate in obese patients. CT/MRI scans are potentially more sensitive, but are associated with increased cost and issues of radiation exposure, so are less widely used. Importantly, AUS has only a 60% sensitivity at identifying curable early-stage HCC.

Based on AASLD guidelines of HCC risk (for hepatitis B/C, ASH and NASH), we estimate that nearly three million patients in the US would be eligible for liver cancer surveillance. Assuming a 20% uptake, this gives a market projection of over $750m in the US assuming two tests per year and a cost per test of $660 (Glycotest data). We note that the average cost of abdominal ultrasonography plus AFP test is around $500. Whether this higher cost/test pricing is achievable remains to be seen and will presumably hinge on the ability of HCC Panel to demonstrate cost-benefit in detecting early-stage HCC. However, growth drivers are likely to come from an increasingly obese population (increasing fatty liver disease and NASH). We estimate the ex-US market potential to be >$3bn, assuming lower uptake (3% of eligible) by a much larger population and a lower cost per test ($300).

Glycotest's commercialisation strategy in the US is to market HCC Panel as a laboratory-developed test (LDT) service; blood samples will be sent by liver specialists to a centralised CLIA-accredited laboratory run by Glycotest. Laboratories testing human samples apply to the Centers for Medicare & Medicaid Services (CMS) for accreditation, which avoids the need for FDA approval for the test itself. Outside the US, Glycotest will seek strategic partnerships, especially for the large Asian liver disease markets.

Timeline/future steps

Glycotest aims to complete the commercial-grade manufacturing methods for its biomarker assays by Q316. In Q416 the company will seek $10m in Series A financing to support its commercialisation strategy, namely team expansion and opening the laboratory, collection of clinical samples (by Q317), complete analytical validation and algorithm training (H117) with the aim of completing clinical validation and obtaining CLIA status for the lab in Q317. Obtaining CLIA status for the lab is reliant on the Series A funding. Glycotest is planning a 500-patient clinical validation study to support its marketing strategy for HCC Panel and has identified investigators and sites. The HCC Panel launch is planned for Q417.

Reimbursement also depends on demonstrating clinical utility and Glycotest plans to seek Medicare coverage through Palmetto GBA's MolDx programme. Private payers are more likely to come on board once the test has Medicare coverage. Reimbursement submissions are expected in late 2018, for potential reimbursement approval in 2019.

Glucosense Diagnostics: Painless blood testing

Glucosense is a Leeds University spin-out that is developing a non-invasive continuous glucose sensor for self-monitoring of blood glucose as an alternative to finger-prick testing, which is an $8bn market. The company employs nano-engineered silica glass with a low-powered laser to provide real-time measurements of blood glucose within 30 seconds. It is developing two device modules: a small, portable device for intermittent measurements and a continuous monitoring wearable device with a hypoglycemia-alert. This could supplement or replace the current invasive/implantable devices. A small-scale validation in 12 patients was positive and Glucosense plans further optimisation in 2016. Assuming success in ongoing testing of the benchtop prototype device, and subsequent clinical trials, European commercial launch is possible in 2019.

Investment and management

As at 31 December 2015, NetScientific had invested £700k and its shareholding was 60.7%; Leeds University owns most of the remainder.

Following the retirement of David Gough at the end of 2015, Glucosense plans to appoint a new CEO following the next clinical evaluation. The timing of a new appointment is likely to depend on hitting forthcoming technical milestones. Mark Rosser, formerly of GE Healthcare, was appointed programme director in May 2015 and continues to lead the product development work for Glucosense.

Technology overview: A 21st century device

Glucosense's device uses proprietary photonics technology which, according to the company, is backed by strong IP. Various patent applications are in place. In July 2015, a key European patent covering the core technology of nano-engineered silica glass (photonic glass) containing ions that fluoresce when stimulated by a low-power laser was awarded. When the glass is in contact with the user's skin, the fluorescent signal varies according to the concentration of blood glucose, enabling a direct measurement of glucose levels in less than 30 seconds.

The current prototype is a desktop device for intermittent testing. A small trial in 12 Type 1 diabetics was run over eight hours comparing Glucosense to standard continuous monitoring and finger-prick testing. The data showed a clinical accuracy rate of 77% and a clinically acceptable accuracy rate of 96.5%, indicating that the device has the potential to be at least as accurate as current methods. Further device development and miniaturisation is underway (see Future steps).

Market opportunity for glucose testing

Diabetes is a growing global problem. Over 380 million people are estimated to have diabetes at a cost of $500bn to healthcare providers. By 2035, this number is expected to rise to nearly 600 million adults worldwide. Regular monitoring of glucose levels five to eight times daily is essential for Type I diabetics. Some 27% of Type 2 diabetics require insulin, so should test their glucose levels. This is most commonly done by finger pricking with a lancet – an uncomfortable and messy process. As a result, many people do not test themselves as often as they should.

With the rise in diabetes, the global blood sugar monitoring market could be worth more than $12bn by 2017, comprising predominantly of hand-held glucose meters and testing strips (GlobalData). The US self-monitoring blood glucose market is estimated to be over $4.2bn in 2016 (Frost & Sullivan), although generic competition and cuts in reimbursement by Medicare from $0.64/strip to $0.21/strip have put the testing strips market under pressure. The market leader is LifeScan (J&J, c 40% share); the rest of the market is dominated by Roche, Abbott and Bayer.

However, research has shown that trend data are more useful than snapshot (intermittent) monitoring in determining the long-term treatment regimen for diabetes. Several companies are

therefore investing in continuous monitoring technologies, as well as non-invasive methods of testing. In this competitive and evolving market, Glucosense's technology has the potential for both.

Exhibit 11: Self-monitoring of blood glucose (SMBG) for diabetes

Aspect	Notes
Types of diabetes	**Type I** diabetes is an autoimmune disease that destroys the insulin-producing cells. Patients do not produce insulin so have to test glucose many times a day and inject insulin. **Type 2** is a metabolic condition linked to obesity and excess carbohydrate in the diet. Patients become steadily unresponsive to their insulin. Eventually, insulin production fails and, like Type 1, they need insulin.
How many	In the US, there are about 1.3 million Type 1 diabetics and perhaps 13 million known Type 2 of whom 3.7 million use insulin (source: Dexcom). Note that there are believed to be many undiagnosed Type 2 cases, perhaps another 14 million.
Why monitor glucose?	Chronically high glucose levels over time cause multiple problems with circulation, eyesight and peripheral nerves. Acutely low levels result in rapid coma and death.
How accurate are the monitors?	Glucose is normally present in small amounts, about 5g in 8 litres of blood. Glucose meters for patient use are not required to be very accurate. The FDA standards are for ±20% accuracy at high levels (over 75 mg/dl) and ±15% at lower levels.
Cost of monitoring	Average $772 per patient (testing strips/supplies); approx cost per testing strip $0.98.(J Manag Care Pharm. 2012 Jan-Feb;18(1):21-32)

Source: Edison Investment Research

Continuous monitoring devices are available in the US and are used to complement finger-stick glucose strips tests. They are not reimbursed by Medicare, but are currently private or insurer-funded purchases. They use implanted sensors linked to external monitors, often with digital health functionality and server connectivity. New sensors last a few days and need regular calibration with glucose strips. For example, the Abbott FreeStyle Navigator II (not FDA approved, some EU sales) uses a sensor, inserted just under the skin, which lasts five days. Dexcom (a US continuous sensing company) has developed its G4 Platinum system with seven-day sensor life and gained FDA approval as a supplement to glucose strips in 2012. In 2014 Dexcom had direct sales of $257m (+ 63%). In April 2015 Dexcom announced a partnership with Google to develop cloud-connected, bandage-sized wearable, albeit not non-invasive, glucose sensors.

Invasive finger-stick testing currently complements the use of continuous monitoring devices; however, in the longer term, these may ultimately lose market share to continuous devices and could also be replaced by non-invasive devices. In view of the competitive oligopolistic nature of the market, a viable commercial route, in our view, is for Glucosense to partner (or be sold to) one of the three major glucose diagnostic players. Glucosense's partnering strategy may evolve as discussions progress, although current thinking is to find the optimal partner with the appropriate strengths for each device type in development.

Timeline/future steps

2015 saw the successful validation of the prototype benchtop device. Glucosense is currently optimising the optical components and working on miniaturising the sensor head technology so it can be used in two distinct forms of the device: a portable device for intermittent testing and a wearable continuous monitoring device. Candidate suppliers have been shortlisted for contract manufacturing of the glass, with supplier evaluations ongoing to select a preferred partner.

It is anticipated that testing of the benchtop device could produce a readout in end-June and end-December 2016, leading to the next clinical phase in H117. Further clinical studies are planned, but timelines will be driven by clinical results and are dependent on a fund-raising in Series A and B rounds. We expect that a CE mark could be gained by end-2018, with a possible commercial launch in Europe in 2019. We assume that FDA approval will need a full clinical validation under the stringent pre-market approval (PMA) route, and hence US launch will follow approximately 12 months later, contingent on the timing of clinical trials. Trial design and size will depend on the results obtained from prototype testing. The company plans to discuss the study design with the FDA to ensure all regulatory requirements for the US market are addressed.

The portable device will be an all-in-one device that collects, processes, stores and displays data, with a wireless connection for data transfer to PC/smartphone. The wearable device will consist of a sensor head to measure and collect the data, combined with a separate hand-held display and data

processing/storage unit. This could give continuous glucose readings and, as a non-invasive system, would have a major market advantage with potential clinical gains from better glucose control. The current strategy is to launch the portable device, with the wearable device following at a later stage. The precise timelines for the wearable version will depend on partnering progress and further funding requirements.

PDS Biotechnology: Cancer vaccines

PDS Biotechnology is a biopharmaceutical company focused on the development of novel cancer immunotherapies and vaccines for infectious diseases. PDS intends to initiate up to five or six Phase II clinical programmes in oncology in 2017. PDS's products are based on the company's proprietary and novel T-cell activating platform, Versamune. Three of the forthcoming Phase II trials will be run in collaboration with the US National Cancer Institute (NCI). One preclinical programme, which will feed into two or three additional Phase II clinical trials, is also in progress in collaboration with the NCI. Successful clinical trials and regulatory decisions will be followed by sales and marketing of the products, which the company may choose to undertake on its own or with a suitable marketing partner. A licensing deal has already been concluded with Merck KGaA; PDS is in discussions with other large pharma companies regarding clinical development partnerships.

Investment and management

PDS is one of the portfolio investments in which NetScientific has a minority position, and where the investment was made with an existing management team in place. As at 31st December 2015, NetScientific had invested £1.8m and held a 14.85% equity stake. In addition, it recently invested a further $500,000 via a convertible loan note instrument. The current CEO, Frank K Bedu-Addo PhD, was one of the founders of the company in 2006. PDS has a small core group of drug development scientists based at its New Jersey facility and multiple third-party collaborators (academic, government and industrial) who perform the testing and manufacturing of the products under development. Although the core strategy is to continue to operate as a semi-virtual company, PDS has recently strengthened its senior management team with the recruitment of a chief medical officer and VP of drug development and manufacturing.

Technology overview

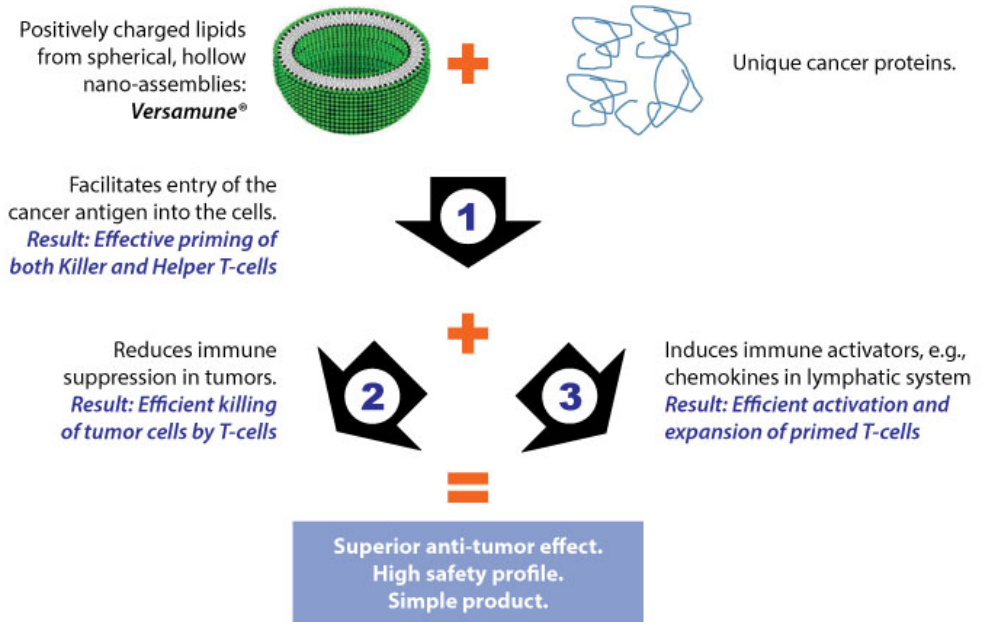
Versamune is a nanoparticle antigen technology based on the use of synthetic positively charged (cationic) lipids. The Versamune platform overcomes a major hurdle in immunotherapy by enabling the unique cancer proteins (antigens) to enter the cytoplasm of the immune dendritic cells directly. This leads to effective priming of tumour-specific killer (CD8+) T-cells to recognise and attack the tumours, leading to tumour cell death. The unique lipid used in the Versamune platform acts as a potent immune activator, which induced proliferation and activation of the primed T-cells.

In contrast to other cancer vaccines, the Versamune-based products are able to reduce the population of certain immune-suppressor cells that could inactivate T-cells. The ability to induce high levels of potent killer T-cells (tumour attack) while simultaneously reducing the number of immune-suppressor cells (tumour defence) allows the product to overcome immune suppression leading to high anti-tumour efficiency.

The Versamune technology platform has demonstrated a clean safety profile in humans and is the first synthetic immunotherapy demonstrated to activate all three critical mechanisms required for effective immunotherapy (Exhibit 12):

- delivery into the cytoplasm for effective antigen cross-presentation;
- potent immune activation; and
- reduction of the population of immune suppressive cells.

Exhibit 12: Versamune activates three critical mechanisms for additive immunological effect



Source: PDS Biotechnology

Market opportunity

The nature and potential advantages of the technology mean that PDS management sees Versamune-based products as having the ability to overcome significant shortcomings of existing immunotherapy approaches. Cancer vaccines have been sub-optimal in their ability to treat cancers largely due to their inability to facilitate antigen-cross presentation via the MHC Class I pathway to killer T-cells, which is compounded by inability to overcome tumour immuno-suppression. CAR T-cells and checkpoint inhibitors, due to their safety profiles, target the very late stage/terminal cancer patients; hence there is a clear therapeutic gap with earlier-stage cancer patients who may be the most treatable by immunotherapy. However, for such subjects a safer immunotherapeutic approach is needed. PDS0101's Phase I indicated strong T-cell potency and safety, which lends it to targeting early-stage cancer.

Limitations of the current approaches to immunotherapy have shifted the focus to combination immunotherapy. However, this brings additional challenges such as compounding of toxicity by combining two products with sub-optimal safety (potentially further restricting the target patient population) and the high cost associated with combining two (or more) expensive drugs (with additional implications for reimbursement), Due to their simplicity (low cost of goods) and indicative clinical profile (safety and potency shown in Phase I) the Versamune-based products have the potential to overcome such issues with the development of combinations with checkpoint inhibitors. In addition, the induction of antigen-specific T-cells shown in humans, coupled with the potential ability to reduce immune suppressor cell levels (eg regulatory T-cells – Tregs - and myeloid-derived suppressor cells [only shown preclinically to-date]) may allow for dose sparing of the checkpoint inhibitor, reducing toxicity and therefore potentially addressing a wider patient population.

Value could develop quickly though deals and licensing now that the PDS0101 Phase I has successfully completed; the clinical data show excellent safety and immunogenicity. Collectively, HPV16 is the cause of about 60% of cervical cancer cases in western markets. Adding an HPV18 candidate increases the coverage to about 75%. PDS has been given FDA approval to start Phase II studies. The studies are planned to start in early-2017and run until late 2019.

Phase II clinical trials for PDS0101 will be in (1) CIN and AIN 2/3 precancerous patients; (2) stage III cervical cancer patients; and (3) late-stage HPV-positive head and neck cancer in combination with a checkpoint inhibitor. Note that AIN/CIN 2/3 are now termed high-grade squamous intraepithelial lesion (HSIL). This type of lesion (CIN 3) is cured surgically, so patients in the proposed study may be at risk of cervical cancer. Most studies establish a therapeutic effect in low-grade squamous intraepithelial lesion (LSIL) patients. PDS management (based on commissioned independent market research) estimates a market for treatment of high-grade precancerous cervical, anal, vulvar and vaginal lesions of $1.1bn in the fifth year after launch, at a 40% market penetration in the US, EU and Japan. In addition, sales into metastatic anal, cervical and oropharyngeal cancer markets in the same geographies were estimated by PDS management at $180m, $430m and $330m respectively. The overall market is therefore potentially $2bn. Management is positioning PDS0101 as the first immunotherapy to provide the safety, cost and potency to potentially replace surgery as the first-line treatment for HSIL. It could also be applied to LSIL, where patients currently do not get treated due to the risk-benefit of surgery. Other projects, currently in Phase I in collaboration with the US National Cancer Institute, are in prostate, breast cancer and ovarian cancer.

Potential direct competitors would include cancer immunotherapy/infectious disease vaccine company, Bavarian Nordic, whose lead cancer programme, Prostvac, is currently in Phase III and is subject to an option with Bristol-Myers Squibb in return for a $60m upfront fee.

Annual growth in the global oncology drug and supportive care market is expected to be 7.5-10.5%, with the overall market reaching $150 billion by 2020. One unrelated estimate suggests that the global market for prostate cancer (the second most common type of cancer affecting American men) therapeutics alone may reach $8.2b by 2023. Breast cancer is the commonest form of malignancy diagnosed among women in the US and globally.

Timeline/future steps

PDS is on track to initiate multiple Phase II studies in HPV-related cervical cancer, head and neck cancer, and pre-cancerous lesions (the latter in collaboration with the National Cancer Institute) in the next 12 months. These trials are scheduled to run until late 2019, with an interim data readout in 2018. Phase III trials will normally take three years, so data in 2023 and approval in 2024-25 may be possible. Three projects in breast, prostate and ovarian cancer are planned to enter Phase II in mid- to late-2017 (once again in collaboration with the National Cancer Institute). The company will have to raise additional funds to progress the studies over this period.

Financials and valuation

NetScientific's FY15 post-tax loss was £12.7m (FY14: loss of £7.1m), which was primarily attributable to **continuing operations** (FY15: loss of £11.2m, FY14: loss of £6.2m) and reflected the ongoing investment into a portfolio of pre-commercialisation and therefore currently loss-making companies. Post-tax loss from **discontinued operations** was £1.5m (FY14: loss of £0.9m), which included the operating loss incurred by the 10 discontinued subsidiaries[2] subject to disposal during 2015, the share of loss from associates and JVs and a £0.3m net loss recorded on disposal.

Significant investment was made into the development of underlying technologies and products of the core portfolio companies, in particular Vortex and Wanda, as indicated by R&D spend of £7.3m in FY15 (FY14: £3.1m). General and admin costs for the year were £3.2m, which includes a significant proportion of subsidiary management by NetScientific executives; the increase on FY14

[2] Frontier Biosciences, MOF Technologies, Morphodyne, Qlida Diagnostics and RoboScientific were the principal disposals in FY15.

(£2.5m) was driven by increased sales and marketing costs and admin spend at the portfolio level. Headcount across the group also increased from 28 to 47, excluding non-executive directors. Exceptional costs of £0.9m (FY14: £0.7m) include redundancy and restructuring costs related to the strategic review and a non-recurring impairment charge related to Triventis. We forecast a significant rise in expenditure in FY16 to £15m (vs £10.4m), with R&D investment rising to £11m as portfolio assets progress towards commercialisation and potential value realisation events. Funds from the 2015 equity raise have been specifically earmarked to accelerate the development of Vortex and Wanda.

FY15 revenues of £78.6k were predominantly generated through the sale of ELISA kits to the research market by ProAxsis, an evaluation fee from a corporate booked by Glucosense and Vortex cartridge sales for research use of VTX-1 at universities. Our FY16 forecast includes further modest revenues generated from the sale of VTX-1 cartridges associated with KOL placements and ProAxsis research kits, as well as c £0.5m connected to Wanda functionality delivery. Exhibit 13 outlines historic financials and summary forecasts. Note that these forecasts do not reflect future fund-raising plans of the individual portfolio companies; as such, a c £6m funding shortfall in 2017e is included in the summary as £10m illustrative short-term debt.

Funding and structure

NetScientific had cash on the balance sheet of £23.2m at 31 December 2015 (FY14: £16.9m), which included the £17.1m net proceeds from the capital raise. Operating cash outflow for the year as reported by the company was £11.0m (FY14: £8.8m). At end-March 2016, cash stood at £19.5m.

At IPO, NetScientific issued 18.75m new shares at 160p to raise £30m gross, £28.6m net. Post the November 2015 placing (15.2m new shares at 120p to raise £18.2m gross), the three Azima Family Trusts representing the former CEO (Zahra, White Mustard and Cyrus) held 20.4% of the company's issued share capital; this has been reduced from 47.9% of the post-IPO equity. NetScientific's free float now stands at 16.2%.

Valuation

NetScientific presents a valuation dilemma. Portfolio value is the most important financial metric for investors; however, unlike other classic investment companies, NetScientific does not provide a portfolio NAV that could be compared with the company market cap. This reflects the relatively modest level of investment that the company has made into its portfolio companies, which has been leveraged by grant funding. However, NetScientific offers the potential for significant value creation from the maturation of its portfolio of equity holdings in digital health, diagnostics and therapeutics companies.

Typically, investment companies with quoted investments can be valued by the underlying asset value and compared to the market value to determine any discount or premium, with unquoted portfolio companies being valued per International Private Equity and Venture Capital Valuation guidelines. These guidelines allow a portfolio company to be valued at the last funding round, at cost for early-stage investments or at the director's discretion.

The NetScientific Capital Markets Day on 14 June should provide more information on the underlying portfolio companies and their forthcoming newsflow, allowing us to make an assessment of the intrinsic value of each. Additionally, with Series A rounds on the horizon for Wanda, ProAxsis and Glycotest, successful fund-raisings will not only provide growth capital, but also allow for an explicit fair value for these companies in NetScientific's future accounts. The evolution of the carrying value of NetScientific's portfolio as these assets approach commercialisation should drive an uplift in share price. Ultimately, however, NetScientific's investment case rests on the potential for significant value creation through realisation, ie exit through IPO or trade sale of its maturing

portfolio companies. An exit would enable the return of capital to shareholders and/or reinvestment into new pipeline opportunities.

Exhibit 13: Financial summary

£'000s	2014	2015	2016e	2017e
Year-ended December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Sales	0	79	696	3,359
Cost of Sales	0	(6)	(382)	(2,109)
Gross Profit	0	73	313	1,251
R&D	(3,098)	(7,256)	(11,000)	(11,000)
Other costs	(2,471)	(3,139)	(4,000)	(4,000)
EBITDA	(5,502)	(10,137)	(14,537)	(13,599)
Operating Profit (before amort. and except.)	(5,568)	(10,267)	(14,687)	(13,749)
Intangible Amortisation	(2)	(55)	0	0
Exceptionals	0	(906)	0	0
Share-based payments	(717)	(171)	(200)	(200)
Operating Profit	(6,286)	(11,399)	(14,887)	(13,949)
Net Interest	77	78	70	45
Profit Before Tax (norm)	(5,490)	(10,189)	(14,617)	(13,704)
Profit Before Tax (as reported)	(6,209)	(11,322)	(14,817)	(13,904)
Tax	30	94	89	83
Profit After Tax continuing operations (norm)	(5,526)	(10,226)	(14,678)	(13,771)
Profit After Tax continuing operations (as reported)	(6,179)	(11,228)	(14,728)	(13,821)
Loss from discontinued operations	(948)	(1,518)	0	0
Profit After Tax (norm)	(6,474)	(11,743)	(14,678)	(13,771)
Profit After Tax (as reported)	(7,127)	(12,746)	(14,728)	(13,821)
Average Number of Shares Outstanding (m)	35.9	38.2	51.1	51.1
EPS - normalised (p)	(13.4)	(21.8)	(25.0)	(22.9)
EPS - normalised and fully diluted (p)	(12.6)	(20.1)	(23.6)	(21.6)
EPS - (IFRS) (p)	(17.9)	(28.4)	(25.1)	(23.0)
Dividend per share (p)	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	91.8	45.0	37.2
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	3,040	2,946	3,593	3,893
Intangible Assets	10	1	1	1
Tangible Assets	348	285	585	885
Investments	2,681	2,660	3,007	3,007
Current Assets	17,720	23,799	8,932	5,261
Stocks	0	0	0	350
Debtors	853	560	560	520
Cash	16,867	23,239	8,372	4,391
Other	0	0	0	0
Current Liabilities	(1,324)	(2,206)	(2,306)	(12,306)
Creditors	(1,281)	(2,156)	(2,156)	(2,156)
Short term borrowings	(43)	(50)	(150)	(10,150)
Long Term Liabilities	(740)	0	0	0
Long term borrowings	(687)	0	0	0
Other long term liabilities	(53)	0	0	0
Net Assets	18,696	24,538	10,219	(3,153)
CASH FLOW				
Operating Cash Flow	(3,679)	(6,697)	(10,752)	(14,607)
Net Interest	67	38	70	45
Tax	19	83	85	85
Capex	(337)	(136)	(450)	(450)
Acquisitions/disposals	(273)	(34)	(100)	0
Financing	0	17,147	0	0
Dividends	0	0	0	0
Net Cash Flow	(7,170)	7,297	(15,002)	(14,004)
Opening net debt/(cash)	(25,069)	(16,137)	(23,189)	(8,222)
HP finance leases initiated	0	0	0	0
Other	(1,762)	(245)	35	23
Closing net debt/(cash)	(16,137)	(23,189)	(8,222)	5,759

Source: Edison Investment Research, NetScientific accounts

Contact details	Revenue by geography
NetScientific 30 St Mary Axe London – EC3A 8BF United Kingdom Tel: +44 (0)20 3514 1800 http://netscientific.net/	N/A

Management team

CEO: Dr François Martelet	Chairman: Sir Richard Sykes
François Martelet, chief executive officer, joined NetScientific in 2015. He was previously a senior advisor to the CEO at Stallergenes. Before this, he was CEO at Topotarget, and prior to that CEO of Avax Technologies. He has also held senior-level commercial positions at Merck, Novartis Pharma, Schering-Plough and Eli Lilly. François gained a doctorate in medicine and a Master's degree in Business from Dijon University, and holds a degree in Legal Medicine from R Descartes University School of Medicine, Paris. He is a graduate of the Advanced General Management Programme at INSEAD.	Sir Richard was CEO of GlaxoSmithKline from 1995 to 2000 and chairman until 2002. He was rector of Imperial College from 2000 to 2008. He has held a number of directorships since 2002 and became the chairman of NetScientific in 2013. He holds a BSc in microbiology from London University and a PhD in microbial metabolism from Bristol University.
CFO (elect): Ian Postlethwaite	**CIO: Vijay Barathan**
Ian Posthethwaite was FD of Allergy Therapeutics from 2002 to 2016. He is a former director of Ellerman Investments, CEO of AFS, FD of several start-up technology companies and held senior finance positions with Ericsson and Philips Electronics. He is a qualified accountant and a Fellow of the Association of Chartered Certified Accountants. Ian has a BSc (Hons) in geological sciences from Aston University.	Vijay Barathan joined NetScientific in January 2014 to lead corporate development and investments, before being appointed as CIO in July 2015. He previously worked in healthcare investment banking at Peel Hunt and Piper Jaffray, and as a medical doctor. He has advised numerous UK listed healthcare companies in medtech, digital health, diagnostics and biotech, completing IPO, M&A and fund-raising deals. He holds a degree in Medicine and a BSc in Developmental Neurobiology from Guy's, King's and St. Thomas' Medical School in London.

Principal shareholders	(%)
Woodford Investment Management	45.1
Invesco Asset Management	18.1
Zahra Holdings	11.7
JO Hambro	9.2
White Mustard Investments	6.2

Companies named in this report

Vortex; Wanda; ProAxsis; Glycotest; Glucosense; PDS Biotechnology