EDISON

Angle

Data from ovarian cancer studies in Q217

H117 results and company outlook

Pharma & biotech

Angle's H117 business update revealed that R&D activities are progressing well, while the company booked further research use sales. The first prospective clinical studies with Angle's liquid biopsy system Parsortix in ovarian cancer reported positive early evaluation results and are due to report headline data in Q217. Our SOTP-based valuation is increased modestly to £140.3m or 188p/share. The main 2017 catalysts are the results from the ovarian cancer studies; an acceleration of research use sales; any new data from Angle's multiple KOLs and customers investigating Parsortix; and progress with the FDA analytical and clinical studies.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
04/15	0.00	(3.55)	(7.50)	0.0	N/A	N/A
04/16	0.36	(5.03)	(7.97)	0.0	N/A	N/A
04/17e	1.09	(7.71)	(10.24)	0.0	N/A	N/A
04/18e	3.62	(5.23)	(6.67)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of intangibles, exceptional items.

Positive early evaluation in ovarian cancer studies

Currently two clinical studies (n=200 each) are running in parallel in Europe and the US. They aim to explore Parsortix's efficacy in triaging women with ovarian masses before surgery to determine whether the tumour is benign or malignant, allowing for appropriate intervention. On 26 January 2017, Angle announced a positive interim evaluation of the ovarian cancer studies after the first 50 patients were enrolled in each trial. Headline results from both studies are expected in Q217. The trials are based on the work of Angle's partners at the Medical University of Vienna, which in 2015 reported from a small trial "unprecedented sensitivity and specificity" of the use of Parsortix for ovarian cancer detection, with reported sensitivity of 80% using seven RNA markers and 100% using 30 markers, while specificity was 100% in both cases.

Research use sales – a commercial milestone

Angle initiated research use sales with £361k and £219k booked in H216 and H117 respectively. While small numbers in absolute terms, these represent a commercial milestone and in line with the company's strategy of research use sales being a near-term goal, while clinical use provides the largest potential. Notably, the contract signed with the Cancer Research UK (CRUK) Manchester Institute in May 2016 indicates a potential boost to research use sales in the near term.

Valuation: Increased to £140.3m or 188p/share

We value Angle at £140.3m or 188p/share, up from £129.6m or 173p, as rolling our model forward was partially offset by the lower net cash position, while our long-term clinical use sales were revised upwards after positive early evaluation of ovarian cancer studies. The main catalysts in 2017 are full results from the ovarian cancer studies, expected pick-up of research use sales, any new data from Angle's KOLs and customers investigating Parsortix and progress with the FDA analytical and clinical studies.

14 February 2017

Price	**50.50p**
Market cap	**£38m**

Net cash (£m) at end-October 2016	9.7
Shares in issue	74.8m
Free float	90%
Code	AGL
Primary exchange	AIM
Secondary exchange	OTC QX

Share price performance

%	1m	3m	12m
Abs	2.5	(14.4)	(15.1)
Rel (local)	2.8	(20.8)	(32.9)
52-week high/low		78.5p	47.8p

Business description

Angle is a specialist diagnostics company. The proprietary Parsortix cell separation platform can be used for detecting and harvesting very rare circulating tumour cells from blood samples. The resulting liquid biopsy enables the analysis of these cells for precision cancer care. Angle has identified ovarian cancer, prostate cancer and metastatic breast cancer as the most likely indications.

Next events

Pilot KOL data in cancer indications	H117
Headline results from ovarian cancer clinical trials	Q217
H217 results	July 2017

Analysts

Jonas Peciulis +44 (0)20 3077 5728

Lala Gregorek +44 (0)20 3681 2527

healthcare@edisongroup.com

Edison profile page

Investment summary

Company description: Liquid biopsy for CTCs

Angle is a diagnostics business focused on the proprietary cell separation system, Parsortix, which can be used to capture and harvest very rare CTCs from blood for analysis, including cancer and foetal cells. The product has been launched for the research market, where it is generating the first research use sales, and is being investigated in two large prospective ovarian cancer studies. Parsortix has CE mark regulatory approval for the clinical market in Europe and Angle is working on an updated submission to the FDA for the approval in the US. The company is listed on the London Stock Exchange and trades on the AIM market. The company has also established a Level 1 ADR programme in the US, which is traded on the OTCQX market. Since its IPO in 2004, Angle has raised c £39.6m, including £9.6m (net) from an equity raise in May 2016. Angle is headquartered in Guildford, England and employs 34 people.

Financials

In H117 Angle's research use sales were £219k versus £361k in H216 (£0 in H116). We keep our sales estimates of £1.1m and £3.6m of FY17 and FY18 respectively, but note that while the company has a strong prospects list for H217, given budgets are often tied to calendar year-ends, there is also a risk that customer evaluations could take longer than expected. After the positive early evaluation of ovarian cancer studies, we upped our expected clinical use market penetration from 20% to 25%. Angle's total operating spend in H117 was £3.1m compared to a total of £5.7m in FY16. We keep our forecast of operating costs increasing to £9.2m in FY17 due to an increase in R&D activities primarily related to key clinical studies, although we note that if the FDA approval process takes longer than expected costs may roll over into the following year. End-October 2016 cash (no debt) was £9.7m, boosted by the £9.6m net equity raise in May 2016.

Valuation: Upped to £140.3m or 188p/share

We value Angle at £140.3m or 188p/share, based on an SOTP approach. Rolling our model forward was partially offset by the slightly lower net cash position, while our long term clinical use sales were revised upwards after the positive early evaluation of the ovarian cancer studies. Our SOTP valuation includes a DCF model for Angle's core operations running the organisation, research use sales and ovarian cancer application. We have already included two additional applications after Angle provided more details about the use of Parsortix for prostate cancer and metastatic breast cancer.

Sensitivities: Diagnostics R&D and commercialisation

As a new technology in a fast-emerging market, Angle's greatest challenge will be communicating and convincing customers of the advantages of Parsortix, to ensure widespread adoption and achieve sales forecasts. The diagnostics field is highly competitive, with a number of large companies able to apply significant resources to promotion and commercialisation activities. In addition, as CTCs are an emerging technology, adoption may be slow and market penetration may be limited. Key to widespread adoption of Parsortix in the clinical markets, and therefore substantial sales, is the continued positive evaluations of the system and demonstration of its clinical utility by KOLs and the data from the initiated prospective clinical studies. Any delays or negative decisions by the FDA will affect estimated timelines and clinical sales in the US, so will have an impact on our valuation as the US market is likely to be key. Angle is reliant on external manufacturers to maintain GMP standards, scale and continuity of production, and to maintain current margins. As sales rise and demand increases, we would anticipate dual sourcing and strategic stocks to mitigate the risk of supply interruptions.

Outlook: Clinical data and research use sales in 2017

Angle is a specialist medical diagnostic company, with a focus on cancer diagnostics. The proprietary Parsortix cell separation system is able to capture CTCs, which are outnumbered by healthy blood cells by over one billion to one. The capture of CTCs from a blood sample could potentially negate the need for further invasive biopsies and allow the patient's cancer treatment to be tailored toward the specific mutations of their tumour, thus fulfilling the objectives of precision medicine. The development of precision (or personalised) medicine providing 'the right patient with the right drug, at the right dose, at the right time' is a core mission for the FDA and governments worldwide. In addition, CTCs have potential for use in screening tests, and as an aid to decision making. Angle has recognised that to secure widespread use of the Parsortix system in the diagnosis and treatment of cancer, endorsement of its medical utility must be provided by KOLs. Parsortix has been evaluated by multiple KOLs and a number of endorsements and its competitive advantages have already been reported, particularly its ability to capture different types of CTCs, its applicability to multiple cancer types, the easy harvesting and high purity of captured cells.

The landscape of cancer care is shifting from non-specific cytotoxic drugs to targeted and immunotherapy approaches that promise to improve treatment efficacy and reduce toxicity. Increasingly, treatment decisions will be based on the molecular abnormality profile of a tumour, gained through analysis of the patient's cancer cells, to predict the patient response to these therapies. Angle's Parsortix system offers the potential for the harvesting of these cells for analysis from a simple blood test (liquid biopsy).

Headline data from ovarian cancer studies due in Q217

2017 could be a transformational year for Angle, with the data from the first clinical trial in ovarian cancer due any time now. As announced in July 2016, the first patients were recruited into two clinical studies that are running in parallel in the US and Europe and explore Parsortix's efficacy in triaging women with ovarian masses before surgery (looking at whether the tumour is benign or malignant to estimate the extent of the necessary surgery). Both studies seek to recruit 200 patients. In Europe, blood samples from the first half of the patients will be used as training to optimise the use of RNA markers for malignancy, which were identified during the successful pilot trial at the Medical University of Vienna. The blood samples from the rest of the patients will be used for verification. The design of the US study is slightly different and will also evaluate clinical information (eg demographics, imaging results, etc) for the estimation of the risk of malignancy.

On 26 January 2017 Angle announced positive interim evaluation of ovarian cancer clinical studies after the first 50 patients were enrolled in each of the trials. The purpose of this evaluation was to optimise the set of RNA markers, which would allow for maximum accuracy with a minimal required number of RNA markers. Although only minimal details were released, the company indicated that the early evaluation from both clinical trials suggests researchers are able to accurately differentiate between women with a malignant pelvic mass and those with benign tumours. In addition, Angle revealed that the European study is over 95% enrolled and expected to be completed in February 2017. This is slightly behind schedule due to a slower than expected recruitment rate. The patient recruitment into the US study is ahead of plan and now 70% enrolled, with the goal of completion in April 2017. Headline results from both studies are expected in Q217.

Breakthrough ovarian cancer pilot data from Vienna

Of the three potential clinical applications, using Parsortix for triaging women with ovarian masses before surgery is the most advanced. In January 2015, the Medical University of Vienna reported the results of a patient study supporting the use of Parsortix for ovarian cancer detection, demonstrating "unprecedented sensitivity and specificity". Parsortix-harvested CTCs were analysed

for CTC-specific RNA markers. The results indicated sensitivity[1] of 90% for primary epithelial ovarian cancer (which constitutes 90% of ovarian cancers), and a specificity of 100%. Previous CTC enrichment technologies used by the university (including many technologies listed in Exhibit 2) had been limited by high levels of white blood cell contamination, with just 24.5% the best sensitivity achieved.

In April 2015, the results of the extended study (n=65, which also included endometrial [n=5], cervical [n=6] and breast [n=7] cancers) were presented at the American Association for Cancer Research. Analysis of seven RNA markers again demonstrated 100% specificity. The sensitivity for ovarian cancer was 80%. The sensitivity for metastatic breast cancer was 71% (versus 40% for the standard CTC diagnostic approach). As part of the study, 13 patient samples were reanalysed using 30 RNA markers, resulting in an improved sensitivity, with a 92% average across all cancer types and 100% sensitivity for the seven ovarian cancer patients.

Unmet need in the management of ovarian masses

The American Cancer Society estimates that there were 21,000 new diagnoses of ovarian cancer in the US in 2015. Of the c 200,000 surgeries performed on pelvic masses each year, 11% could be ovarian cancer. In 2012, c 239,000 women worldwide were diagnosed with ovarian cancer (65,600 in Europe; source: Cancer Research UK). As there are limited symptoms in the early stages, the cancer is often at an advanced stage at diagnosis. For those with Stage III or Stage IV at diagnosis, five-year survival rates are just 19% and 3% respectively, whereas for Stage I it is 90%. Hence, there is a strong need for early diagnosis.

Patients with very early stage ovarian cancer benefit from the removal of the mass intact, since opening the mass results in a more advanced stage (through dissemination), adversely effecting prognosis.[2] Thus, it is essential that an appropriate surgical approach is used and the procedure is performed by a gynaecological oncologist. In advanced disease, surgery performed by a gynaecological oncologist resulted in a six- to nine-month median survival benefit.[2] Success in the study could lead to the use of Parsortix to identify patients at high risk of ovarian cancer, aiding surgical management decisions, which can be critical to the patient's prognosis. Going one step further, future upside in ovarian cancer could come from the expansion of Parsortix use for diagnosis, screening in high risk patients, treatment stratification and monitoring and remission surveillance. However, these applications will likely require additional data.

The best-studied serum biomarker for ovarian cancer, CA-125, is elevated in c 85% of women with advanced ovarian cancer but its sensitivity is only c 50% in early-stage disease and the specificity is poor, meaning that serum levels are raised in a number of benign conditions and other cancers.[3] The FDA-approved OVA1 (Vermillion) is a blood test and software algorithm used to evaluate ovarian masses for malignancy before surgery. OVA1 has a sensitivity of c 95% but a specificity of just c 40%, resulting in a significant level of false positives which results in women often 'over-diagnosed' leading to 'over-preparation' for the surgery.

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1 Sensitivity: the ability to correctly detect patients who have a disease (ability to avoid false negatives). Specificity: the ability to correctly classify an individual as disease-free (ability to avoid false positives).

2 Michael G Muto. 2014. Management of an adnexal mass. Available at: http://www.uptodate.com/contents/management-of-an-adnexal-mass

3 Fritsche HA, et al. (1998). CA-125 in ovarian cancer: advances and controversy. Clinical Chemistry. 44(7):1379-1380.

Liquid biopsy and circulating tumour cells

The current 'gold standard' procedure for obtaining information about a tumour is a solid biopsy. However, this is not without limitations, including:

- The primary tumour is not always easily accessible, for example a brain tumour. Even when it is, the invasive procedure is often painful and carries risk of infection and bleeding.
- Continual monitoring of tumour evolution is hampered once the primary tumour has been removed, with metastatic disease sites often difficult to access.
- Single-site biopsy may not provide a complete genomic landscape of the tumour due to intra-tumour heterogeneity, with anatomically distinct areas within a primary tumour, and the metastases, exhibiting clear differences in genomic architecture.[4] For instance, in breast cancer, where HER2 status guides therapy, overt distant metastases and CTCs are found to have discordant HER2 statuses compared with the primary tumour in up to 30% of cases.[5]

CTCs are cells that have been shed from a solid tumour into the vasculature. They can be found even in patients with no overt evidence of metastasis and in whom the primary tumour has been completely removed. This population of cells includes viable tumour cells capable of initiating metastasis and the presence and quantity of CTCs has been shown to be indicative of patient prognosis in a number of cancers.[6] CTCs also hold valuable information about the tumour, including the genetic mutations that drive the tumour's growth and resistance mechanisms, the very information that makes each tumour unique. Thus, CTCs could serve an important role in putting precision medicine into practice, namely in diagnosis, treatment stratification on the basis of molecular characterisation, real-time monitoring of treatment efficacy and remission surveillance.[6]

In addition to the information they can provide, the appeal of CTCs is that they can be harvested from a peripheral blood sample, or liquid biopsy, which is significantly less invasive and better suited for serial sampling. However, CTCs are extremely rare with estimates of just one CTC per 10^7 white blood cells per millilitre of blood.[6] Therefore, their detection and capture is not straightforward.

CellSearch is the only FDA-approved CTC capturing device approved for CTC enumeration in breast, prostate and colon cancers. It isolates CTCs using magnetic particles coated with antibodies that bind to a cell surface marker called anti-epithelial cell adhesion molecule (EpCAM). Once extracted, CTCs are enumerated and their concentration has been proven to have prognostic value for progression-free survival and overall survival in primary and metastatic disease of patients. However, CTCs are heterogeneous and may express fewer cell surface markers, like EpCAM, in a process called epithelial-to-mesenchymal transition (EMT). The exact process of metastasis is still unclear, but emerging data in this field point to EMT transition being involved. EMT is the process in which malignant epithelial cells gain migratory and invasive properties.[2] Due to EMT, circulating tumour cells may express fewer cell surface markers, like EpCAM. Also many cancers have weak epithelial expression, such as ovarian. Therefore, antibody-based systems, such as CellSearch, which are limited to detecting epithelial markers may fail to capture key subsets of CTCs, which are of particular clinical relevance.

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4 Mahoney KM, et al. (2015) The next immune checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. Clin. Ther. 37(4):764-782.

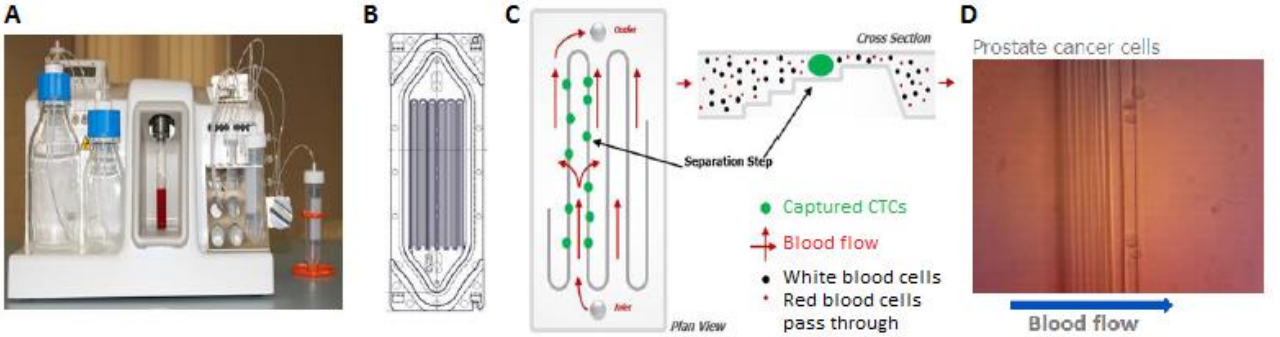
5 Alix-Panabières et al. (2014) Challenges in circulating tumour cell research. Nat. Rev. Cancer. 14(9):623-631.

6 Krebs MG, et al. (2014) Molecular analysis of circulating tumour cells – biology and biomarkers. Nat. Rev. Clin. Oncol. 11:129-144.

Parsortix solution

Angle's Parsortix system is a platform technology for harvesting rare cells from blood. The system uses a patented step-based microfluidic technology in the form of a disposable cassette, to capture and harvest the CTCs. The system processes the patient blood sample (volumes of <1ml up to 50ml) through the cassette, taking 60 to 90 minutes per standard 10ml sample. Based on their morphology, namely that they are less deformable and larger than other blood components, CTCs are caught in the cassette while the other blood components are able to pass through. The CTCs can then either be fixed and stained in the cassette for identification and enumeration, or can be harvested from the cassette to allow for external staining, genetic analysis and culture, Exhibit 1.

Exhibit 1: Parsortix system overview



Source: Angle. Note: (A) The Parsortix system. (B) Diagram of the disposable isolation cassette. (C) Isolation principle inside the cassette. (D) Captured prostate cancer cells. The lines are the Parsortix cell separation steps.

The Parsortix system, comprising a desktop machine and one-time use consumables, can be purchased for use on site alongside existing analysis platforms. In contrast, many of the competitor systems are so complex that the sample must be sent to a CLIA certified laboratory for processing. This has commercial downsides as it requires large in-house investment, is less scalable and deprives the hospital of the reimbursement, which instead goes to the external laboratory. The Parsortix system has potential to offer a number of advantages over other CTC enrichment technologies, particularly antibody-based approaches. These include the low cost and simplicity of the capture process, and the high purity of harvested cells, with minimal white blood cell contamination. In addition, the Parsortix system offers three important advantages:

- It is marker-independent and therefore is not limited by cell marker bias. It is able to capture multiple CTC types, including mesenchymal CTCs. Antibody-based approaches, including CellSearch (Janssen Diagnostics), the only FDA-approved system for CTC detection, rely on cell surface markers to select CTCs, often with an epithelial phenotype. As a result, these approaches are limited to certain types of CTCs and cancers. Furthermore, this approach may result in false negatives in cases where the cancer cells have undergone an EMT transition that results in reduced expression of the target markers. This is particularly important, as EMT cells have been implicated in the process of cancer metastasis.[6]
- Many of the other approaches have limited potential for the easy harvesting of CTCs, thus preventing genome analysis (CellSearch's approval is limited to enumeration for prognostic purposes). A possible alternative is cell-free DNA (cfDNA), which is released as fragments from necrotic and apoptotic tumour cells, and can be detected from blood plasma for analysis using next generation sequencing. However, the analysis is limited to DNA only, whereas CTCs allow for analysis at the DNA, RNA and protein levels, providing more information.
- CTCs harvested using Parsortix are not subject to antibody binding or other chemical reactions. In some of the pilot trials captured CTCs have been found to be viable after harvesting; in contrast, many of the antibody-based systems lead to damage to, or death of, the cell, which can limit detailed analysis. A number of Angle's collaborators are now investigating the potential

to culture the CTCs, which could allow for the testing of proposed treatments prior to patient administration.

There a number of CTC detection systems in development. Exhibit 2 lists a selection of these.

Exhibit 2: 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	Anti-EpCAM antibody-coated functionalised medical wire which is placed directly into the antecubital vein for 30 minutes 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 (ADnaGen AG)	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.
MagSweeper (Illumina)	Validation	Enriches CTCs using a magnetic rod stirred through a blood sample pre-labelled with anti-EpCAM antibody-coated magnetic beads. In one study mean capture of spiked cells was 81%, also able to isolate viable CTCs with high purity. Limited to epithelial CTCs.
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.
CTC-iChip (Veridex-partnered)	Prototype	Magnetic bead capture of WBCs combined with microfluidic inertial focusing to isolate CTCs. Not limited to epithelial CTCs and cells are viable after capture, however purity is reported to be low as a result of WBC contamination
Lung and breast cancer offering (Biocept)	Lab-run test	Dual platform of proprietary antibody-based enrichment technique and cfDNA capture. The latter is also innovative with an extra sample preparation step that ensures almost all the DNA it sequences comes from the mutant cells shed by tumours. Enriched CTCs can be checked for certain surface biomarkers.
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 (RareCell 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.
Centrifugation and Vortex flows		
DeanFlow Fractionation	Prototype	Size-based selection using centrifugal force. Reported recovery of CTCs >85% with high purity. High throughput, no issues with clogging. Captured CTCs are easily harvested for further analysis and are viable.
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.
Vortex Biosciences (NetScientific)	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.
Microfluidic		
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. See text for further details.

Source: Edison Investment Research., company websites. Note: Published data is 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.

Potential in prostate and metastatic breast cancers

Over the course of 2016, Angle released more KOL initiated pilot data, which led Angle to add two additional clinical applications in its further R&D pipeline: prostate cancer and metastatic breast cancer. Breakthrough pilot data for prostate cancer was gathered by Angle's KOL partner Barts Cancer Institute (BCI) and by the University of Southern California (USC) Norris Comprehensive Cancer Center for metastatic breast cancer.

Barts Cancer Institute and prostate cancer

In September 2015, the BCI published the results of a pilot study in which it evaluated the Parsortix system for CTC harvest in prostate cancer. The study compared Parsortix to CellSearch and to IsoFlux, another antibody-coated magnetic bead-based CTC isolation system that relies on cell surface markers to select CTCs. The study included only 19 prostate cancer patients and 17

healthy controls, therefore statistical interpretation is limited; however, the trends and conclusions were as follows:

- The investigators highlighted the **ease and speed of use** of the Parsortix system.
- **Higher purity and comparable capture in matched patient samples.** In spiked samples, capture and harvest rates by Parsortix were comparable to reported recovery rates by CellSearch, but lower than those of IsoFlux. However, in matched patient samples, the Parsortix system harvested comparable numbers of CTCs to IsoFlux, and significantly more than CellSearch, and the purity of the CTC harvest was significantly higher using Parsortix than IsoFlux. White blood cell contamination can make downstream CTC analysis very difficult.
- **Parsortix harvested a range of CTC phenotypes, including mesenchymal cells and cell clusters.** Like mesenchymal CTCs, CTC clusters are reported to have increased metastatic potential, and to be more resistant to apoptosis and correlated with poorer prognosis.[7]
- **Parsortix-captured CTCs were found to be undamaged and viable**. Capture of viable cells not only allows for detailed analysis, but could also enable the culture of the cancer cells. In contrast, the use of magnetic beads for capture can lead to damage to, or death of the cell, which can limit detailed analysis and impede culture. In the future, culturing a patient's cancer could eventually allow for the testing of proposed treatments prior to patient administration.

Furthermore, in March 2016, Angle announced that the BCI presented additional data from the prostate cancer pilot study with 52 patients. The final data are yet to be published, but headline results indicated that Parsortix could potentially perform as well as or better than current standard of care in terms of detecting early-stage prostate cancer and assessing its severity, and can do so with a simple blood test. This prompted Angle to select prostate cancer as a second clinical application to be explored in clinical studies. The main conclusions included:

- **Parsortix detected CTCs in 100% of the metastatic prostate cancer patients**.
- Parsortix was able to harvest **CTCs in 75% of men with the early stage of the disease**, although for these patients it was deemed that an intervention was not necessary (active surveillance only).
- There was a **good correlation between the number of mesenchymal CTCs harvested by Parsortix and the Gleason scores** suggesting that Parsortix may be able to provide the same or similar information as the biopsy in assessing the aggressiveness of the cancer. Gleason score is one of the most established indicators of prognosis for prostate cancer patients. It is calculated based on the histological findings after solid biopsy.
- Finally, the results suggest that **Parsortix may be able to indicate the progressive metastatic or localised status of the disease with a higher level of accuracy than the Gleason score**, which is the established method for determining the aggressiveness of the cancer, but requires an invasive solid biopsy. In November 2016, at the National Cancer Research Institute (NCRI) annual conference, the BCI provided more data on this topic using 80 samples from men with prostate cancer. When compared to epithelial CTCs or EMT, mesenchymal CTCs performed the best in correlation with serum PSA (most widely used prostate cancer biomarker) level and Gleason score and were an independent risk factor for overall survival in prostate cancer patients with progressive disease.

Many prostate cancer patients have low-risk disease and are on "watchful waiting" and the disease may not necessarily progress to advanced cancer. Historically, often false positive screening and fear of incurable and unpredictable metastasis led to overtreatment of localised disease and

[7] Xu L, et al. (2015). Optimisation and evaluation of a novel size-based circulating tumour cell isolation system. PLoS One. 10(9):e0138032.

avoidable harm to patients. Therefore, better prediction and knowledge of the biology of metastasis can improve care across the spectrum.[8]

Management of prostate cancer starts with screening, which is based on digital rectal exam and blood test for prostate-specific antigen (PSA), which so far has been the cornerstone for the decision to refer patients to prostate biopsy. This is typically trans-rectal and in total can require up to 18 samples of tissues, which means 18 aspirations with a biopsy needle. Overall, screening of prostate cancer is controversial to say the least. This is because PSA has low specificity and leads to large number of false positives, which results in a number of unnecessary biopsies. Estimates (cancer.gov) suggest that less than 10% of solid prostate biopsies indicate the need for treatment with around 80% showing a benign tumour. CTC analysis can fulfil the role of a biomarker by serving as an accurate, non-invasive measure of disease and can be followed throughout the course of the disease.

Next steps

Since only headline results were released from the BCI study, it is premature to pinpoint the positioning of Parsortix in management of prostate cancer patients; however, two clear directions of use seem to be the detection of the cancer and the assessment of the aggressiveness, which affects the interventional treatment. In particular the finding that Parsortix may be able to indicate the metastatic or localised status of the disease with a higher level of accuracy than the Gleason score looks to be striking, but this will still need to be replicated in larger-scale trials. Angle now intends to work with BCI and other cancer centres to conduct clinical studies to validate the use of the Parsortix system as a clinical application in the routine detection, assessment and treatment of prostate cancer patients. The company expects to take at least 18 months to complete the studies, while financial details remain undisclosed.

University of Southern California and breast cancer

In April 2016, Angle's KOL partner USC presented patient data from its metastatic breast cancer study at the American Association for Cancer Research Annual Meeting (AACR). The study involved 12 patients with metastatic breast cancer, who underwent metastatic tissue biopsy. To understand whether CTCs are similar to cancer metastases, researchers used RNA sequencing (RNA-Seq) to compare expression signature of 192 genes. Gene signature is the combined expression pattern of a specific group of genes and is unique to a specific medical condition. RNA-Seq was performed on samples from metastatic tissue biopsy, Parsortix's harvested CTCs and, as a control, peripheral blood of each of eight patients. Headline findings include:

- Parsortix was able to capture CTCs from all the patients.
- A statistically significant correlation between gene expression profiles of CTCs and the tissue samples from secondary sites of the metastatic breast cancer, thus confirming that CTCs actually reflect the biology of the metastasised cancer, which can be different to the primary tumour. American Society of Clinical Oncology (ASCO) guidelines recommend a biopsy of a metastatic site to guide the decision for treatment.[9]
- Typically tissue biopsy is used to obtain breast tumour biomarkers (oestrogen and progesterone receptors, HER2 oncogene) to decide on the most suitable therapy. While there are a number of ways to assess the biomarkers, the USC researchers were able to demonstrate similarly significant correlation of expression of 66 clinically actionable genes

[8] B. Hu et al. Circulating Tumor Cells in Prostate Cancer. Cancers 2013, 5, 1676-1690; doi:10.3390/cancers 5041676.

[9] C. Van Poznak et al. "Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 33. 2015 by American Society of Clinical Oncology.

comparing CTCs to tissue biopsy samples. These genes code targets, for which a drug is already available or in late-stage development, therefore could be used in guiding the treatment for the patients.

Although the results need to be replicated in larger-scale studies, these new data imply that Parsortix could replace invasive biopsy in managing breast cancer patients. Subsequently Angle announced that metastatic breast cancer was chosen as a third application and that the first FDA clearance in the US will be pursued for this indication. According to preliminary plans, the clinical trial will enrol 392 patients, split equally between healthy volunteers and breast cancer patients. Angle believes the data could be obtained next year.

Numerous other KOL studies evaluating the Parsortix system

Collaboration with a network of KOLs is at the core of Angle's R&D strategy, which also increases awareness among the leading intuitions. For example, in May 2016 Angle announced that the Clinical and Experimental Pharmacology group at Cancer Research UK (CRUK) Manchester Institute will adopt Parsortix in routine use in clinical trials and research. CRUK has been evaluating Parsortix since 2012 and is currently using the system in 16 clinical trials. Notably, CRUK is running around 620 clinical trials, so there is significant potential for Parsortix to be used in more studies. This is the first KOL that will adopt Parsortix for routine use and will generate recurring research use revenues for Angle. Exhibit 3 summarises a selection of other collaborations.

Exhibit 3: Selected recent KOL collaborations for the Parsortix system

Indication	Collaborator	Notes
Lung cancer	Cancer Research UK Manchester Institute	CRUK Manchester Institute published the results of a study comparing Parsortix to CellSearch for CTC isolation in small cell lung cancer (SCLC). The study found that CellSearch (83% ±6%) and Parsortix (79% ±11%) capture rates were comparable using blood samples spiked with EpCAM positive cancer cell line, but using low EpCAM expression cancer line Parsortix (41% ±1%) was significantly superior to CellSearch(0.35% ±0.05%).
Ovarian, lung, breast and prostate cancers	University Medical Centre Hamburg-Eppendorf (UKE)	UKE researchers compared Parsortix to CellSearch in cell separation efficiency from blood samples from healthy donors spiked with tumour-derived cell lines and blood samples of various cancer patients. The study focused on cell capture rates, feasibility to harvest and viability of the cells. The results show that cell capture rates of Parsortix ranged from an average of 42% to 70% in blood samples spiked with various tumour cell lines; harvest rates ranged from an average of 54% to 69%; virtually all (99%) harvested cells were shown to be viable and suitable for culture and molecular analysis; and when comparing Parsortix to CellSearch, Angle's system captured a similar number of epithelial CTCs as CellSearch. However, Parsortix is additionally able to capture clinically relevant mesenchymal CTCs that cannot be captured by CellSearch.
Prostate and breast cancer patients	University Medical Centre Hamburg-Eppendorf (UKE)	Research study published by UKE compared the use of Parsortix and CellSearch in prostate and breast cancer patients. Parsortix allowed better profiling of CTCs in order to understand tumour response to chemotherapy. This represents a new utility for Parsortix to identify whether patients respond to anticancer therapy or not.
Breast cancer	University of Texas MD Anderson Cancer Center	Four different breast cancer cell lines were spiked in healthy donor blood with the goal to validate the isolation of spiked cells with Parsortix and then perform molecular characterisation using two different gene expression analysis methods (Quantigene Assay/Affymetrix and PrimePCR AssayBiorad). The authors confirmed the ability to perform advanced molecular analysis on breast cancer cells isolated from blood samples.
Pancreatic cancer and colorectal cancer	Cancer Research UK-Manchester Institute	Initial evaluation of the ability of Parsortix to capture and harvest CTCs from healthy blood samples spiked with cultured cells. Results showed a good level of capture (>80%). Using an optimised enrichment protocol, the system delivered high harvest efficiency (c 45%) with very low levels of WBC contamination, providing an "ideal starting point" for single cell isolation and molecular analysis.

Source: Edison Investment Research. Note: PSA: prostate specific antigen; EMT: epithelial mesenchymal transition.

Routes to commercialisation

Regulatory pathways

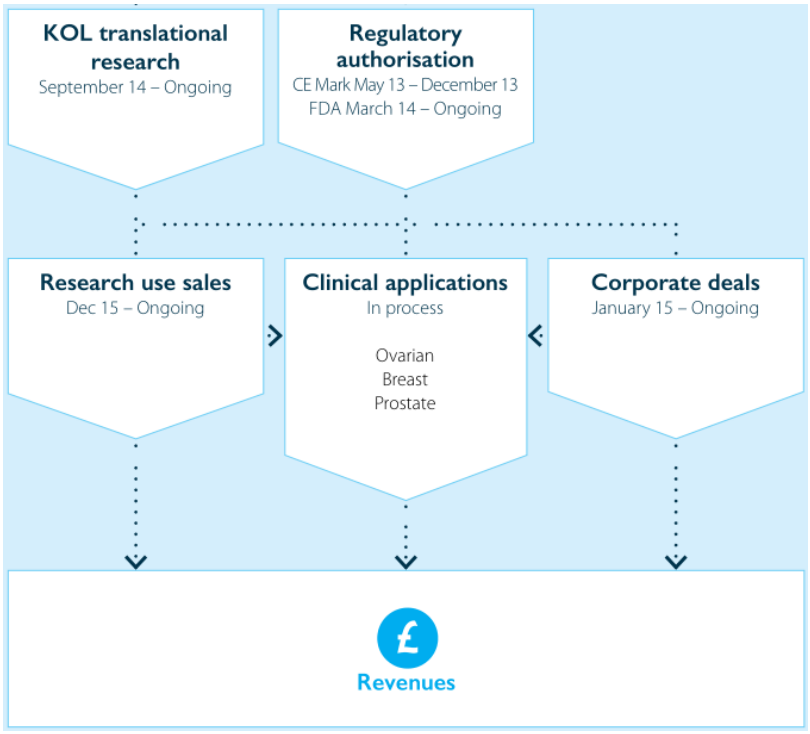
Parsortix is CE mark authorised in Europe. If the data from the ovarian cancer study is positive (triaging women before surgery), Angle plans to start offering Parsortix to accredited European hospitals via a laboratory developed test (LDT) pathway, which means that the laboratories would be required to validate the test under their own quality control system. Centres that already are investigating Parsortix are likely to be early adopters. As LDT pathway is an additional hurdle for the customers and may limit the potential of Parsortix, Angle plans to conduct a second prospective clinical study to validate the clinical utility of Parsortix, which would "upgrade" the existing CE mark for this specific indication, thus eliminating the need for internal validation at the hospitals.

In March 2014, Angle submitted a 510K application to the FDA for the use of Parsortix as a platform for the capture and harvesting of cells from the blood for the purpose of analysis. Angle reported that the ongoing dialogue is positive and noted that the completed work on the system's analytical validation will not be needed for every clinical application, thus likely shortening the review timelines for other applications. Angle is currently conducting an analytical study and will use breast cancer indication as the first Parsortix application to get FDA approval. Preparation for the clinical trial is in the final stages and will involve 200 metastatic breast cancer patients and 200 healthy volunteers. The study will be carried out in three US cancer centres, with the study plan finalised in H117. Both the analytical and clinical studies are expected to be finished in 2017. In Europe, if the data from the ovarian cancer study is positive, Angle plans to start offering Parsortix to accredited European hospitals via a laboratory developed test (LDT) pathway and centres that already are investigating Parsortix are likely to be early adopters. A planned second validation clinical study would allow a more widespread adoption eliminating the need for LDT pathway. As previously, Angle envisions that one more validation study will be required in the US and Europe each to gain regulatory approvals.

Commercial strategy

In the long term, Angle's revenues will be generated from three distinct streams: clinical applications; research use for drug trials; and corporate deals. While clinical applications will provide the bulk of revenues in the long term, these are not anticipated to begin until the completion of the Vienna and the Rochester clinical studies (headline data due in Q217). Successful evaluations of Parsortix by KOLs have already led to Parsortix being specified in a number of clinical trials and research studies, with first research use sales booked and one of the key KOLs, CRUK, adopting Parsortix in routine use in clinical trials and research. With an estimated addressable market of c 800 Phase II and III cancer drug trials initiated each year (based on a search of clinicaltrials.gov), there is significant opportunity for the use of Parsortix in a variety of indications. Further, positive trial outcomes could lead to the adoption of Parsortix as a companion diagnostic and monitoring system for the development of new drugs.

Exhibit 4: Angle's path to commercialisation



Source: Angle

CTCs harvested using the Parsortix system can be analysed using a variety of existing analytical platforms, including quantitative PCR (Roche) and next generation sequencing (Illumina). Angle plans to form commercialisation partnerships with established diagnostic companies, whereby combining the analytical system with the Parsortix system provides a 'complete solution' to the oncologist, and thus provides an additional source of revenue to the diagnostic company. This could lead to revenues through upfront payments, milestone payments, royalty income and/or sales revenues.

Valuation

We value Angle at £140.3m or 188p/share, up from £129.6m or 173p, based on a sum-of-the parts (SOTP) approach. Rolling our model forward was partially offset by the lower net cash position, while our long term clinical use sales were revised upwards after the positive early evaluation of ovarian cancer studies. Our SOTP valuation includes a DCF model for Angle's core operations running the organisation, research use sales and the ovarian cancer application, assuming a discount rate of 10% and terminal growth of 2%. We have already included two additional clinical applications after Angle provided more details about the development of Parsortix for prostate cancer and metastatic breast cancer. For the two new applications in earlier stages we use a risk-adjusted NPV model with the breakdown shown in Exhibit 5. We keep all our product assumptions and financial forecasts unchanged and as discussed in detail in our 1 August 2016 report.

Exhibit 5: Risk adjusted NPV-based valuation of early-stage projects for Parsortix

Indication	Launch	Peak sales (£m)	Value (£m)	Probability	rNPV (£m)	NPV/share (p)
Metastatic breast cancer	2019	60	116.2	7.5%	7.7	27.0
Prostate cancer	2020	140	193.5	5.0%	8.9	31.1

Source: Edison Investment Research

Exhibit 6: Sum-of-the parts valuation of Angle

Key assumptions	NPV (£m)
DCF valuation (core operations, research use sales and ovarian cancer application)	
Free cash flow model FY17-26e	24.2
Tapering growth free cash flows FY26-35e	44.8
Terminal value (2% growth rate assumed)	49.5
NPV	118.5
Discount rate	10%
Tax rate	20%
rNPV valuation	
Metastatic breast cancer	7.7
Prostate cancer	8.9
Discount rate	12.5%
Net cash (estimate at April 2017)	5.3
Valuation (£m)	**140.3**
Valuation/share (p)	**187.6**

Source: Edison Investment Research

Financials

In H117 Angle's research use sales were £219k versus £361k in H216 (£0 in H116). We keep our sales estimates of £1.1m and £3.6m of FY17 and FY18 respectively. However, after the positive early evaluation of ovarian cancer studies, we upped our expected clinical use market penetration (which partially discounted the remaining R&D risk) from 20% to 25%, in turn increasing long term potential (for more detailed discussion of our assumption see our initiation report). Angle mentioned that many potential clients have business cycles based on the calendar year and the company expects sales to increase substantially in H217. Research use sales came from both existing

relationships with KOLs, which were converted into paying customers, and new clients. The Cancer Research UK (CRUK) Manchester Institute, a flagship customer, which adopted Parsortix for routine use in clinical trials in May 2016, has already processed 1,100 patient samples in 16 clinical trials, up from 10 clinical trials last May. As an example of the scale of the opportunity, The Christie NHS Foundation Trust is one of the partners behind CRUK Manchester Institute and runs around 620 cancer trials currently. In our view, an important 'side effect' of the growing research use customer base is that it is using Parsortix for investigations into new uses of the device, which increase awareness and expand the potential. In line with the company's strategy, sales for research use are the near-term goal, while the largest potential is in clinical use of Parsortix, currently being explored in clinical trials.

Angle's total operating spend in H117 was £3.1m compared to a total of £5.7m in FY16. We keep our forecast of operating costs to go up to £9.2m in FY17 due to an increase in R&D activities, primarily in relation to clinical studies, although we note that if the FDA approval process takes longer than expected costs may roll over into the following year. End October 2016 net cash (no debt) was £9.7m, boosted by the £9.6m net equity raise in May 2016. We calculate cash at £5.3m by end-FY17. Our model suggests that this should be sufficient to fund operations through to 2019. We assume £3.2m of illustrative financing will need to be included nominally as long-term debt (as per Edison policy) on the balance sheet in 2019. We anticipate profitability in 2021 (on net income).

Exhibit 7: Key changes to our financial forecasts

£m	2016	2017e			2018e		
	Actual	Old	New	Change (%)	Old	New	Change (%)
Revenue	0.361	1.085	1.085	+0%	3.620	3.620	+0%
Gross Profit	0.254	0.762	0.762	+0%	2.545	2.545	+0%
Operating Profit	(5.449)	(8.493)	(8.468)	-0%	(6.057)	(5.956)	-2%
Profit Before Tax (rep)	(5.427)	(8.478)	(8.443)	-0%	(6.057)	(5.936)	-2%
Profit After Tax (rep)	(5.086)	(8.278)	(8.243)	-0%	(5.857)	(5.736)	-2%
EPS (p) (rep)	(8.64)	(11.29)	(11.25)	-0%	(7.77)	(7.61)	-2%

Source: Angle accounts, Edison Investment Research

Exhibit 8: Financial summary

£'000s	2014	2015	2016	2017e	2018e
Year-end 30 April	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	0	0	361	1,085	3,620
Cost of Sales	0	0	(107)	(322)	(1,075)
Gross Profit	0	0	254	762	2,545
Research and development	(900)	(1,600)	(2,470)	(4,750)	(4,125)
EBITDA	(1,994)	(3,452)	(4,858)	(7,445)	(4,889)
Operating Profit (before amort. and except.)	(2,051)	(3,563)	(5,056)	(7,734)	(5,250)
Intangible Amortisation	(99)	(204)	(187)	(254)	(225)
Share-based payments	(61)	(111)	(238)	(480)	(480)
Other	0	0	32	0	0
Operating Profit	(2,211)	(3,878)	(5,449)	(8,468)	(5,956)
Net Interest	13	9	22	25	20
Profit Before Tax (norm)	(2,038)	(3,554)	(5,034)	(7,709)	(5,230)
Profit Before Tax (FRS 3)	(2,198)	(3,869)	(5,427)	(8,443)	(5,936)
Tax	0	0	309	200	200
Discontinued operations	960	(18)	32		
Net Income (norm)	(1,078)	(3,572)	(4,693)	(7,509)	(5,030)
Net Income (FRS 3)	(1,238)	(3,887)	(5,086)	(8,243)	(5,736)
Average Number of Shares Outstanding (m)	45.1	47.6	58.9	73.3	75.4
EPS - normalised (p)	(2.39)	(7.50)	(7.97)	(10.24)	(6.67)
EPS - normalised and fully diluted (p)	(2.39)	(7.50)	(7.97)	(10.24)	(6.67)
EPS - (IFRS) (p)	(2.74)	(8.16)	(8.64)	(11.25)	(7.61)
Dividend per share (p)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	70.4	70.3	70.3
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	1,882	1,572	1,801	2,200	2,475
Intangible Assets	1,142	1,149	1,346	1,704	2,090
Tangible Assets	139	423	455	496	385
Investments	601	0	0	0	0
Current Assets	4,278	9,648	4,938	6,789	1,552
Stocks	52	197	376	532	442
Debtors	328	1,008	489	691	496
Cash	3,898	8,443	3,764	5,256	305
Other	0	0	309	309	309
Current Liabilities	(645)	(1,131)	(1,504)	(1,917)	(2,211)
Creditors	(645)	(1,131)	(1,504)	(1,917)	(2,211)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	0	0	0	0	0
Long term borrowings	0	0	0	0	0
Other long term liabilities	0	0	0	0	0
Net Assets	5,515	10,089	5,235	7,072	1,816
CASH FLOW					
Operating Cash Flow	(1,899)	(3,413)	(4,762)	(7,418)	(4,309)
Net Interest	(4)	5	23	25	20
Tax	0	0	0	227	200
Capex	(83)	(325)	(186)	(330)	(250)
Acquisitions/disposals	4,326	126	577	0	0
Financing	0	8,257	1	9,600	0
Other	(270)	(105)	(332)	(612)	(612)
Dividends	0	0	0	0	0
Net Cash Flow	2,070	4,545	(4,679)	1,492	(4,951)
Opening net debt/(cash)	(1,828)	(3,898)	(8,443)	(3,764)	(5,256)
HP finance leases initiated	0	0	0	0	0
Other	0	0	0	0	0
Closing net debt/(cash)	(3,898)	(8,443)	(3,764)	(5,256)	(305)

Source: Angle accounts, Edison Investment Research. Note: Historical reported revenues relate to the legacy business, which has now been divested. FY14 has been restated to exclude discontinued operations.

Contact details	Revenue by geography
Angle 3 Frederick Sanger Road Guildford, Surrey GU2 7YD United Kingdom +44 (0)1483 685830 www.angleplc.com	N/M

Management team

Chief Executive: Andrew Newland	Non-Executive Chairman: Garth Selvey
Andrew Newland is the founder and chief executive of Angle. He has over 25 years' experience building technology-based businesses, serving as chairman or on the board of several specialist medtech companies. He has an MA in engineering science and is a qualified chartered accountant.	Garth Selvey joined Angle as non-executive director in 2006, becoming non-executive chairman in September 2007. He has spent 36 years in the computer industry, previously serving as managing director of TIS Applications and group chief executive of Comino Group. He has a BSc in physics and electronics engineering.
Finance Director: Ian Griffiths	**Non-Executive Director: Brian Howlett**
Ian Griffiths joined Angle in 1995, and has been finance director since 2003. He has specialised in technology commercialisation for over 20 years, previously working at KPMG from 1986-93 where he worked within their high technology consulting group. He has a BSc in mathematics with management applications and is a qualified chartered accountant.	Brian Howlett joined Angle as non-executive director in January 2013. He also has roles on the boards of Vascular Flow Technologies, Michelson Diagnostics and Accentus Medical. He was formerly CEO of Lombard Medical Technologies, and has had prominent roles at Boston Scientific, Cobe Laboratories and Fisons.

Principal shareholders	(%)
Jupiter Investment Management Group	9.76
Andrew Newland	9.43
Henderson Group	8.25
Hargreaves Lansdown Asset Management	8.21
Toronto-Dominion bank	4.32
Walker Crips Group	3.87
Smith & Williamson Holding	3.80

Companies named in this report

Janssen Diagnostics (Johnson & Johnson, JNJ); Illumina (ILMN); NetScientific (NSCI); Biocept (BIOC)

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
245 Park Avenue, 39th Floor
10167, New York
US

Sydney +61 (0)2 8249 8342
Level 12, Office 1205
95 Pitt St, Sydney
NSW 2000, Australia