Angle

Initiation of coverage

Cells for precision medicine

Pharma & biotech

Angle has transformed into a pure-play diagnostics business. Parsortix, its proprietary cell separation system, can be used to capture and harvest very rare cells from blood for analysis, including circulating tumour cells. Information gained from these cells is essential to a precision medicine approach, a key initiative aiming to improve clinical outcomes. In the near term, Parsortix is being evaluated for use in the pre-surgery triaging of ovarian masses, which could see clinical sales as early as FY H217. Parsortix is launched for the research market and, and for the clinical market has a CE mark in Europe. An FDA application is in progress for the US. We value Angle at $143m or $24/ADS.

Year end	Revenue (US$m)	PTP* (US$m)	EPADR ($)	DPADR ($)	P/E (x)	Gross Yield (%)
04/14	0.0	(3.2)	(0.37)	0.0	N/A	N/A
04/15	0.0	(5.5)	(1.15)	0.0	N/A	N/A
04/16e	0.53	(7.9)	(1.29)	0.0	N/A	N/A
04/17e	3.37	(5.0)	(0.79)	0.0	N/A	N/A

Source: Note: Converted at US$1.54 to £1. Investors should consult their tax advisor regarding the application of any domestic and foreign tax laws.

Potentially transforming how cancer care is delivered

The precision medicine approach aims to improve treatment efficacy and outcomes by tailoring the treatment to the individual, and unique, characteristics of the patient and their disease. Circulating tumour cells (CTCs) provide information about the individual's cancer, which can be used for prognostic, dia14gnostic and treatment stratification purposes as part of this approach. However, CTCs are very rare and difficult to isolate. Parsortix offers the potential to harvest these cells for analysis from a simple blood test (liquid biopsy), on a minimally invasive, repeatable basis.

"Unprecedented" sensitivity in ovarian cancer

The Parsortix system is being evaluated in a variety of clinical applications by a number of Key Opinion Leaders (KOLs). In H115, the Medical University of Vienna reported the "unprecedented sensitivity and specificity" of an approach using Parsortix alongside their RNA markers in the diagnosis of ovarian cancer, with 100% sensitivity and specificity with analysis of 30 RNA markers. A clinical study utilising this approach for the pre-surgery triaging of ovarian masses is now being planned. Success of the study could provide validation for the Parsortix system and lead to clinical sales for use in this indication in Europe as early as FY H217.

Valuation: DCF valuation of $143m or $24/ADS

We value Angle at $143m or $24/ADS, based on a three-phase DCF valuation using comprehensive forecasts for the period through to 2025, with less detailed cash flows to 2035 followed by a terminal growth rate of 2%. Our valuation is based on sales of Parsortix for use in research and clinical sales for the pre-surgery triaging of ovarian masses, with no contribution from other potential applications or the technology platform. Cash of $13m at FY15 should be sufficient to allow Angle to operate through to end-2017. We anticipate profitability in 2019.

10 September 2015

Price	**US$14.85**
Market cap	**US$87.6m**
	ADR/Ord conversion ratio 1:10
Net cash ($m) at April 2015	13
ADRs in issue	5.9m
ADR Code	ANPCY
ADR exchange	OTCQX
Underlying exchange	AIM
Depository	Bank of New York Mellon
52-week high/low	US$13.38 US$15.78

Business description

Angle is a pure-play specialist diagnostics company. The proprietary Parsortix cell separation platform can be used for the detection and harvesting of very rare cells from a blood sample, including circulating tumour cells (CTCs). The resulting liquid biopsy enables the analysis of these cells for precision cancer care.

Next events

Results from KOL studies in various cancer indications	H215
Start of ovarian cancer clinical study with the Medical University of Vienna	Q415

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Investment summary

Company description: Now a pure-play diagnostics business

Angle is now a pure-play diagnostics business following the focus on the proprietary cell separation system, Parsortix, and subsequent wind-down of the legacy management services business (remaining contracts completed on 31 March 2015). The Parsortix system can be used to capture and harvest very rare cells from blood for analysis, including cancer and foetal cells. The product is launched for the research market and has CE mark regulatory approval for the clinical market in Europe. Angle is listed on the London Stock Exchange (AGL) and trades on the AIM market. The company has also established a Level 1 ADR program in the US and ADRs are traded on the OTCQX market. Since its IPO in 2004, Angle has raised c $46m, including $12.6m (net) from an equity raise in H115. Angle is headquartered in Guildford, England and employs 22 people.

Valuation: DCF valuation of $143m or $24/ADS

We value Angle at $143m or $24/ADS, based on a three-phase DCF valuation assuming a discount rate of 10% and a long-term tax-rate of 20%. Our DCF includes comprehensive forecasts for the period through to 2025, with less detailed cash flows to 2035, followed by terminal growth of 2%. We have adopted conservative assumptions in our modelling; for instance, the valuation includes only the sales of Parsortix for use in research and clinical sales in ovarian mass triaging, with no value assigned to its use in other indications, neither does it consider the inherent value of the technology platform. We feel this is currently appropriate as Angle is operating in a frontier area of medical diagnostics; however, as visibility improves we envisage employing less cautious assumptions, leaving significant room for upside. Clearly as progress is achieved, we would expect to revisit the model and anticipate the valuation would reflect this.

Financials: Funded through to key value inflection points

Angle's revenues have previously been driven by the legacy management services business, which has now been wound down, and so historic financial information has little relevance to Angle's prospects (the $1.1m balance of the Geomerics sale will be received in December 2015). Our revenue forecasts are based solely on our assumptions for sales of Parsortix in research initially, followed by clinical sales for the triaging of ovarian masses.

Following the $12.6m net equity raise in February and March 2015, Angle finished the FY15 with $13m cash, Angle has no debt. Our model suggests that this should be sufficient to fund operations through to 2017. We forecast $2m of illustrative financing included nominally as long-term debt on the balance sheet in 2018 (as per Edison policy). We anticipate profitability in 2019. The increase in net loss to $6m from $3.4m in 2014 reflects the planned increase in operating expenditure on the Parsortix system.

Sensitivities: similar, but lower, risks to drug development

With the existing positive KOL evaluations of Parsortix, the biggest sensitivity for Angle relates to execution rather than technical risk. As a new technology, Angle's greatest challenge will be communicating and convincing customers of the advantages of Parsortix, so as to ensure widespread adoption and achieve sales forecasts. We have assumed a conservative, but consistent, uptake of Parsortix, such that any significant delays could have a negative impact on our valuation. Also in the near term, the outcome of the Vienna clinical study and the continued progress of the FDA application, will affect its eventual commercial potential. Angle relies on the continued positive evaluations of the Parsortix system by KOLs, and the demonstration of its clinical utility in clinical trials.

Outlook: Separating the wheat from the chaff

Angle is a pure-play specialist medical diagnostic company, with a focus on cancer diagnostics. The proprietary Parsortix cell separation system is able to capture circulating tumour cells (CTCs), which are outnumbered by healthy 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. In addition, CTCs have potential for use in screening tests, and also as an aid to decision making. The planned clinical study will investigate an approach incorporating Parsortix for the pre-surgery triaging of ovarian masses. Parsortix has a CE mark for the clinical market in Europe, with an FDA approval process underway for the US. In the meantime, revenues will be generated through sales for use in research.

Identifying and harvesting cells for precision cancer care

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, in order to predict 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). This minimally invasive, repeatable approach could transform the treatment of cancer, enabling precision medicine to improve outcomes and minimise costs and morbidity associated with ineffective treatment and avoidable adverse events.

Angle has recognised that, in order 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. Translational research is now underway in a variety of clinical indications, including at the Medical University of Vienna and the Cancer Research UK Manchester Institute. A number of endorsements and competitive advantages of Parsortix have already been reported, in particular its ability to capture different types of CTCs, applicability to multiple cancer types, and the easy harvesting and high purity of captured cells. Angle believes that Parsortix has the potential to be more simple, effective and affordable than competing technologies.

"Unprecedented" findings in ovarian cancer study

The Medical University of Vienna has reported the "unprecedented sensitivity and specificity" of an approach to ovarian cancer diagnosis which combines the Parsortix system with molecular analysis of captured CTCs for RNA markers. The approach achieved sensitivity of 80% with analysis of seven markers, and 100% with analysis of 30 markers. Previous studies using the best competing CTC enrichment technologies had sensitivity levels of just 24.5%. The University will now lead a full clinical study investigating this approach for the triaging of patients with ovarian masses who are undergoing surgery (cancerous versus benign), aiding the decision regarding surgical management. Success in the study could provide validation of Parsortix and lead to European clinical sales as early as FY H217.

A platform technology with multiple applications

In addition to capturing CTCs, the Parsortix technology has the potential for deployment with several other important cell types, including the capture of foetal cells from maternal blood. Non-invasive foetal diagnostics could replace procedures such as amniocentesis, which is not only invasive and painful, but also carries a risk of miscarriage. Thus, the Parsortix technology has potential to be broadly applicable across multiple conditions that require the capture and isolation of specific cells from a blood sample to aid in analysis for diagnosis.

Circulating tumour cells: The needle in the haystack

No two cancers are the same. Not only is a patient's cancer unique to them, the same cancer evolves and changes over time. It stands to reason therefore, that the heterogeneous nature of cancer should be recognised when deciding a patient's treatment, not just initially, but throughout the disease course. 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. The goal is to streamline clinical decision making by distinguishing in advance those patients most likely to benefit from a given treatment, from those who will incur cost and suffer side effects without gaining benefit (Precision Medicine Initiative). This is ever more topical, as immunotherapies such as Opdivo (BMS) and Keytruda (Merck) receive as much attention for their hefty price tags as they do for their remarkable clinical benefits. With a course of each drug costing $150,000, and yet only one in five patients likely to respond,[1] the ability to identify those responders in advance is increasingly sought by patients, doctors and payers alike.

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.[2] 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.[3]

CTCs are cells that have been shed from a solid tumour into the vasculature. CTCs 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 and establishing metastasis.[2] The presence and quantity of CTCs has been shown to be indicative of patient prognosis in a number of cancers.[2] 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.[2]

In addition to the information they can provide, the great 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. CTCs however, are extremely rare with estimates of just one CTC per 10^7 white blood cells per millilitre of blood.[2] Therefore, their detection and capture is not straightforward.

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

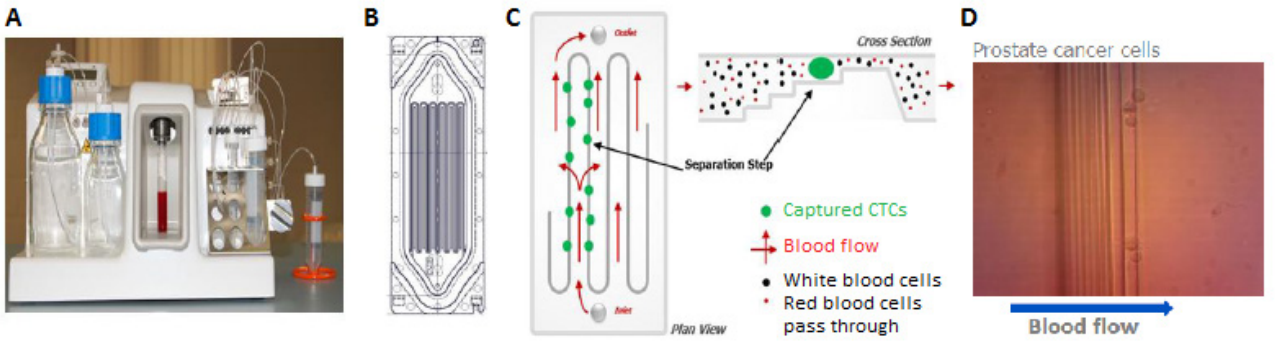
[2] Krebs MG, et al. (2014) Molecular analysis of circulating tumour cells – biology and biomarkers. Nat. Rev. Clin. Oncol. 11:129-144.

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

Parsortix technology

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 Parsortix 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, Edison Investment Research. (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, 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 epithelial-to-mesenchymal transition (EMT) 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.[2]
- 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. In addition, having come from dead cancer cells, information from cfDNA may not be as clinically relevant.
- CTCs harvested using Parsortix are not subject to antibody binding or other chemical reactions. Captured CTCs have been found to be viable and undamaged; 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.[2]
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 in to the antecubital vein for 30min 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
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.
VortexBiosciences (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. 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.

Ovarian cancer: "Unprecedented sensitivity and specificity"

In January 2015, the Medical University of Vienna reported the "sensational" 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[4] of 90% for primary epithelial ovarian cancer, and a specificity[4] 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 the best sensitivity achieved only 24.5%. 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.

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

In 2012, c 239,000 women worldwide were diagnosed with ovarian cancer (65,600 in Europe; 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 medical need for early diagnosis. 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.[5] Furthermore, the specificity of CA-125 is poor, with serum levels raised in a number of benign conditions and other cancers. The FDA-approved 'OVA1' (Vermillion), is a blood test and software algorithm used to evaluate ovarian masses for malignancy prior to surgery. OVA1 has a sensitivity of c 95% but a specificity of only c 40%, resulting in a significant level of false positives.

In women with a BRCA1/2 mutation, up to 39% will develop ovarian cancer and up to 65% will develop breast cancer by the age of 70 years. As a result, some women resort to risk-reducing surgeries such as ovarian removal and mastectomies. As part of the Vienna study, a blood sample of a woman with the BRCA1/2 mutation who had opted for risk-reducing ovarian removal was analysed. Although asymptomatic, and appearing disease-free on the basis of ultrasound and CA-125 levels, she had elected for surgery. The Parsortix blood sample taken prior to surgery indicated that the woman was positive for ovarian cancer. Although initially thought to be a false positive, following surgery she was in fact found to have ovarian cancer. While this requires validation in larger studies, Parsortix could form part of a screening process in these high risk women.

First clinical study being planned

The Medical University of Vienna will now lead a full clinical study of the Parsortix system together with their RNA markers, for the pre-surgery triaging of patients with ovarian masses. This multi-centre study (one site in the US) is due to start in Q415, with the European side of the study expected to complete in 12 months. Angle believes that some of the costs of running the European side may be borne by a third party, due to various European research programs targeting the area.

The American Cancer Society estimates that there will be 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 an ovarian cancer. Patients with very early stage ovarian cancer benefit from removal of the mass intact, since opening the mass results in a more advanced stage (through dissemination), adversely effecting prognosis. [6] Thus, it is essential that an appropriate surgical approach is used and that the procedure is performed by a gynaecological oncologist. Furthermore, gynaecological oncologists have been found to be significantly more likely to perform optimal staging in early-stage disease.[6] In advanced disease, surgery performed by a gynaecological oncologist resulted in a six to nine month median survival benefit.[6] Success in the study could lead to the use of Parsortix to identify patients at high risk for ovarian cancer, aiding surgical management decisions, which can be critical to the patient's prognosis. Validation would also provide a strong rationale for its use for diagnosis, screening in high risk patients, treatment stratification and monitoring and remission surveillance.

Discussions with the FDA

The Parsortix system is CE mark authorised for clinical sales in the European Union. In March 2014, Angle submitted an 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 reports that the ongoing dialogue is positive. CellSearch is the only CTC system to have been approved, but its use is limited to enumeration only and to certain cancer types. As a marker-independent system that also allows for the harvesting of CTCs, Parsortix offers a number of advantages over CellSearch. In

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

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

light of Parsortix's synergy with a precision medicine approach, Angle hopes that Parsortix will be the first FDA-approved device for the harvesting of CTCs.

Numerous KOL studies evaluating the Parsortix system

Angle is collaborating with a total of nine KOLs in leading cancer institutes around the world to investigate new clinical applications for the Parsortix system in a number of cancers. Exhibit 3 summarises a selection of these collaborations, most of which have already provided positive evaluations of Parsortix. Through these collaborations Angle hopes to gain validation of the Parsortix system, laying the foundations for commercialisation through clinical sales.

Exhibit 3: Collaboration agreements for the Parsortix system

Indication	Collaborator	Notes
Ovarian cancer	Medical University of Vienna	Investigating a potential diagnostic tool incorporating Parsortix and their RNA markers to triage patients with ovarian masses who are undergoing surgery. See text for further details.
Metastatic breast cancer	Sidney Kimmel Cancer Centre, Thomas Jefferson University	Parsortix system evaluated in combination with the single cell analysis DEPArray system to isolate single cancer cells from blood spiked with cultured breast cancer cells, and from blood samples of patients with metastatic breast cancer. CTCs were successfully harvested using Parsortix, with high levels of purity. Individual cells were successfully manipulated and analysed using PCR to identify two breast cancer related genes on the cells. The researchers will now analyse Parsortix-harvested CTCs using NGS in specific disease status and treatment settings to better identify clinical applications for more effective treatment of metastatic breast cancer.
	University of Southern California Norris Comprehensive Cancer Center	Investigating the potential of liquid biopsies as an alternative to surgical biopsy of secondary cancer sites in metastatic breast cancer. Parsortix would be used to capture and harvest CTCs from the liquid biopsy for RNA analysis to determine the disease status of the metastatic sites. In addition, they will profile the biology of the CTCs over a time period to see whether this provides information on treatment-resistance. Results expected in H215, and if positive, will be followed by a large-scale clinical study.
Prostate cancer	Barts Cancer Institute (BCI)	Initial study used the Parsortix system to harvest CTCs from prostate cancer patient samples (n=52: 44 metastatic and 8 localised). CTCs were harvested from 100% of patients, and included both epithelial and mesenchymal cells. Further, the number of mesenchymal cells harvested showed better correlation with simultaneous PSA levels (current gold standard biomarker used to assess cancer progression). This work is now being expanded with more patient numbers and ongoing follow-up. In addition, BCI is investigating the viability of Parsortix-harvested CTCs and the potential to culture them, and the molecular biomarkers in the CTCs in order to predict prostate cancer outcome and response to therapies.
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. Now using the Parsortix system to undertake pilot studies in both colorectal and pancreatic cancer.
Colorectal cancer	MD Anderson Centre	Evaluating the use of Parsortix to harvest CTCs from the blood samples of 50 metastatic colorectal cancer patients. The harvested CTCs will be investigated for: (a) key markers for use as a companion diagnostic to indicate which patients will benefit from Merck Serono's Erbitux (cetuximab); (b) the number of CTCs that have been through the EMT phase and are involved in the process of metastasis; and (c) the potential to culture the CTCs for investigation eg chemo-sensitivity testing.

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

In addition, Angle has recruited a number of influential Scientific Advisors, reflecting its commitment to demonstrating the clinical utility of Parsortix. This also provides independent endorsement of the technology. These include, Dr James Reuben, a Professor at The University of Texas MD Anderson Cancer Centre and Dr Daniel Danila, an oncologist at Memorial Sloan Kettering Cancer Centre. Each is a leader in the development of CTCs for use in breast and prostate cancer, respectively.

Routes to commercialisation

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 FY H217 at the earliest (following the completion of the Vienna clinical study).

Successful evaluations of Parsortix by KOLs have already led to Parsortix being specified in a number of clinical trials and research studies. Angle expects to receive revenues from the sale of machines and cassettes for use in research in FY H216. With 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 new drug (see the recent FDA approval of therascreen (Qiagen) as a companion diagnostic for AstraZeneca's Iressa).

CTCs harvested using the Parsortix system can then 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. In addition, Angle could also take advantage of the existing distribution channels, thereby containing their own costs. Angle has entered into two such collaborations in the last year:

- With a diagnostics division of a large pharmaceutical company, who will investigate the combination of the Parsortix system with their single cell analysis system.
- With EKF Diagnostics. EKF will investigate the combination of Parsortix with their PointMan DNA enrichment technology and will explore ways to offer the systems as a combined solution.

Angle outsources manufacturing to specialist organisations, with whom they have entered into long-term supply partnerships. The agreements ensure that Angle's regulatory commitments are met, and have capacity for upscaling and holding stock. The cassettes are custom-made to Angle's specific designs by a German specialist manufacturer with established, large scale, multi-site manufacturing capability. The machines are constructed from readily available electronic, fluidic and mechanical components by a UK-based contract manufacturer.

Sensitivities

The positive evaluations of Parsortix already reported and the research trials incorporating Parsortix provide independent validation of the technology and its utility, thus reducing the investor risk profile. Therefore, the biggest sensitivity for Angle relates to execution, rather than technical risk. 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. We have assumed a conservative, but consistent, uptake of Parsortix, such that any significant delays could have a negative impact on our valuation.

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. In particular, the outcome of the Medical University of Vienna clinical study evaluating its use in ovarian cancer will influence regulatory decisions and the uptake of Parsortix in other cancers and applications, thus determining eventual commercial potential. However, as Parsortix is a marker-independent system, negative or inconclusive data in one cancer indication should, in theory, not have negative read-across to other cancer indications and other potential applications of Parsortix. Angle has reported positive ongoing discussions with the FDA regarding their application. Any delays or negative decisions will affect estimated timelines and clinical sales in the US and therefore have an impact on our valuation, as the US market is likely to be key.

Angle are reliant on external manufacturers to maintain GMP standards, scale and continuity of production, as well as to maintain current margins. As sales rise and therefore demand increases, we would anticipate dual sourcing and strategic stocks to mitigate the risk of supply interruptions.

Valuation

We value Angle at $143m or $24/ADS, based on a three-phase DCF model, assuming a discount rate of 10%, terminal growth of 2% and a long-term tax rate of 20% (reflecting the expected benefit

of the Patent Box incentives). The breakdown of our valuation is shown in Exhibit 4. We have adopted conservative assumptions in our modelling; for instance, the valuation includes only the sales of Parsortix for use in research and clinical sales in ovarian mass triaging, with no value assigned to its use in other indications, neither does it consider the inherent value of the technology platform. We feel this is currently appropriate as Angle is operating in a frontier area of medical diagnostics; however, as visibility improves we envisage employing less cautious assumptions, leaving significant room for upside. Clearly as progress is achieved, we would expect to revisit the model and anticipate the valuation would reflect this.

Exhibit 4: Assumptions for base case DCF valuation

Key assumptions	NPV ($m)
Free cash flow model FY16-25	25.9
Tapering growth free cash flows FY26-35	53.0
Terminal value (2% growth rate assumed)	51.1
Total NPV	130.0
Net cash (FY15)	13.0
Valuation ($m)	**143.0**
Valuation/ADS ($)	**24.2**
Discount rate	10%
Tax rate	20%

Source: Edison Investment Research

For research use, we have forecast peak sales of $14.6m in 2021, based on only 5% of Phase II and Phase III cancer drug trials incorporating the use of Parsortix by 2021. Due to the variable and unpredictable nature of clinical trials we have had to make assumptions regarding revenues per trial. We have assumed only one machine per trial, with 300 cassettes per Phase II trial (n=100, 3 cassettes per patient) and 5,000 cassettes per Phase III trial (n=1000, 5 cassettes per patient). It is likely that the larger Phase III trials will require more than one machine, leaving room for upside.

The Medical University of Vienna study will investigate the use of Parsortix for the pre-surgery triaging of patients with ovarian masses. For this indication, we have forecast peak sales of c $25.4m in 2030. This is based on the Vienna study completing in Q416, allowing for launch in Europe in 2017 where a CE mark is already granted, and a 2019 launch in the US given the pending FDA approval. Our sales forecasts are based on the assumption that Parsortix will be used in 20% of cases at peak. In lieu of the fact that this is a new technology with penetration difficult to predict, we have assumed a conservative uptake, taking 9 years to reach peak penetration in Europe and the US. We have made assumptions regarding the cassette capacity of the Parsortix machine, and used this to calculate machine sales. The cassette cost of $300 in the US, is based on a premium to the EU price of £150, and is below the Medicare reimbursement for OVA1 ($516/test), which is approved for the same market. We assume that the findings of the initial Vienna study will be replicated, demonstrating significant specificity advantage of Parsortix (100% vs 40%), allowing for capture of some of OVA1's market share.

Looking at the cost side of the model, we forecast c $14m in R&D spend over the next three to four years in order to secure EU and US approval for clinical sales and to fund clinical trials in other applications. We assume that Angle will bear the full cost of the ovarian clinical study, leaving room for upside should funding be available under various European research programs. Our valuation assumes that Angle will market Parsortix directly, and that manufacturing costs remain as projected, driving an effective product margin of 80%.

Financials

Angle's revenues have previously been driven by the legacy management services, which have now been wound down, thus historic financial information has little relevance to Angle's prospects.

Our revenue forecasts, as detailed above, are based solely on our assumptions for Parsortix sales in research initially, followed by clinical sales for the triaging of ovarian masses. After the $12.6m net equity raise in February and March 2015, Angle finished the FY15 with $13m cash, Angle has no debt. Our model suggests that this should be sufficient to fund operations through to 2017. We forecast $2m of illustrative financing included nominally as long-term debt on the balance sheet in 2018 (as per Edison policy). We anticipate profitability in 2019. The increase in net loss to $6m ($3.4m in 2014) reflects the planned increase in operating expenditure on the Parsortix system.

Exhibit 5: Financial summary

USD:GBP	1.54	$'000s	2013	2014	2015	2016e	2017e
Year end April			IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS							
Revenue			1,492	0	0	525	3,366
Cost of Sales			0	0	0	(157)	(999)
Gross Profit			1,492	0	0	367	2,367
Research and development			(462)	(1,386)	(2,464)	(4,743)	(3,785)
EBITDA			(1,038)	(3,071)	(5,316)	(7,711)	(4,745)
Operating Profit (before amort. and except.)			(1,068)	(3,159)	(5,487)	(7,962)	(5,030)
Intangible Amortisation			(474)	(152)	(314)	(527)	(563)
Share-based payments			(109)	(94)	(171)	(693)	(739)
Other			0	0	0	0	0
Operating Profit			(1,651)	(3,405)	(5,972)	(9,182)	(6,333)
Net Interest			64	20	14	51	23
Pre-tax profit (norm)			(1,004)	(3,139)	(5,473)	(7,911)	(5,007)
Pre-tax profit (FRS 3)			(1,587)	(3,385)	(5,958)	(9,131)	(6,310)
Tax			0	0	0	308	308
Discontinued operations			0	1,478	(27)	0	0
Net Income (norm)			(1,004)	(1,660)	(5,501)	(7,603)	(4,699)
Net Income (FRS 3)			(1,587)	(1,907)	(5,986)	(8,823)	(6,002)
			0	0	0	0	0
Average Number of ADS Outstanding (m)			41	45	48	59	59
Earnings per ADS - normalized ($)			(0.25)	(0.37)	(1.15)	(1.29)	(0.79)
Earnings per ADS - normalized and fully diluted ($)			(0.25)	(0.37)	(1.15)	(1.29)	(0.79)
Earnings per ADS - (IFRS) ($)			(0.39)	(0.42)	(1.26)	(1.49)	(1.01)
Dividend per ADS ($)			0.0	0.0	0.0	0.0	0.0
Gross Margin (%)			n/a	n/a	n/a	70.0	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			5,512	2,899	2,421	1,908	1,455
Intangible Assets			1,663	1,758	1,769	1,402	999
Tangible Assets			213	215	651	505	455
Investments			3,636	926	0	0	0
Current Assets			5,870	6,588	14,858	6,864	2,549
Stocks			95	80	303	308	385
Debtors			699	505	1,552	627	922
Cash			2,815	6,003	13,002	5,929	1,242
Other			2,261	0	0	0	0
Current Liabilities			(931)	(993)	(1,742)	(1,365)	(1,859)
Creditors			(931)	(993)	(1,742)	(1,365)	(1,859)
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			10,452	8,493	15,537	7,407	2,145
CASH FLOW							
Operating Cash Flow			(2,080)	(2,924)	(5,256)	(7,090)	(4,623)
Net Interest			169	(6)	8	51	23
Tax			0	0	0	231	308
Capex			(214)	(128)	(501)	(105)	(236)
Acquisitions/disposals			237	6,662	194	0	0
Financing			3,180	(416)	12,554	0	0
Dividends			0	0	0	0	0
Net Cash Flow			1,292	3,188	6,999	(6,913)	(4,527)
Opening net debt/(cash)			(1,523)	(2,815)	(6,003)	(13,002)	(5,929)
HP finance leases initiated			0	0	0	0	0
Other			0	0	0	(160)	(160)
Closing net debt/(cash)			(2,815)	(6,003)	(13,002)	(5,929)	(1,242)

Source: Company accounts, Edison Investment Research. Note: Historic 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/A

Management team

Non-Executive Chairman: Garth Selvey	Chief Executive: Andrew Newland
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.	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.
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 1986-1993 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	(%)
Andrew Newland	9.67
Henderson Global Investors	5.22

Companies named in this report

Janssen Diagnostics (Johnson & Johnson, JNJ); Illumina (ILMN); NetScientific (NSCI); Qiagen (QGEN); EKF Diagnostics Holdings (EKF LN)