Trinity Delta

ANGLE plc

Initiation of coverage

Parsortix commercial traction would be transformational

11 May 2021

ANGLE is progressing its proprietary Parsortix cancer diagnostic platform through several key inflection points over the next 24 months, most notably FDA approval. In parallel, it has initiated commercialisation through the creation of two clinical laboratories (in the UK and US), which can offer services to the pharma industry and LDTs (Laboratory Developed Tests) for the clinical market. Parsortix is an elegant microfluidic device that captures circulating tumour cells (CTCs) for analysis. Such liquid biopsies will be employed increasingly not only in initial diagnosis, but to monitor and guide treatment. Our DCF-based valuation is £549m, or 255p per share.

Year-end: December 31	2019*	2020	2021E	2022E
Revenue (£m)	0.6	0.8	2.3	5.5
Adj. PBT (£m)	(9.1)	(13.8)	(20.5)	(19.3)
Net Income (£m)	(7.9)	(11.6)	(18.2)	(17.4)
Adj. EPS (p)	(4.7)	(6.7)	(8.3)	(7.9)
Cash (£m)	18.8	28.6	7.9	6.2**
EBITDA (£m)	(8.4)	(12.3)	(19.8)	(17.8)

Source: Trinity Delta Note: Adjusted numbers exclude exceptionals * FY19 covers an eight-month period. **includes assumed £15m financing proceeds.

- **CTCs offer an invaluable insight** Targeted therapies are poised to transform the treatment of many solid cancers, but as they become more specific and tailored so the need for more relevant and timely diagnostic information rises. Various liquid biopsy approaches, such as ctDNA, provide valuable genomic insights in a non-invasive manner. CTCs offer a more complete picture, but challenges of harvesting such rare cells consistently and reproducibly have been a limiting factor to date.
- **Parsortix addresses clear unmet needs** The Parsortix system is an elegantly simple automated system that can rapidly detect and harvest a whole range of CTCs from a patient blood sample, effectively a true liquid biopsy. The platform has been extensively validated by many renowned research centres, with impressive results published in peer reviewed journals. However, a key inflection point will be the US FDA approval, a first in the CTC harvesting field, which is expected later in 2021.
- **Commercial opportunities are sizeable** Management has embarked on a multi-faceted approach to address the various opportunities. In parallel with seeking FDA approval, it is now offering CTC analysis services to pharma companies and plans to launch LDTs that will be run in its own CLIA and ISO certified laboratories. These not only bring near-term revenues, but also act as demonstrators of clinical utility and accelerators of market awareness and adoption. In April 2021, the first large-scale pharma services deal was announced, worth $1.2m over 18 months, for longitudinal monitoring of prostate cancer clinical trials. Partnerships with established diagnostic players are also being explored.
- **rNPV model suggests a valuation of 255p/share** We have used a three-phase DCF model based on the various forecast revenue streams, which are then netted against cash. This generates a value of £549m, equivalent to 255p/share, with further upside as value inflection points, notably FDA approval and further pharma services contracts, are reached.

Price	111p
Market Cap	£239.1m
Enterprise Value	£210.5m
Shares in issue	215.4m
12 month range	39.8-120.0p
Free float	62.5%
Primary exchange	AIM
Other exchanges	OTC QX
Sector	Healthcare
Company Code	AGL
Corporate client	Yes

Company description

ANGLE is a specialist diagnostics company. Its proprietary Parsortix technology can capture and harvest very rare cells, including CTCs (circulating tumour cells), from a blood sample. The FDA approval for its clinical use to guide precision cancer care will open up further multiple commercial opportunities.

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Investment case

Focussed exclusively on CTCs, with a highly attractive platform

ANGLE is a specialist diagnostics company developing its proprietary Parsortix cell capture platform. This elegant system employs microfluidics to physically separate viable cells from a simple blood sample. Although it can be tuned to capture other rare circulating cells, for instance foetal, it is being developed mainly to harvest circulating tumour cells (CTCs). The key clinical programme, in metastatic breast cancer, has been filed with the FDA, with approval expected later in 2021. Continuing research applications have provided invaluable external validation, which coupled with FDA approval and the establishment of clinical service laboratories, sets the stage for multiple commercialisation opportunities. ANGLE is listed on the LSE AIM (AGL), though an eventual NASDAQ listing is possible. It is headquartered at the Surrey Research Park in Guildford, with operations in Canada and the US and employs over 100 people across the group. To date, ANGLE has raised c £60m, including £18.5m (net) in Q420, most of which has been directed to research and development activities.

Valuation

DCF model uses conservative assumptions and gives a value of £549m, 255p per share

We use a three-phase DCF-based model with detailed medium-term forecast revenues to 2031, followed by a ten-year trending period, and a 2.5% terminal growth rate. These income streams are discounted back and netted against the net cash position, resulting in a valuation of £549m, or 255p per share. In line with our policy, we employ conservative assumptions throughout. A clear value inflection point is FDA approval of the first clinical indication, currently anticipated during H221. As the emphasis shifts from development activities to commercial execution, we expect several value-inflection points in the coming 18-24 months.

Financials

Current cash and supportive investors underpin forecast medium-term funding needs

ANGLE had £28.6m in liquid funds at end-December 2020, with the receipt of a £2.1m R&D Tax Credit expected during FY21. Planned investment in establishing the CLIA/ISO accredited laboratories and creating LDTs, together with continued support of studies that expand the Parsortix system's utility, suggests, on our forecasts, a cash runway that extends to at least mid-FY22. There are multiple value-inflection points expected over the near-term and we believe there will be ample support for any equity raise from existing and new investors.

Sensitivities

Regulatory aspects paramount, closely followed by execution and financing risks

In common with most innovative healthcare companies, ANGLE's three main sensitivities relate to development and regulatory timelines, execution of the commercialisation plans, and the financial resources required to accomplish these. Impressively, considering the limited resources available, the key near-term sensitivity is the likelihood of FDA approval, the first in this field. Such *de novo* applications often encounter obstacles, but commercialisation plans are not dependent on a rapid approval. The development of the pharma services business line and the launch of its first LDT from the newly established clinical laboratories should mitigate this risk through nearer term revenue generation.

ANGLE: at the centre of CTC liquid biopsies

ANGLE is approaching a defining moment as its proprietary Parsortix platform is set to gain FDA clearance. This would be the first CTC harvesting system approved and only the third product authorisation for any liquid biopsy. CTCs carry vital information on a tumour's status and Parsortix allows their easy, reliable, and consistent capture. Commercialisation initiatives are already underway, with the development of a pharma services business and the expected launch of LDTs (Laboratory Developed Tests) from newly established clinical services laboratories in the US and UK. These act as invaluable demonstrators of how the Parsortix system enables targeted treatments, monitoring of responses, and improved patient outcomes. These activities are even now bearing fruit, with the first sizeable pharma services contract announced in April. Our DCF-based valuation is £549m (255p/share), which should rise materially as visibility on commercialisation initiatives and Parsortix's positioning becomes clearer.

ANGLE is a low risk play on the emerging field of targeted cancer treatments

ANGLE is well placed to benefit from the changes impacting many aspects of cancer care across the world. The greater understanding of the causes and drivers of cancer demonstrates clearly that it is a complex, dynamic, and, importantly, a heterogeneous disease. The multiple gene and environment interactions, and the involvement of numerous and variable biological pathways, means that any drug therapy needs to be targeted precisely to maximise efficacy. To achieve the goal of such precision medicines, reliable, robust, and affordable non-invasive diagnostic testing will be required. This clear need has led to the development of numerous liquid biopsy approaches.

Parsortix is a simple and effective platform to harvest CTCs for diagnostic testing

The Parsortix system is a simple, elegant, and versatile technology platform that can capture circulating tumour cells (CTCs). A compact benchtop system separates and collects the cells; these are easily harvested, and appropriate downstream tests are then used to identify the nature, status, and susceptibility of the tumour. Unlike competing technologies, such as ctDNA, the CTCs allow RNA and protein expression, giving a complete and accurate picture of the cancer, whether primary or metastatic. The entire process has been validated extensively by numerous leading cancer research institutions across a variety of tumour types, with the results published in respected peer-reviewed journals. The expected FDA clearance should transform awareness and help drive adoption into the various sizeable market segments, ranging from pharmaceutical services for cancer drug trials to clinical tests to support patient management.

FDA approval to accelerate the multiple routes to commercial success

However, management is aware that realising the opportunities presented by liquid biopsies requires more than being the first- or best-in-class technology. The supporting research and clinical evidence for the Parsortix system are now compelling and mounting. Regulatory approval will accelerate ANGLE's ability to form collaborations and partnerships with leading diagnostic players; but it is the establishment of CLIA and ISO accredited laboratories and LDTs (Laboratory Developed Tests) that demonstrate the Parsortix system's utility and facilitate the receipt of essential reimbursement codes in the important US market. We believe the successful interplay of these initiatives will determine the Parsortix system's positioning and scale of commercial success. It should be noted that even a relatively small share of such large opportunities would be transformative for ANGLE.

Right at the heart of the cancer revolution

Understanding of the drivers of cancers is growing daily

The revolution in cancer treatment has taken decades to come to fruition but finally we are on the cusp of a shift from "carpet bombing" with aggressive cytotoxic regimens to targeted therapies that reflect the current status of an individual cancer. This is driven by the wealth of knowledge unleashed by increasingly accessible genomic data, which has led to genuine insights into how tumours differ from each other and how they themselves evolve over time. Although it is the potential of novel therapies that harness the body's immune system that are making the headlines, equally important progress is being made across other fronts that enable these changes to clinical practice.

Tumour genomic profiling will decide the optimal therapy

Targeted therapies, such as immune checkpoint inhibitors (CPIs), have already started to transform the cancer treatment landscape and offer the hope of greater efficacy with fewer toxicities and side-effects. However, to truly realise their clinical value such selective drug regimens require a more thorough understanding of the nature of the tumour (and its metastatic offspring). It is now evident no two cancers are precisely the same and as a cancer can change over time susceptibility to treatment differs across patients (heterogeneity) and over time (longitudinally)[1]. This means a detailed initial appraisal and regular follow-up testing is a prerequisite for the effective deployment of this new era of precision medicines, both clinically and in terms of cost-benefit.

Exhibit 1: Comparison of solid and liquid biopsy properties

		Solid tissue biopsy		Liquid biopsy	
Source		**Primary tumor**	**Metastatic site**	**CTCs[1]**	**ctDNA[2]**
Sample type		Intact cells	Intact cells	Intact cells	Fragmented DNA
Procedure		Invasive	Invasive	Non-invasive[3]	Non-invasive[3]
Sample accessibility		Not always accessible	Less accessible	**Accessible using Parsortix[4]**	Accessible
Tumor heterogeneity		Site of biopsy sampling	Site of biopsy sampling	Multi-site sampling	Multi-site sampling
Patient recovery time		Varies	Longer	None	None
Test costs		Varies	Higher	Lower	Lower
Test turnaround time		Varies	Longer	Shorter	Shorter
Longitudinal monitoring[5]		Difficult	Very difficult	Easy	Easy
Molecular analysis	DNA	Yes	Yes	Yes	Yes
	RNA	Yes	Yes	Yes	Difficult
	Protein	Yes	Yes	Yes	No
Live cells	Cell culture	Yes	Yes	Yes	No
	Xenograft	Yes	Yes	Yes	No
Standard of care		Proven	Proven	Not yet proven	Not yet proven

1. CTCs (circulating tumor cells) are live cancer cells circulating in blood
2. ctDNA is cell-free circulating tumor fragments of DNA from dead cells, which may be found in the plasma component of blood
3. Tissue obtained from simple peripheral blood draw
4. Access to CTCs from blood is technically challenging given the low number of CTCs present and historically has been very difficult. ANGLE's Parsortix system has been specially designed to address this issue
5. Solid tissue biopsy information is a one-time snapshot and rapidly becomes outdated and does not reflect response to treatment and current mutational status. Liquid biopsy information is dynamic as tests can be repeated to provide real time information to monitor changes over time

Source: ANGLE

Tissue biopsy is still the gold standard but has drawbacks

For the majority of solid tumours, a tissue biopsy remains the "gold standard" and is the first step in confirming a diagnosis and obtaining a genomic profile to guide treatment. However, for some tumours (eg lung and brain) performing a biopsy can be challenging and in some cases impossible. Even where access is practicable, the incidence of complications can be an issue. More pertinently, where possible, the goal in most solid cancers is to surgically remove the primary tumour which hampers the repeat sampling that is required to monitor treatment efficacy.

[1] Molecular profiling for precision cancer therapies. Malone et al. Genomic Medicine 12 art 8 (14.1.2020)

Similarly, where metastatic disease is present it can be difficult to identify the distal tumour sites, let alone access them.

Aside from the practical difficulties, procedural risks, and patient discomfort, obtaining a tissue biopsy can be time consuming and costly. A straightforward biopsy can range from $500 to $2,000 in direct costs alone (Value in Health Journal, 2016). Hence the widespread pursuit for viable alternatives that are relevant, accurate, reproducible, accessible, relatively rapid, and cost effective.

Liquid biopsies are now a genuine alternative

The search for non-invasive assessment methods have led to a variety of "liquid biopsy" techniques, with over 50 companies known to be developing novel products and technologies. Typically, these centre on blood samples, but could include any appropriate and easily attainable bodily fluid. These exploit the fact that cancers tend to shed many elements ranging from intact circulating tumour cells (CTCs) through cell-free DNA (cfDNA) to RNA and exosomes. Consequently, these can be grouped into three main categories:

- **ctDNA (circulating tumour DNA):** Cancer patients have significantly higher levels of cell-free DNA compared with healthy individuals (up to three times) because tumours tend to have elevated cell turnover rates (due to apoptosis) and many more necrotic cells relative to normal tissue. The relative levels of ctDNA have been shown to correlate with tumour burden and the fragmentation pattern of ctDNA reflects its biology. Analysis of a blood sample can yield large amounts of important genetic information about the tumour, particularly using NGS (Next Generation Sequencing). Their high relative frequency and ease of detection has made cfDNA a popular method for testing mutation status (eg for KRAS).
- **CTCs (circulating tumour cells):** Simplistically CTCs are cancer cells that are shed into blood vessels from tumours which have the potential to develop metastases. As more is known about them, their complexity and roles suggest their biological signatures may be invaluable sources of clinical information. Initially collection was performed by chemical means, but since these tend to alter a cell's signature the consensus is shifting towards physical separation methods that leave a cell's biology intact. Subsequent downstream analysis, employing any preferred methodology, can then be performed as desired.
- **Exosomes and other extracellular particles:** Exosomes are small membrane-enveloped vesicles containing functional particles such as proteins, RNA, and DNA. Their role is still being elucidated but they are known to act in intracellular communication. Tumour-derived exosomes are thought to help prepare a favourable microenvironment at future sites of metastasis (called the premetastatic niche). Exosomes and other extracellular particles (including circulating RNA and proteins) are viewed as potentially attractive biomarkers due to their high stability in fluids. Whilst these may eventually become important diagnostic tools, their early stage means their biological significance is not fully understood and their clinical relevance is unproven.

A host of novel tumour detection technologies have appeared over the last few years, with the field becoming increasingly crowded, but none has yet emerged as a conclusive preferred methodology.

Circulating Tumour Cells hold the key to so much

A window into the tumour that can guide clinical practice through all stages of disease

Circulating Tumour Cells (CTCs) are extremely rare; they are outnumbered by normal, healthy blood cells by between one million and one billion to one[2]. Understandably, the challenge of locating a single CTC has been described as repeatedly searching for the proverbial needle in a haystack and finding it consistently and reliably. Although their relative number has been shown to be predictive of prognosis in breast cancer patients[3], it is the more recent advances in understanding a tumour's genetic make-up that has now brought them to the fore. Their real value lies in the amount of critical information they hold, particularly the information on RNA and protein expression that drive tumour growth, therapeutic sensitivity, forecast resistance mechanisms, and predicted aggression.

CTCs are heterogenous and understanding of their role(s) is growing

The existence of CTCs has been known for some time, with their role in metastasis first postulated by the Australian pathologist Thomas Ashworth in 1869[4]. An increasing variety of CTCs are being identified, with extensive heterogeneous sub-populations. These include viable cells that have been shed from a primary tumour into the blood circulation that can initiate and sustain metastases[5]. Another important group is the CTCs going through epithelial-mesenchymal transition (EMT) which are associated with heightened resistance and malignancy.

Similarly, the cancer stem cells and cell clusters that are also present may have important diagnostic and clinical roles. Work at the University of Basel suggests cell clusters are 50 times more likely to generate metastasis than individual CTCs and these are linked to the state of hypoxia in the original tumour. The findings[6] suggests that intra-tumour hypoxia creates conditions that stimulate formation of an increased size and number of CTC clusters, which may increase (rather than decrease) metastatic spread. This is clinically important as c 90% of patients that die of cancer die of metastatic spread, not due to the primary tumour.

Many ingenious approaches developed, with viable cells being the goal

Over the past two decades an impressive array of imaginative strategies has been developed to capture CTCs. These employ selection methods based on physical characteristics (such as size, density, deformability, and electrical charge) or cell-specific factors (such as cell surface marker expression), with varying degrees of efficacy. Many technologies have focussed on explicit markers (or sets) which proved to be exquisitely precise; however, growing understanding of the substantial heterogeneity of CTCs means their probable clinical utility has diminished. Increasingly capture methods are required that are able to collect pure and viable cells that are representative of the CTC subpopulations.

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[2] Circulating tumour cells: will they be clinically useful? J Natl Cancer Inst,102, 146-148 (2010) Nelson NJ et al

[3] Circulating tumour cells, disease progression, and survival in metastatic breast cancer. N Engl J Med 351(8):781-791 (2004) Christofanilli M et al

[4] A case of cancer in which cells similar to those in the tumours were seen in the blood after death. Aust Med J 14: 146–149 (1869) Ashworth T

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

[6] Hypoxia Triggers the Intravasation of Clustered Circulating Tumor Cells Cell Reports 32 108105 Sept 2020 Donato et al

A variety of CTC harvesting methods, but most have drawbacks

The various techniques for CTC capture include:

- **positive capture:** antibodies against CTC surface markers;
- **negative capture:** usually antibodies against leukocyte cell surface markers;
- **cell size separation** or **exclusion filtration:** smaller blood cells filtered out using membranes or novel nanostructures;
- **density gradient** separation;
- **dielectrophoresis:** separation via an electric field; and
- **spiral microchannels** (separation via drag forces).

Unfortunately, these methods often suffer from a lack of sensitivity[7] or poor specificity[8]. Notably, antibody-based separation can be problematic due to non-specific binding to non-tumour non-epithelial cells or binding to naturally circulating epithelial cells unrelated to the cancer.

Performance criteria for detection systems are well established

The key metrics[9] for CTC detection platforms are that they must be repeatable, reliable, rapid, cost-effective, and suited to large-scale production and clinical use. In addition, they need to capture extremely rare cells from clinically relevant blood volumes, usually 7.5ml to 10.0ml. These requirements have formed the basis for standardised performance criteria used to evaluate and compare the various CTC technologies: capture efficiency, purity, enrichment, throughput, cell viability, and release efficiency. It is worth noting that the Parsortix system scores highly on all six of these parameters.

Parsortix platform is proven and well documented

A deceptively simple solution that addresses CTC issues

The Parsortix system is an elegantly simple system that employs a standardised cassette, intentionally sized to be the same as a routine microscope slide, to separate circulating cells from a blood sample. The process has been engineered to rapidly collect highly enriched populations of CTCs, undamaged by labels or reagents. At its heart is a disposable plastic casing enclosing a series of three-dimensional steps that blood is channelled through. The patented technology uses micro-fluidics to capture, and subsequently harvest, CTCs based on their larger size and less deformable nature in comparison to other blood components.

Compact, flexible, automated, and easy to use

The system consists of a compact fully automated benchtop machine that processes a blood sample, in volumes ranging from >1ml to up to 50ml, without any additional reagents or stages. A standard 10ml sample takes 60 to 90 minutes.

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[7] **Sensitivity** (also called the true positive rate) measures the proportion of positives that are correctly identified. Put another way, if a disease test is highly sensitive and the test result is negative you can be nearly certain that disease is not present.
[8] **Specificity** (also known as the true negative rate) measures the proportion of negatives that are correctly identified. In other terms, if the disease test result for a highly specific test is positive you can be nearly certain that disease is present.
[9] Clinical and biological significance of circulating tumour cells in cancer. Molecular Oncology Vol 10 Iss 3 pp 408-417 (2016). Takaaki Masuda et al

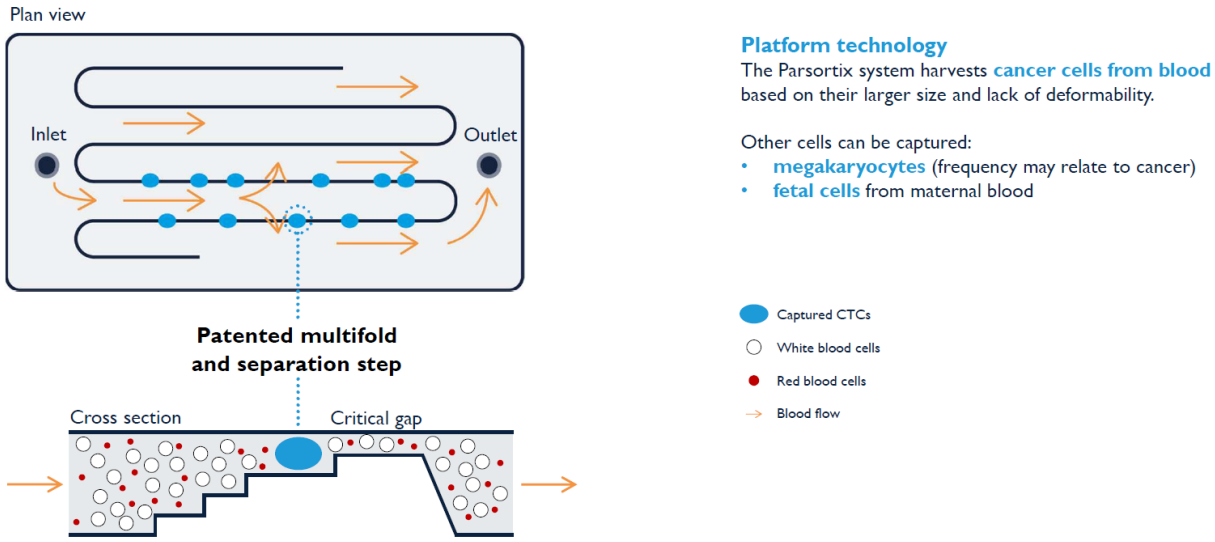
The CTCs can be harvested with a simple reverse flush into any external container. There is extensive intellectual property protection around key elements of the system.

Straightforward to use and consistently high quality outputs

The process has been deliberately designed to be straightforward so that limited technical expertise is required for routine operation. Although Parsortix will be used in central laboratories, the system is intended to be easily placed alongside other analytical equipment in a hospital laboratory (hence offering the potential of retaining the diagnostic test reimbursement within the clinic).

The Parsortix platform can capture all types of CTCs, including mesenchymal and cell clusters (which other microfluid-based system struggle with). The harvested CTCs tend to be of high purity, with minimal white blood or other cellular contamination, and ready for further downstream processing (eg morphological and cytological examination, immunofluorescence, FISH, DNA, RNA, and protein expression). Importantly, the recovered CTCs are intact, undamaged, and viable and so allow for great flexibility in subsequent testing.

Exhibit 2: Parsortix platform overview



Source: ANGLE

In summary, the Parsortix system is simple, effective, affordable, and solves the challenges of harvesting CTCs typical of membrane- and antibody-based systems. Historically, CTC capture technologies have been limited by complex sample processing, poor scalability, low sample purity, reliance on cell surface proteins for isolation, and dilute output volumes that require additional cell concentration steps. The ability of Parsortix to isolate CTCs without damaging the cells in the process is increasingly important, notably for personalised medicine applications when detailed genomic analysis may be desirable. It is these developments that underpin the shifts that should see cancers treated according to tumour status rather than tissue location.

No single liquid biopsy approach set to dominate

Effective liquid biopsies are a paradigm shift in cancer diagnosis and monitoring

Effective liquid biopsies will clearly play a central role in future diagnoses and their impact will affect several disciplines across the spectrum from drug development (as clinical trials are optimised through improved patient recruitment), to

diagnostics (with faster and more accurate screening), and treatment (as earlier diagnosis and targeted treatment improves outcomes). The attractions, both clinical and commercial, of a practical and reliable liquid biopsy has understandably drawn numerous players to the space. As discussed earlier, these employ a multitude of differing technologies that compete either directly (eg other CTC capture systems such as antibodies) or indirectly (eg analysing the genetic make-up through ctDNA). Exhibit 3 summarises how Parsortix is differentiated from other existing CTC platforms.

Exhibit 3: Parsortix compared to selected competitive platforms

Technology	Name	Simple and flexible process	Low cost	Captures all types of cancer	Captures mesenchymal CTCs involved in metastasis	Easily harvests cells for analysis	High purity of harvest	Cell viability (alive)	CTC Clusters
Microfluidic step	**Parsortix**	✓	✓	✓	✓	✓	✓	✓	✓
Antibody-based	CellSearch (only FDA authorised CTC system - enumeration)	✗	✗	✗	✗	✗	✗	✗	✗
	AdnaTest Biocept CTC iChip Cynvenio Gilupi Isoflux	✗	✗	✗	✗✓	✗✓	✗	✗	✗
Membrane-based	CellSieve ISET Microsieve Screencell	✓	✓	✓	✓	✗	✗	✗✓	✗
Field Flow Fractionation	Biolidics	✓	✓	✓	✓	✗	✗	✗✓	✗

Source: ANGLE

Clinical applications expected to increase as liquid biopsies become established

The clinical market is expected to grow both horizontally (more cancer types tested) and longitudinally (patients monitored more frequently) as liquid biopsies become better validated and their utility demonstrated. Initially the drivers will be the identification of proven biomarkers in selected solid tumour types to better guide treatment decisions. Over time this will broaden into exploring drug resistance and monitoring therapy response, as well as expanding into other cancer types. In the longer-term, liquid biopsy has the potential to improve the early detection of cancer overall and, as early diagnosis is usually closely linked to better survival, to dramatically alter mortality rates.

Collaborative technologies required to address the differing clinical needs

We expect the liquid biopsy segment to continue to evolve rapidly as results from large well-run studies help shape clinical practice. The decreasing cost of analysing genomic information, which appears to be following Moore's Law, should allow personalised diagnostics to be affordable, even by cash-strapped health systems, and greatly assist the rate of adoption of precision medicine. While possible, the emergence of one technology to dominate above all others is, in our view, unlikely. The diversity of clinical need means that we foresee certain applications becoming the choice in some segments but not others. For instance, we can see highly automated ctDNA being employed widely in the initial patient profiling, but the greater information available with CTCs means their role would be to provide a larger and more complete picture.

Parsortix is complementary to alternative liquid biopsies

A key point, in our view, is the Parsortix CTC harvesting system should be viewed as complementary to the emerging platforms, such as ctDNA, since the two can be easily performed from the same blood draw. The amount of clinically relevant

information generated is materially greater and would support better economics (typically reimbursement codes in the US) than either test in isolation. Realistically, the question from an investment perspective is how does Parsortix stack up against alternative CTC harvesting systems? The wealth of published data, coupled with key opinion leader support and forthcoming FDA approval suggests the Parsortix system is the acknowledged leader in its field.

The market opportunity is sizeable and growing

Cancer remains a major killer and economic burden is material

The cancer market is large, being the leading cause of mortality in economically developed countries and the second leading cause of death in developing countries, and growing, with incidence rising due mainly to ageing populations and environmental/life style factors. This is despite valiant sustained efforts to curtail known risk factors, notably smoking but also programmes such as HPV vaccination for cervical cancers. The incidence of 19.2m new cancer cases worldwide in 2020 is projected to rise by 43.2% to reach 27.5m cases by 2040. It is estimated that over one in three people in Western countries will be diagnosed with a form of cancer during their lifetime. Understandably, the costs of treatment and to society in general are huge. For instance, in the UK the direct cost to the NHS is over £5bn and the societal costs are over £18bn.

Different approaches but similar conclusions are reached

Against this backdrop the opportunity for liquid biopsy diagnostics is substantial. Multiple market research companies have published reports examining the current situation and forecasting likely sales for the various technologies. For instance, Verified Market Research estimates a 23.1% CAGR to a $5.03bn value between 2020 and 2027; Adroit Market Research sees the market growing at 33.4% CAGR to reach $6.01bn by 2025; Report Linker forecasts it reaching $12.9bn by 2030; and Research and Markets expects a $4.02bn increase between 2020-2024 alone. Interestingly, several earlier market research reports are, with the benefit of hindsight, seen to have been too conservative despite what were deemed aggressive forecasts at the time.

US set to be the early adopter and biggest market, with CTCs forecast as largest category

Although methodologies differ, a number of common themes emerge: the US is expected to be the largest market with rapid adoption once regulatory approvals help reimbursement clearance; lung cancer is a key target due to the difficulties with tissue biopsies, followed by metastatic breast cancer; CTCs will over time become the largest category as their flexibility and high amount of clinical data overtakes the rapidity and ease of ctDNA tests; vesicles and other promising technologies (including RNA testing and platelets) are likely to become important only later in the forecast periods; and the larger players will seek to claim a slice of this either through internal development or M&A.

Leading liquid biopsy players are committed

Current industry heavyweights endorse positive outlooks

Market research forecasts may appear ambitious, but they are reasoned. Guardant Health expects the current c 700k patients undergoing systemic treatment for advanced cancers to generate around $6bn/year in the US alone; with a further c $15bn over the medium term once the c 15m patients with neoadjuvant/adjuvant and recurrence monitoring indications are included; and over $30bn when, in the longer term, early-stage detection in the over 65m “at-risk” individuals is also factored in. Similarly, when Illumina sought to (re)acquire Grail in September 2020

(for $8bn) the accompanying presentation highlighted how the oncology testing market is expected to reach $75bn/year by 2035; driven by c 7m tests for therapy selection, c 20m tests for monitoring therapeutic response or disease recurrence, and over 150m to screen the asymptomatic "at risk" populations. It is worth noting that, in April 2021, the FTC challenged the proposed acquisition on competition grounds.

Four key activities required for commercial success

Guardant Health management sees the following four steps as critical prerequisites to the widespread adoption of liquid biopsy:

- the generation of compelling clinical evidence;
- gaining FDA regulatory approvals;
- establishing attractive reimbursement; and
- ensuring widespread oncologist adoption is achieved.

These key steps are reassuringly similar to the activities that ANGLE management has been working through over the past decade.

First key enablers for commercialisation are in place

Research publications form the bedrock to future clinical use

With such a disruptive device and, at the time, novel approach the creation of an extensive and powerful series of research evaluations was an essential external validation of Parsortix's utility. This has been fruitful with a number of very supportive publications from prestigious cancer research centres, such as MD Anderson Cancer Center and Barts Cancer Institute, and tie-ups for research use with renowned organisations such as Cancer Research UK (CRUK) Manchester Institute. To date, 42 papers from 26 leading cancer centres and across 24 differing cancer types have been published in peer-reviewed journals.

Generating proof of concept and great insights into potential applications

ANGLE has generated modest revenues from the sale of instruments and disposable cassettes for these research programmes; however, the real value has been in creating a compelling (and growing) body of evidence, generating proof of concepts across various cancer types, optimisation and standardisation of workflows, and reproducibility of results across multiple centres. Management calls this "leveraged research", as it generates far more valuable results than it could have funded directly. CTC clusters provide a pertinent example as the Parsortix platform has been a critical enabler in their identification and understanding of the roles they play in metastatic disease.

A well thought out path to commercialisation

Examining the "in-house" work, ANGLE's management has followed a pragmatic approach in preparing for commercialisation:

- The first phase saw numerous pilot studies carried out in various clinical applications to assess the Parsortix system's performance, which was used to guide development in the most promising areas;
- Larger, and more comprehensive, patient studies were initiated to document and validate how Parsortix works in a clinical setting, providing supporting evidence for the important regulatory process;
- Finally, after extensive dialogue with the FDA to prepare for the *de novo* regulatory submission, a successful 400 subject trial in metastatic breast cancer was undertaken with four prominent US cancer centres.

FDA approval will be a major achievement

Gaining FDA approval is a major undertaking but worth the effort

Parsortix is set to be the first system for harvesting CTCs from a blood sample to be approved by the FDA. The lead indication is metastatic breast cancer (MBC) but, once the initial data package has been reviewed, the subsequent indications will be more straightforward to process. The regulatory package for Class II clearance was made in September 2020 and followed a Q-Submission process to clarify the expected requirements for an uneventful review. The package included a review of over 15,000 samples and over 400 technical documents and reports. The analytical studies had to demonstrate that parameters such as precision, reproducibility, sensitivity, specificity, accuracy, and linearity, were all in place and robust when performed across multiple systems and centres.

Robust clinical studies at the heart of the submission

A key element was a 400-subject (200-patient) blinded clinical study performed by the University of Rochester Wilmot Cancer Center, together with the University of Texas MD Anderson Cancer Center, University of Southern California Norris Cancer Center, and Robert H Lurie Cancer Center Northwestern University. The primary objective was demonstrating the capture and harvesting of CTCs from MBS patient blood and demonstration of downstream analysis of the CTCs using cytopathological evaluations, FISH testing for HER-2 status, and RT-qPCR and cDNA libraries for RNA-seq assays.

Approval timelines uncertain but could be as soon as H221

Assuming smooth progress, the FDA clearance could be granted as early as H221. The Q-Submission process identified and addressed many known regulatory requirements; in March 2021 ANGLE announced that the FDA had issued an Additional Information Request (AIR) asking for some targeted additional analytical studies. Management believes these can be completed and the response submitted in May 2021. We note that the FDA has stated, in response to COVID pressures, it is extending the timelines in which it is processing certain submissions including *de novo* applications.

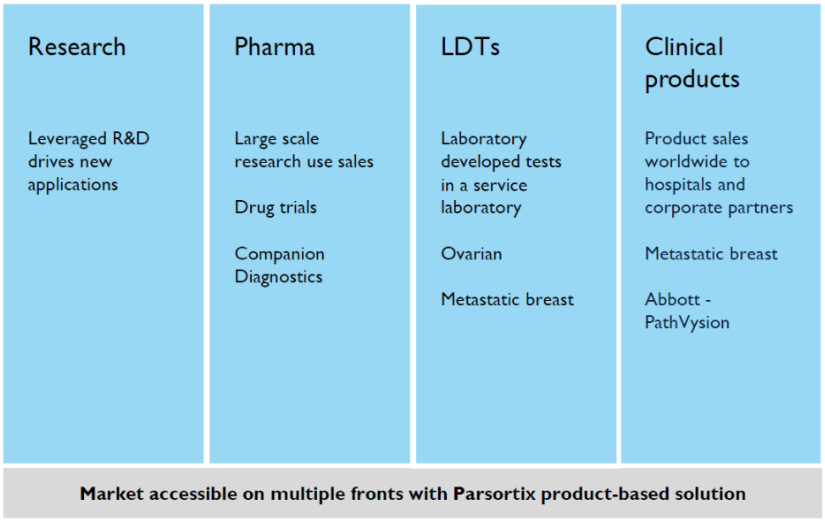
It should be remembered this is the first ever submission for the harvesting of CTC cells for subsequent analysis and we believe only the third product-based liquid biopsy that the FDA has cleared. Hence, over and above any COVID-related pressures, there is an inherent uncertainty as to the actual timings; although subsequent filings for additional cancer indications will be able to follow the 510(k) predicate device route, which should be more rapid and predictable. The importance of achieving FDA approval should not be underestimated as it validates the Parsortix system as a clinical device, opening up larger commercial opportunities.

Focus shifts from development to execution

Broad applicability across many points of the diagnosis and treatment journey

As mentioned earlier, Parsortix can be employed at multiple points in the emerging cancer treatment pathways, providing actionable decision-making information. This can range from the initial diagnosis to therapy selection and monitoring, recurrence monitoring and potentially, in the longer term, patient screening. This versatility, coupled with its ability to be used in conjunction with most downstream assays, means the commercial opportunities are significant, varied, and numerous. The challenge is to focus on the prospects that have the highest likelihood of rapid adoption and gaining of market traction, rather than simply those with the greatest theoretical revenue potential.

Exhibit 4: Four commercial streams targeted by Parsortix



Source: ANGLE

Four main commercial streams, as both product and service

Management is aiming to capture meaningful revenues through four streams:

- Research use (RUO);
- Pharma services, offering CTC analysis in clinical trials;
- Laboratory Developed Tests, offered from the clinical laboratories; and
- Clinical products, including through partners.

The flexible approach adopted makes this possible; for instance, the Parsortix system (instrument and disposables) can be bought as a stand-alone unit and integrated into a client's workstreams or a "sample to answer" approach can be provided, where ANGLE's own HyCEAD diagnostic platform provides the desired analysis, as both a product and as a service.

Research use – academic and industry

Research Use Only is easiest and quickest to address

Grant of FDA approval would be expected to broaden the existing research use only (RUO) to a wider audience and, in turn, generate further original papers and applications that would help cement the Parsortix system's position as a leading CTC harvest platform. To our minds, the value of RUO is to broaden awareness of the Parsortix system among the academic and research community and, through the publication of peer-reviewed papers, extend its utility and applicability. Hence, whilst being invaluable for credibility and validation, we do not view this as a major revenue stream when viewed in the context of the other commercial opportunities.

Pharmaceutical services

Clinical trial services are a near-term revenue opportunity

In contrast, use in oncology clinical trials could be a sizeable revenue stream. All pharmaceutical companies developing cancer therapies are seeking better biopsy tools, notably for patient targeting and monitoring, for use in their clinical trials. The clinical laboratories established in the UK (Guildford, Surrey) and USA (Plymouth Meeting, Pennsylvania) are well placed to provide these services. Blood samples from study patients would be sent to either location (the ability to maintain sample integrity for 96 hours means a global service can be provided), with the analyses ranging from simple enumeration to imaging to gene expression.

This is priced between $1,000 to $2,000 per sample, reflecting the degree of evaluation desired. Importantly, as this is deemed a RUO application, no external accreditation or regulatory approval is required.

First commercial oncology clinical trial deal struck

These business development efforts have already begun to bear fruit. In April 2021 the first large-scale services contract covering a clinical trial programme was announced. Reflecting the clear market need, an unnamed but sizeable pharmaceutical company is employing ANGLE and Parsortix to perform patient longitudinal monitoring in a large Phase III prostate cancer trial. The contract, worth c $1.2m over 18 months, also covers two Phase I studies that, if successful, would also involve longitudinal monitoring in later Phase II and Phase III trials. A key factor in the customer's selection criteria was the ability to also capture mesenchymal cancer cells and CTC clusters; since these may have important roles in the progression of disease, metastasis, and drug resistance.

Clinical trials could be a sizeable market, especially if study programmes are successful

Business development activities target companies developing the relevant oncology programmes and, pertinently, the CROs running the trials. Management is flexible in how these clinical trial CTC analyses are delivered; it can be either a direct service or a white label for the CROs to offer and bill. The commercial opportunity is sizeable as oncology trials are set to remain one of the most numerous clinical activities. Longer term, assuming successful clinical trial outcomes, these could help establish Parsortix as a routine test for patient and therapy selection once the drug candidate has been approved.

Our forecasts are based on conservative assumptions

We have modelled this revenue stream conservatively. We expect the initial typical contracts would address the earlier stages of clinical development, where patient numbers are smaller, with revenues becoming more significant when used in Phase III trials and beyond. It can be argued that FDA approval will be the gateway to widespread adoption by drug developers, but there is a need that ANGLE is already seeking to address. We expect these high-profile applications will be a valuable shop window and provide real-world evidence of the value-add a Parsortix analysis brings, Additionally, the revenues generated should provide a useful income stream to bridge across to the larger, but later, opportunities.

Laboratory Developed Tests for the clinical market

Clinical laboratories are where majority of tests are performed

We view the development of a clinical laboratory presence as a key element in the establishment of the Parsortix system as a liquid biopsy of choice. Given the clinical value is, arguably, easily demonstrated, we believe there are two critical steps that need to be addressed if Parsortix is to become adopted widely for the treatment and management of patients. The first is the establishment of economically attractive US reimbursement codes and the second is demonstration of commercial demand. Both are best addressed by developing and providing tests that are patient-relevant and market-ready.

In-house laboratory facilities to demonstrate and accelerate

The clinical laboratories in the UK and US would act as demonstrators of the services that can be offered, including complete workflows, and help accelerate the development and uptake of integrated diagnostic testing. Accreditation by CLIA (Clinical Laboratory Improvement Amendments) and ISO15189 is planned by year-end. This will allow the provision of commercial services and provide an important proof of concept for the larger CLIA laboratory networks. Once fully established, these sites will each have capacity to process around 2,000 tests per

month; they will initially service the expected clinical trial work mentioned earlier but will also provide the patient management tests once they are established (eg pelvic mass triage).

Successes here will pave the way for genuine commercial traction

Development of in-house Laboratory Developed Tests (LDT) will allow dialogue with US clinical payors to establish dedicated reimbursement codes (CPT codes), which are an essential step in driving widespread adoption and becoming established clinical practice. Assays for several of the more common diagnostic procedures are being developed, first as part of the pharma services offering and, once clinical studies have been successfully completed, as LDTs. These include enumeration of epithelial and mesenchymal CTCs and CTC clusters (features Menarini's Cellsearch cannot perform), monitoring PD-L1 status, and, when employed with its proprietary HyCEAD technology, multiplex expression profiling of up to 100 genes. Importantly, a pelvic mass assay to differentiate between a benign mass and ovarian cancer is also in late-stage development (see later).

Clinical products through partners

Partnerships with key diagnostic players to be a major element

In parallel with these activities, ANGLE has been cultivating relationships with major diagnostic players such as Abbott, Philips, and Qiagen to develop clinical products. The Abbott collaboration is an apt example, with the PathVysion HER-2 FISH Probe kit being used in the metastatic breast cancer studies. Between 20-25% of the 1.2m women diagnosed with breast cancer globally each year have amplification of the HER-2 gene. Treatment guidelines, such as National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO), recommend HER-2 assessment for all invasive breast cancers. PathVysion is the leading global HER-2 test and, once FDA approval is gained, both parties will be exploring how to optimise the routine testing of HER-2 status throughout treatment. For context, current thinking suggests the availability of a simple blood test would allow a four-fold increase in testing.

Parsortix development programmes

Comprehensive criteria used to select clinical programmes

The Parsortix system is agnostic as to the cancer type the CTCs originate from; however, management has carefully selected the indications for its initial clinical development. The primary goal was to achieve FDA approval of the platform and the metastatic breast cancer indication was ideal, but all the principal programmes being pursued are in areas where there is a specific need that cannot be easily addressed by potential alternative technologies. The criteria employed to select which clinical indications to progress was broad and comprehensive, including factors such as:

- Clear differentiation from other detection methods such as ctDNA, antibody- and label-based CTC assays, and any known emerging tests;
- Good access to current Key Opinion Leaders (KOLs) in the disease area (for expertise, relationships, patients, etc) and successful pilot data;
- A poor existing standard of care with significant problems (high unmet medical need); or
- A recognised existing test or current standard of care available for benchmark comparison;
- Required studies are easy to organise, recruit patients, have well-defined endpoints, and shorter timelines to results; and

- For the US, an existing CPT code to act as an administrative precedent and aid with reimbursement discussions; also
- Other considerations including barriers to market entry such as established clinical practice, cost, and vested interests.

Pelvic mass triage is a great showcase for Parsortix benefits

These criteria are showcased by the ovarian cancer test in development to triage women set to undergo surgery for an abnormal pelvic mass. The intention is to distinguish between a benign and malignant growth ahead of surgery and so direct the patient to the appropriate treatment option. Most women have benign masses and can be treated in local non-specialist units with conservative surgery (typically laparoscopy, since this is associated with lower morbidities and shorter hospital stays). However, for ovarian cancer patients the most important prognostic factors are accurate surgical staging, cytoreductive surgery, and the expertise of the gynaecological oncologist who performs the operation. Hence, these women should be referred directly to specialist centres.

Misallocation results in either a poor prognosis or unnecessary procedures and costs

However, the difficulty of an accurate pre-operative assessment means that many end up in non-specialist centres, resulting in a poorer prognosis, or, conversely, many women are operated on unnecessarily in a specialist centre, with longer recoveries, wasted resources, and higher costs. Various approaches have been tried to make an effective differential diagnosis, with physical examination, CA 125 and HE4 levels (ROCA scores), OVA1 testing, and ultrasound examination (trans-vaginal and colour Doppler sonography) being most commonly used. All have limitations and no system, or combination of approaches, performs to the desired standards in terms of specificity and/or sensitivity.

Clinical trials demonstrate good sensitivity and specificity

Two 200-patient clinical trials, ANG-001 in Europe and ANG-003 in the US, have reported positive results. ANG-001 was led by the Medical University of Vienna, with Vivantes and Charité, and ANG-003 was led by the University of Rochester Medical Center, Wilmot Cancer Institute. Parsortix showed a high degree of sensitivity (correctly identifying cancer) of up to 95% whilst at the same time achieving a higher specificity (low false positive rate) than existing tests (CA-125).

Developing an LDT allows more rapid commercialisation

The performance of the test has been optimised, with a larger number of RNA markers, and a 200-patient clinical verification study is underway with the University of Rochester Wilmot Cancer Center. Patient enrolment has completed, and patient status will remain blinded until the analysis is concluded. Headline results are expected during Q421. The test will be developed as an LDT that can be performed in an accredited laboratory, using the HyCEAD platform at ANGLE laboratories or third-party laboratories. If the study delivers as expected, management is hoping to launch an LDT around the end of 2021. The pelvic mass triage application is one of the three key commercial indications targeted by management.

The three priority addressable markets

Targeting segments with clear needs and fewer barriers to entry

The creation of CLIA and ISO-accredited clinical laboratories allows management to have direct control over a number of its commercialisation activities. Three priority applications have been identified and marketing plans are in place, with the provision of PD-L1 testing for immunotherapy clinical trials across multiple solid tumours the closest to fruition. Exhibit 5 details the size of the opportunity and management's assessment of its addressable market.

Exhibit 5: Pharma services PD-L1 addressable market

	PD-L1 Drug Trials	Price per sample (US$)	Number of patients per trial	Number of trials	Number of patients in trials	Number of repeat samples per patient	Addressable number of samples	Addressable market per annum	Target market entry
1	Phase 1	$1,200	84	273	22,932	2	45,864	$55 million	CY21
2	Phase 2	$1,200	102	867	88,434	3	265,302	$318 million	CY22
3	Phase 3	$1,200	719	233	167,527	4	670,108	$804 million	CY23
				1,373	278,893		981,274	$1,178 million	

Note: the same assay can be used for all three Phases. However sales will generally progress through the trial phases. Hence early sales will typically be Phase 1 trials.
Note: revenues shared with contract research organization providing the test. Note: successful drug trials may lead to ongoing clinical revenues as a companion diagnostic.

Data from Clinical Trials.gov. Search completed at 14.28pm on 09/10/2020. Search terms - Cancer and PD-L1 interventional trials which are enroling, in progress or active

Source: ANGLE

Assessing PD-L1 status in immunotherapy clinical trials

The PD-L1 status of a tumour is a critical determinant in selecting the appropriate immunotherapy regimens and, conversely, for clinical trials it is essential for selecting patients that will likely respond to the drugs under evaluation. PD-L1 status is typically established by tissue biopsy but, as discussed earlier, accessing the primary tumour is often difficult and, importantly, the tumour's status often changes materially over time. The importance of selecting appropriate and relevant patients for these studies, especially at the earlier stages when patient numbers are small and a single "rogue" result can significantly skew the data, means the benefits of a liquid biopsy are better understood and the barriers to adoption are lower.

Phase I trials are the ideal entry point, with larger studies to follow later

Once chosen for Phase I studies it would be expected that liquid biopsies would be employed through to the later clinical stages, with the number of samples growing to reflect the greater patient numbers and longer trial durations. Management is targeting the key development companies and CROs, with terms and scope for the first such service contract being negotiated.

Breast cancer is a major opportunity to highlight Parsortix

The second area is clinical testing for breast cancer, where the benefits of a liquid biopsy are clear, which will follow the FDA approval. ASCO (American Society of Clinical Oncology) guidelines on the use of biomarkers in treatment decisions for metastatic breast cancer reflect the growing understanding that a cancer's sensitivities will likely have altered during disease progression so treatment must change to reflect this. The two main issues are that many metastatic sites are not suitable for routine (and regular) biopsy and that the biomarkers currently examined (eg oestrogen [ER], progesterone [PR], and HER2) may not provide a sufficiently complete picture of a tumour's current sensitivities to direct effective treatment.

A large and obvious need that lacks an answer

An effective and validated liquid biopsy would make a significant difference to the outcomes of many women. Around 2.3m women are diagnosed with breast cancer annually, which now represents 11.7% of all cancers and has overtaken lung cancer (11.4%). Although the statistics are, arguably, not robust, around 6-10% of new breast cancer cases are initially Stage IV or metastatic and a further 20-30% of women with earlier stage disease become metastatic. A study by the National Cancer Institute (NCI) found that these numbers are rising as a combination of greater incidence and more women living longer with metastatic disease, concluding there is a consequent need for more resources and effort to be directed to their continuing diagnosis and treatment.

Exhibit 6: Breast cancer clinical tests addressable market

	Application	Reimbursement potential (US$)	Number of patients p.a. (US)	Number of tests per patient p.a.	Addressable number of tests per annum	Addressable market per annum	Target market entry
1a	MBC CTC harvesting (initial assay where biopsy not possible), analysis undertaken by clinical lab	$500	42,000	1	42,000	$21 million	CY21
1b	MBC presence, monitoring and therapy selection (complete assay offered)	$1,500	84,000	4	336,000	$504 million	CY22
2	Primary BC presence and monitoring	$1,000	280,000	4	1,120,000	$1,120 million	CY23
3	Remission monitoring in first 5 years after diagnosis	$500	985,000	2	1,970,000	$985 million	CY23
3	Remission monitoring beyond 5 years	$500	2,615,000	1	2,615,000	$1,308 million	CY23
					6,041,000	$3,917 million	

Note: revenues shared with the clinical laboratory providing the test.

Source: ANGLE

A sizeable addressable market

Exhibit 6 details the size of the opportunity and management's assessment of the addressable market. It should be noted that in all these assessments the revenues indicated would be shared with the actual test providers.

Pelvic mass triage is a real opportunity, both clinically and commercially

The third area is ovarian cancer testing, where the initial application would be triage of abnormal pelvic masses. Placing the magnitude of the issue into context: approximately one in five women will develop a pelvic mass sometime in their lives; yet only one in 72 will have ovarian cancer[10]. In the US, and other Western countries are similar, a woman has a 5-10% lifetime risk of undergoing surgery for suspected ovarian cancer, of which 13-21% are found to have ovarian cancer[11]. It is also worth noting that early diagnosis improves survival tremendously; a diagnosis at Stage I has a 90% survival, whilst at Stage III or Stage IV it drops to 19% and 3% respectively.

OVA1 combination test is the current best performer

Various approaches have been tried to make an effective differential diagnosis; all of which have limitations. No system, or combination of approaches, performs to the desired standards in terms of specificity and/or sensitivity. One of these, the OVA1 commercial test combines CA-125, transthyretin, transferrin, β-microglobulin, and apolipoprotein A1 and generates a single-number result. The combination of OVA1 test and physical assessment had a sensitivity of 96% in predicting malignancy, compared to only 75% for physical assessment alone and 93% for OVA1 test alone. However, specificity was lower, at between 35% and 55% for OVA1 and combined OVA1 test and physical assessment.[12]

Aspira Women's Health shows the scope of the ovarian cancer opportunity

As a useful peer comparator, OVA1 is Aspira Women's Health's largest product, with 12,898 tests performed in 2019 and 3,849 in Q420 (COVID dampened testing during 2020/1). The CPT reimbursement price for OVA1 is set at $897 (the related OVERA test is $950) and over half of all US women now have positive coverage. Aspira Women's Health is NASDAQ listed (ticker AWH), with a market cap of $566m. Their latest investor presentation presents a convincing overview of the US commercial opportunity for an effective ovarian cancer diagnostic.

[10] Siegel R et al. Cancer statistics, 2013. *CA Cancer J Clin.* 2013;63: 11-30
[11] ACOG Practice Bulletin. Management of adnexal masses. *Obstet Gynecol* 2007;110: 201–214
[12] Ueland FR et al. Effectiveness of a multivariate index assay in the preoperative assessment of ovarian tumors. *Obstet Gynecol* 2011;117:1289–1297

Exhibit 7: Ovarian cancer clinical tests addressable market

Application	Reimbursement potential (US$)	Number of patients p.a. (US)	Number of tests per patient p.a.	Addressable number of tests per annum	Addressable market per annum	Target market entry
1 Pelvic mass surgery triage	$1,000	200,000	1	200,000	$200 million	Q4 CY21
2 Watchful waiting monitoring	$1,000	550,000	2	1,100,000	$1,100 million	CY22
3 Remission monitoring	$1,000	230,000	2	460,000	$460 million	CY23
		980,000		1,760,000	$1,760 million	

Note: revenues shared with the clinical laboratory providing the test.

Source: ANGLE

Exhibit 7 shows ANGLE's assessment of the addressable market. As with Aspira Woman's Health's experience, the market opportunity increases materially beyond the initial triage diagnostic testing (notably for the "watchful waiting" monitoring, where the numbers of test opportunities are significantly larger).

For our modelling we have focussed on these three applications as the main elements of the clinical services and products offered (since they reflect management priorities), although other revenue streams, such as research use, will continue to accrue.

Sensitivities

Overall risks now reduced as Parsortix awaits FDA regulatory approval

In common with most innovative healthcare companies, the three main sensitivities relate to development and regulatory aspects, execution of commercialisation plans, and the financial resources required to accomplish these. The key near-term focus is on the likely timelines for FDA approval but, importantly, the emphasis is shifting from development to commercialisation.

The specific sensitivities, both on the upside and downside, are as follows:

Liquid biopsy is a fast moving and competitive technology area

In our view ANGLE has a noteworthy advantage over other CTC players; however, the liquid biopsy space in general is a complex, crowded, and competitive arena and there is a material risk that advances in technology could leapfrog Parsortix and bypass or reduce the need for a CTC capture platform.

Gaining market traction in the clinical settings will be key

Whilst Parsortix has been the subject of many positive publications, posters, articles and KOL endorsements, its true commercial value lies in its adoption in clinical practice. FDA approval does provide invaluable validation of the platform, but it will be its use in routine clinical settings (where even a small overall share represents sizeable volumes) that will drive meaningful revenue and profit growth.

Reimbursement codes are a prerequisite for significant clinical adoption

Accessing the clinical setting requires a multi-faceted approach. A critical step in the important US healthcare system is access to suitable reimbursement codes. Whilst some applications and LDTs may be initially reimbursed under existing codes, the novel, and more relevant to long-term success, applications will likely require new codes. This can be a lengthy and tortuous process, possibly requiring economic models that demonstrate compelling benefit. Although the clinical outcomes are, in our view, clear, the administrative processes will need to be navigated.

Protecting the intellectual property can be difficult

Parsortix's mode of action is elegantly simple and effective. ANGLE has employed a multi-layer IP strategy, having filed numerous patents covering the cassette and key elements of the platform and with some in the process of being granted. Nonetheless, as is common in this field, litigation risk remains an ever-present sensitivity.

Gaining traction against larger and well-funded competitors will be challenging

Much planning and effort has gone into commercialisation but addressing such large and competitive markets with novel technologies requires relevant clinical programmes to validate and support the technology and sizeable commercial teams to perform initial launches and indication roll outs. Such efforts are time consuming and expensive, with competitors being larger and well-funded. The concern is that unless rapidly partnered, Parsortix may struggle to gain traction.

A large opportunity, where even a small share would be transformational

However, these risks, whilst tangible, are in our view containable. Importantly, the company has worked well to mitigate these factors and the commercial opportunity, even if capturing only a small fraction of the overall market potential, is sufficiently attractive to merit attention.

Valuation

Our DCF-approach values ANGLE at £549m, equivalent to 255p per share

As ANGLE transitions from development of the Parsortix platform to execution of its commercial strategy so our preferred valuation methodology shifts from an rNPV approach to a DCF model. We employ a three-stage DCF based on comprehensive forecast cash flows to 2031, followed by a ten-year trending period, and a modest 2.5% terminal growth rate. We separately forecast cash flows for three business lines (research use, pharma services and LDTs, and clinical products) to reflect the differing markets, revenue potential, growth profiles, and R&D investment requirements that these represent. These are summed and netted against the central costs of running the business and current net cash/debt. Using conservative assumptions throughout, our model generates a valuation of £549m, equivalent to 255p per share (Exhibit 8).

Exhibit 8: Three-phase DCF valuation of ANGLE

Business line	NPV (£m)	NPV ($m)	rNPV (£m)	rNPV ($m)	rNPV/ share (p)	Notes
Research use	18.8	24.4	18.8	24.4	8.7	
Pharma services & LDTs	155.5	202.1	132.2	171.8	61.4	Includes priority LDT applications for PD-L1 and ovarian cancer triage. Overall 85% risk adjusment to reflect development and commercialisation risks.
Clinical Products	478.3	621.8	382.7	497.5	177.7	First meaningful sales FY23, following metastatic breast cancer launch in FY22; 90% risk adjustment for mBC programme.
Operating costs	(13.0)	(16.9)	(13.0)	(16.9)	(6.0)	
Net cash at FY20	28.6	37.2	28.6	37.2	13.3	
Total	**668.2**	**868.7**	**549.3**	**714.0**	**255.0**	

Source: Trinity Delta Note: 12.5% discount rate, 2.5% terminal growth rate, 20% tax rate, and $1.3/£ FX rate. mBC = metastatic breast cancer

Parsortix is an acknowledged leader in CTC capture

CTC-based diagnostics are likely to be employed across multiple clinical segments including as non-invasive assays for early detection of cancer; as prognostic tools for cancer survival and the prediction and monitoring of response to therapies; and in the development of new drugs for cancer. These are broad indications and large market opportunities but, as discussed earlier, the field is still immature, crowded, and no industry standard has yet emerged. As the clear leader, Parsortix is well placed to capture meaningful share of these indications, however, in line with our conservative philosophy, we employ modest assumptions in our modelling.

Our forecasts based on visible programmes only, with remainder leaving upside

For instance, we base our revenue assumptions on the three target areas detailed by management: PD-L1 testing as a service for immunotherapy clinical trials; liquid biopsy clinical testing for breast cancer, initially for the presence of metastatic disease then rolling out increasingly into monitoring and therapy selection; and ovarian cancer clinical testing, with the initial focus on pelvic mass triage and expanding into monitoring of the various resulting groups. Sales from RUO (Research Use Only) are also included but, as previously detailed, we do not assume these to be substantial in the context of the clinical revenue potentials.

Whilst we are arguably being overly cautious, it does leave scope for significant potential upside in our valuation as visibility increases with the execution of the commercialisation and partnering strategy.

Financials

FY20 results have year-end changed to December

ANGLE's FY20 results cover the 12 months to 31 December 2020, following the decision in January 2020 to change from the previous April year-end. The restated FY19 period covers the eight months to 31 December 2019.

Continued investment in technology platforms and infrastructure

FY20 revenues of £0.8m (FY19: £0.6m) consisted mainly of Research-Use Only sales (Parsortix systems and disposables), in line with management expectations as COVID restrictions limited work at customer sites. Operating costs of £14.4m (FY19: £9.5m) reflect the continuing spend on the development and validation of Parsortix's clinical application and commercial uses as well as the phasing in of investment required in its new clinical laboratories and pharma services business. Net loss for the full year was £11.6m (FY19: £7.6m loss).

Supportive UK and US investors

ANGLE's cash and short-term deposits of £28.6m at end-FY20 (FY19: £18.8m) were strengthened by the £19.6m gross (£18.5m net) share placing to new and existing US and UK institutional investors in November. FY20 R&D tax credits of £2.1m (FY19: £3.4m) are due to be received in FY21.

Numerous commercial opportunities as both product supplier and service provider

ANGLE's positioning as both an equipment supplier and a service provider mean that it is well placed to exploit multiple segments of the liquid biopsy market. The Parsortix platform is highly attractive, and has already been significantly de-risked; the company is now focused on commercialization with the goal of building a sizeable business. At the time of the share placing the company earmarked use of funds as follows:

- £7m to complete the FDA approval process in metastatic breast cancer, to finish the ovarian cancer LDT programme, and general working capital;
- £5m, in addition to a previous £2m investment, to establish the two clinical laboratories in the UK and US that will develop and perform the LDTs and clinical services that underpin near-term commercial plans;
- £6m to develop new assays and clinical studies to expand Parsortix's utility and applications; and
- £2m to support the measures to establish US reimbursement codes, expand sales, marketing, and business development activities, and to encourage further partnerships agreements.

Importance of accelerator and demonstrator roles should not be underestimated

The importance of the investment in the clinical laboratories should not be under-estimated. Pharma services and LDTs, which will be delivered through ANGLE's facilities, represent key near-term revenue opportunities; however, they also have a crucial role as demonstrators and accelerators for the more ambitious proposals to capture broader indications and applications, and the development and expansion of a product-based offering in parallel.

The liquid biopsy market is diverse and offers a multitude of opportunities. ANGLE's planned investments will help to position it as both an attractive service provider and/or enabling partner for players across the sector. Potential partners span medtech (downstream analysis), pharma (companion diagnostics), Clinical Research Organisations (drug trials) and/or reference laboratories (Laboratory Developed Tests). Securing future corporate parentship deals such as these will further catalyse and transform ANGLE's financial prospects.

Exhibit 9: Summary of financials

Year-end: Dec 31	£'000s	2018*	2019**	2020	2021E	2022E
INCOME STATEMENT						
Revenues		**628**	**581**	**762**	**2,315**	**5,469**
Cost of goods sold		(169)	(142)	(165)	(651)	(1,547)
Gross Profit		**459**	**439**	**597**	**1,664**	**3,922**
Operating expenses		(9,444)	(9,512)	(14,407)	(21,993)	(22,932)
Underlying operating profit		**(8,985)**	**(9,073)**	**(13,810)**	**(20,328)**	**(19,010)**
Share-based payments		(324)	(333)	0	(375)	(383)
Exceptionals		0	0	0	0	0
Other revenue/expenses		52	61	79	87	96
EBITDA		**(8,467)**	**(8,441)**	**(12,310)**	**(19,843)**	**(17,792)**
Operating Profit		**(9,257)**	**(9,345)**	**(13,731)**	**(20,617)**	**(19,297)**
Financing costs/income		8	(26)	(14)	(124)	(254)
Profit Before Taxes		**(9,249)**	**(9,371)**	**(13,745)**	**(20,741)**	**(19,551)**
Adj. PBT		**(8,977)**	**(9,099)**	**(13,824)**	**(20,452)**	**(19,264)**
Current tax income		1,387	1,482	2,139	2,574	2,188
Net Income		**(7,862)**	**(7,889)**	**(11,606)**	**(18,167)**	**(17,363)**
EPS (p)		**(8.2)**	**(4.8)**	**(6.5)**	**(8.4)**	**(8.1)**
Adj. EPS		**(8.0)**	**(4.7)**	**(6.7)**	**(8.3)**	**(7.9)**
DPS (p)		**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Average no. of shares (m)		95.5	163.7	178.0	215.4	215.4
BALANCE SHEET						
Current assets		**11,219**	**23,579**	**32,930**	**12,344**	**10,386**
Cash and short-term deposits		7,645	18,766	28,618	7,901	6,164
Trade and other receivables		828	627	1,443	1,078	1,199
Inventories		599	788	742	802	848
Other current assets		2,147	3,398	2,127	2,562	2,176
Non-current assets		**7,063**	**6,996**	**6,119**	**8,008**	**7,573**
Property, plant & equipment		1,475	1,508	1,176	2,648	1,839
Intangible assets		5,588	3,974	3,710	3,620	3,487
Other non-current assets		0	1,514	1,233	1,740	2,247
Current liabilities		**(2,398)**	**(2,777)**	**(3,777)**	**(2,872)**	**(17,459)**
Short-term debt		0	0	0	0	(15,000)
Trade payables		(2,398)	(2,425)	(3,343)	(2,574)	(2,407)
Other current liabilities		0	(352)	(434)	(298)	(53)
Non-current liabilities		**0**	**(1,201)**	**(928)**	**(928)**	**(928)**
Long-term debt		0	0	0	0	0
Other non-current liabilities		0	(1,201)	(928)	(928)	(928)
Equity		**15,884**	**26,597**	**34,344**	**16,552**	**(428)**
CASH FLOW STATEMENTS						
Operating cash flow		**(7,136)**	**(8,699)**	**(7,848)**	**(18,054)**	**(15,668)**
Profit before tax		(9,249)	(9,371)	(13,745)	(20,741)	(19,551)
Non-cash adjustments		1,074	1,498	2,268	1,273	2,142
Change in working capital		538	(767)	228	(601)	(578)
Interest paid		0	0	0	(124)	(254)
Taxes paid		501	(59)	3,401	2,139	2,574
Investing cash flow		**(5,466)**	**(15,564)**	**(1,966)**	**(2,156)**	**(563)**
CAPEX on tangible assets		(1,861)	(595)	(506)	(2,156)	(563)
Acquisitions/disposals		(3,613)	0	0	0	0
Other investing cash flows		8	(14,969)	(1,460)	0	0
Financing cash flow		**14,391**	**16,675**	**18,143**	**(507)**	**14,493**
Proceeds from equity		14,391	16,921	18,650	0	0
Increase in loans		0	0	0	0	15,000
Other financing cash flow		0	(246)	(507)	(507)	(507)
Net increase in cash		**1,789**	**(7,588)**	**8,329**	**(20,717)**	**(1,738)**
Cash at start of year		5,536	11,010	3,757	12,080	(8,637)
Cash at end of year		**7,321**	**18,766**	**28,618**	**7,901**	**6,164**
Net cash at end of year		**7,645**	**18,766**	**28,618**	**7,901**	**(8,836)**

Source: ANGLE, Trinity Delta. Note: Adjusted numbers exclude exceptionals. * FY18 relates to 12 month period ending 30 April 2018, ** FY19 relates to 8 month period ending 31 December 2019. £15m need to finance shown as illustrative short-term debt in FY22e.

Company information

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Key personnel

Person	Position	Biography
Garth Selvey	Non-Executive Chairman	Appointed Chairman in 2007, having joined as a non-executive director in 2006. Previously Group Chief Executive of Comino Group plc from 1997 until its sale to Civica plc in 2006. Prior roles include Managing Director of TIS Applications Ltd from 1984 until its sale to Misys plc in 1989. Holds a BSc in Physics and Electronics Engineering from the University of Manchester.
Andrew Newland	CEO	Founded ANGLE in 1994. Over 28 years' experience in creating and building technology-based businesses. Founded Acolyte Biomedica, a medical diagnostic company spun out of the Defence Science and Technology Laboratory Porton Down, and Provexis, a specialist nutraceuticals company spun of the Rowett Institute. From 1982 to 1994 worked for KPMG. Holds an MA in Engineering Science from the University of Cambridge and is a Chartered Accountant.
Ian Griffiths	Finance Director	Joined in 1995. Previously KPMG for seven years, both within the accountancy practice and High Technology Consulting Group. Holds a BSc in Mathematics with Management Applications from Brunel University and Chartered Accountant.
Paul Smith	VP, CEO ANGLE Biosciences	Joined in 2017. CEO of ANGLE Biosciences Inc. Previously CEO of Axela Inc and Vice-President, Sales Europe and North America and Director, European Operations for Ciphergen Biosystems Inc. Over 30 years experience in sales and marketing in life science instrumentation.

Top institutional shareholdings

	% holding
Conifer Management LLC	9.62%
Morgan Stanley Investment Management	6.50%
Dermot Keane	5.93%
Fidelity International Ltd	5.25%
Chelverton Asset Management Limited	3.95%
Andrew Newland (Management)	3.28%
M E Denning	3.02%
Top institutional investors	**37.55%**
Other shareholders	62.45%
Total shareholders	**100.00%**

Source: ANGLE

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Disclaimer

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