Liquid biopsy
Cells for precision medicine
January 2016
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Precision medicine

Cancer Research UK: “One in two people born after 1960 in the UK will be diagnosed with some form of cancer during their lifetime.”

- Each patient’s cancer is different
- Patient’s cancer changes over time
- Effective treatment requires personalised care
- Reducing healthcare costs

- Major pharma developing more selective drugs
  - Colorectal cancer KRAS- Erbitux (Merck Serono)
  - Lung cancer EGFR+ Iressa (AstraZeneca)
  - Breast cancer HER2+ Herceptin (Genentech)
### Obtaining cancer cells for analysis

#### Existing approach: solid tumour biopsy

- Clinicians cut out part of the tumour and analyse the cancer cells
  - Breast cancer mastectomy or lumpectomy
  - Colorectal cancer colonoscopy tumour biopsy
  - Prostate cancer fine needle biopsy and prostatectomy

- Difficulty in accessing some tumours
  - Pancreatic cancer, Lung cancer, Brain cancer

- Repeat tumour biopsy problematic

#### New approach: liquid biopsy

- Harvest intact cancer cells from blood
- Non-invasive, repeatable, real time, cost effective
- But only one CTC in one billion blood cells

Whole blood from a simple peripheral blood draw contains approximately one cancer cell per ml of blood. The cancer cells are circulating tumor cells shed by the primary tumour in the process of metastasis. The CTCs travel in the blood and if they take root in another organ are the cause of a secondary cancer at a new location.
Animation showing Parsortix patented steps
Video showing blood flowing in Parsortix cassette
ANGLÉ’s patented Parsortix system

- Stepped, microscale cell separators for fluid flow and cell separation
- Two granted US Patents
  - Granted patents in China, Canada and Australia
- Patents pending worldwide
  - European patent expected later this financial year
Market size and drivers

- Total addressable market for liquid biopsy US$ 14 billion in the United States market alone by 2025

- Four key market segments
  - Diagnostic screening
  - Therapeutic decision-making
  - Minimal residual disease
  - Post treatment monitoring

- Liquid biopsy comprises ctDNA and CTCs
  - “Whole cells (CTCs) offer the advantage of providing a clinician access to cellular morphology along with other genetic content such as RNA”
  - “CTCs are exceedingly rare … and more difficult to isolate the ctDNA”


**ANGLE is changing the paradigm by making it easy to isolate CTCs from patient blood for a wide range of cancers**
## Competitive differentiation in a $ multi-billion market

ANGLE is offering customers a Parsortix system for purchase comprising a desktop machine and a one-time use consumable. Many competitor systems are so complicated that they have to offer a CLIA (certified laboratory) solution where the customer sends them the sample and they operate the system and provide a result. This approach is commercially less attractive as it requires large in-house investment, is less scaleable and deprives the clinical customer of much needed revenue in processing the samples.

### Technology Comparison Table

<table>
<thead>
<tr>
<th>Technology</th>
<th>Name</th>
<th>Simple process</th>
<th>Low cost</th>
<th>Captures all types of cancer</th>
<th>Captures mesenchymal CTCs involved in metastasis</th>
<th>Able to easily harvest cells for analysis</th>
<th>High purity of harvested cells</th>
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<tr>
<td><strong>Microfluidic step</strong></td>
<td>Parsortix</td>
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<td>✓</td>
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<td>Antibody-based system</td>
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<td>Centrifugation</td>
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<td>Cell-free DNA</td>
<td>Alternative process using plasma from blood</td>
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<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>N/A (1)</td>
<td>✗</td>
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</tbody>
</table>

(1) Cell free DNA techniques can only analyse DNA, not RNA or proteins.
Path to commercialisation

Translational research for clinical applications
Ovarian cancer: Vienna
Breast cancer: USC Norris
Prostate cancer: Barts
Colorectal cancer: MD Anderson
Lung cancer: CRUK
Pancreatic cancer: Cambridge
Others being developed
Research use sales to support drug trials and other research

Following successful evaluations of the system by KOLs, ANGLE commenced research use sales in Q4 CY15 addressing a research use market of $375m p.a.

Secondary market providing establishment revenues, building market awareness and third party evidence to support clinical applications in multiple cancer types

750 addressable Phase II cancer drug trials p.a.
- typically 100 patients two years 3 blood tests per patient
- each trial potential to generate >$150,000 revenue for ANGLE

120 addressable Phase III cancer drug trials p.a. initiated each year
- typically 1,000 patients three years 5 blood tests per patient
- each trial potential to generate >$1m revenue for ANGLE

Securing 5% of the Phase II and Phase III trials as customers offers potential Parsortix revenues of $12m p.a.

Cancer drug trials leading to a new drug may lead to the adoption of Parsortix as a companion diagnostic (CDx) for that drug

<table>
<thead>
<tr>
<th></th>
<th>Machine</th>
<th>Cassette</th>
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<tbody>
<tr>
<td>Price</td>
<td>£40,000</td>
<td>£150</td>
</tr>
<tr>
<td>Cost</td>
<td>£12,000</td>
<td>£17</td>
</tr>
<tr>
<td>Margin</td>
<td>70%</td>
<td>89%</td>
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</table>

1. High margins allow flexibility in pricing for competitive advantage
2. Includes maintenance, technical support, sales and distribution
Sales of the Parsortix system for clinical use is the primary objective for commercialisation of the business.

Estimated clinical market available to ANGLE in excess of $12 billion p.a.

Requires both regulatory authorisation and patient data.

ANGLE has a comprehensive strategy to deliver clinical sales:
- regulatory authorisation
- key opinion leaders
- patient studies
- corporate partnerships

Multiple KOL studies in progress to investigate new clinical applications for the treatment of patients.
Ovarian cancer: clinical application in development

Medical University of Vienna

- Highly successful patient study
  - 100% specificity in primary epithelial ovarian cancer (no false positives)
  - 78/80% sensitivity with 7 RNA markers
  - 100% sensitivity with 30 RNA markers

- Parsortix results “sensational”
  - best CTC alternative only 24.5% sensitivity

Clinical application in triaging patients with abnormal pelvic mass
- to identify those at high risk of ovarian cancer
- in US, 200,000 women p.a. have surgery on abnormal pelvic masses c. 10% have cancer
- Medicare reimbursement of $516/test

Clinical study over 18 months

Ovarian sales potential >$450m p.a.

Parsortix effectiveness compared to other tests

Sensitivity
The test correctly identifies those with the disease (true positive). A low sensitivity means the test may miss many people who have cancer (false negative).

Specificity
The test correctly identifies those without the disease (true negative). A low specificity means patients are told they may have the disease when they do not (false positive).

Key
- Green: Sensitivity
- Blue: Specificity
- Dashed line: Target level

Test Result
<table>
<thead>
<tr>
<th>Cancer</th>
<th>No cancer</th>
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<tr>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Positive</td>
<td>True Positive</td>
</tr>
<tr>
<td>Negative</td>
<td>False Negative</td>
</tr>
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</table>

1. Target for clinical studies
2. Vermillion Inc.
3. Patient.co.uk / Fritsche HA, et al. (1998); CA-125 in ovarian cancer advances and controversy. Clinical Chemistry, 44(7):1379-1380
Prostate cancer: mesenchymal cells

Barts Cancer Institute

- CTCs harvested in 100% of patients (n=52)
- Barts study demonstrates Parsortix harvested cells are clinically relevant in prostate cancer
- Mesenchymal cells (involved in metastasis) as well as epithelial cells
- Clinically relevant cells harvested

- Barts researchers now investigating molecular biomarkers on the harvested cells to guide effective treatment

Figure 3. Representative images for different populations of detected cells in prostate cancer patients. The upper row: a CK+/Vimentin+/CD45- cell surrounded by CD45+ lymphocytes. The middle row: a CK+/Vimentin+/CD45- cell next to a CD45+ lymphocyte. The lower row: a CK+/Vimentin+/CD45- cell surrounded by CD45+ lymphocytes.
Breast cancer: metastatic biopsy comparison

University of Southern California Norris Comprehensive Cancer Center

- CTCs harvested for RNA Seq analysis in 100% of patients
- CTCs from Parsortix liquid biopsy had similar patterns of gene expression to the traditional biopsy of cancer cells from metastatic sites in all cases (n=4)
- Parsortix liquid biopsy also provides additional clinical information beyond the biopsy of a single metastatic site
- Metastatic biopsies invasive, often requiring surgery, expensive and may delay treatment

Hierarchical two dimensional heat map of 214 genes differentially expressed in CTC and met vs peripheral blood.
Lung cancer: out-performs other systems

Cancer Research UK Manchester Institute and Christie Hospital

- CTCs harvested 100% patients (n=12)
  - Parsortix harvested >5 cells from 100% of patients compared to 58% by leading competitive system
- Suitable for at least four days at room temperature
- Simple plug and play device
- Enables analysis of CTCs not detected by epitope dependent technologies
- Parsortix enables processing a single blood sample for both CTCs and cfDNA

Ged Brady, Cancer Research UK Manchester Institute
“The Parsortix system has a unique combination of features making it suitable for routine clinical analysis of patient blood samples. We have now incorporated the Parsortix workflow into multiple clinical trials and have been accumulating many hundreds of stored enriched samples that will be of immense value in our future CTC studies.”
Corporate collaborations with diagnostics companies

Cost-effective distribution channel
Parsortix “open source” as a front end for existing analytical platforms deployed worldwide giving them new revenues

So far two commercial collaborations announced

Diagnostics division of a large pharmaceutical company
- combine Parsortix CTC harvesting platform with their single cell analysis system
- Parsortix system may be sold as a source of patient samples for analysis using the Collaborator’s analytical platform

EKF Diagnostics Holdings plc
- combine Parsortix CTC harvesting platform with EKF’s PointMan™ DNA enrichment technology: liquid biopsy to identify genetic variation in the cancer
- explore ways to offer the systems as a combined solution from blood to medical result

ANGLE’s commercialisation strategy is to establish a series of partnerships with major medtech players such as Roche, Illumina, Abbott, Life Technologies, Qiagen, Hologic, Agilent, Siemens Healthcare, bioMérieux etc
Summary

Parsortix patented system provides cells for precision medicine changing the paradigm in a $ billion emerging market

- High performance in ovarian, prostate, breast and lung cancers
- Growing research use sales with a clear competitive advantage
- CE Mark authorised. FDA approval in process
- Ovarian cancer first clinical application in development

Parsortix system + key opinion leader + patient data + regulatory authorisation + clinical application = $bn market
Contact details

Andrew Newland
ANGLE plc
3 Frederick Sanger Road
The Surrey Research Park
Guildford GU2 7YD
United Kingdom
Tel:  +44 1483 685830
Email:  andrew.newland@ANGLEplc.com
Website:  www.ANGLEplc.com

3711 Market Street
University Science Center 8th floor
Philadelphia PA 19104
USA
Tel:  +1 (267) 265 6761