

Early Detection Biomarkers workshop

Workshop Report



Workshop summary

14 delegates from a variety of specialities attended the one-day workshop, held at Imperial College London.

Chaired by Prof. Bob Brown (Former Chair of NCRI Biomarkers and Imaging CSG) the workshop aimed to:

- 1. Outline and define the clinical unmet need in early detection**
- 2. Highlight what initiatives are underway**
- 3. Explore which samples and technologies exist which are fit for purpose**
- 4. Initiate a collaborative project**

The workshop has been summarised below:

Introduction

On 17th June, 2014, the NCRI Biomarkers and Imaging Clinical Studies Group ran a closed workshop with an aim to attract delegates who are current researchers within various scientific fields applicable to early diagnosis. The main purpose of the workshop was to bring together a small group, representing cross-disciplines, to explore potential for a national study on early detection of cancer, with a particular focus on high risk patients linked with Primary Care groups. In these initial stages, the workshop was kept small, however, there is scope to involve the wider community as this moves forward.

The workshop agenda was composed of two sessions; the first, a series of short 10 minute presentations summarising current state of the art science and technologies, work in progress and current bottlenecks or challenges in early detection research. The second session was a structured discussion, to map out where the major clinical unmet needs are and what is realistic to achieve in the area of early detection biomarkers.

Sessions

A brief summary of each session is given below

1. Session One - Summary of current status and challenges

Chair: Professor Robert Brown, Imperial College London

Session one included presentations on the following:

1. Clinical unmet need: The NCRI Primary Care CSG Perspective
2. Current status: SPED Perspective
3. Biomarker challenges: The NCRI Biomarker & Imaging CSG Perspective
4. Surgery and imaging
5. Genetics risk markers
6. Epigenetic risk markers
7. The Exposome and Environmental biomarkers
8. Circulating DNA/RNA
9. Metabonomic profiling of patients
10. Cancer Research Technologies/CRUK perspective
11. MRC perspective

1.1 Clinical unmet need: the NCRI Primary Care CSG perspective

Professor Richard Neal, University of Bangor & Dr Fiona Walter, University of Cambridge

Professor Neal and Dr Walter highlighted the current unmet need in diagnosis and early diagnosis in primary care practice. With 75% of cancers being diagnosed after symptomatic presentation and a small proportion through emergency admission, there is a great need for additional diagnostic tools in primary care, especially for those cancers which are difficult to diagnose.

There are few biomarkers used to diagnose cancer and the standard biomarkers generally used detect 'clinically unimportant' cancers. What we consider to be a biomarker was also discussed: Prostate Specific Antigen (PSA), a current biomarker for prostate cancer, detects many prostate conditions and results of PSA assays produce many false positives. Significant improvements are needed for more biomarkers in antecedent, screening and diagnostic contexts.

1.2 Current status: SPED perspective

Professor Mahesh Parmar, NCRI SPED Chair; NIHR CRN; Medical Research Council

Professor Parmar gave an overview of the NCRI Screening, Prevention and Early Diagnosis Group (SPED), which was established in response to poor submissions of new ideas and studies in this area. The Group has representation from each Clinical Studies Group (CSG) and helps all CSGs to converge, providing a forum for discussion, study generation and collaboration.

SPED also aims to act as a nurturing environment to encourage further development and maximise potential for new studies, i.e. covering more than one cancer type. Success or efficacy performance for SPED is difficult to measure; however a number of studies are under discussion and are being taken forward. SPED will also hold an open workshop, welcoming proposals from outside investigators who wish to gain expert opinions on their studies. Prof. Ian Cree has presented at SPED which may bear some commonalities with the aims of this workshop.

1.3 Biomarker challenges: The NCRI Biomarker & Imaging CSG perspective

Professor Craig Robson, Newcastle University

Professor Robson highlighted challenges in biomarker research, including deciding which biomarker is the best to use. There are many current initiatives run by the former Biomarkers and Imaging CSG, which include further workshops, CTAAC advisory panel, advice on clinical trials e.g. BRITROC, i-Knife analysis and advice to other CSGs such as attendance to the Prostate CSG strategy day.

The Biomarkers and Imaging CSG has undergone restructure and a number of work streams will be delivered across two expert advisory groups: Imaging Advisory Group (Chair: Dr Fiona Gilbert) and the Molecular Biomarker Advisory group (Chair: Professor Craig Robson). The Molecular Biomarkers Advisory Group aims to continue working with CSGs, advise on funding and create a bank of national leads in particular areas of biomarkers.

1.4 Surgery and imaging

Dr Sadaf Ghaem-Maghani, Imperial College, London

Dr Ghaem-Maghani presented on dilemmas in surgical treatment of cancer, particularly ovarian cancer. There are no predictive bio-indicators for surgical outcome, to help decide on treatment paths. Presently, diagnosis of ovarian cancer can be complex in ovarian masses. There are no definitive diagnostic conclusions across many ovarian cancer diagnoses for both pre-and post menopausal women, which may provide predictive measures for surgical intervention.

Combining OMICS (i.e. genomics, proteomics or metabolomics) with imaging is worth exploring in addition to improving sensitivity and specificity on current potential biomarkers. Programmed death-ligand 1 (PD-L1) has also shown potential as an indicator for ovarian cancer; however, it is still difficult to define a cut-off point from a benign to a malignant tumour.

1.5 Genetics risk markers

Dr Paul Pharoah, University of Cambridge

Dr Pharoah discussed polygenic cancer risk, the importance of identifying risk in the population and targeting intervention towards those at risk. The talk highlighted various analyses for predicting risk, which gave emphasis on the importance of using the correct predictive model. The talk outlined that very few women are at sufficiently high risk to warrant surgery or MRI. Analysis has shown some women are at fairly low risk, with half of 50 year old women have <2% chance of dying from breast cancer before age 80. Those at low risk may consider that the harms of screening outweigh the benefits.

1.6 Epigenetic risk markers

Dr James Flanagan, Imperial College London

Dr Flanagan presented on epigenetics and the study of the epigenome for use in identifying cancer risk. The talk outlined epigenetics as code for how much of a gene is made and the complexity of the epigenome being one Human Genome Project vs. four million Epigenomes Project.

Epigenome-Wide Association Studies (EWAS) analysis has been shown for smoking status, using both blood and lung tissue. Results are measured using a Methylation Index to predict former smokers, quantify past exposure and possible smoking-associated risk with potential for improved accuracy of risk prediction, e.g. Attributable risk (AR) for breast cancer in non-smokers is -0.2% and current smokers is 10%. Overall, 10% of the risk of breast cancer associated with smoking is due to methylation at this marker. What about other cancer risk exposures?

1.7 The exposome and environmental biomarkers

Professor Paolo Vineis, Imperial College, London

Professor Vineis presented on 'exposomics' as a new paradigm for studying the environmental causes of disease. The talk outlined the strengths in exposome research and applications in Personal Exposure Monitoring (PEM) and international partnerships via extensive cohort resources. Research looks promising in this new area with further resources being made available via the MRC-NIHR National Phenome Centre and further research in metabolomics, adductomics and epigenomics. Ongoing studies include:

Exposure comparisons (UFP) from suburban homes to the city/working environment. Exposomics might be applied to early diagnosis in many ways such as exposure characterization to early disease markers.

1.8 Circulating DNA/RNA

Dr Jacqui Shaw, University of Leicester

Dr Shaw gave an overview of circulating tumour DNA (ctDNA) as a tool for early detection of cancer. Plasma and ctDNA samples can vary by patient; standardisation across sample handling, condition, testing and patients is required. The talk described how ctDNA can assist in the 'curable period' as ctDNA is detected in this time and it may also be useful in tracking mutations in metastatic disease. There are, however, some challenges for this technique such as standardisation of approaches, pre-analytical processing, low levels of ctDNA in early stage disease, assay sensitivity and homogeneity of shedding.

1.9 Metabonomic profiling of patients

Dr Hector Keun, Imperial College London

Dr Keun gave an overview of metabolic profiling (metabolomics/metabonomics) and the work of the MRC-NIHR National Phenome Centre & Clinical Phenome Centre. Future projects include supporting activity of NIHR Biomedical Research Centres. Future research also includes investigation into biofluids, high-throughput MS, solid-state (tissue) MAS-NMR, in addition to tissue metabolomics and imaging using mass spectrometry.

1.10 Cancer Research Technologies/CRUK perspective

Dr David Jenkinson, Cancer Research Technologies

Dr Jenkinson gave an overview of Cancer Research Technologies (CRT) programmes in early diagnosis. The Abcodia/CRUK/CRT consortium is running a longitudinal discovery programme. This programme uses the sample set of a controlled trial, the UK Collaborative Trial of Ovarian Cancer Screening (UCTOCS), which gives up to 3 time-points per case and has a pilot phase to determine technologies to use. There are currently four cancers of interest: Lung, Colorectal, Oesophageal and Pancreatic.

The consortium is making steady progress, with the beginning of a discovery phase anticipated in late 2014. Early diagnosis strategy continues to be developed with increased funding and discovery of new routes to diagnosis.

1.11 MRC perspective

Dr Louise Jones, Medical Research Council

Dr Jones presented on potential models for an early diagnosis platform and gave an overview of similar programmes employed by the Medical Research Council, such as the MRC UK Dementias Platform (UKDP). The UKDP is a national, collaborative and managed 5yr + programme to assemble the world's biggest dementia research cohort and a resource for the scientific community. The aim of this programme is to identify the molecular determinants of neurodegenerative disease, integrate knowledge of co-morbidities, translational research and public health interventions. This model seeks to drive partnership between academia, industry and make international links.

Dr Jones also presented on the UKDP cohorts and methods development covering a wide range of activity including informatics, the design of clinical trials, the derivation of cell lines etc. This platform model may provide a guide for discovery in early detection.

2. Session two – discussion and summary of current status and challenges in early detection biomarkers

Chair: Professor Robert Brown, Imperial College London

Session two included discussions on the following:

1. Defining the clinical unmet need

Specific areas of clinical interest:

What is needed at the point of first patient contact – Primary care?

- GPs are interested in risk stratification
- Primary Care – envisage a model based on various factors including lifestyle, medicine and history.

- Can look to the Symptom Study:
 - Gathered clusters of symptoms
 - Recruited patient cohorts with and without specific cancer symptoms
 - Symptoms were measured from presentation to time and of diagnosis and stage of disease.
 - One of the streams is tackling the issue of recruitment at the interface of primary and secondary care
 - potential for collection of colorectal samples from patients in the primary care setting. In 18 months, over 900 patients were recruited.
 - The biggest challenge in patients presenting with abdominal symptoms. More biomarkers are needed to refine strategies.

2. Defining the resources available

a) Retrospective samples

- ECMC sample collection should be followed up for scope

b) Prospective samples

- Biobanking – ECMC should be focused on this; currently looks at early phase studies and has a remit of looking at biomarkers in phase III trials.
- Need standardisation in testing processing and storage. Good Clinical Laboratory Practice (GCLP) needed. Can happen across samples, e.g. blood and sputum.
- Need to decide on process and storage techniques, which leave samples fit for purpose.
- **Working Group: FW to ask Paul Little and Lucy Brindle**

3. Defining the technologies that are clinically applicable

- Many different technologies exist - is there a way to question or bring together a collective way forward to bridge technologies and techniques?
- Could look to companies in the UK – use of integrated diagnostics; defined panels for mass spectrometry aid with sorting patients for biopsy

4. Defining a collaborative project... or not!

The key question is in symptoms and biomarkers

- Implement a diverse programme
 - Important that there are multiple endpoints
 - need population studies
 - Need to assess how difficult it would be to add cancers and diagnostic pathways.
- Study design – Non-specific early detection of cancer in symptomatic patients for 3-4 disease areas.
Should be a large cohort, bigger than The Symptom Study, with a biobanking element.
- Operates on molecular work and sampling
- What is the predictive value of the biomarker? Stringency on markers – cannot validate all
- What is our priority? Symptomatic population; Genetic and epigenetic studies.

- Structures – Cohorts current being developed in Wales - **RN to look into CPRD database**. This has an automatic ongoing follow-up with samples. People can be recruited on the basis of symptoms and which can be stratified.
- Pan-symptoms/pan-cancer might be a better study. There is value in keeping it broad – may also address rarer cancers

Key points of the day– next steps

Chair: Professor Robert Brown, Imperial College London

1. Discuss how we take things forward:
 - enhance biobanking, e.g. ECMC funding
 - Primary Care
2. Decide what endpoints are to be used
3. Samples - must be fit for purpose. Discuss collection and standardisation measures
4. Establish further links in genetics and epigenetics
5. Establish links with existing studies
6. May help to inform more studies, e.g. Acordia; systematic reviews of relevant biomarkers; establish a panel
7. Feasibility – need to examine
8. This may coincide with other major projects
9. Now is a good time to strategise for the future