Consensus statement between CM-Path, CRUK and the PHG Foundation following on from the Liquid Biopsy workshop on the 8th March 2018

Summary:

This document follows on from the findings of the CM-Path "The Liquid Biopsy: ctDNA, Circulating Tumour Cells and Bloodborne Biomarkers" workshop on the 8th March 2018 at the Royal Society of Medicine with emphasis on the role of cellular pathologists in supporting the implementation of innovative technologies into diagnostic pathways across the NHS.

The meeting highlighted:

- The potential for genomic analysis to be performed on a minimally-invasive blood sample has several advantages over conventional biopsy, potential for widening access to personalised treatment in patients with inaccessible tumours and also improving follow up by allowing repeat sampling over time.
- CtDNA testing is currently in clinical use in a small number of NHS laboratories as a companion diagnostic for targeted therapy to treat non-small cell lung cancer both at diagnosis and for detection of resistance mutations.
- Potential near future applications include greater use of ctDNA to direct targeted therapy in a wider range of solid tumours as well as monitoring response to treatment and detecting molecular residual disease.

Challenges:

- Several challenges are identified for the greater application of this technology in an equitable way across the NHS. These include:
    - Awareness and availability of expertise
    - Validation and logistics
    - Cost
- Many of these challenges can be addressed through improved communication and better dissemination of technical information between laboratories and across the NHS.

The role of Pathologists:

- Pathologists have an essential role to play in the cancer diagnostic pathway, even with the advent of innovating testing modalities such as liquid biopsy. Detection of ctDNA is easier and more accurate if a genetic tumour profile is available from a morphologically defined histopathology tumour sample prior to plasma analysis. This is true whether analysing blood for stratification to target therapy or attempting to monitor for early disease recurrence. Pathologists can contribute to the wider uptake of this technology in multiple ways:
    - Ensuring best practice in the collection of histological biopsy samples for subsequent molecular analysis.
    - Research into histopathological features of tumours related to ctDNA detection.
    - Assisting with integration of molecular information into histopathology reports and discussion at multi-disciplinary cancer team meetings.
    - Pathology laboratories may be well positioned for wider integration of this technology across the NHS in areas distant from genomic hubs.

- CM-Path are aiming to develop a network of pathology laboratories to help ensure grass roots pathology services are equipped to enable the wider integration of molecular pathology into patient diagnostic pathways.

- We recommend that the Royal College of Pathologists ensures that histopathology training is able to produce pathologists that can lead this integration of molecular and histological pathological information into a comprehensive "morpho-molecular" pathology approach.

Introduction

On 8th March 2018 the Cellular Molecular Pathology Initiative, CM-Path, in association with PHG Foundation and Cancer Research UK, held a "liquid biopsy" workshop attended by pathologists, oncologists, scientists and pharma. The goal of the meeting was to highlight advances in liquid biopsy research to the pathology community, to examine how this technology could be integrated into clinical care and research and to explore collaborative opportunities. Increasing understanding of molecular testing technology and its clinical implications within the wider pathology community will be important in encouraging the wider adoption of molecular testing and encouraging pathology research.

Molecular pathology and genomic assessment of cancers is dependent upon well preserved biopsy samples usually obtained via an invasive procedure. This material provides the basis for tests to determine diagnosis, prognosis and eligibility for targeted therapy. The potential for this genomic analysis to be performed on a minimally-invasive blood sample has several advantages over conventional biopsy, potential for widening access to personalised treatment in patients with inaccessible tumours and also improving follow up by allowing repeat sampling over time. The meeting aimed to explore the potential for this technology, the overlap with cellular pathology and the barriers to wider adoption in the UK.

This document is a summary of the findings from the workshop with emphasis on the role of cellular pathologists in supporting the implementation of innovative technologies into diagnostic pathways across the NHS.

What is happening now?

- ctDNA testing is currently in clinical use provided by a small number of NHS laboratories for targeted therapy to treat non-small cell lung cancer. It is currently used in two situations:
    - At diagnosis, if insufficient material is present from the diagnostic sample, to determine EGFR mutation positivity. If present then tyrosine kinase (TKI) therapy can be prescribed.
    - At progression on first line TKI therapy to determine if resistance is due to EGFR resistance mutation (T790M). If so then second line therapy can be prescribed (Gefitinib license extended to plasma testing in 2014)[1].

- While there are currently no guidelines on the use of ctDNA testing in the UK, a National Institute for Health and Care Excellence (NICE) Medtech Innovation Briefing published in January 2018[1] provides advice on its use.

What is coming up in the next 3-5 years

- Directing therapy
    - CtDNA testing is being used for the detection of genetic biomarkers to direct stratified therapy in other tumour types e.g. breast cancer[2].
    - Broad analysis of ctDNA to detect oncogene expression using NGS panels in a range of solid tumours to direct treatment is also being explored.

- Monitoring response to treatment:

- ctDNA amplifies longitudinal monitoring of a mutation profile of a tumour potentially allowing alteration of treatment plans to adapt to the changes in the tumour, as being explored in the TRACERx study [2,3,4]

- Detecting molecular residual disease[5]
  - This approach is likely to benefit patients with intermediate stage tumours undergoing curative treatment with a high risk of recurrence e.g. c-TRAK TN trial in triple negative breast cancer patients.

The future – Beyond the next 5 years

- Primary diagnosis of conditions or screening using cell free DNA is still experimental and whilst great advances are being made in the sensitivity of these assays it is unlikely they will be able to enter into clinical use in the next 5 years.

- Circulating tumour cells are currently used as a research tool and show potential for wider clinical application[6]. However, the technology is expensive and only small numbers of circulating tumour cells (CTCs) are routinely detectable.

With advances in technology and the advantages afforded with a simple blood test, it is likely that ctDNA testing will be more widely available as part of the mainstream care of cancer patients, not just to aid with drug prescribing but also to monitor patients after treatment; to detect relapse of disease or emergence of resistance to treatment.

What are the barriers to future implementation and possible solutions?

Whilst ctDNA technology is already being used on a small-scale in clinical practice in the NHS, there are a number of issues that will affect current and future implementation. We highlight below key areas where action is required and what initiatives CM-Path are delivering that will have an impact on these areas:

Awareness and Expertise–

Increased awareness and knowledge of ctDNA and its clinical applications is needed for oncologists and patients to request the tests. Effective communication between laboratories, clinicians and healthcare staff is vital if centralised genetic testing is to be widely utilised across the NHS. We welcome the role of NICE in promoting testing through their recent Medtech innovation briefing[1]. Pathologists are key members of MDT meetings and there is great potential for pathologists to play a key role in raising awareness of testing. CM-Path aim to create a grass-roots network of pathologists and pathology departments well positioned to disseminate information about the options for molecular pathology testing within the health system.

Validation & Logistics –

There is still technical uncertainty over what is the optimal test method. This includes which blood collection tube to use, which sequencing platform to use and methods of sample processing such as centrifugation protocol [7] and DNA extraction and quantification methods. There is a need for guidance on this issue and publication of standards would greatly assist laboratories looking to introduce this technology. Both the International Quality Network for Pathology (IQNPath) and the Association for Clinical Genomic Science (ACGS) potentially have a role here in reviewing data from international studies and UK based laboratories to help develop standards in this area. The recent literature review and guidelines by Merker et al. provides a comprehensive evidence based

review for some of the pre-analytical variables and analytical validity but does call for more research into assay robustness and performance characteristics[8].

The introduction of a new test requires extensive validation of tubes and platforms. EDTA tubes have historically been used but if not processed within 2 hours these tubes can lead to lysis of white blood cells and dilution of the ctDNA by genomic DNA. Specialised blood tubes have been used effectively over longer periods of time but require validation. The CM-Path workshop highlighted that this validation work is being duplicated across the country unnecessarily. Wider communication of validation results carried out within genomic centres would be useful and bodies such as the ACGS or NICE may be well placed to assist in the dissemination of this information. There is further onus on manufacturers to support the use of their products and to guarantee compatibility of their own tubes and platforms.

UKNEQAS already offer a quality assurance program for EGFR mutation testing in lung cancer using ctDNA and it is hoped this could be easily expanded as other tests become available.
Whilst producing standards for genetic testing is beyond the scope of CMPath, we are working with the confederation for cancer biobanks to develop a quality improvement tool that will also include standards for processing and preserving samples for ctDNA analysis.

Cost –

It is not clear where the extra resource would come from to support the wider implementation of ctDNA testing routinely in the NHS. In the longer term there are potential cost savings from reduction of tissue biopsies or reduced need for post treatment monitoring but the health economics are not currently well defined.

Ethical –

There is potential to detect germline mutations. Guidelines on how to counsel patients pre-sampling and to deal with the situation according to ethical principles are needed. Anecdotally this has arisen as an issue in a research setting for cancer patients who have consented to take part in clinical trials where appropriate genetic counselling is easily accessed. This would be a more significant issue if detected during a screening test rather than in a patient with a known cancer.

What is the role of pathologists in the implementation of liquid biopsy technologies?

- Pathologists have an essential role to play in the cancer diagnostic pathway, even with the advent of innovating testing modalities such as liquid biopsy. Detection of ctDNA is easier and more accurate if a genetic tumour profile is available from a morphologically defined histopathology tumour sample prior to plasma analysis. Use of primary tissue samples is still essential to assist with detection of ctDNA as it is easier to detect a small amount of ctDNA if mutations are known. This is true whether analysing blood for stratification to target therapy or attempting to monitor for early disease recurrence. Close communication between pathologists and genomic scientists will be important to facilitate this process.

- CM-Path is developing a network of pathology laboratories to help ensure best practice in the collection of samples for subsequent molecular analysis. Standardising the collection of tumour histopathology samples for both FFPE and fresh tissue in pathology laboratories across the country through initiatives such as the 100k Genome Project will help to facilitate subsequent ctDNA detection (as described above).

- Our understanding of the biology of ctDNA is rapidly increasing. It appears that ctDNA may be more easily detectable from some tumour phenotypes than others[9] and from some tumour sites than others e.g. brain metastases are harder to detect using this method. Pathological analysis will be useful in research aimed at identifying features in the primary tumour that can affect the quantity or quality of ctDNA present. This is a key area where pathology focussed research could have an impact on our understanding of the histopathological factors involved in tumour metastasis.

- Genomic laboratory services are currently undergoing a process of reconfiguration and consolidation and it remains to be seen how ctDNA testing will fit into this new service model. Given these changes, cellular pathology laboratories may be well placed to site this technology in the future.

- The role of the future pathology workforce should also be considered given that pathologists are well placed to disseminate and interpret results at a local level and could engage with and integrate reporting of molecular assays into histopathology reports.

- We therefore recommend that the Royal College of Pathologists guarantees that pathology training enables trainees to spend time with clinical genomic scientists and bioinformaticians during training and develop a grounding in molecular pathology that ensures that future pathologists are able to produce truly integrated morpho-molecular tumour pathology reports for the benefit of local clinicians and patients. This type of approach is vital to ensure that diagnostic pathways are able to integrate innovative technologies into working practice without becoming fragmented.

About us:

CM-Path is an initiative set up by the NCRI to reinvigorate academic pathology and enable development of innovative diagnostics and widespread integration of molecular pathology into standard practice.
CRUK are a cancer research charity who fund research aimed at improving treatments and patient outcomes across the range of cancer diagnoses.
PHG Foundation is a health policy think tank with a focus on helping decision makers deliver the benefits of biomedical innovations to all, through providing evidence, analysing policy and advocating for change. For our work on ctDNA see: www.phgfoundation.org/project/ctDNA

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