The Foundation for Science and Technology
Debate Record Note

Cancer diagnostics: can cancer be diagnosed earlier and if yes what are the consequences?

Date and Location:	11th July, 2017 at The Royal Society
Chair:	The Earl of Selborne GBE FRS Chair, The Foundation for Science and Technology
Speakers:	Sir Harpal Kumar Chief Executive, Cancer Research UK
	Billy Boyle Chief Executive Officer, Owlstone Medical
	Dr Clare Turnbull Clinical Lead for the Genomics Enland 100,000 Genomes Cancer Programme
Panellists:	Dr Suzanne Jenkins Director, Diagnostics Expert, Personalised Healthcare & Biomarkers AstraZeneca
	Sara Hiom Director of Early Diagnosis & Health Professional Engagement, Cancer Research UK
Sponsors:	AstraZeneca, The Kohn Foundation and the National Physical Laboratory
Audio Files:	www.foundation.org.uk
Hash tag:	#fstcancerdiagnostics

SIR HARPAL KUMAR said the imperative for early diagnosis of cancer was clear. Even without new technologies it would improve both outcomes and resource utilisation. In bowel cancer, for example, 5 year survival rates were 90% for early stage disease, but less than 10% for late stage diagnosis. The differentiation was similarly stark in the case of lung cancer. This was compounded by the fact that, for these tumours, the rate of last stage diagnosis was higher than in comparable countries – over 50% in the case of bowel cancer. Moreover the average cost of treatment for a patient with early stage cancer was £3,373. For a patient with late stage cancer it was £12,000.

A range of possibilities suggested themselves as approaches to improving rates of early diagnosis. There was scope for better uptake in the current screening programmes – particularly for bowel cancer – if patient factors, system issues and the test quality could be addressed. Regional variations in diagnosis rates and variations related to gender, age, socio economic factors and efficiency were obvious opportunities. Lengthy waiting times for pathology and imaging services (operating with less resource than comparable health systems internationally) were a significant contribution

to late diagnosis – which could and should be addressed by increased investment. A faster standard for time to diagnosis – 4 weeks – had now been established; and a series of other measures to improve diagnostic pathways, including new rapid, one–stop-shop diagnostic assessment centres for people with non-specific symptoms, were being developed and piloted across the system. There was certainly scope for more active surveillance of patients in higher risk groups. Finally and encouragingly, new technologies were emerging which showed promise for supporting earlier, faster and better diagnosis – including circulating biomarkers, volatile compounds, new imaging modalities such as low dose CT and ultra sound, cell capture and AI/machine learning (using existing large datasets).

Earlier diagnosis had consequences both for patients and individuals and for the health system. For patients there were risks associated with both false positives and false negatives. In one recent programme, for example, the use of low dose CT for diagnosing lung cancer had reduced mortality by 20% but, astonishingly, resulted in a false positive rate of 96% - with all the risk that carried of individuals going forward for unjustified and potentially harmful interventions. On the other hand increased volumes of early diagnosis might increase the risk of false negatives: giving unwarranted assurance to a patient which might inhibit them responding to symptom development, leading to late stage presentation. There was always a risk, too, of over diagnosis, particularly with slow growing cancers. For example, there was clear evidence that the breast screening programme saved lives (1300 – 1500 a year in the UK). But it was also the case for every life saved 3 women were diagnosed and often given extensive, treatment for cancer that left undetected or unrelated would not affect their life span. On the other hand earlier diagnosis might offer real possibilities for better identifying the tissue of origin in cases where later presentation made that intrinsically more different.

For the health system, earlier diagnosis would require investment in new technology and workforce expansion to support growth in the diagnostic infrastructure. It would also lead to more surgical treatment. This shift in resource should, however, be balanced by significantly reduced costs in the treatment of metastatic disease. There would be implications, too, for primary care. On the one hand its role might diminish if better symptom awareness and more diagnostic capacity could lead straight to testing. On the other hand it could increase if community based testing became practicable. All this pointed to a clear conclusion: earlier diagnosis of cancer should lead to better outcomes and better resource utilisation; and progress was achievable if the current and future possibilities for improvement were explored and consequences for patients and the system were recognised and carefully managed. For that reason CRUK would be prioritising research in this area as it looked to the future.

BILLY BOYLE said that this his company, Owlstone Medical, was seeking to develop the science of breath biomarkers to support earlier, more accessible and non-invasive diagnosis of cancer. The company had its origins in a spin out from Cambridge University which had developed applications for military use. This further spin-out into the medical field was, therefore, founded on well-established technology and a proven team. The technology – current and next generation – for capturing good samples of breath biomarkers and analysing them to high levels of sensitivity existed. The challenge now was to move to collection at scale with samples that were stable enough for analysis.

He agreed with Sir Harpal that early detection was our greatest opportunity. One in two of us would be diagnosed with cancer in our lifetime. Sir Harpal had already highlighted the poor outcomes in lung and colon cancer linked to late stage diagnosis. Both tumour types were obvious opportunities for improvement through early detection; and his company were currently targeting specific programmes in those areas. They were running a trial (LuCID) for a lung cancer breathalyser with the aim of improving rates of early diagnosis. The opportunity was clear. Over three years an increase in detection rates of stage 1 disease from the current 14.5% to 25% could save over 9,500 lives and £246m. The trial, funded by the NHS, was the largest breath biomarker trial ever undertaken in the world, recruiting up to 3,000 patients from 21 clinical sites across the UK and Europe. Moreover, this was a global opportunity. China had for example, had more lung cancer cases and deaths than any other country because of the rise of its population, with mortality highest in urban East China.

He echoed, however, Sir Harpal's comments about some of the problems associated with earlier detection, also citing the high volume of false positives associated with the US national lung cancer screening trial using low dose CT (LCDT) and the

consequent overtreatment of indeterminate lung modules and the associated harms (with 17% of low risk patients having a biopsy and 28% having surgery , and with surgery being performed on 35% of benign modules irrespective of assessed risk). Breath biopsy could, therefore, definitely have a role in the management of indeterminate pulmonary modules revealed by LDCT: using a non-invasive technology offering high compliance could be used at least rule out tests for a suspicious module.

The nature of the diagnostic test also really mattered. Again, Sir Harpal had already referred to the low compliance rate in current colon cancer programmes (48%). That was undoubtedly related to the nature of the test. Low compliance rates were then compounded by poor test sensitivity (66%) – which meant that out of 100 patients with colon cancer only 31 cancers were detected. Their Intercept programme was therefore targeted at early detection of colorectal cancer through breath biopsy.

However, early detection was a financial engineering problem as well as a scientific one. The funding 'valley of death' between product development and testing and market authorisation was wide and deep for all medical technologies. However, even when compared to other health technologies, diagnostics had been historically a poor asset class. There were essentially two ways through this: to raise a lot of money initially to bridge the gap and vicissitudes of the market; or the route his company were proposing for breath biopsy, which was to develop a deep pipeline with a mix of near and longer term recurring revenue streams. But one way or the other solutions had to be found to the need to attract funding and investment in the diagnostics class of products if 'our greatest opportunity' in cancer – early detection – was to be realised.

DR CLARE TURNBULL confirmed that patients presenting with advanced cancer usually died of their cancer and were very expensive to treat. Sophisticated cancer drugs were used to extend life in the case of advanced cancer; but they were not typically curative, usually only extending life, which may only be by months. These drugs are typically expensive and may cost £10,000s per treatment round. Moreover cancer was ruthlessly Darwinian and evolved against the selective pressure of drugs. Resistant mutation occurred; and the resistant sub clone in the tumour had selective advantage and expanded. Indeed evolutionary modelling suggested that a key mutational event was followed by aggressive and unbridled cellular replication. When a patient was cured of cancer it was, typically, as a result of surgery – which meant catching a tumour when it was small (enough), localised and before it 'bolted'. Earlier detection across the population enabled more frequent successful surgical resection; enabling cure and reducing costs. Prevention was, of course, even better than early detection.

This pointed to the need for the delivery of effective screening programmes; for public education around uptake of screening symptoms awareness; for public health intervention around life-style change (smoking, alcohol and obesity); for expansion and development of vaccine programmes; and for the expansion of chemoprevention. In addition, targeting sub-populations at elevated risk would improve early detection and prevention. For example, screening was currently focussed by age and gender. It should be possible to use genetics (and non-genetic factors) to focus screening on those at higher risk.

There are genetic susceptibility factors underlying all common cancers: focusing screening and interventions on individuals at the higher end of the genetic risk distribution curve may, for a given resource, enable identification or prevention of a higher proportion of the cancers. Next generation technologies for genetic sequencing is cheaper, and much more rapid and high throughput – making a case for lowering the thresholds for offering genetic testing, which would result in a significant expansion of testing.

From a pedigree it is possible to identify individuals likely to have Lynch syndrome, a genetic condition conferring about an 80% lifetime cancer risk (mainly colorectal, endometrial and ovarian cancers), which is amenable to application of screening, early detection and prevention to save lives. Screening options included a colonoscopy every 18 months from the age of 25 and preventive interventions ranging from chemoprophylaxis (aspirin and potentially, immunomodulation drugs or even vaccines) to surgery.

Individuals at risk of hereditary breast and ovarian cancer due to BRCA1/BRCA2 can be identified through the pedigrees. Those carrying a change (mutation) in BRCA1/BRCA2 can be offered screening and early detection (through MRI and mammography annually from age 30) and again, offered preventive treatment including surgery and chemoprophylaxis (where RANK –Ligand inhibitors showed potential as a potential target for protection in BRCA1-mutation carriers). In both scenarios, expansion of genetic testing to all individuals with

the relevant cancers at time of diagnosis, would offer improved and earlier detection of mutation carriers, rather than mandating the need for extensive family history to trigger a test. Page 4 www.foundation.org.uk to build a genetic architecture of cancer susceptibility based on the frequency and relative risk of the underlying genetic factors. This meant, for example, that genetic and non-genetic factors could be used to target breast cancer screening by risk category rather than just by age– this could reduce screening volumes with very modest impact on cancer detection rates. However, the 'missed' cases would be in those currently receiving breast screening who are estimated to be at 'low risk' – which raised, of course, issues for debate.

In short genetic risk profiling using sets of common variants (SNPs), in combination with nongenetic factors, should be further explored to target resources for early detection and prevention. Additionally, we should expand genetic testing to look for individuals carrying in high penetrance cancer susceptibility genes (Lynch, BRAC1/2 and others). Colorectal cancer was, in her view, a very tractable model for both success in screening prevention and early detection.

All this did give rise, however, to a series of questions and challenges. Could changes to screening programmes legitimately take away screening from those at lower genetic risk? Might it be possible to create 'registries' of individuals at increased genetic risk in order to manage them effectively to learn which interventions were effective in which groups and to improve data linkage? And would we be able to fund the required large-scale long-term longitudinal genetic cohort studies and screening implementation studies?

DR SUZANNE JENKINS, who joined the panel at this stage, supported the emphasis on developing less invasive technologies for diagnosis in early stage disease - to complement drug discovery and the new targeted therapies that showed so much promise. The challenge, however, was to get the test characteristics right – both in terms of sensitivity and specificity.
In discussion, a number of contributors emphasised the need for better informed and balanced public debate about the nature of risk in the diagnosis and treatment of cancer. This was needed to support the necessary shift in resources towards better screening, prevention and early diagnosis to reducing invasive and debilitating treatment at the end of life - which had a negative impact on well-being and did not necessarily prolong life beyond what could be achieved with effective palliative care.

This was not straightforward, as the speakers had highlighted. The benefits of prevention were not always easy to frame; and mischief could always be made about rationing - whether related to risk profiling for screening programmes or access to the most expensive drugs to prolong life. But cancer remained a high cause of mortality; and there were significant gains to be made, as the speakers had made clear in both presentation and treatment. Value based healthcare – balancing clinical effectiveness and sound as well and economic factors should be the goal.

The importance of ensuring effective patient and public engagement in the development and evaluation of new health technologies was emphasised. CRUK were putting and increasing emphasis on this, as were NICE, NIHR and other national bodies in this field. At the level of the individual, too, those involved in genetic screening and the associated counselling services were deeply engaged in supporting individuals and their families to understand risk and to make informed decisions about it. There was also a strong case for awareness of symptoms among the general public – and pharmacies and other primary care practitioners as well as GPs could have a role to play here.
The importance of specificity in testing, particularly when the test itself was invasive, was endorsed. As testing for susceptibility improved, confirmatory testing became a bigger issue. Sequencing tumour material was complex; and the number of mutations that could currently be targeted by drugs was limited. However, as research on the whole genome developed there was clear potential for progress.

The issue of whether the private sector had a role to play in risk profiling for health was raised. Although there might be scope for collaboration with companies involved in gathering genetic information at the population level, it was agreed that this was very unlikely to be helpful at an individual level – and, potentially misleading and unhelpful. Companies that had tested this market had withdrawn, at least in respect of advising individuals on disease genetics.

Contributors supported the introduction of 'one-stop-shops' (on the 'Danish model' but which CRUK had championed for some time) which provided rapid access to diagnostic assessment for individuals with non-specific systems. This would reduce multiple, separate and consecutive testing for such individuals and support earlier diagnosis. Five pilot centres had been established and the results should be

known in 18 months.

Hard to diagnose high risk cancers – such as pancreatic cancer – should also be prioritised; and there was considerable interest in whether volatile compounds would support early diagnosis of such cancers. The potential shown by sniffer dogs, had for example, pointed the way to the research on the use of breath biomarkers for lung cancer described earlier; and the question of whether biomarkers for other cancer types such as pancreatic cancer could be found was very much a feature of that research. Whether targeted therapies for more high risk cancers would become available was another question, not least because tumours responded in the way Dr Turnbull had described. But there were promising signs that targeted therapy could work at a molecular level; and it was suggested that the new technologies combining effective monitoring with combinations of therapies to treat re-occurrence offered promise for the future.

There was no link, it was agreed, between preventive surgery to cure inherited cancer in an individual and subsequent inheritability. Reproductive interventions on the other hand could guarantee that high risk mutations were not passed on; but IVF was expensive and carried other risks, not least that conception might not occur.

Capacity issues were raised by a number of contributors. Radiology and radiography were crucial to cancer diagnosis and treatment, but current services were over stretched and under-resourced. Workforce and technology issues had to be addressed. AI and machine based learning were seen as having real potential for interpreting data, in genetic screening and to support radiology (where Singapore was already using AI effectively). It was important to highlight needs in this area – and look internationally for investment and support.

There was general enthusiasm for the potential of new technologies to support early diagnosis, particularly where these were non-invasive and easily accessible. Access to capital for innovations in this field was recognised as a rate-limiting factor – and not just in the UK. However, the NHS did, arguably, set a higher bar for wide scale adoption than, for example the healthcare system in the US, because it looked for value across the whole chain – from screening through testing to treatment. However, there were signs that the position had been picking up over the last ten months; and momentum on prioritising research and funding on early detection was unquestionably building. The Chief Medical Officer had, for example, prioritised the issue in her latest annual report.

The challenge now, it was agreed, was to maximise the possibilities outlined in the presentations: more collaboration was needed both on the development of bigger data sets to support risk stratification and better targeting thus reducing the burden on the health system and improving clinical effectiveness and more nimble approaches to trials on new health technologies to support better diagnosis with high predictive value and treatment. Longitudinal research studies would, it was agreed, be particularly important. Patient confidentiality was, of course, crucial; but patients would be horrified if the system was not using data to support these developments in early diagnosis which held so much promise for the future.

Concluding the debate, the Earl of Selbourne noted that the discussion had been particularly, wide ranging – from the scope for using primary care and pharmacies more effectively to inform and support the public, through deficits in capacity in key areas such as radiology, to the clear potential that existed for exciting new developments in early diagnosis of cancer.

Sir Hugh Taylor KCB

Useful Reports and URLs

Diagnosing Cancer Earlier: Evidence for a National Awareness and Early Diagnosis Initiative
www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@hea/documents/generalcontent/cr_044142.pdf

Annual Report of the Chief Medical Officer 2016: Generation Genome
www.gov.uk/government/publications/chief-medical-officer-annual-report-2016-generation-genome

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Faculty of Medical Leadership and Management
www.fmlm.ac.uk

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www.fom.ac.uk

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www.rcgp.org.uk

Royal College of Radiologists
www.rcr.ac.uk

Royal College of Obstetricians and Gynaecologists
www.rcog.org.uk

Royal College of Ophthalmologists
www.rcophth.ac.uk

Royal College of Paediatrics and Child Health
www.rcpch.ac.uk

Royal College of Pathologists
www.rcpath.org

Royal College of Physicians of Edinburgh
www.rcpe.ac.uk

Royal College of Physicians of London
www.rcplondon.ac.uk

Royal College of Physicians and Surgeons of Glasgow
www.rcpsg.ac.uk

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www.rcpsych.ac.uk

Royal College of Surgeons of England
www.rcseng.ac.uk

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www.rcsed.ac.uk

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www.ahrc.ac.uk

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www.bbsrc.ac.uk

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www.epsrc.ac.uk

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www.esrc.ac.uk

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www.mrc.ac.uk

Natural Environment Research Council
www.nerc.ac.uk

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www.stfc.ac.uk

Companies, Research Organisations and Academies:
Association of Innovation, Research and Technology Organisations (AIRTO)
www.airto.co.uk

Academy of Medical Royal Colleges
www.aomrc.org.uk

Academy of Medical Sciences
www.acmedsci.ac.uk

AstraZeneca
www.astrazeneca.co.uk

British Academy
www.britac.ac.uk

British Medical Association
www.bma.org.uk

Cancer Research UK
www.cancerresearchuk.org

Catapult Programme
www.catapult.org.uk

Department for Business, Energy and Industrial Strategy
www.gov.uk/government/organisations/department-for-business-energy-and-industrial-strategy

Department for Communities and Local Government
www.gov.uk/government/organisations/department-for-communities-and-local-government

Department for Culture, Media & Sport
www.gov.uk/government/organisations/department-for-culture-media-sport

Department for Education
www.gov.uk/government/organisations/department-for-education

Department for Health
www.gov.uk/government/organisations/department-of-health

Francis Crick Institute
www.crick.ac.uk

Genomics England
www.genomicsengland.co.uk

Government Office for Science
www.gov.uk/government/organisations/government-office-for-science

GSK
www.gsk.com

Higher Education Division, Department for Education, Northern Ireland Government
www.economy-ni.gov.uk/articles/higher-education-division

Higher Education Funding Council for England
www.hefce.ac.uk

Higher Education Funding Council for Wales
www.hefcw.ac.uk

Independent Doctors Federation
www.idf.uk.net

Innovate UK
www.gov.uk/government/organisations/innovate-uk

Institute of Cancer Research (ICR)
www.icr.ac.uk

Joseph Rowntree Foundation
www.jrf.org.uk

King's Fund
www.kingsfund.org.uk

Knowledge Transfer Network
www.ktn-uk.co.uk

Learned Society of Wales
www.learnedsociety.wales

National Physical Laboratory (NPL)
www.npl.co.uk

Owlstone Medical
www.owlstonemedical.com

Pfizer
www.pfizer.co.uk

Research Councils UK
www.rcuk.ac.uk

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www.raeng.org.uk

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www.royalsociety.org

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www.rse.org.uk

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www.rsm.ac.uk

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