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The role of germline genetic profiling for risk-based prevention and cancer screening

Workshop Report

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WORKSHOP REPORT

The role of germline genetic profiling for risk-based prevention and cancer screening

In July 2015, the Independent Cancer Taskforce published a report 'Achieving world-class cancer outcomes: a strategy for England, 2015-2020' outlining a vision for the NHS to improve survival rates and achieve world class outcomes for those affected by cancer. Of the 96 recommendations outlined in the report, 11 were specific to research, including recommendation 14.

Recommendation 14: NHS England and Public Health England should work with NIHR and research charities to develop research protocols to evaluate the potential for risk-based prevention and surveillance programmes based on genetic germline profiling

This report outlines a workshop entitled 'The role of germline genetic profiling for risk-based prevention and cancer screening' organised by the NCRI and NHS England. The workshop was funded by NHS-England with additional funding from Breast Cancer Now. The aim of the workshop was to define research questions to evaluate the potential for risk-based prevention and surveillance programmes based on germline genetic profiling.

The day brought together a group of geneticists, clinical cancer specialists, academics, consumers[1], representatives from Breast Cancer Now, Prostate Cancer UK and Bowel Cancer UK, and others with specialist interest in this area. The day was organised around an information- sharing session in the morning, followed by guided parallel breakout sessions in the afternoon, to develop recommendations in six tumour types; Breast, Colorectal, Gynaecological, Lung, Prostate and Skin.

Professor David Baldwin from University of Nottingham, the Chair of the workshop, introduced the day, which was followed by talks from Dr Anne Mackie of the National Screening Committees, Professor Tony Howell from University of Manchester and Dr Nicholas McGranahan from University College London.

The workshop focused on surveillance programmes rather than prevention programmes. Targeted prevention programmes could be developed to compliment surveillance programmes that stratify the population into levels of risk of developing cancer.

What key questions do the UK National Screening Committee need to know the answers to?

Dr Anne Mackie introduced Screening. It is the process of identifying healthy people who may be at increased risk of disease or condition. Those at risk are offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition. Screening therefore supports individuals, from invitation right through to referral for treatment and/or advice. Dr Mackie outlined the review process in place for a new test to be used in a screening programme for a new condition or to replace a test in an existing condition. She also provided information on how to submit a proposal to the UK National Screening Committee[2].

[1] Patients, carers and others affected by cancer

[2] https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/appendix-d-how-to-submit-a-proposal-to-the-uk-nsc

How can genetic markers improve the benefit from screening programmes? Factors associated with mortality, overdiagnosis and preventable disease

Professor Tony Howell outlined the current risk assessment in the breast screening programme, and gave an overview of PROCAS[3] (Predicting Risk Of Cancer At Screening), a study using the Tyrer-Cuzick model to predict which women are at the highest risk of developing breast cancer by gathering information on women at the time of their mammography. He also gave an overview of visually assessed mammographic density as a risk factor, using the Breast Imaging Report and Data System (BIRADS), and discussed visual versus automatic systems for assessing breast density. Risk-associated SNPs for breast cancer and approaches to the use of genetic and other markers to define risk, outlining the potential added value of further SNPs for stratified screening was also discussed.

TRACERx: lung cancer genome evolution

Dr Nicholas McGranahan spoke about tumour evolution and tumour heterogeneity, both between tumours and within single tumours. He gave an overview of the TRACERx (TRAcking non-small-cell lung Cancer Evolution through therapy, Rx) Consortium and study. TRACERx is a multicentre, UK-wide prospective study involving multi-region sequencing of primary tumours, sequencing non-small-cell lung cancer (NSCLC) from diagnosis to relapse, to track the clonal evolution of tumours. He discussed the heterogeneous landscape of NSCLC and showed evidence to suggest that intratumour genetic heterogeneity is likely to be a prominent factor contributing to intertumour, intratumour and intercellular heterogeneity. Dr McGranahan also delved into the clonal status and timing of driver events during NSCLC evolution.

[3] https://www.preventbreastcancer.org.uk/wp-content/uploads/2014/08/Prediction-Projects-Page-1-PROCAS.pdf

Breakout sessions

Following on from the information-sharing session, participants attended parallel breakout sessions focusing on Breast, Colorectal, Genealogical, Skin and Lung cancers.

1. Breast breakout session, chaired by Professor Dan Rea

The Breast breakout session focussed on the morning presentation from Professor Howell. As well as looking at the risk of developing a breast cancer they also focussed on the risk of dying from breast cancer. Information on lifestyle, SNPs and breast density would feed into a refined way of categorising patients into high, intermediate and low risk groups.

Augmenting the existing screening programme

The group discussed the possibility of reconfiguring the breast screening programme so patients would have a SNP-test and information collected to enter into the Tyrer-Cuzick breast cancer risk evaluation tool before or as they approach their screening date. This information could then be used to stratify women into high, moderate, average and low-risk of breast cancer populations. The group outlined how this stratification might influence the tests and pathways. For instance, the high-risk group, annual MRI and Full Field Digital Mammography (FFDM) screening might be used. The high-moderate risk group could be further sub-grouped by breast density with different timing and forms of screening used. The average risk group might follow the current three yearly FFDM screening programme. Women with low risk of breast cancer could choose to be screened less often or undertake the current three yearly FFDM. A strong psychosocial assessment for each group would be needed to understand what sense the women are making of the options with which they are presented.

The group suggested that, as well as SNPs, a platform might be developed to give BRCA status at the same time to identity BRCA-positive women. BRCA-positive patients make up around one in 300 of all breast cancer patients but if BRCA-positive women could be identified at screening it would make a big difference to that group.

A separate interrogation project would be helpful to understand the relationship between baseline factors, SNPs and the type of cancers diagnosed through this augmented screening proposal.

The Group felt it would be possible to develop a trial and grant proposal based on the discussions outlined above to investigate if the existing breast screening programme could be further augmented. The trial would dovetail into an existing European pilot project that will help inform the work.

2. Colorectal breakout session, chaired by Professor Ian Tomlinson

The colorectal breakout session discussions were based on the existing bowel cancer screening programme. There is currently a two-yearly faecal occult blood testing (FOBT) moving to faecal immunochemical testing (FIT) for 60-74 years. Bowel scope (flexible sigmoidoscopy) is also being rolled out from the age of 55, alongside the FIT and colonoscopy based programme. FIT is a quantitative measure, and is used to indicate who might benefit from a colonoscopy. There is debate around the appropriate threshold level of FIT, above which a colonoscopy would be performed. The major issue for screening is colonoscopy capacity.

Colorectal cancer genetics and epigenetics

In terms of colorectal cancer genetics, there are approximately 50 known SNPs and roughly 15 high-risk (Mendelian) genes. It would be ideal to test SNPs and high-risk genes together, whether

by custom array or by sequencing. Individuals could provide a saliva sample at the same time as providing a stool sample.

The group also discussed whether risk profiling can be shared with other cancer types, but for now this is difficult to put in practice.

Non-genetic risk factors

There was debate around the key non-genetic risk factors and how much data could be obtained given survey participation drops off considerably when there are more than five to eight questions. Pilot work is required to assess the feasibility of capturing all the major risk factors. Eventually electronic records could be utilised rather than questionnaires, but initially an online questionnaire would be used to capture at least five of the major risk factors.

Other non-genetic risk factors were discussed, such as the microbiome, physical activity and diet. The group regarded these as being a possibility to capture in the future but hard to do in the short term as they are difficult to parameterise.

Use of risk score

There is a great burden on colonoscopy services at present. It is therefore important to try to reduce the burden through better targeting of screening aiming for similar or lower costs. It might also be possible for those at the highest risk score, irrespective of Mendelian gene status, to have a colonoscopy first rather than occult blood testing and to consider no screening for low-risk individuals. Also varying the frequency of screening should be considered, as two-yearly screening is frequent compared with other screening programmes.

Pilot work needs to be done to demonstrate the risk score has positive predictive value in those with a positive FIT test.

Suitability of colorectal cancer for risk stratification

There is little doubt that screening for colorectal cancer can be refined using other data (e.g. age, sex, FIT sensitivity, ethnicity and perhaps previous screening history). The bowel screening programme has set up a group to look at this. It is possible that genetic information might prove useful in improving the risk stratification.

Colorectal cancer has a few advantages in terms of its suitability for risk stratification. As there is a defined premalignant lesion (colorectal adenoma or other polyps), early detection and removal is beneficial. Early carcinomas detected in the screening programme have over a 95% chance of being cured. Screening is non-toxic in that individuals are not being irradiated and highly invasive methods are not used.

More research is needed to prove that this approach would be efficacious, the risk score developed and health economics explored before going to a trial. A pilot study is required and is possible to do and further discussion and thought is required to develop such a study.

3. Gynaecological breakout session, chaired by Dr Ranjit Manchanda

Ovarian is following breast cancer in the context of validating risk models for predicting ovarian cancer risk, which incorporates SNPs, epidemiological and germline profiling. A number of groups have developed models but there is a need for validated risk models to predict ovarian cancer risk in the same way as breast cancer risk.

Predicting risk of ovarian cancer

The PROMISE[4] programme (Predicting Risk of Ovarian Malignancies, Improved Screening and Early detection) is a programme being run from 5 centres to develop algorithms to predict ovarian malignancy, and identify new screening biomarkers to update biomarker driven screening strategies as well as offering downstream options of prevention. There is also a health behaviour aspect to develop a decision tool for women that provides information on their risk of cancer. An ongoing pilot study (PROMISE Feasibility Study)[5] is now looking at the acceptability and feasibility of screening and stratifying the population for ovarian cancer risk using germline and epidemiological information. The recently defined risk threshold for preventive surgery is about 5% and there is cost effectiveness data on this. The cost effectiveness of doing unselected population testing for ovarian and breast cancer gene mutations is being evaluated but these data are not yet published. Also discussed was the need for better confidence intervals around the risk estimates for newer gene mutations to implement models and thresholds. Research is needed to look at improving the outcome measures to help drive clinical practice.

Data

The group discussed the lack of data on concordance of germline and somatic tumour testing to drive downstream management pathways. The also spoke of the need to have a national or international database to ensure good outcome data in relation to surveillance and preventive surgery.

Targeted prevention strategies

From a prevention point of view the group spoke about new targeted prevention strategies, such as salpingectomy in pre-menopausal women and a delayed oophorectomy for after menopause. A salpingectomy maintains oestrogen levels so there are reduced long term detrimental health consequences, such as osteoporosis and cardiovascular disease. Funding has been received to start a national trial on this which is aiming to start later this year.

A trial for germline testing

The group also discussed the option and highlighted the importance of a general population intervention study taking forward the pilot data generated over the next year which would look at germline testing for the whole population. This has the potential to cover mutations for multiple cancer types. The design for this was discussed, questions which need addressing include acceptability, uptake, psychosocial issues, quality of life, health behaviour, uptake of screening and prevention strategies as well as cost effectiveness. It remains to be established whether long term outcomes are going to be similar to if they were ascertained through other means, such as high-risk settings. This study will be discussed and developed further.

4. Lung and Skin breakout session, chaired by Professor David Baldwin and Dr Fiona Walter

The Lung and Skin breakout sessions merged on the day. Selecting who to screen for lung cancer is an important area, with broad criteria currently recommended in the US and Canada. There are multivariate models that have been shown to be much more cost effective, but even these might be improved. These models are important to select people that are at intermediate risk that cannot be selected merely based on smoking and age. Inevitably, some patients will be ineligible but still develop lung cancer. For these people, we need biomarkers that, on their own or in

[4] https://eveappeal.org.uk/our-research/our-research-programmes/promise-2016

[5] http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/study-looking-possible-test-all-women-to-find-risk-developing-ovarian-cancer-promise-fs

combination with other factors, can more precisely predict risk and allow people to enter screening programmes.

The group identified concerns that the UK is not tackling prevention of skin cancer. Prevention strategies have been successful in Australia, after forty years of campaigning. Screening for skin cancer is an area with limited evidence but a German study performed a one-off screen of the population and found a big surge in pick up rate. There are a few models worldwide, looking at stratified screening for skin cancer, but none are currently UK-based.

Augmentation and refinement of existing risk prediction models

Identification of biomarkers that predict risk of lung cancer is an ongoing area of research, whereas in skin cancer, work is more focussed on identifying malignant disease in skin lesions. In both lung cancer and skin cancer, the use of the germline to predict risk has so far been unexplored or unsuccessful. The work done in lung cancer has shown a multitude of SNPs but no consistent finding that could predict risk of cancer or identify subgroups. There are some genetic diseases (mendalian) that are risk factors for skin cancer, but these are rare. Thus, no specific recommendations were made for germline testing. It was noted that some of the work on somatic mutations and their evolution has not considered the role of the germline in predisposition for mutations. This is a possible area of further research.

Aggressiveness of tumours and prognosis

As in other tumours, it was noted that predictive biomarkers should really predict who would be harmed by the disease, to minimise the impact of overdiagnosis.

Other potential areas for research

The protective effects of the germline, in contrast to added risk, was considered a potential area for research. This could be done by identifying a very high-risk group that have not developed cancer. For example, in lung cancer this would be current smokers over the age of 70. The concept of looking at the whole genome as opposed to just identifying SNPs was discussed. The group also discussed the concept of using big data, learning software to make sense and improve accuracy of the statistical predictions.

Chemoprevention

The group also discussed the need to improve chemoprevention across the board. Further research into the germline mutations could offer rationales for developing chemoprevention drugs. If the link between germline mutation and the tumour development is understood agents could be developed to block the process. There is not a lot of research in this area currently.

5. Prostate breakout session, chaired by Dr Liz Bancroft

The major problem with prostate cancer is overdiagnosis and the associated treatments and side effects. Risk stratification using genetic profiling could be used to tease out the individuals at highest risk of developing lethal cancers for screening.

There are around 170 genetic variants that are known to influence prostate cancer as well as a small number of rare variants with intermediate risk. 27 variants are associated with aggressive and early-onset disease. It may be that adding genetic factors to other characteristics could make a screening programme more effective

A critical issue for prostate cancer is around what screening test could be used. To date, Prostate Specific Antigen (PSA) has been the sole prospect for a screening test. There are a number of other markers that are being investigated in relation to screening programmes. It was also noted

that there are issues around accurate diagnosis and prognosis. MRI is becoming standard in the diagnostic pathway, with or without biopsy depending on results of the MRI. Regarding treatment we need to be thinking of how to use the genetic markers to aid prognosis to ensure the right men are getting the right treatment.

Patient preferences need to be an essential component of developing protocols, looking at communication, information, psychosocial issues, health behaviour, choice and adherence.

The group discussed the STOCKHOLM-3[6] study, the only study to date in prostate cancer which has incorporated genetic profiling into a screening algorithm. Protein markers, genetic markers and clinical data were used to produce a formula about an individual's risk of developing prostate cancer. Through this the research group managed to demonstrate a reduction in the number of men sent for biopsy, an equal number of men being diagnosed, a decrease in the number of clinically insignificant disease being detected, and 44% less biopsies in men without cancer. The study didn't include MRI in the algorithm, and the group thought that replicating this study using MRI could be worthwhile to further improve the results.

Prostate Cancer UK is working on a risk assessment tool within primary care. At present, it does not incorporate genetics, but this could be incorporated in the future.

Two genetic profiling studies are ongoing at the Institute of Cancer Research, the BARCODE 1[7] study looking at using risk-based profiling in a general population cohort, and the PROFILE[8] study offering prostate screening to men in two high risk groups based on ethnicity and family history. The PROFILE study is retrospectively evaluating the use of a polygenic risk score in these cohorts to detect clinically significant disease.

[6] https://prostatecanceruk.org/about-us/news-and-views/2015/11/stockholm-study-heralds-major-change-in-assessing-cancer-risk

[7] http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-genetic-profile-identify-men-increased-risk-prostate-cancer-barcode-1

[8] http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-to-find-out-if-looking-at-gene-changes-could-be-part-of-prostate-cancer-screening-profile

Workshop recommendations

Breast cancer

Prof Dan Rea should ensure the trial design discussed at the workshop to augment the current breast cancer screening programme is discussed and further developed into a grant proposal by the NCRI Breast Cancer Clinical Studies Group. Potential funders, psychosocial experts and people who attend screening should be involved in developing the grant proposal.

Colorectal cancer

The NCRI Colorectal Cancer Clinical Studies Group should invite Professor Ian Tomlinson to discuss the idea of a pilot study looking at the use of mendelian genes in risk stratification for colorectal cancer screening that was explored at the workshop. Potential funders, psychosocial experts and people who could be part of such a trial should be involved in the discussions.

Gynaecological cancer

The NCRI Gynaecological Cancer Clinical Studies Group should invite Dr Ranjit Manchanda to discuss a trial for germline testing in relation to gynaecological cancers that was explored at the workshop. Potential funders, psychosocial experts and people who could be part of such a trial should be involved in the discussions.

Lung and Skin cancer

Lung and skin cancer research in this area is in its infancy. Research into the relevance of the germline in predicting skin and lung cancer should consider using large data solutions in rationalising the potential predictive SNPs and combinations. Germline research in people who do not develop cancer despite being at very high risk should be developed. Research into the use of germline data in combination with other data that predict risk should be conducted.

Prostate Cancer

The NCRI Prostate Cancer Clinical Studies Group should invite Dr Liz Bancroft to discuss the findings of the workshop and the Group should explore if any further studies should be developed.

Cross cutting

Prof David Baldwin should investigate the feasibility of creating a pan-cancer genetic germline profiling platform with the NCRI Screening, Prevention and Early Diagnosis Advisory Group and the Chairs of the Chairs of the NCRI Breast, Colorectal, Lung and Skin Cancer Clinical Studies Groups.

Research funders, such as Breast Cancer Now, Bowel Cancer UK and Prostate Cancer UK, should explore with researchers and people who attend screening how the gaps in knowledge identified at the workshop can be filled to allow the design of trials to evaluate risk-based prevention and surveillance programmes based on genetic germline profiling.

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