Cancer Genetics Group

With

European Hereditary Tumour Group

Spring Meeting

Monday 24th and Tuesday 25th May 2021

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UK CANCER GENETICS GROUP & EHTG SPRING MEETING
Monday 24th and Tuesday 25th May 2021

DAY 1 – Monday 24th May

09.25	Welcome and Housekeeping Feedback from CGG Council	**Professor Marc Tischkowitz**
09.40-10.45	**Session 1: Dermatology**	**Chair: Dr Anju Kulkarni**
09.40-10.05	Saturation Mutagenesis of Melanoma Predisposition Genes	**Dr David Adams**
10.05-10.30	Xeroderma Pigmentosum: a unique disease model for UV radiation-induced skin cancer	**Dr Hiva Fassihi**
10.30-10.55	Why, who and how we should screen for melanoma	**Dr Katie Lacy**
10.55-11.25	**Session 2: Lightening talks**	**Chair: Dr Terri McVeigh**
10.55	A day in the life of a Clinical Psychologist working with hereditary breast and ovarian cancer families	**Dr Clare Firth**
11.00	Attenuated phenotype in PTCH1-related Gorlin Syndrome	**Dr Helena Carley**
11.05	Parental views on the experience of a childhood *TP53* surveillance programme	**Dr Shereen Tadros**
11.10	TP53 Clinical Management - are we doing it right?	**Ms Madeline Gale**
11.15	Implementation of the Very High Risk breast surveillance guidelines in women age 25-29 - experience of the East Anglian Clinical Genetics Service	**Ms Bev Speight**
11.20	Patient and public collaboration in research: An exemplar from the CanGene-CanVar project developing decision aids to assist with understanding of hereditary cancer risk and management options	**Ms Kelly Kohut**

11.25-11.35 TEA BREAK

11.35-12.50 Session 3: Submitted abstracts Chairs: Ms Hannah Musgrave and Ms Bev Speight

11.35-11.50 The IMPACT study Lynch Syndrome cohort – results after first round of screening
Professor Ros Eeles

11.50-12.05 Development of a comprehensive prediction model for future prostate cancer risk
Dr Tommy Nyberg

12.05-12.20 The BARCODE1 Pilot Study: The use of polygenic risk score for targeted prostate cancer screening in men in the general UK population **Dr Jana McHugh**

12.20-12.35 Patient-centred changes to BRCA genetic test reports lead to better comprehension
Dr Gabriel Recchia

12.35-12.45 Q and A session

12:45 **Day 1 meeting close**

UK CANCER GENETICS GROUP & EHTG SPRING MEETING
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DAY 2 – Tuesday 25th May

09.25 Welcome and Housekeeping **Dr Helen Hanson**

9.30-10.40 **Session 4: Equality and Diversity in Cancer Genetics** **Chair: Dr Katie Snape**

9.30- 9.55 Person-centred care for trans and gender diverse people accessing cancer genetics
Dr Alison Berner, Ms Beth Coad and Ms Josephine Giblin

9.55-10.20 Men of differing ancestry: Diversity in Prostate Cancer screening
Dr Jana McHugh

10.20-10.45 Reflecting on cancer communication with diverse groups
Ms Sasha Henriques

10.45-10.55 TEA BREAK

10.55-12.10 **Session 5: European Hereditary Tumour Group**
Chairs: Professor Julian Sampson and Professor Gabriela Moeslein

10.55-11.20 Lynch syndrome cancer evolution – implications for immune prevention and immunotherapy **Dr Matthias Kloor**

11.20-11.45 Gene-specific clinical guidance for colorectal cancer in Lynch syndrome
Dr Toni Seppälä

11.45-12.10 Functional MMR testing in diagnosis and screening for Lynch syndrome.
Professor Sir John Burn and Dr Richard Gallon

12.10.12.55 **Session 6: Keynote Lecture** **Chair: Professor Marc Tischkowitz**

Lynch syndrome: the gynaecologist's perspective **Professor Emma Crosbie**

12.55 **Meeting close**

DAY 1 - Monday 24th May 2021

Session 1: Dermatology

Saturation Mutagenesis of Melanoma Predisposition Genes

Dr David Adams. Experimental Cancer Genetics, Wellcome Sanger Institute, Hinxton, Cambs. Email: da1@sanger.ac.uk

Melanoma remains one of the most difficult tumours to treat at advanced stages meaning that identifying individuals at high risk and managing them through screening is critically important. The major melanoma predisposition genes include *CDKN2A, CDK4, BAP1 and POT1*. While there are well established pathogenic variants in these genes that associate with melanoma predisposition, gene panel sequencing experiments have identified a large number of variants of unknown significance (VUS). These VUS represent a challenge for patience management since it is often unclear which individuals should receive screening and which individuals and their family members would receive no benefit. To facilitate clinical decision making we are performing saturation genome editing of all melanoma predisposition genes. In my talk I will outline the approach of saturation genome editing, provide examples of how we are using this method to identify all possible disruptive variants in the abovementioned genes and describe how we are scaling this approach to tackle the challenge of all cancer genes. I will also provide clinical examples of how the functional data we have generated can aid decision making and also further our biological understanding of genes and proteins. As part of my talk I will also provide an update on our large-scale melanoma cohort sequencing studies, including our analysis of the tumours of Leeds melanoma cohort of over 500 cases and also germline sequencing of over 2,000 individuals as part of the same study.

Xeroderma Pigmentosum: a unique disease model for UV radiation-induced skin cancer

*Dr Hiva Fassihi. Clinical Lead National XP Service and Consultant Dermatologist, St John's Institute of Dermatology, Guy's and St Thomas' Hospitals NHS Foundation Trust. Honorary Reader, King's College London. Email: hiva.fassihi@gstt.nhs.*uk

Xeroderma pigmentosum (XP) is a rare inherited disorder of DNA repair characterized by increased susceptibility to UV radiation (UVR)-induced skin pigmentation, skin cancers, ocular surface disease, and, in some patients, sunburn and neurological degeneration. Genetically, it is assigned to eight complementation groups (XP-A to -G and variant).

Since 2010, the National XP Service, at Guy's and St Thomas' Hospital in London, has provided follow-up for about 120 XP patients, representing most of the XP patients in the United Kingdom. Causative mutations, DNA repair levels, and more than 60 clinical variables relating to dermatology, ophthalmology, and neurology have been measured, using scoring systems to categorize disease severity. This deep phenotyping has revealed unanticipated heterogeneity of clinical features, between and within complementation groups.

Skin cancer is most common in XP-C, XP-E, and XP-V patients, previously considered to be the milder groups based on cellular analyses. These patients have normal sunburn reactions and are therefore diagnosed later and are less likely to adhere to UVR protection. XP-C patients are specifically hypersensitive to ocular damage, and XP-F and XP-G patients appear to be much less susceptible to skin cancer than other XP groups. Within XP groups, different mutations confer susceptibility or resistance to neurological damage.

In an XP-C patient with advanced metastatic cancer arising from an angiosarcoma, molecular analysis of the tumour DNA suggested that immunotherapy, not normally recommended for angiosarcomas, might in this case be successful, and indeed the patient showed a dramatic recovery following immunotherapy treatment.

Our findings on this large cohort of XP patients under long-term follow-up reveal that XP is more heterogeneous than has previously been appreciated. Our data now enable provision of personalized prognostic information and management advice for each XP patient, as well as providing new insights into the functions of the XP proteins.

Why, who and how we should screen for melanoma

Dr Katie Lacy. Consultant Dermatologist, Guy's and St Thomas' Hospitals NHS Foundation Trust. Email: Katie.Lacy@gstt.nhs.uk

Melanoma represents a major public health issue with rising incidence and mortality worldwide. It is one of the commonest causes of cancer in young adults. If caught early, excision can provide >95% chance of cure however overall 20% of patients will go on to develop metastatic disease where life expectancy is often limited. It is not currently recommended in the UK that all individuals seek screening however guidance on who should be screened is inconsistent. In addition to environmental exposure to UV, risk factors for the development of melanoma include the presence of >50-100 naevi, dysplastic naevi, a previous history of melanoma and a family history of melanoma. Testing for genetic susceptibility to melanoma can help to identify individuals at significant risk of melanoma however a substantial proportion of families with a strong history of melanoma will not have a gene that is currently identifiable on panel testing. In this talk I will discuss strategies for the identification of individuals at high risk for melanoma and their screening.

Session 2 – Lightening session

A day in the life of a Clinical Psychologist working with hereditary breast and ovarian cancer families

Presented by Dr Clare Firth. Clinical Psychologist, Guy's and St Thomas' Hospitals NHS Foundation Trust. Email:clare.firth@gstt.nhs.net

The Genetics service at Guy's hospital is unique in having a dedicated in-house clinical psychology team aimed at supporting patients from when they embark on a genetics risk assessment including testing through to coping with the repercussions of a genetic diagnosis. As part of this role, the psychology team provides appointments at our multidisciplinary 'one-stop' clinic for patients with a family history of hereditary breast and ovarian cancer (HBOC clinic). The psychology clinic appointment serves as a screening appointment as well as a brief support session, and approximately half of patients attending the clinic opt for this appointment. Issues discussed range from making risk management decisions, talking to family about the genetic mutation, preparing for risk reducing surgery or coping with cancer treatment, for example. Clinic patients present with a variety of psychological complexity and severity and some require further psychology sessions which consist of up to six sessions of goal-focused therapy, such as cognitive behavioral therapy. Also, all patients opting for risk reducing mastectomies after their HBOC clinic appointments are offered further psychological support in line with NICE guidelines. The psychology team also contributes to the clinic MDT discussions to provide psychological perspectives about patients. Clinical psychologists play a highly integral and useful role in providing psychosocial support for HBOC clinic patients and we will provide patient data and case examples from a typical clinic day to support this.

Attenuated phenotype in PTCH1-related Gorlin Syndrome

Presented by Dr Helena Carley. South West Thames Regional Genetics Service, St George's University Hospitals NHS Foundation Trust. Email: helenacarley@nhs.net

We present an extended pedigree with a predominant basal cell carcinoma phenotype, and a pathogenic missense variant in PTCH1 c.3062A>G p.Tyr1021Cys.

Two branches of this family have been independently ascertained with onset of multiple basal cell carcinomas in adult life without significant sun exposure. To our knowledge, there are nine confirmed or obligate mutation carriers within this family of which six have had multiple BCCs. Age of onset of BCCs ranges from 30s to 60s, with two individuals having around 80-100 BCCs each.

Of the seven family members known to our department, six are confirmed mutation carriers. Only one individual is known to have macrocephaly, and one has a reported jaw keratocyst. Other features of Gorlin Syndrome, such as palmar pits, characteristic skeletal x-ray findings and congenital anomalies are notably absent. Furthermore, three adults identified through predictive testing thus far have no BCCs and have normal head circumferences. Collectively, the evidence is suggestive of an attenuated Gorlin phenotype.

We present the evidence for variant pathogenicity and review the literature surrounding hypomorphic missense variants in PTCH1-related Gorlin Syndrome. We also discuss the complexities surrounding predictive testing and screening in children in families with attenuated phenotypes.

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Parental views on the experience of a childhood *TP53* surveillance programme

Presented by Dr Shareen Tadros. North East Thames Regional Genetics Service, Great Ormond Street Hospital for Children. Email:shereentadros@nhs.net

Background
Carriers of *TP53* pathogenic variants have up to 41% tumour risk by the age of 18 years.[1]
Recently published UKCGG Guidelines recommend childhood surveillance for carriers of *TP53* pathogenic variants including annual whole body and brain MRI, 3-4 monthly abdominal ultrasound and review in a dedicated clinic.[2]

Such surveillance has been ongoing at Great Ormond Street Hospital (GOSH) for over three years. However, it has long been recognised that hospital attendance may be source of anxiety for children and their families.[3]

Aim
To gain information about children and families' experience of the TP53 surveillance clinic.

Method
24 families under the care of the GOSH TP53 clinic were invited to take part in an anonymous semi-structured online survey.

Results
16/24 families responded. Of these, one third had children affected with a tumour, all of which had been identified prior to starting surveillance.
14/16 felt satisfied or very satisfied with the surveillance programme as a whole. The degree of satisfaction with MRI scans was in line with other aspects of the programme.
75% of children and parents were relaxed or very relaxed about attending surveillance appointments and half of parents reported feeling higher levels of optimism about their child's diagnosis since joining the clinic.

Conclusion
Overall, there was a very high degree of satisfaction with being part of the surveillance clinic and negative aspects were felt to be outweighed by benefits.
Further work will clarify the longer term impact.

[1] Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. J Clin Oncol. 2015;33(21):2345-2352. doi:10.1200/JCO.2014.59.5728
[2] Hanson H, Brady AF, Crawford G Consensus Group Members, et al UKCGG Consensus Group guidelines for the management of patients with constitutional TP53 pathogenic variantsJournal of Medical Genetics 2021;58:135-139.
[3] Bachanas P J, Roberts MC. Factors affecting children's attitudes toward health care and responses to stressful medical procedures, Journal Pediatric Psychology, 1995, vol. 20 (pg. 261-275)

TP53 Clinical Management - are we doing it right?

Presented by Ms Madeline E Gale. STP trainee, NW Thames Regional Genetics Service. London North West NHS Healthcare Trust Email: madeline.gale@nhs.net

In 2020 the UKCGG Consensus Group published guidelines for the management of patients with constitutional TP53 pathogenic variants[1] which are associated with Li-Fraumeni syndrome (LFS). An audit was undertaken to evaluate the clinical management of patients with LFS seen in the North West Thames Regional Genetic service against local and national protocols.

Patient records were reviewed. Patients and referring clinicians were contacted where necessary to assess the following outcome measures:

1) Females age 20-70 had had bilateral mastectomy or had been referred for annual breast MRI
2) Patients were provided with a 'To Whom It May Concern' letter to support them to inform at-risk relatives, where appropriate
3) Parents/carers of children affected or at risk of LFS were aware of the specialist LFS clinic at Great Ormond Street Hospital
4) Annual dermatology review from age 18 years had been recommended
5) "Red flag" symptoms and lifestyle choices had been discussed

In addition we assessed the number patients eligible for annual whole body MRI and brain MRI as such surveillance is not yet available within our region but it is hoped this work will help support the provision of this unmet need. We reflect on the successes of the clinical management of our LFS patients, highlight areas of potential errors, and evaluate these in regards to changes to our guidelines and protocols within our service.

1. Hanson H et al. UKCGG Consensus Group guidelines for the management of patients with constitutional TP53 pathogenic variants. J Med Genet 2021;58:135–139.

Implementation of the Very High Risk breast surveillance guidelines in women age 25-29 – experience of the East Anglian Clinical Genetics Service

Presented by Ms Beverley Speight. Principal Genetic Counsellor, East Anglian Clinical Genetics Service, Cambridge University Hospitals NHS Foundation Trust Email: Beverley.Speight@addenbrookes.nhs.uk

The current surveillance protocols for women at very high risk of breast cancer were published in February 2021 by Public Health England. This revised guidance states that women aged 25-29 with a 10-year breast cancer risk of ≥8% should be included in the very high risk surveillance programme. To identify the women most likely to be eligible in our region, we searched a local database of predictive test patients to select women currently age ≤29 with a germline pathogenic variant in BRCA1, BRCA2 or PALB2. 84 women met these criteria: BRCA1 = 29, BRCA2 =50, PALB2 = 5, age range 19-29 years. A letter outlining the new surveillance guidelines and a health questionnaire were sent to 62 women. Of the other 22 women, five had moved outside of our region, 12 had undergone or were soon to have bilateral risk-reducing mastectomy, four were close to their 30th birthday and therefore referred for breast MRI and one woman had died. Health questionnaire information was returned for 56 of the 62 women (response rate 90%). The 10-year breast cancer risk between ages 25-29 was calculated using CanRisk and included genetic status, family history and hormonal/lifestyle information. 39/56 (70%) women met the 10-year risk threshold between age 25-29 (BRCA1 = 17, BRCA2 =22). 13 of these 39 women (33%) were eligible at their current age and were referred for breast MRI. We are using our experience to inform the development of a clinical register for women eligible for very high risk breast surveillance

Patient and public collaboration in research: An exemplar from the CanGene-CanVar project developing decision aids to assist with understanding of hereditary cancer risk and management options

Presented by Ms Kelly Kohut. Consultant Genetic Counsellor, St George's University Hospitals NHS Foundation Trust, University of Southampton,. Email: Kelly.kohut@stgeorges.nhs.uk

Introduction: CanGene-CanVar (CGCV) is funded by Cancer Research UK to ensure coordinated, safe, effective delivery of clinical cancer susceptibility genetics enabling best outcomes for patients. Patients have been involved from the conception stage, and work alongside researchers to strengthen research quality and relevance. We are developing decision aids to help patients understand personalised risk for hereditary cancer and make decisions about screening, prevention, and risk-reduction.

Methods: A Patient Reference Panel (PRP) of 10 patient advocates was appointed to consult on clinical guidelines, ethical issues and research design. Two collaborative meetings were held with researchers and the PRP to evaluate and develop decision aids. These included interactive group discussions, small breakout rooms, and feedback to improve future activities.

Results: Patient involvement has shaped the direction of our research, including search strategy for a systematic literature review, on which the PRP chair is co-author. Sixty publications describing 42 patient decision aids were identified. The PRP scrutinised selected decision aids and fed back on written forms and in the group discussions. Priorities for future prototypes were identified, along with suggestions for the research programme, e.g. the need to work with groups from target communities.

Conclusions: The PRP are guiding development of patient decision aids for use in clinical practice, tailored according to cancer diagnosis, family history and gene(s) tested. Psychological theory and patient preference for risk communication will underpin design. This will ensure maximum benefit to care pathways, including in mainstream oncology settings and follow-up care of pathogenic variant carriers in clinical genetics.

Session 3 – Submitted abstracts

The IMPACT study Lynch Syndrome cohort – results after first round of screening

Presented by Professor Rosalind Eeles. Professor of Oncogenetics, The Institute Of Cancer Research & The Royal Marsden NHS Trust, London, UK.
Email:ros.eeles@icr.ac.uk

Introduction:
Mutations in the mis-match repair genes (MMR) have been reported to increase the risk of early-onset aggressive prostate cancer (PrCa). The IMPACT study is prospectively evaluating PSA screening in men with germline *MMR pathogenic variants (PVs)*. Here we report the utility of PSA screening, PrCa incidence and tumour characteristics after the first year's screening.

Methods:
Men aged 40–69 years with germline PVs *in MSH2, MSH6 and MLH1 genes* and male controls testing negative for a familial PV in *these genes* underwent PSA screening and if PSA >3.0ng/ml, were offered prostate biopsy.

Results:
204 *MLH1* carriers, 199 *MLH1* non-carriers, 305 *MSH2* carriers, 210 *MSH2* non-carriers,135 *MSH6* carriers, 177 *MSH6* non-carriers were recruited. After 1 year's screening 56 men had PSA>3.0ng/ml, 35 biopsies were performed, and 18 PrCas diagnosed (13 *MSH2* carriers, 1 *MSH2 non-carrier*; 4 *MSH6* carriers; 0 cancers in *MSH6* non-carriers, and *MLH1* cohort). Cancer incidence was higher in *MSH2* carriers (4.3% vs 0.5%;p=0.01) and *MSH6* carriers than non-carriers respectively (3% vs 0%;p=0.04). *MSH2* carriers were diagnosed younger (60 vs 66years) and more likely to have clinically-significant disease than non-carriers (85% vs 0%p=0.2). *MSH6* carriers were diagnosed at 64 years (median) and 75% had clinically significant disease.

Discussion:
After one year's screening, carriers of *MSH2 and MSH6 PVs* had a higher incidence of PrCa, were diagnosed at a younger age and had more clinically significant disease compared with non-carriers.

Development of a comprehensive prediction model for future prostate cancer risk

Presented by Dr Tommy Nyberg, Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge. MRC Biostatistics Unit, University of Cambridge. Email: tommy.nyberg@mrc-bsu.cam.ac.uk

Prostate cancer (PCa) risk assessment is largely determined by family history, ethnicity and the presence of pathogenic variants (PVs) in *BRCA2* or *BRCA1*. Several PCa susceptibility variants have been identified, including rare moderate-to-high-risk PVs and common low-risk variants which jointly explain 40% of the excess familial relative risk (FRR). To date, no multifactorial PCa risk prediction model exists that incorporate current knowledge on PCa susceptibility.

We developed a genetic risk prediction model, using genotypic and family history information on 16,633 European ancestry PCa cases included in the UK Genetic Prostate Cancer Study. We used a kin-cohort study design and complex segregation analysis, assuming a multiplicative model for PCa incidence for the relative risks (RRs) associated with PVs, a polygenic risk score (PRS) based on 174 common variants, and unexplained PCa family history.

The best-fitting model includes the effects of PVs in*BRCA2* ($RR_{age<65}$=7.0, $RR_{age\geq65}$=3.8, carrier frequency [CF]=0.2%), *HOXB13* ($RR_{born<1930}$=3.0, $RR_{born\geq1930}$=5.4, CF=0.5%) and *BRCA1* ($RR_{age<65}$=1.9, $RR_{age\geq65}$=0.9, CF=0.1%). The model further includes a rare recessively inherited risk of early onset PCa (RR=104, CF=0.2%) and a polygenic component with age-dependent standard deviation ($SD=2.11\times0.985^{(age-70)}$), which imply higher familial relative risks (FRRs) at younger ages, and from affected brothers over fathers. The PRS was estimated to explain on average 35% of the polygenic component. The predicted FRRs are consistent with those reported in observational studies. External validation is ongoing.

If successfully validated, the model will most likely enhance genetic counselling for men by providing more tailored risk estimates compared to currently available risk-prediction tools.

The BARCODE1 Pilot Study:

The use of polygenic risk score for targeted prostate cancer screening in men in the general UK population

Presented by Dr Jana McHugh. Clinical Research Fellow at the Institute of Cancer Research, London and the Royal Marsden Hospital, Oncogenetics Department. Email: jana.mchugh@icr.ac.uk

Introduction:
A significant proportion of prostate cancer (PrCa) risk is attributable to heritable risk factors. A large proportion of PrCa arises from the combined effect of multiple low risk variants. Approximately 170 single nucleotide polymorphisms (SNPs) associated with PrCa risk have been identified in Europeans. While each confers a low/moderate risk of PrCa, the cumulative risk (polygenic risk score, PRS) of increasing numbers of these risk alleles may confer substantial relative risk. PRS in PrCa genetic profiling could be used to target population-screening to those at highest risk. BARCODE1 is the first study to prospectively review utilising genetic profiling in PrCa screening in the UK population.

Patients and Methods:
Our pilot study invited healthy males aged 55-69 to participate through General Practitioners. Genotyping was carried out after DNA extraction from saliva samples using a study specific assay and PRS was calculated. Prostate MRI and biopsy were offered to men in the top 10% of PRS distribution.

Results:
1434 men were invited to participate in the pilot; uptake was 26%. Data were available for 297 men following genotyping and quality control checks. Of 25 participants with PRS in the top 10%, 19 underwent prostate MRI, and 18 underwent systematic prostate biopsy. There were 7 diagnoses of PrCa (38.9%). Cancers detected were low/intermediate-risk. Follow up is ongoing.

Conclusions:
The BARCODE1 pilot has shown the feasibility of this population-based study, with an uptake of 26% and cancer incidence of 38.9%. The BARCODE1 full-study results will be important in defining the role of PRS genetic profiling in targeted PrCa screening.

Patient-centred changes to BRCA genetic test reports lead to better comprehension

Presented by Dr Gabriel Recchia. Winton Centre for Risk and Evidence Communication, University of Cambridge. Email:glr29@cam.ac.uk

With increased mainstreaming of BRCA testing through primary care, and much prior research showing that BRCA genetic test results are frequently misunderstood by clinicians and patients alike, there is an opportunity for BRCA genetic test reports to help facilitate effective communication of test results to clinicians, to assist clinicians in explaining results to patients, and to serve as tools that individuals can use to explain test results to family members. We undertook user-centered design research, including four rounds of interviews with a total of 42 past patients, laypersons, and clinicians, to produce six template reports for different BRCA test outcomes. A separate study (N=456) found that lay participants viewing the new reports rated them significantly more actionable, comprehensible, and effective at communicating key information than reports currently in use. They were also more likely to correctly understand that pathogenic BRCA variants can be passed to children by fathers as well as mothers, that it is possible for both children of someone who carries a BRCA1 pathogenic variant to be carriers themselves (i.e., understanding that the 50% risk applies to each child, and that the total percentage of affected children will not necessarily be exactly 50%), and that full siblings of a carrier have a 50% chance of being affected. Our results imply that improving genetic test result templates may offer real benefits for patient safety and understanding. They also suggest general principles for improving genetic test result templates that could facilitate understanding across a wide variety of genetic tests.

DAY 2- Tuesday 25th May 2021

Session 4 - Equality and Diversity in Cancer Genetics

Person-centred care for trans and gender diverse people accessing cancer genetics

Dr Alison Berner. Tavistock and Portman NHS Foundation trust. Email: alison.berner@nhs.net.
Ms Beth Coad, Genetic Counsellor, St Georges Hospital NHS Trust. Email: Beth.Coad@stgeorges.nhs.uk.
Ms Josephine Giblin, Genetic Counsellor. Wessex Clinical Genetics Service and Central and South GMSA. Email: josephine.giblin@nhs.net

An increase in referrals for transgender and gender diverse (T&GD) patients with inherited cancer risk has been reported for cancer genetics services across the UK. To best support these patients, we must adapt our practice to consider their unique needs including tailored risk assessments and management recommendations.

We will discuss the experiences and management of T&GD patients accessing UK cancer genetics services, providing a background to gender identity care in the UK, and tips for seeing T&GD patients in clinic. We will also highlight some cases from which recommendations for risk assessment, screening and surgical management guidance has been suggested.

Further work is required to improve cancer genetics services for these patients. We will outline ongoing initiatives and consider areas for improvement such as the need for an expert MDT, national guidelines, and internationally collaborative research into better risk estimations.

Diversity in Prostate Cancer Screening

Dr Jana McHugh. Clinical Research Fellow at the Institute of Cancer Research, London and the Royal Marsden Hospital, Oncogenetics Department. Email: jana.mchugh@icr.ac.uk

Introduction

Prostate cancer (PrCa) is the second most common solid tumour worldwide. Currently, there is no population screening programme in the UK for PrCa, or in many countries across the globe. The use of prostate specific antigen (PSA) remains controversial with false positive and false negatives an ongoing issue. The known risk factors for PrCa are age, race/ethnicity, family history and germline genetic mutations eg. *BRCA* and Lynch Syndromes.

PrCa is the most common cancer affecting men of African and African-Caribbean ancestry. Since there are issues with using PSA alone as a screening tool and the basis for certain men being at higher risk for PrCa has at least a 50% genetic component, therefore research in combining genetic risk scores and imaging will be important in PrCa screening in men of differing ancestries.

Background

Studies conducted in the USA and UK have shown that men of African ancestry are more likely to develop PrCa at a younger age and the disease is likely to behave more aggressively. PrCa appears to have a lower prevalence in men of Asian ancestry. Men of non-European ancestry are less likely to take part in clinical studies and work is ongoing to improve engagement with these groups. Such diverse populations are under-represented in GWAS studies and so we established a global consortium, PRACTICAL, involving ~133 groups globally. In collaboration with Professor Haiman (USC), a recent trans-ancestry meta-analysis of 107,247 cases and 127,006 controls (10,368 cases; 10,986 controls of African ancestry and 8611 cases; 18,809 controls of East Asian ancestry) discovered 86 novel SNPs associated with PrCa risk. Men of African ancestry were estimated to have a mean PRS that was 2.18-times higher and men of East Asian ancestry 0.73-times lower than men of European ancestry. This paper showed that the current polygenic risk score (PRS) profile has 269 variants. These 269 capture 40% of the 2-fold familial relative risk.

The PROFILE study

The PROFILE study (NCT02543905) set out to investigate targeted screening in men at higher risk of PrCa in the UK. The aims of this study are to investigate the role of targeted PrCa screening in men at a higher genetic risk and its association with specific genetic profiles and biomarkers (both biological samples and imaging). The primary endpoint of the study is to determine an association between the genetic risk profile and the prostate biopsy result. We have invited (i) men of African and African Caribbean ancestry (with four grandparents of the same ancestry) and (ii) men of European ancestry with a family history of PrCa to participate in the study; 350 men will each be recruited into parts (i) and (ii). All men are offered mpMRI and prostate biopsy and biological samples are taken. Early results will be presented in the talk.

Conclusion

It will be important to incorporate emerging data from more diverse groups in order to provide a more complete and comprehensive risk profile useful in targeted PrCa screening across populations to inform public health programmes

Reflecting on cancer communication with diverse groups.

Ms Sasha Henriques. Principal Genetic Counsellor. Clinical Genetics. Guys and St. Thomas' NHS Foundation Trust. Email: sasha.henriques@nhs.net

Although there have been initiatives to ensure the equitable and ethical practice of genetic services disparities still exist. One of the areas where further research and intervention may be needed is in genetic cancer services. Genetic testing for the risk of hereditary cancer can help patients to make important decisions about prevention or early detection. Differences in access to genetic services and the uptake of screening may explain some of the disproportion in cancer outcomes seen across different groups in the UK.

Literature in this area has highlighted a place for a range of culturally appropriate interventions for cancer prevention. Through this presentation we will look at some of the challenges highlighted in the UK and reflect on the approaches suggested to address them. We will also examine some of the communication skills and practical tools clinicians in cancer genetic services can implement to meet the needs of diverse groups.

Session 5 - European Hereditary Tumour Group

Lynch syndrome cancer evolution – implications for immune prevention and immunotherapy.

Dr Matthias Kloor. Department of Applied Tumor Biology, Institute of Pathology Heidelberg University Hospital. Email: matthias.kloor@med.uni-heidelberg.de

Lynch syndrome is caused by monoallelic germ line variants of the DNA mismatch repair (MMR) genes. During life, somatic mutation events (second hits) lead to loss of MMR function in proliferating cells, including crypts within the colonic mucosa. From thousands of such MMR-deficient crypt foci, however, only a very small part develops into clinically manifest cancers. These cancers are mostly diploid, but characterized by the microsatellite instability (MSI) phenotype, i.e. the accumulation of numerous insertion/deletion mutations at repetitive microsatellite sequences. Mutations affecting microsatellites in tumor suppressor genes promote MSI tumor development in Lynch syndrome. Using a bioinformatics-based model, we have identified a set of coding microsatellite mutations with likely driver function. These mutations also lead to shifts of the translational reading frame and to the generation of MMR deficiency-related frameshift peptides (FSPs). The well-defined pattern of MMR deficiency-induced mutations and neoantigens has wide-ranging implications on the clinical course of the disease: as the same mutations recurrently occur in the same tumor suppressor genes, Lynch syndrome cancers share a small and predictable set of highly immunogenic FSP neoantigens. Immune responses against these FSP neoantigens can already be detected in tumor-free Lynch syndrome carriers, suggesting that there is a lifelong interaction between the immune system and emerging precancerous cell clones. Recent observations of tumor mutation patterns have provided additional evidence for elimination of pre-cancerous MSI cell clones by the immune system. Immune surveillance therefore likely contributes to the limited penetrance of Lynch syndrome and may be boosted by vaccination with FSPs. We demonstrated in a phase I/IIa clinical trial that vaccination with specific FSP neoantigens is safe and induces pronounced immune responses. Preliminary data suggest that FSP vaccination has a tumor-preventive-effect in a pre-clinical model of Lynch syndrome, particularly in combination with chemoprevention.

Gene-specific clinical guidance for colorectal cancer in Lynch syndrome

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The observational data from the Prospective Lynch Syndrome Database (PLSD) has clarified the organ-, gene-, gender- and age-specific risks related to Lynch syndrome. It is warranted that this new knowledge is transferred into clinical guidelines, replacing the previous 'one size fits all' -approach. The European Hereditary Tumor Group (EHTG) and the European Society of Coloproctology (ESCP) have established the European recommendations for colorectal cancer screening and management in Lynch Syndrome.

EHTG and ESCP developed a multidisciplinary working group consisting of surgeons, clinical and molecular geneticists, pathologists, epidemiologists, gastroenterologists, and patient representation to conduct a graded evidence review. The previous Mallorca guideline format was used to revise the clinical guidance. Consensus for the guidance statements was acquired by three Delphi voting rounds. Recommendations for clinical and molecular identification of Lynch syndrome, surgical and endoscopic management of Lynch syndrome-associated colorectal cancer, and preventive measures for cancer were produced. The emphasis was on surgical and gastroenterological aspects of the cancer spectrum. The guidelines are designed to empower patients and clinicians to enable informed and individu- alized decision-making, recognizing that there is no universal approach to the care of those who carry pathogenic mismatch repair variants (*path_MMR*) and have LS, and therefore personalized care is critical.

Colonoscopy is recommended every 2 or 3 years for *path_MLH1*, *path_MSH2* and *path_MSH6 carriers*, unless they have had colorectal cancer before, after which biennial colonoscopy is recommended. For *path_PMS2* carriers, 5-yearly surveillance may be considered. Colonoscopy surveillance is recommended starting at age 25 years for *path_MLH1* and *path_MSH2* carriers, and at age 35 years for *path_MSH6* and *path_PMS2* carriers.

Extended surgery is recommended for *path_MLH1* and *path_MSH2* carriers at the time of first diagnosis of a colon cancer. Ileosigmoidal/ileorectal anastomosis is preferable to standard resection to reduce the risk of metachronous CRC. For a *path_MSH6* or *path_PMS2* carrier with a first colon cancer, standard/segmental colon resection should be offered. A decision on extended colorectal surgery for CRC should not be based on dMMR immunohistochemistry (loss of MLH1, MSH2, MSH6 or PMS2) and BRAF staining/*MLH1* hypermethylation from the preoperative endoscopic biopsy only.

Patients with *path_MMR* should be advised that there is a high probability that daily aspirin will reduce their cancer risk. The recommended aspirin dose should be a minimum of 75–100mg daily. This dose should be increased for people with above-average body mass.

Functional MMR testing in diagnosis and screening for Lynch syndrome.

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Despite NICE guidance issued four years ago, MisMatch Repair (MMR) deficiency testing of all colorectal cancers (CRCs) to screen for Lynch Syndrome (LS) remains inadequate. Existing technology is a barrier to widespread deployment of screening guidance[1]. The Newcastle MSI-PLUS assay can improve uptake of LS screening, providing both MSI analysis, *BRAF* and *RAS* analysis in one low cost and scalable test[2]. The assay has been deployed in the YNE GLH Newcastle laboratory, and a single technologist can process up to 4000 cases per annum with a turnaround under 14 days. Roll out to other GLHs is being pursued.

Practitioners should be aware of limitations to MMR deficiency testing of CRCs to identify LS. Screening will miss ~4% of LS cases that are MMR proficient, and ambiguous genetics testing and Lynch-like syndrome can result in uncertain diagnoses and management. The focus on CRC means that screening opportunities are missed. Resected tumour analysis also fails to provide a diagnosis prior to surgery, and testing of all biopsy blocks should be considered. The MSI-PLUS assay has capacity to test the broader LS tumour spectrum, and is being further developed with a more sensitive marker set for pan-cancer application and for use with low DNA yield from biopsy samples.

Novel applications of MMR deficiency testing include the development of *in vitro* assays to interpret MMR variants, or assays to assess MMR function of patient fibroblast culture as a direct LS carrier test. MSI analysis has repeatedly been detected in the normal tissues of patients with Constitutional Mismatch Repair Deficiency[3], and suggests MSI analysis of normal tissues may be an alternative LS carrier test. The Newcastle MSI-PLUS assay can detect increased MSI in the urine of LS patients with urothelial cancer, providing a surveillance tool for the third most common cancer in LS gene carriers.

1. Gallon R et al Cancers 2021; 13: 406-43
2. Gallon R et al Human Mutation. 2020;41:332–341
3. Perez-Valencia et al Gen Med 2020;22:2081-8

Session 6 - Keynote Lecture

Lynch syndrome: the gynaecologist's perspective .

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The gynaecological manifestations of Lynch syndrome have received little attention until recently. The Manchester International Consensus meeting aimed to address this gap by convening an expert group to develop clear and comprehensive clinical guidance regarding the management of the gynaecological sequelae of Lynch syndrome. In this keynote lecture, I will present the evidence underpinning new NICE recommendations that all people with endometrial cancer should have access to Lynch syndrome testing. I will present the results of the PETALS study, which investigated who, how and when endometrial cancer patients should be tested for Lynch syndrome. I will discuss risk reducing surgery and gynaecological surveillance for healthy carriers with Lynch syndrome, how current practice varies across the UK and new discoveries that could offer hope for the non-invasive detection of endometrial cancer in high risk women.