Cancer Network Newsletter

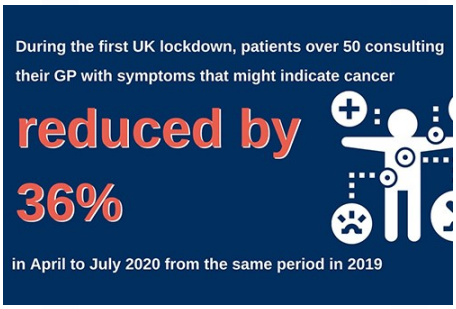
2021: Issue 2

Bristol Cancer Research Network

Pandemic saw fall in symptoms reporting

A team of National Institute for Health Research (NIHR)-funded researchers analysed anonymous information from 21 GP practices in Bristol, North Somerset and South Gloucestershire, covering 124,000 patients over the age of 50. They compared data from April-July 2020 with the same period in 2019. During April-July 2019, 56% of over 50s who were registered with the GP practices had a consultation and 17% reported potential cancer symptoms. In April-July 2020, this had reduced to 45% of over 50s having a consultation and 11% reporting cancer symptoms.

In 2019, potential cancer symptoms were reported in 21% of face-to-face GP consultations in over 50s, compared to 13% of remote consultations. In 2020, this was 17% face-to-face and 14% remotely. Of the most commonly reported potential cancer symptoms, reporting of chest infections, fever, coughs, fatigue and urinary tract infection reduced most dramatically. The eight alarm symptoms (blood in the urine, poo or vomit, coughing up blood, yellowing of the skin or eyes, breast lump, post-menopausal bleeding in women aged 55 and over, and difficulty swallowing) saw a less pronounced decline, but still reduced by 27% overall.



During the first UK lockdown, at-risk groups such as older people and those shielding tended to access GP consultations more frequently. However, these consultations did not result in higher levels of reporting of potential cancer symptoms. This suggests that these consultations were mostly for existing or routine issues rather than new health problems.

The findings reinforce an earlier Cancer Research UK survey where GPs felt they were receiving fewer reports of cancer symptoms during the first UK lockdown.

Cancer Research UK have published information for patients on common cancer symptoms to look out for.

Scott L *et al*. (2021). Changes in presentations with features potentially indicating cancer in primary care during the COVID-19 pandemic: a retrospective cohort study. *BMJ Open*.

Image © OneCare

Inside this issue:

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University of BRISTOL

Elizabeth Blackwell Institute for Health Research

EVENTS

3rd Crick International Cancer Conference
4 - 5 October 2021, The Francis Crick Institute, 1 Midland Road, London, NW1 1AT

A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance
4 October 2021, 11.00 - 12.30, online

Modulation of humoral immunity during immunization through control of vaccine kinetics
5 October 2021, 13.00 - 14.00, Professor Darrell Irvine (MIT), online

Invention for innovation seminar series: Patient & public involvement and stakeholders
6 October 2021, 13.00 - 14.30, online

CRUK's Prevention and Population Research funding opportunities webinar
6 October 2021, 14.00 - 14.45, online

Early Detection of Cancer Virtual Conference
6 - 8 October 2021, online

NIHR Pre-doctoral Clinical Academic Fellowship information webinar
6 October 2021, 17.00 - 18.00, online

Emerging Options in the Treatment of Waldenstrom's Macroglobinemia
7 October 2021, 9.00 - 17.00, online

Molecular Analysis for Precision Oncology Virtual Congress
7 - 9 October 2021, online

UK CLL Forum Clinical Sciences Day
8 October 2021, 9.30 - 17.15, Hybrid Event from the Cavendish Conference Centre, London

University of Bristol Inaugural Lectures: Professors Valeska Ting and Adam Perriman
8 October 2021, 16.30 - 20.00, Profs Valeska Ting & Adam Perriman, Queen's Building, BS8 1TR

Bristol Health Partners AHSC virtual conference
12 October 2021, 13.00 - 15.00, online

Invention for innovation seminar series: Clinical evaluation and validation
13 October 2021, 13.00 - 14.30, online

Virtual Summer School in Translational Cancer Research
13 - 14 October 2021, online

#Idea2Pitch Event
13 October 2021, 13.30 - 17.00, Rick Chapman, SETsquared Boardroom, Engine Shed, Bristol

SEE ALL EVENTS ON THE CANCER RESEARCH NETWORK WEBSITE

NEWS

University Cancer Research Fund

The University Cancer Research Fund holds an annual funding call which supports early-stage, innovative projects of up to £5,000 that have the promise to develop into high impact research. Between 2015 and 2020 the fund awarded a total of £120,886 which contributed to attracting £1,859,485 in follow-on funding - a return of £15 per £1 investment. The fund is overseen by the Cancer Research Network's steering group. The 2021-22 funding round supported the following projects:

- Dr Hannah Serrage (Bristol Dental School): *Examining the role of* Fusobacterium nucleatum *extracellular DNA in colorectal cancer pathogenesis*
- Prof Harry Mellor and Dr Mark Dodding (Biochemistry): *Targeting rhoj in tumour angiogenesis*
- Dr Caroline Bull (Cellular and Molecular Medicine [CMM]): *Formulating cell culture media to reflect the metabolic environments of obesity and type 2 diabetes*
- Dr Anna Chambers (Biochemistry): *Regulation of HELLS chromatin remodelling enzyme by phosphorylation*
- Dr Claire Perks (Bristol Medical School): *Interaction between T cell exhaustion, cancer-specific immunity and exercise in men with prostate cancer*
- Dr Philip Haycock, Carolina Borges and Tracey Collard (Bristol Medical School): *Understanding the mechanism linking polyunsaturated fatty acid desaturase activity to risk of colorectal cancer*
- Dr Vanessa Tan (Bristol Medical School): *Exploring the mechanisms linking acetate and breast cancer*
- Prof Christoph Wülfing (CMM): *Metabolic control of cytotoxic T cell function in tumour cell spheroids*
- Prof Karim Malik (CMM): *Targeting aberrant alternative splicing in neuroblastoma using Combinatorial protein arginine methyltransferase inhibition*

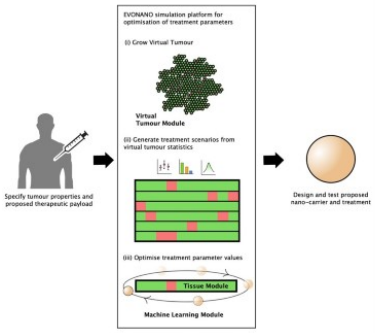
Read more about the fund and find out how you can contribute to the continuing fight against this terrible disease.

External engagement

Dr Siddhartha Kar (Bristol Medical School) presented his work at the American Association for Cancer Research (AACR) annual meeting on 21 May 2021. Held virtually over one week in April and one week in May, the conference allows scientists, clinicians, other health care professionals, survivors, patients, and advocates to gather and share the latest advances in research and medicine. The session he was involved in, *The Promise and Pitfalls of Genome-Wide Association Studies (GWAS), Transcriptome-Wide Association Studies, and Beyond*, included talks from Hae Kyung Im of the University of Chicago and Peter Kraft of Harvard University. Siddhartha spoke on advances in GWAS of cancer risk. He is a cancer epidemiologist studying how a wide range of everyday factors, such as exercise and diet, as well as the human body's physiology and biochemistry, relate to the molecular characteristics of tumours in cancer patients.

Growing and treating virtual tumours with AI

The EVONANO platform allows scientists to grow virtual tumours and use artificial intelligence to automatically optimise the design of nanoparticles to treat them.
The ability to grow and treat virtual tumours is an important step towards developing new therapies for cancer. Using the new EVONANO platform, the team were able to simulate simple tumours, and more complex tumours with cancer stem cells, which are sometimes difficult to treat and lead to relapse of some cancer patients. The strategy identified nanoparticle designs that were known to work in previous research,



as well as potential new strategies for nanoparticle design.

In the future, creating a digital twin of a patient tumour could enable the design of new nanoparticle treatments specialised for their needs, without the need for extensive trial and error or laboratory work, which is often costly and limited in its ability to quickly iterate on solutions suited for individual patients.

Stillman N *et al*. (2021). Evolutionary computational platform for the automatic discovery of nanocarriers for cancer treatment. npg *Computational Materials.*

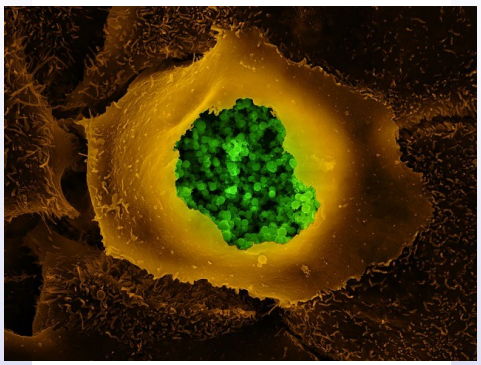
Image: The EVONANO platform can grow virtual tumours and use AI to automatically optimise the design of nanoparticles to treat them.

How chlamydia might increase cancer risk

A review of evidence by researchers at the University of Bristol and University of Edinburgh has suggested a possible new means by which chlamydia could lead to an increased risk of cancer and ectopic pregnancy.

The analysis of the studies' findings suggests that chlamydia induces a particular type of change in reproductive tract cells known as 'epithelial to mesenchymal transition' (EMT), which can lead to inflammation and cell growth. Their hypothesis is that this chlamydia-triggered cell change contributes to the development of further disease.

The researchers think that the association of chlamydia with ovarian and cervical cancer could be explained by the persistence of EMT changes in



combination with DNA damage caused by chlamydia following chlamydia infection. If correct, the hypothesis would support the English National Chlamydia Screening Programme's shift to earlier testing of women, as the shorter the duration of infection, the lower the risk of developing EMT changes. Further down the line, this could lead to the development of new tests for identifying women at increased risk of ovarian cancer and ectopic pregnancy and interventions that could reduce these risks.

Horner P *et al*. (2021). Is There a Hidden Burden of Disease as a Result of Epigenetic Epithelial-to-Mesenchymal Transition Following Chlamydia trachomatis Genital Tract Infection?. *Journal of Infectious Diseases.*

Funding successes and prizes

Dr Henkjan Gersen (Physics) was awarded £70,881 from **Cancer Research UK** and the **Engineering and Physical Sciences Research Council** for *TEP-eDx: Validating the use of Tumour Educated Platelets for early cancer diagnosis*.

Prof Linda Wooldridge (Bristol Veterinary School) received £42,983 from **Research England** for *Immunomodulation using artificial membrane binding proteins (AMBPs) to improve T cell responses to melanoma*.

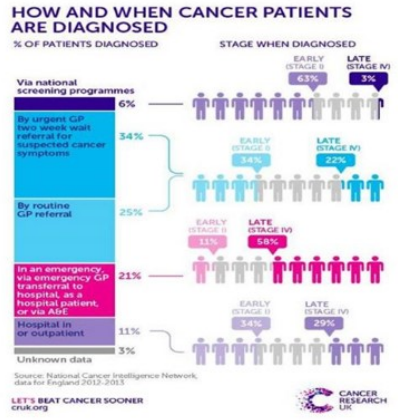
The Elizabeth Blackwell Institute/Development and Alumni Relations Office joint funding scheme for COVID-19 for early career researchers saw Katherine Fairhurst (Academic Clinical Lecturer, Bristol Medical School) awarded funds for *The RESTORE-C19 Study: Exploring the experiences and outcomes of patients not offered immediate breast REconstruction after maSTectOmy for bREast cancer during the COVID-19 pandemic*.

Dr Carina Owen was awarded the Association of Cancer Physicians McElwain Prize 2021. Carina is an academic medical oncology SpR who completed a sub-specialty fellowship in melanoma, during which she led two international multi-centre studies. These high-impact studies contribute significantly to the published literature on clinical management of immunotherapy resistance and toxicity. She is continuing to develop these research interests as an Academic Clinical Fellow in Medical Oncology at the University of Bristol.

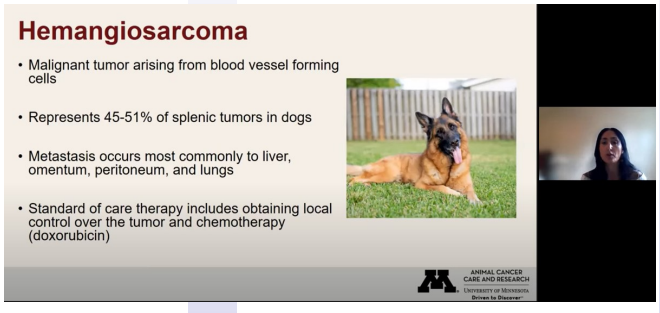
Prof Karim Malik (Cellular and Molecular Medicine) was awarded £199k from **Children's Cancer and Leukaemia Group** for *Combined inhibition of autophagy and epigenetics as a novel therapeutic strategy for poor prognosis neuroblastoma*.

Early detection and prevention of cancer

The Bristol Cancer Research Network, alongside the Somerset, Wiltshire, Avon and Gloucestershire (SWAG) Cancer Alliance, hosted an online early detection and prevention of cancer symposium on 16 September 2021.



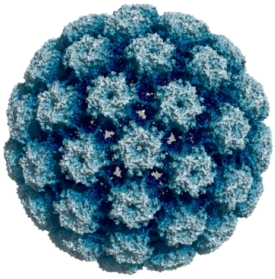
Eight invited speakers discussed a variety of topics, including how to detect brain tumours earlier on so they can be treated before becoming fatal; how to prevent the growth of tumours in the lower gastrointestinal tract by developing new drug therapies; and how to encourage minority groups to take part in screening and prevention programmes such as bowel screening and the Human Papilloma Virus (HPV) vaccine. This was the first in a series of planned events that will be exploring the cancer disease pathway from prevention to treatment, with follow-up events anticipated in 2022.



Watch the recording on YouTube.

The effect of sexual behaviour on oropharyngeal cancer risk

Human papilloma virus infection is known to influence oropharyngeal cancer (OPC) risk, likely via sexual transmission. However, sexual behaviour has been correlated with other risk factors including smoking and alcohol, meaning independent effects are difficult to establish. Here we evaluate aspects of sexual behaviour in relation to the risk of OPC (2,641 cases and 6,585 controls), using genetic variants associated with age at first sex (AFS) and number of sexual partners (NSP) to perform Mendelian randomization (MR) analyses. While univariable MR showed a causal effect

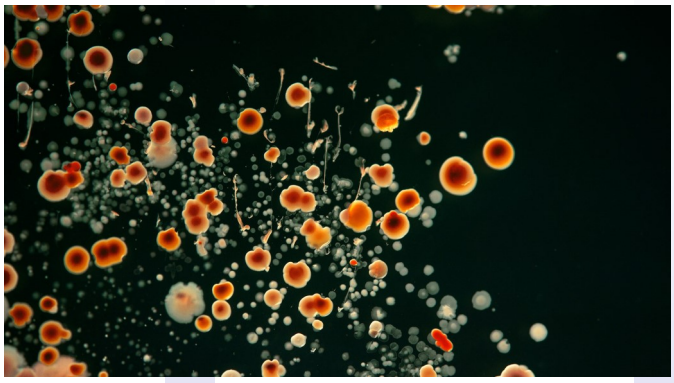


of both later AFS and increasing NSP on OPC, results attenuated in the multivariable models (AFS IVW OR 0.7, 95% CI 0.4, 1.2, p= 0.21; NSP IVW OR 0.9, 95%CI 0.5 1.7, p= 0.76). We also found evidence for correlated pleiotropy in the genetic instruments for sexual behaviour, emphasising the need for multivariable approaches when performing MR of complex behavioural traits and the triangulation of evidence.

Gormley M *et al*. (preprint). Investigating the effect of sexual behaviour on oropharyngeal cancer risk: a methodological assessment of Mendelian randomization. *medRxiv*.

The difficulties of linking the microbiome to cancer

Variations in the human gut microbiome have been linked to cancer – an exciting prospect for cancer prevention, but teasing apart causation from correlation is no easy task, according to Dr Kaitlin Wade (Bristol Medical School) in a Cancer Research UK research feature from 2 June 2021.



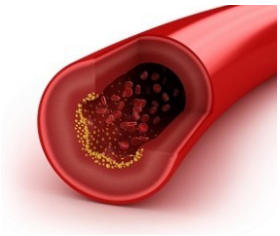
We know the gut microbiome can have a substantial impact on host metabolism, inflammation, and immune response to external infections, so there are many plausible biological mechanisms by which it could influence cancer development and progression. However, findings have been inconsistent, or even contradictory, and very few hypotheses have been reliably supported with data from multiple model organisms.

The appropriate application of Mendelian randomisation to interrogate causality of the gut microbiome in cancer has begun to show promise. However, early work has also highlighted the importance of inter-disciplinary collaboration between population health, genetic and basic sciences. A triangulation of evidence to unpick causation from correlation is essential; any research conducted within one discipline cannot provide concrete evidence to support or challenge the role of the gut microbiome in cancer aetiology.

See also: Wade K *et al*. (preprint). Applying Mendelian randomization to appraise causality in relationships between nutrition and cancer. *OSF Preprints*.

Cholesterol and clear cell renal cell carcinoma

Clear cell renal cell carcinoma (ccRCC) is characterised by large intracellular lipid droplets (LDs) containing free and esterified cholesterol; however, the functional significance of cholesterol accumulation in ccRCC cells is unknown. We demonstrate that genes encoding cholesterol biosynthetic enzymes are repressed in ccRCC, suggesting a dependency on exogenous cholesterol. Mendelian randomization analyses performed on 31,000 individuals indicate a causal link between elevated circulating high-density lipoprotein (HDL) cholesterol and ccRCC risk. Depriving ccRCC cells of either cholesterol or HDL com-



promises proliferation and survival in vitro and tumour growth in vivo; in contrast, elevated dietary cholesterol promotes tumour growth. Scavenger Receptor B1 (SCARB1) is uniquely required for cholesterol import, and inhibiting SCARB1 is sufficient to cause ccRCC cell cycle arrest, apoptosis, elevated intracellular reactive oxygen species levels and decreased PI3K/AKT signalling. Collectively, we reveal a cholesterol dependency in ccRCC and implicate SCARB1 as a novel therapeutic target for treating kidney cancer.

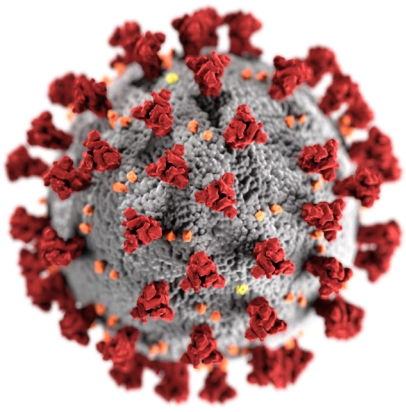
Riscal R *et al*. (2021). Cholesterol auxotrophy as a targetable vulnerability in clear cell renal cell carcinoma. *Cancer Discovery*.

Understanding the risk of cancer after SARS-CoV-2 infection

A Jean Golding Institute (JGI) blog post written by Dr Pau Erola, Professor Tom Gaunt and Professor Richard Martin (Bristol Medical School) based on a JGI seed corn-funded project. This a brief extract:

In this pilot study we used the graph database EpiGraphDB to link the recently mapped host-coronavirus protein interaction in SARS-CoV-2 infections with the existing knowledge of cancer biology and epidemiology. Coronaviruses are known to target the respiratory system. We have reconstructed the molecular network for lung cancer risk, as many patients recovering from SARS-CoV-2 suffer from long-term symptoms due to damage of the walls and linings of the lungs.

We found 93 human genes targeted by SARS-CoV-2, represented in pink, which are oncogenic or interact with onco-



genic genes. These were clustered based on high connectivity to enrich the network visualization, where each cluster is depicted as two columns, one for SARS-CoV2 interacting genes and one for cancer genes. Then we searched for molecular pathways that may be perturbed by each gene set. Our results suggest potential alterations in Wnt and hippo signalling pathways, two important pathways frequently linked to cancer due to their roles in cell proliferation, development and cell survival. The risk of perturbations in telomere maintenance and DNA replication may affect the integrity of the DNA favouring it's degradation and preventing the repair of damaging events like gene fusions. There may also be a possible impact on gene function through changes in the mRNA splicing process, impeding translation into working proteins.

Cost-effectiveness models in prostate cancer

There is currently no formal prostate cancer screening programme in the UK. Early detection using age-based prostate-specific antigen (PSA) testing is unlikely to be cost-effective due to limited mortality benefit and harms associated with over-detection. However, the discovery of new prostate cancer specific biomarkers and more accurate diagnostic strategies could improve the outcomes of screening.

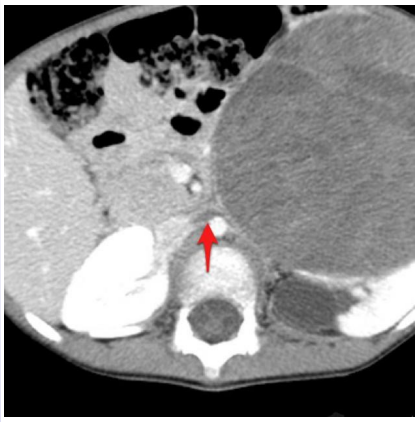
A systematic review was conducted to assess the evidence base on cost-effectiveness of such innovations and areas for further development. To identify model-based economic evaluations of screening and diagnostic tests for prostate cancer, a systematic review of the literature using the NHS Economic Evaluation Database, Medline, EMBASE, HTA databases, NICE guidelines, and UK National Screening Committee guidance was carried out, between 2009 and 2019. Relevant data were extracted on study type, model inputs, modelling methods and cost-effectiveness conclusions and the results narratively synthesised.

This review brings together the cost-effectiveness literature for novel screening and testing methods used in the diagnosis of prostate cancer. Several limitations of the published models were identified. The models generally either compared new biomarkers or new imaging techniques which highlights the importance of future work in this area, as biomarkers and imaging are likely to be used in combination.

Keeney E *et al*. (preprint). Systematic Review of cost-effectiveness models in prostate cancer: exploring new developments in testing and diagnosis. *Research Square*.

The regulator that suppresses Wilms tumour

Wilms tumour (WT), an embryonal kidney cancer, has been extensively characterised for genetic and epigenetic alterations, but a proportion of WTs still lack identifiable abnormalities. To uncover DNA methylation changes critical for WT pathogenesis, we compared the epigenome of foetal kidney with two WT cell lines, filtering our results to remove common cancer-associated epigenetic changes, and to enrich for genes involved in early kidney development. This identified four hypermethylated genes, of which ESRP2 (epithelial splicing regulatory protein 2) was the most promising for further study. ESRP2 was commonly repressed by DNA methylation in WT, and this occurred early in WT development (in nephrogenic

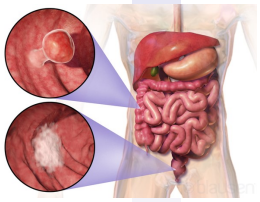


rests). ESRP2 expression was reactivated by DNA methyltransferase inhibition in WT cell lines. When ESRP2 was overexpressed in WT cell lines, it inhibited cellular proliferation in vitro, and in vivo it suppressed tumour growth of orthotopic xenografts in nude mice. RNA-seq of the ESRP2-expressing WT cell lines identified several novel splicing targets. We propose a model in which epigenetic inactivation of ESRP2 disrupts the mesenchymal to epithelial transition in early kidney development to generate WT.

Legge D *et al*. (2021). The epithelial splicing regulator ESRP2 is epigenetically repressed by DNA hypermethylation in Wilms tumour and acts as a tumour suppressor. *Molecular Oncology*.

Reducing parastomal hernia risk after colostomy

Parastomal hernia (PSH) is a common problem following colostomy. Using prophylactic mesh during end colostomy creation may reduce PSH incidence, but concerns exist regarding the optimal type of mesh, potential long-term complications, and cost-effectiveness of its use. We evaluated the cost-effectiveness of mesh prophylaxis to prevent PSH in patients undergoing end colostomy creation for rectal cancer.



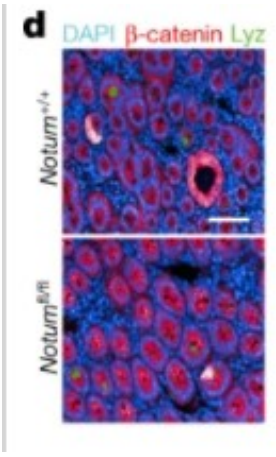
We developed a decision-analytical model, stratified by rectal cancer stages I–IV, to estimate the lifetime costs, quality-adjusted life-years (QALYs) and net monetary benefits (NMBs) of synthetic, biologic and no mesh from a UK NHS perspective.

Synthetic mesh was the most cost-effective strategy to prevent the formation of PSH in patients after end colostomy for any rectal cancer stage; however, conclusions are dependent on which subset of Randomised Clinical Trials are considered to provide the most robust evidence.

Mohiuddin S *et al*. (2021). A semi-Markov model comparing the lifetime cost-effectiveness of mesh prophylaxis to prevent parastomal hernia in patients undergoing end colostomy creation for rectal cancer. *Colorectal Disease*.

NOTUM from Apc-mutant cells in colorectal cancer

The tumour suppressor *Apc* is the most commonly mutated gene in colorectal cancer. Loss of Apc in intestinal stem cells drives the formation of adenomas in mice via increased WNT signalling, but reduced secretion of WNT ligands increases the ability of Apc-mutant intestinal stem cells to colonise a crypt (known as fixation). Here we investigated how Apc-mutant cells gain a clonal advantage over wild-type counterparts to achieve fixation. We found that Apc-mutant cells are enriched for transcripts that encode several secreted WNT antagonists, with NOTUM being the most highly expressed. Conditioned medium from Apc-mutant cells suppressed the growth of wild-type organoids in a NOTUM-dependent manner. Furthermore, NOTUM-secreting Apc-mutant clones actively inhibited the proliferation of surrounding wild-type crypt cells and drove their differentiation, thereby outcompeting crypt cells from the niche. Genetic or pharmacological inhibition of NOTUM abrogated the ability of Apc-mutant cells to expand and form intestinal adenomas. We identify NOTUM as a key mediator during the early stages of mutation fixation that can be targeted to restore wild-type cell competitiveness and provide preventative strategies for people at a high risk of developing colorectal cancer.

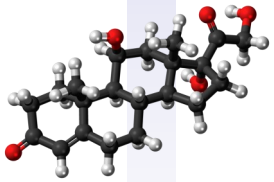


Flanagan DJ *et al*. (2021). NOTUM from Apc-mutant cells biases clonal competition to initiate cancer. *Nature*.

Image: Immunofluorescence staining for β-catenin (red) and lysozyme (Lyz; green) of representative whole-mount Apc-mutant clones (red) from Notum +/+ and Notum fl/fl mice

The role of cortisol in cancer

Cortisol's immunosuppressive, obesogenic, and hyperglycaemic effects suggest that it may play a role in cancer development. However, whether cortisol increases cancer risk is not known. We investigated the potential causal association between plasma cortisol and risk of overall and common site-specific cancers using Mendelian randomisation.



Three genetic variants associated with morning plasma cortisol levels at the genome-wide significance level in the Cortisol Network consortium were used as genetic instruments. Summary-level genome-wide association study data for the cancer outcomes were obtained from large-scale cancer consortia. Two-sample Mendelian randomisation analyses were performed using the fixed-effects inverse-variance weighted method. Estimates across data sources were combined using meta-analysis.

There was no significant association between genetically predicted plasma cortisol and risk of other common site-specific cancers, including breast, ovarian, prostate, colorectal, lung, or malignant skin cancer, or overall cancer. These results indicate that elevated plasma cortisol levels may increase the risk of endometrial cancer but not other cancers. The mechanism by which this occurs remains to be investigated.

Larsson SC *et al*. (2021). Assessing the role of cortisol in cancer: a wide-ranged Mendelian randomisation study. *British Journal of Cancer*.

Body size and composition and risk of site-specific cancers

Evidence for the impact of body size and composition on cancer risk is limited. This mendelian randomisation (MR) study investigates evidence supporting causal relationships of body mass index (BMI), fat mass index (FMI), fat-free mass index (FFMI), and height with cancer risk. Associations of the genetic variants with 22 site-specific cancers and overall cancer were estimated from the UK Biobank and with lung, breast, ovarian, uterine, and prostate cancer in large international consortia. Genetically predicted BMI was positively associated with overall cancer; several digestive system cancers: stomach, oesophagus, liver, and pancreas; and lung cancer. For sex-specific cancers, genetically predicted elevated BMI was associated with an increased risk of uterine cancer and with a lower risk of prostate cancer. Genetically predicted BMI was positively associated with digestive system cancers but not with non-digestive system cancers. Genetically predicted FMI was positively associated with liver, pancreatic, and lung cancer and inversely associated with melanoma and prostate cancer. Genetically predicted FFMI was positively associated with non-Hodgkin lymphoma and melanoma. Genetically predicted height was associated with increased risk of overall cancer and multiple site-specific cancers. Results show that the evidence for BMI as a causal risk factor for cancer is mixed. We find that BMI has a consistent causal role in increasing risk of digestive system cancers and a role for sex-specific cancers with inconsistent directions of effect. In contrast, increased height appears to have a consistent risk-increasing effect on overall and site-specific cancers.

Vithayathil M *et al*. (2021). Body size and composition and risk of site-specific cancers... *PLOS Medicine*.

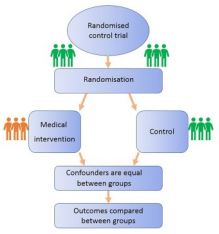
Impact of genetics on epigenetic factors

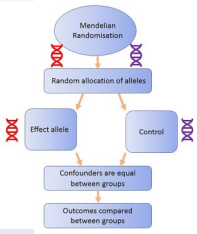
Understanding what causes epigenetic variation could be a step closer thanks to a new atlas of genetic effects on epigenetic factors. The atlas, which has been established by an international consortium led by the University of Bristol, will enable scientists to learn more about the mechanisms underpinning gene regulation. Epigenetic variation exists but it is unclear what causes this variation – is it genetic or is it the environment? It is also unclear how genetic differences that occur between individuals' impact on our epigenomes. The atlas of genetic effects on DNA methylation (DNAm), by the Genetics of DNA Methylation Consortium (GoDMC) of 50 universities and institutes. By providing a world-wide platform for collaboration and combining genetic and epidemiological expertise, the scientists of GoDMC has established a large resource of genetic effects on DNAm (which plays a central role in gene regulation) and how this atlas can be used to understand the genetic basis of DNAm variation.

Min JL *et al*. (2021). Genomic and phenotypic insights from an atlas of genetic effects on DNA methylation. *Nature Genetics*.

Sex hormones and colorectal cancer risk

Epidemiologic studies evaluating associations between sex steroid hormones and colorectal cancer risk have yielded inconsistent results. To elucidate the role of circulating levels of testosterone, and sex hormone-binding globulin (SHBG) in colorectal cancer risk, we conducted observational and Mendelian randomization (MR) analyses.





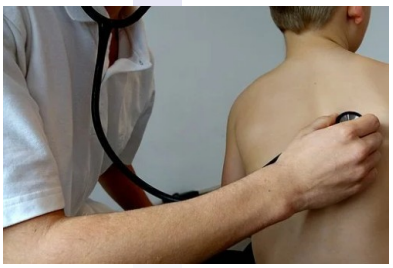
The project included 333,530 participants enrolled in the UK Biobank with testosterone and SHBG measured. For MR analyses, genetic variants robustly associated with hormone levels were identified and their association with colorectal cancer (42,866 cases/42,752 controls) was examined using two-sample MR. In the observational analysis, there was little evidence that circulating levels of total testosterone were associated with colorectal cancer risk; the MR analyses showed a greater risk for women, although pleiotropy may have biased this result. Higher SHBG concentrations were associated with greater colorectal cancer risk for women but was unsupported by the MR analysis. There was little evidence of associations between free testosterone and colorectal cancer in observational and MR analyses.

The team concluded that circulating concentrations of sex hormones are unlikely to be causally associated with colorectal cancer. Additional experimental studies are required to better understand the possible role of androgens in colorectal cancer development.

Dimou N *et al*. (2021). Circulating Levels of Testosterone... *Cancer Epidemiology, Biomarkers & Prevention*.

Funding for the School for Public Health Research

The National Institute for Health Research (NIHR) has reaffirmed its commitment to public health research by awarding a third round of funding to the NIHR School for Public Health Research (SPHR).



The next round of the school, which has been awarded £25 million from April 2022, will advance and extend the school's current research themes of children, young people and families; public mental health; and places and communities.

Established in April 2012, the renewed SPHR is an extended partnership between Bristol University and eight other leading centres of academic public health research excellence across England: University of Sheffield, University of Cambridge, University of Birmingham collaboration with the Universities of Warwick and Keele (PHRESH), London School of Hygiene and Tropical Medicine, Liverpool and Lancaster Universities Collaboration for Public Health (LiLaC), Imperial College Fuse, the Centre for Translational Research in Public Health (Durham, Newcastle, Northumbria, Sunderland and Teesside Universities), and University of Exeter.

With the Government's increasing attention on prevention and public health research and how we recover from the pandemic, the contribution of the school is of strategic importance to the Department of Health and Social Care.

Read the press release

GW4 Doctoral Training Partnership

The GW4 Alliance, comprising Bath, Bristol, Cardiff and Exeter Universities, has been awarded a share of £79 million funding from the Medical Research Council (MRC) to support 64 studentships over the next three years.

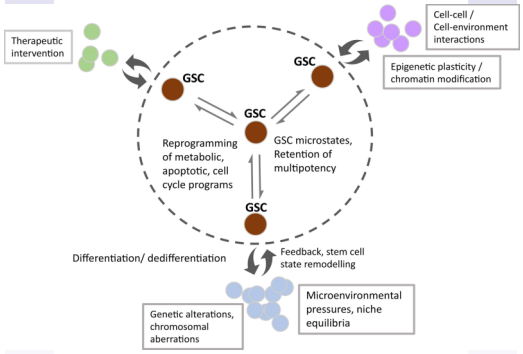
The GW4 BioMed2 MRC Doctoral Training Partnership is one of 17 successful Doctoral Training Partnerships (DTPs) to receive the awards across 34 UK research organisations through the MRC's DTP competition which focuses on scientific excellence, positive research culture and wider training opportunities.

Led by Cardiff University, the Partnership will train postgraduate research students in three main areas: neuroscience and mental health; infection, immunity, antimicrobial resistance and repair; and population health sciences. The programme will focus on three cross cutting strands: data science, interdisciplinary skills and translation and innovation and includes opportunities for students to broaden horizons through industry placements, research visits, public engagement internships and a bespoke online core skills training element. The MRC has awarded 16 notational studentships across the alliance per year for three years. The partnership has also received funding for four iCASE studentships over the three years. These industrial CASE studentships (Collaborative Awards in Science and Engineering) allow postgraduate research students to receive high quality research training in collaboration with commercial or other non-academic partners.

Read the press release

Glioma Stem-Like Cells and Metabolism

Glioma stem-like cells (GSCs) were first described as a population which may in part be resistant to traditional chemotherapeutic therapies and responsible for tumour regrowth. Knowledge of the underlying metabolic complexity governing GSC growth and function may point to potential differences between GSCs and the tumour bulk which could be harnessed clinically. There is an increasing interest in the direct/indirect targeting or reprogramming of GSC metabolism as a potential novel therapeutic approach in the adjuvant or recurrent setting to help overcome resistance which may be mediated by



GSCs. In this review the authors discuss stem-like models, interaction between metabolism and GSCs, and potential current and future strategies for overcoming GSC resistance.

Harland A *et al*. (2021). Glioma Stem-Like Cells and Metabolism: Potential for Novel Therapeutic Strategies. *Frontiers in Oncology*.

Image: Schematic showing the microstate transitions within the GSC population (within the circled dotted line) due to enhanced transcriptional and epigenetic potential, underpinned by extrinsic cues. Double headed arrows represent dynamic transitioning between GSC states, resulting in cellular reprogramming of metabolic, apoptotic and cell cycle programmes.

Drop in surgical activity during COVID winter wave

New research shows the huge pressure anaesthesia and critical care staff in the UK have been under throughout the winter wave of COVID-19, as the number of newly admitted infected patients surged and most planned surgeries, including a substantial number of critical cancer operations, were cancelled. The findings have important implications for understanding what has happened during the COVID-19 pandemic, planning recovery and building a system that will better respond to future waves or new epidemics.

Between October 2020 and January 2021, the authors conducted three national surveys to track anaesthetic, surgical and critical care activity during the second COVID-19 pandemic wave in the UK – the first round as the November 2020 lockdown was being implemented, the second in December 2020 as restrictions were lifted, and the final survey in February 2021 just after the peak of the new year surge caused by the new Alpha variant of SARS-CoV-2. The surveys showed increasing systemic pressure on anaesthetic and peri-operative services due to the need to support critical care pandemic demands.

As long as the UK's exit from lockdown restrictions continues and vaccination rates keep COVID-19 infections low, a rapid decompression is likely to occur whereby critical care units quickly decrease their capacity and the rest of the health system resumes elective and other surgical care. However, tackling the surgical backlog requires working at well above normal capacity for several years and even returning to normality is likely to be challenging.

Kursumovic E *et al*. (2021). The impact of COVID-19 on anaesthesia and critical care services in the UK: a serial service evaluation. *Anaesthesia*.

ELIZABETH BLACKWELL FUNDING

Nurturing Research. Improving Health.

EBI extension and mitigation scheme for early career researchers impacted by the pandemic

The Institute will be launching a funding scheme to support early career academic staff in health research from all Faculties at the University of Bristol impacted by the COVID-19 pandemic.

Provisional launch date 4 October 2021.

Full details of the scheme including eligibility and application process will be published on the website.

EBI Seed Fund: Public Engagement with Health Research

Seed funding is available for health researchers who would like to deliver public engagement events and activities. Applications will be considered on a rolling basis.

EBI Identifying Candidates for Wellcome Trust Investigator Awards

This scheme is designed to support a small number of permanent academic staff at UoB within the first five years of their appointment, who are planning to apply for an Investigator Award from the Wellcome Trust. Applications will be accepted on a rolling basis.

Heads of Schools are asked to nominate members of staff who can be eligible for this scheme by emailing ebi-health@bristol.ac.uk

EBI Workshop support

Support interdisciplinary workshops in health research at new or emerging interface between two or more disciplines. Applications reviewed all year.

Returning Carers Scheme

To support academic staff across all faculties in re-establishing their independent research careers on return from extended leave (16 weeks or more) for reasons connected to caring (e.g. maternity leave, adoption leave, additional paternity leave, leave to care for a dependant.).
Applications reviewed all year.

FUNDING OPPORTUNITIES

Research Professional provides access to an extensive database of funding opportunities. You can set up individualised funding alerts based on keywords or areas of research . UoB staff and students have **FREE** online access to the database.

You can search for funding information by discipline, sponsor, database searches, by recent calls or by upcoming deadlines. Find out more about **Research Professional** on the RED website. Note that some calls may have an internal process; do always remember to check the major bids webpage here to see if there is an internal process.

The following listings represent a *brief selection* of available funding for the Cancer Research community. **Full listings of opportunities** are sent out via School Research Directors, and **are available on the Research Development website**.

Cancer Research UK
Experimental medicine award

Closing date: 21 October 2021 Award amount: £1 million - 5 million

This supports investigator-led studies for translational research conducted in association with a clinical trial or clinical study, with the objective of optimising treatment and maximising patient benefit.

National Cancer Institute, USA
Innovative research in cancer nanotechnology (R01 clinical trial not allowed)

Closing date: 4 November 2021 Award amount: USD$ 2,250,000

These support projects addressing major barriers in cancer biology or oncology using nanotechnology and should emphasise fundamental understanding of nanomaterial or nanodevice interactions with biological systems. The scope includes research concerning the delivery of nanoparticles and nanodevices to desired and intended cancer targets in vivo and characterisation of in vitro detection and diagnostic devices.

National Cancer Institute, USA
Innovative basic research on adducts in cancer risk identification and prevention (R01 clinical trial optional)

Closing date: 4 November 2021 Award amount: USD$ unspecified

This supports research focused on adducts to cellular macromolecules as indicators of exposures to cancer risk factors relevant to human populations. The priority is on projects that focus on adductomic approaches and address some aspects of the totality of adducts. Projects should explore the basic aspects of adducts or adductomics that may have a potential utility in cancer detection, cancer prevention or assessing cancer risks.

World Cancer Research Fund
Regular programme grant

Closing date: 16 November 2021 Award amount: £350,000

This supports research on the link between diet, nutrition, body composition, physical activity, and cancer prevention and survival. These research areas may be approached by either identifying the mechanisms that underpin the effects of diet, nutrition and physical activity on cancer, or by addressing the risk factors that influence individual susceptibility to cancer development, progression and survival, contributing to the evidence on variability between people in outcomes. Two types of grants are available: investigator initiated grants, worth a maximum of £350,000 for up to four years; seed grants worth up to £60,000 over two years.

National Cancer Institute, USA
Clinic and laboratory integration programme grants

Closing date: 1 December 2021 Award amount: USD$ 200,000

These support scientists exploring clinically relevant questions aimed at improving the effectiveness of cancer immunotherapies. Grants support preclinical and translational research that can be directly applied to optimising cancer immunotherapy in the clinic.

Cancer Research UK
Prevention and population research project awards

Closing date: 15 December 2021 Award amount: £500,000

These provide support for focused research proposals centred on key questions in prevention and population research. Grants may be awarded in the following areas:

- population-based studies, including classical, clinical and molecular epidemiological approaches, to help understand risk and disease aetiology, and to test and validate strategies to improve the prevention and control of cancer in patients and the public;
- incidence rates of cancer, including changes over time and geographies;
- methodological and statistical research relating to prevention and population sciences;
- population-level epidemiological studies of secondary physical effects of cancer treatment;
- screening as a form of prevention, including population-level trials of screening approaches;
- risk stratification and associated cancer prevention studies;
- exploratory and confirmatory clinical trials seeking to test the efficacy and safety of chemopreventive agents;
- behavioural and lifestyle interventions to support prevention of cancer, including cancer recurrence, across a range of risk factors, which may include tobacco, alcohol, physical activity, sedentary behaviour, obesity and UV exposure;
- policy-focused research to help develop CRUK's policies and advocacy strategies concerning cancer prevention, including policy research on tobacco control.

FEATURED PUBLICATION

Pleiotropy-guided transcriptome imputation from normal and tumour tissues identifies candidate susceptibility genes for breast and ovarian cancer

Kar SP, Considine DPC, Tyrer JP *et al*. (2021). *HGG Advances*.

Familial, sequencing, and genome-wide association studies (GWASs) and genetic correlation analyses have progressively unravelled the shared or pleiotropic germline genetics of breast and ovarian cancer. In this study, we aimed to leverage this shared germline genetics to improve the power of transcriptome-wide association studies (TWASs) to identify candidate breast cancer and ovarian cancer susceptibility genes. We built gene expression prediction models using the PrediXcan method in 681 breast and 295 ovarian tumours from The Cancer Genome Atlas and 211 breast and 99 ovarian normal tissue samples from the Genotype-Tissue Expression project and integrated these with GWAS meta-analysis data from the Breast Cancer Association Consortium (122,977 cases/105,974 controls) and the Ovarian Cancer Association Consortium (22,406 cases/40,941 controls). The integration was achieved through application of a pleiotropy-guided conditional/conjunction false discovery rate (FDR) approach in the setting of a TWASs. This identified 14 candidate breast cancer susceptibility genes spanning 11 genomic regions and 8 candidate ovarian cancer susceptibility genes spanning 5 genomic regions at conjunction FDR < 0.05 that were >1 Mb away from known breast and/or ovarian cancer susceptibility loci. We also identified 38 candidate breast cancer susceptibility genes and 17 candidate ovarian cancer susceptibility genes at conjunction FDR < 0.05 at known breast and/or ovarian susceptibility loci. The 22 genes identified by our cross-cancer analysis represent promising candidates that further elucidate the role of the transcriptome in mediating germline breast and ovarian cancer risk.

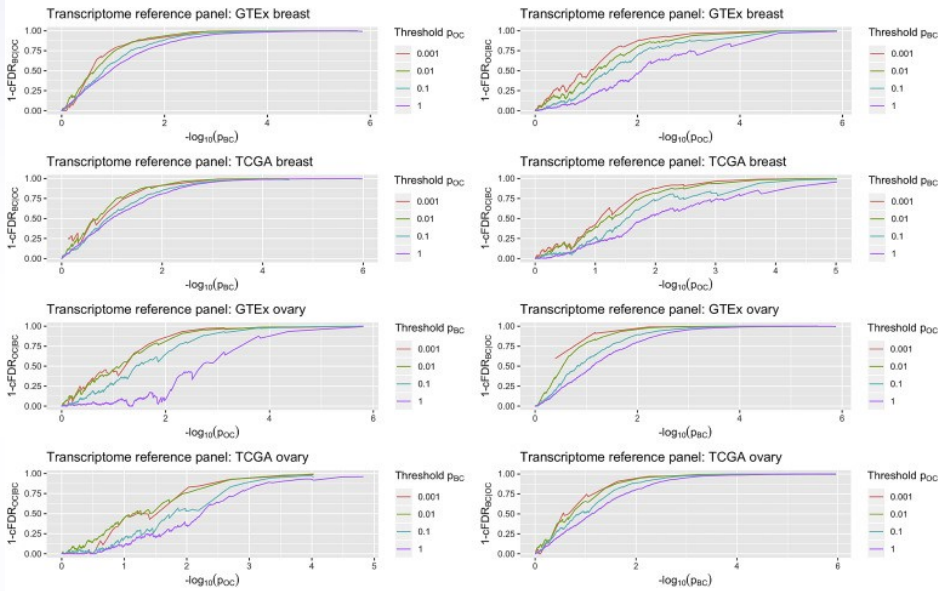


Image: True discovery rate of S-PrediXcan associations for each cancer stratified by associations with the other cancer. True discovery rate against the negative logarithm (base 10) of the p value for each cancer for subsets of genes based on strength of association with the other cancer. The y axis of each plot is the true discovery rate, which is defined as 1 − conditional FDR (cFDR). For a given ordered analytic combination of datasets (e.g., GTEx normal breast tissue as transcriptome reference panel-breast cancer GWAS-ovarian cancer GWAS, plotted in the upper left corner) we observed that, in general, for progressively smaller S-PrediXcan p values of the second cancer type (indicated by the key "Threshold p" next to each plot), the true discovery rate (y axis) for association with the primary cancer type approached 100% at progressively larger S-PrediXcan p values for the primary cancer type (x axis; negative logarithm [base 10] of the p values). Only p values > 10−6 are plotted on the x axis. BC, overall breast cancer risk; OC, all invasive ovarian cancer risk.

Cancer Network

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- Prof Richard Martin, *Professor of Clinical Epidemiology*

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- Dr Sabine Hauert, *Assistant Professor in Robotics*

- Dr Zoë Holland, *Research Development Manager*

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- Dr Timothy Robinson, *Academic Clinical Lecturer in Medical Oncology*

- Prof Ann Williams, *Professor of Experimental Oncology*

- Dr Emma Vincent, *Research Fellow and Early Career representative*

- Dr Helen Winter, *Medical Oncologist*

- Catherine Brown, *Network Administrator*