Cancer Network Newsletter

2021: Issue 1

University of BRISTOL
Elizabeth Blackwell Institute for Health Research

Future Leaders Fellow announced

Four Bristol researchers have been awarded UK Research and Innovation's Future Leaders Fellowships. The awards are designed to establish the careers of world-class research and innovation leaders across the UK to help them tackle major global challenges.

Dr Siddhartha Kar, a cancer epidemiologist it the Bristol Medical School: Population Health Sciences, will study 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. He will then map how these tumour molecular characteristics, in turn, affect survival after a diagnosis of cancer. Some of these everyday factors, particularly those associated with lifestyle, are modifiable through public health interventions. Other physiological and biochemical measures, such as the levels of specific proteins or cholesterol in the blood, and the tumour molecular characteristics themselves, may be amenable to

medical treatment. By establishing the causal chain from these factors or measures to tumour molecular features to cancer progression, Dr Kar's work will inform the development of novel approaches to cancer prevention and therapy.

Entitled *Mapping tumour molecular mechanisms associated with common exposures: a new approach to identifying targets to prevent and treat cancer*, Siddhartha's fellowship, which was awarded £854,281 started in October 2020 and will continue for four years.

UKRI's initiative aims to support the creation of a new cohort of research and innovation leaders who will have links across different sectors and disciplines. Awardees will each receive between £400,000 and £1.5 million over an initial four years. The grant supports challenging and novel projects, and the development of the fellow's career. The funding can also used to support team members, their development, and pay for equipment and other needs.

Read about other University of Bristol FLFs in the press release.

Inside this issue:

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Bristol Cancer Research Network

EVENTS

PolicyBristol: Working with the International Development Select Committee
20 May 2021, 10.00 - 11.30, online

Extracting and deploying intelligence from text-based patient experience data- An open source project using Python and R
20 May 2021, 11.00 - 12.00, Andreas Soteriades (Applied Mathematician) and Milan Wiedemann (data scientist, Clinical Development Unit, Notting-hamshire Healthcare NHS Foundation Trust, pictured right), online

Applying lessons from COVID-19: Shaping the delivery of cancer clinical trials
20 May 2021, 13.00 - 14.15, online

Introduction to public involvement in research for members of the public
21 May 2021, 10.00 - 13.00, online

What's Next for UK Aid: Exploring the Impact of the FCDO Cuts
21 May 2021, 12.30 - 14.00, online

New Frontiers in Healthcare
25 - 27 May 2021, 9.00 - 13.00, online

Turing Fellowship call 2021 information event
25 May 2021, 10.30 - 11.30, online

GW4 3Rs Symposium 2021
25 May 2021, 13.30 - 15.30, online

23rd London Lymphoma Forum Follicular Lymphoma
26 May 2021, 17.30 - 20.30, online

Knowledge exchange seminar: How can researchers and charities work together to improve health outcomes?
8 June 2021, 10.00 - 11.30, online

QIAGEN Virtual Event
9 June 2021, 13.00 - 15.30, Akshay Acharya (Customer Solutions Manager Oxford & South West), online

Inclusive Research Collective: Inclusive Basic Research
9 June 2021, 14.00 - 13.30, Dr Simone Badal (University of the West Indies) & Dr Natasha Karp (Astra Zeneca), online

Athena Swan Best Practice conference

SEE ALL EVENTS ON THE CANCER RESEARCH NETWORK WEBSITE

EVENTS CON'T

16 June 2021, 10.00 - 13.00, online

Systems Approaches to Wound Healing
17 June 2021, 13.00 - 16.00, online

Ageing Futures: Building an inter-disciplinary research agenda
17 June 2021, 14.00 - 16.00, online

Inclusive Research Collective: Inclusive Data Science
17 June 2021, 15.00 - 17.00, Dr Anjali Mazumder (The Alan Turing Institute), Alex Hepburn (University of Bristol) & Dr Malvika Sharan (The Alan Turing Institute), online

CRUK Lung Cancer Centre of Excellence: Future Leaders
17 June 2021, 15.00 - 17.00, online

Inclusive Research Collective: Inclusive Human Participant Research
23 June 2021, 13.00 - 14.30, Pollyanna Sheehan (University of Bristol), online

Research Ethics Conference 2021 (REC2021)
25 June 2021, 9.00 - 17.00, online

Mendelian Randomization Conference: Harnessing the power of population diversity and family relatedness
7 - 9 July 2021, online

Intensive bid support event - Marie Skłodowska-Curie Postdoctoral Fellowship Scheme (MSCA-PF)
8 July 2021, 9.00 - 17.00, online

Public Engagement Masterclass
19 - 21 July 2021, online

Development of the Oxford AstraZeneca Covid-19 vaccine: Elizabeth Blackwell Annual Public Lecture 2021 with Professor Sarah Gilbert
6 October 2021, 13.00 - 14.00, Professor Sarah Gilbert (pictured right)

SEE ALL EVENTS ON THE CANCER RESEARCH NETWORK WEBSITE

NEWS

Dog size and shape and bone tumour risk

Osteosarcoma is a painful and aggressive bone tumour in dogs that is known to be more common in certain breeds than others. Research has now confirmed that larger breeds, such as Rottweiler and Great Dane, have a greater risk of osteosarcoma than smaller breeds, and demonstrated that breeds with shorter skulls and legs have lower osteosarcoma risk. The findings could inform future breed health reforms as well as studies into the way tumours develop from normal bone.

The study, led by Bristol Veterinary School in collaboration with Cardiff University and Royal Veterinary College (RVC) London, and using data from VetCompass™ and Veterinary Pathology Group histology, looked at the epidemiology surrounding which dog breeds get osteosarcoma, and what this means for canine welfare. The project also shows the huge benefits from using dogs as a model to study the cancer.

The team found 27 mainly larger breeds, had an increased risk of osteosarcoma compared to crossbreeds. Thirty mainly smaller breeds, including Jack Russell and Bichon Frisé had reduced risk of osteosarcoma compared to crossbreeds. The findings that bone tumours are more common in certain breeds and conformations indicates that a dog's genetics play a role in bone tumour development. This link between the biology of conformation and the biology of bone tumours in dogs provides valuable opportunities for further study into what causes bone tumours to develop, and how they could be treated in the future.

Edmunds G *et al.* (2021). Dog breeds and body conformations with predisposition to osteosarcoma in the UK: a case-control study. *Canine Medicine and Genetics.*

One Health approach to osteosarcoma

Drs Helen Winter (University Hospitals Bristol and Weston NHS Foundation Trust), Grace Edmunds (Bristol Veterinary School) and Sara Gould (Langford Vets) organised a collaborative webinar alongside ACTAsia, an international organisation working for sustainable social change through education, on 3 November 2020. Aimed at academics, clinicians and veterinarians, the *One Health: Collaborative Cultures* event sought to engage researchers across disciplines to target cancer using a holistic approach. Following a seminar she attended at the University of Oxford (*Health & Well-being: Science & Humanity are One*), human oncologist Helen proposed that vets and medics work together to combat osteosarcoma through comparison of cancer management in human and canine patients. As noted above, osteosarcoma occurs in dogs, particularly larger breeds. Canine bone cancer behaves in a very similar way to human bone cancer and has similar genetics; dogs with osteosarcoma experience similar clinical problems to children with bone cancer, namely significant pain associated with the tumour, secondary lesions developing in the lungs, and similar outcomes after surgery and systemic therapy.

Read more about the partnership on the Integrative Cancer Epidemiology Programme's pages

Helping to beat cancer sooner

A Cancer Research UK (CRUK) award of nearly £8 million, the largest grant awarded by the charity in the city, will allow the Integrative Cancer Epidemiology Programme (ICEP) to continue its essential research. Now its fifth year thanks to previous CRUK funding, the programme has already driven significant advancements in understanding the disease and the factors that cause cancer. This grant will enable further research work to unpick the causes and mechanisms of cancer and why it progresses in some people and not in others.

Co-Leads Profs Caroline Relton and Richard Martin confirmed that in the last five years, the programme developed large scale studies using cutting edge statistical methods and genetic data on tens to hundreds of thousands of people

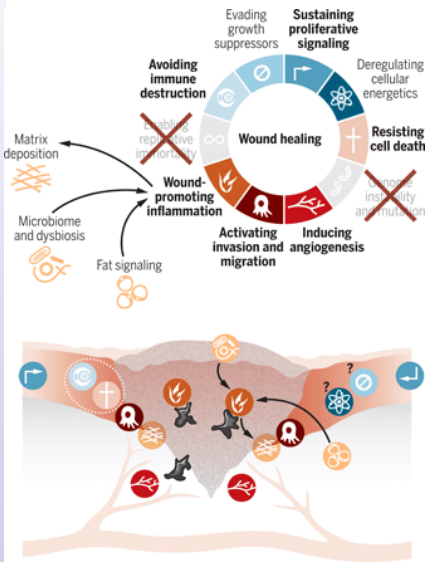
to provide high quality evidence on the causes of nine cancers and their progression. For example, in a genetic study, researchers found strong evidence to suggest that women who take statins in the long term could be less likely to develop ovarian cancer. Their findings highlight body fatness as the most common cause of cancer after tobacco; they also found that obesity causes people to smoke and to smoke more heavily.

Read the full press release

Hallmarks of cancer and wound healing are similar

For over a century it has been noted that tumours appear to behave similar to wounds that fail to heal. In recent years, it has become clear that there are many cellular and molecular parallels indicating multiple shared mechanisms that differ only in their being well regulated during healing of a wound and dysregulated during cancer growth and metastasis. Whereas acute wound repair normally has a resolution phase, tumours behave more similar to a chronic wound, which has no resolution phase. Because of these parallels, the genomic datasets and mechanistic findings gathered from studying wound healing may provide us with potential insights into the processes that are involved in tumorigenesis and vice versa.

MacCarthy-Morrogh L & Martin P (2020). The hallmarks of cancer are also the hallmarks of wound healing. *Science Signaling*.

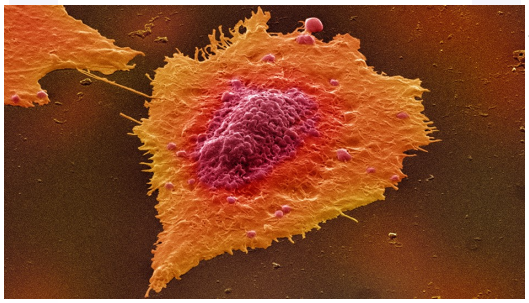


The contribution of the hallmarks and enabling characteristics to wound healing are mapped onto a schematic of a healing skin wound. Cell migration and proliferation drive re-epithelialization, which may also depend on altered cellular energetics. The wounded epithelium must also resist cell death and avoid damage inflicted by inflammatory cells that infiltrate the wound. Damage signals, the microbiome, and fat cells contribute to the inflammatory response, which, in turn, regulates both wound angiogenesis and matrix deposition.

Cancer risk from obesity differs for men and women

A new study, led by researchers at the University of Bristol and the International Agency for Research on Cancer (IARC), has revealed that where fat is on our body may lead to different health outcomes for men and women. The research, co-funded by World Cancer Research Fund (WCRF), Cancer Research UK and Diabetes UK, found that a higher body mass index (BMI) is more dangerous for men, whereas a higher waist-to-hip ratio is more dangerous for women. An increase in BMI of about five kg/m^2 raised the risk of colorectal cancer by 23% for men, but only 9% for women. Whereas an equivalent increase in waist-to-hip ratio raised the risk for women by 25%, this was only 5% for men.

Colorectal cancer is the fourth most common cancer in the UK and the second deadliest, yet it is one of the most preventable cancers by eating a balanced diet, being active and maintaining a healthy weight.



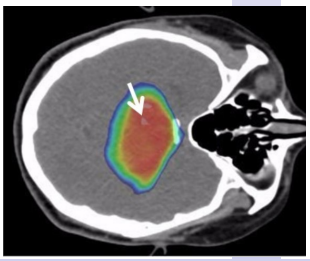
Bull CJ, Bell JA, Vincent EE *et al*. (2020). Adiposity, metabolites, and colorectal cancer risk: Mendelian randomization study. *BMC Medicine.*

The publication has been covered by 21 news outlets, including an article in Physician's Weekly which appeared on 12 January 2021.

The genetics of glioma susceptibility

Genome-wide association studies have discovered 27 sites associated with glioma risk; it is estimated that we have uncovered only about a third of the risk posed by familial or inheritable factors, indicating a large portion of genetic glioma risk is still to be uncovered.

In this study the team used Mendelian randomisation (MR) to assess the causal relationship between genetically predicted gene expression on glioma subtype risk and statistical colocalization, a method that can identify whether a putative causal genetic variant is shared by two traits. They investigated how genetically predicted gene expression affects risk across tissue type (brain and whole blood) and glioma subtype: glioblastoma (GBM) and non-GBM gliomas. The results suggested that genetically predicted increased gene expression of 12 genes were associated with glioma, GBM and/or non-GBM risk, three of which are novel glioma susceptibility genes (RETREG2/FAM134A, FAM178B and MVB12B/FAM125B). The effect of gene expression appears to be relatively consistent across glioma subtype diagnoses. The correlation of MR estimates in brain and blood are consistently low which suggested that tissue specificity needs to be carefully considered for glioma. Results have implicated genes yet to be associated with glioma susceptibility and provided insight into possible causal pathways for glioma risk.



Robinson JW, Martin RM, Tsavachidis S *et al*. (2021). Transcriptome-wide Mendelian randomization study prioritising novel tissue-dependent genes for glioma susceptibility. *Scientific Reports*.

Research funding awards

Prof Mark Dillingham is Principal Investigator on a **Biotechnology and Biological Sciences Research Council** grant totalling £514,041. Alongside Co-Investigator Dr Anna Chambers (both Biochemistry) they will investigate *Structure: Function Correlation in the Human DNA Repair Factor CtIP*.

The **National Institute for Health Research** awarded £233,408 to Prof Jonathan Sterne (Bristol Medical School: Population Health Sciences) for *Adapting Breast Cancer Screening to MAximise Mortality Benefit and Minimise Overdiagnosis harm*. The project started in January 2021 and will continue for two years.

Bristol's **Above & Beyond** charity awarded £29,134 to Dr Adam Chambers (Cellular and Molecular Medicine) for his project *Circulating tumour DNA in rectal cancer.*

Prof Sarah Lewis (Bristol Medical School: Population Health Sciences) received £169,354 from the **World Cancer Research Fund** for *Appraising causal mechanisms underpinning the link between physical activity and cancer risk*. The project started in Dec '20 and will continue for three years.

University of Bristol biotech start-up **CytoSeek** raised £3.5 million to develop new cell therapies to treat solid tumours in cancer patients. Solid tumours account for the majority of deaths from cancer and are notoriously difficult to treat because the tumour suppresses immune cells' ability to kill cancer cells. The funding is led by Science Creates Ventures, a new deep tech EIS fund for science and engineering start-ups.

Dr Sabine Hauert (Engineering Mathematics) and colleagues have received £150k from the **UKRI Trustworthy Autonomous Systems Hub** for *Trustworthy light-based robotic devices for autonomous wound healing*.

Senior Investigator appointment

Prof Richard Martin (Bristol Medical School: Population Health Sciences) has been appointed as a National Institute of Health Research (NIHR) Senior Investigator. Investigators are among the most prominent and prestigious researchers funded by the NIHR and the most outstanding leaders of patient and people-based research within the NIHR research community.

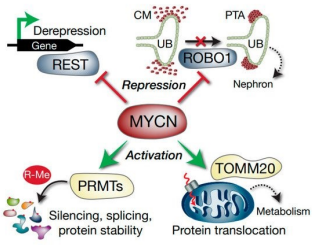
His appointment follows an open competition in which just 31 researchers in the UK were newly appointed as NIHR Senior Investigators in 2021. They are joined by 15 current or previous holders of the award who have been reappointed as Senior Investigators for a second term, bringing the total number of appointments for 2021 to just 46.

NIHR Senior Investigator status is awarded according to the quality and volume of internationally excellent research, its relevance to patients and the public and its impact on improvements in healthcare and public health. It also reflects high quality research leadership, the engagement of patients and the public, as well as the engagement of healthcare policy makers and planners with their research.

Richard leads the world's largest prostate cancer screening trial (CAP), demonstrating that a single PSA-based screening test does not reduce 10-year prostate cancer mortality, but leads to over-detection of indolent- and under-detection of lethal-cancers and is co-Lead of the £11.2 million Integrative Cancer Epidemiology Programme funded by Cancer Research UK.

Potential therapeutics for Wilms' tumour

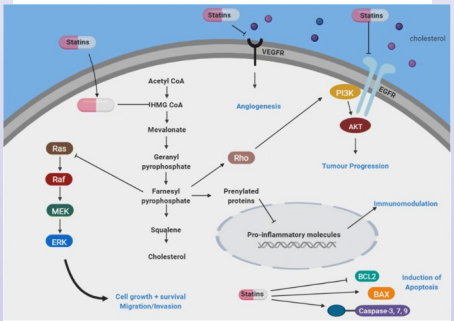
Wilms' tumour (WT) is one of the most common solid paediatric malignancies and arises in the developing kidney. Treatment of most WTs is relatively successful, with the notable exception of tumours with anaplastic histology. Anaplastic WT survival rates can be as low as 30–50%, emphasising the need for a better understanding of their molecular aetiology, in order to facilitate the development of novel therapeutics for poor-prognosis WT. Previous studies have implicated increases in MYCN at the DNA and RNA level in WTs with anaplasia, although the biological functions of MYCN protein have not been reported. In this study, we define the expression pattern of MYCN protein in WTs and also modulate MYCN protein levels in anaplastic WT cell-lines to define the functions of MYCN in WT. We show that MYCN depletion leads to decreased cell growth and identify MYCN-regulated genes and pathways that may represent therapeutic vulnerabilities in poor-prognosis WT.



Szemes M, Melegh Z, Bellamy J *et al*. (2021). Transcriptomic Analyses of MYCN-Regulated Genes in Anaplastic Wilms' Tumour Cell Lines Reveals Oncogenic Pathways and Potential Therapeutic Vulnerabilities. *Cancers*.

Statins as potential therapeutic agents in cancer

Repurposing established medicines for a new therapeutic indication potentially has important global and societal impact. The high costs and slow pace of new drug development have increased interest in more cost-effective repurposed drugs, particularly in the cancer arena. The conventional drug development pathway and evidence framework are not designed for drug repurposing and there is currently no consensus on establishing the evidence base before embarking on a large, resource intensive, potential practice changing phase III randomised controlled trial (RCT). Numerous observational studies have suggested a potential role for statins as a repurposed drug for cancer chemoprevention and therapy, and we review the strength of the cumulative evidence here. Findings show that whilst most pre-clinical and observational evidence appears to support the use of statins in the prevention of cancer, results from the randomised vascular setting, pharmaco-epidemiological research using a target trial design, and evidence from Mendelian randomization have all been less convincing in most tumour types. There is little supportive evidence of the beneficial effects of statins as a treatment for cancer from phase III trials; however, most inferences have been limited to the non-curative setting.



Joharatnam-Hogan N, Alexandre L, Yarmolinsky J *et al*. (2021). Statins as Potential Chemoprevention or Therapeutic Agents in Cancer: a Model for Evaluating Repurposed Drugs. *Current Oncology Reports*.

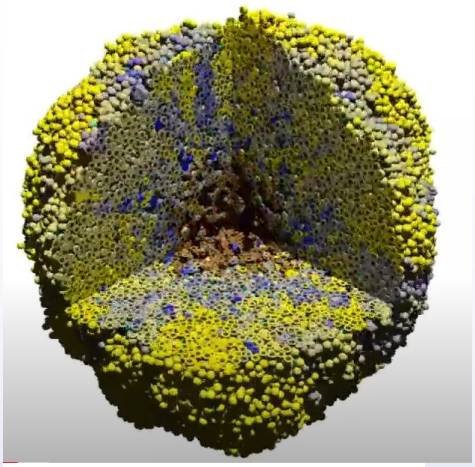
Image shows the mevalonate pathway and possible mechanism of action of statins

Polygenic hazard scores for prostate cancer

Genetic risk models have emerged as useful tools that identify individuals with greater risk for being diagnosed with prostate cancer, and so help inform if and when to initiate screening for an individual. A subset of these models called polygenic hazard scores (PHS) seeks to directly identify associations between common genetic variants and the age of diagnosis of prostate cancer by utilising the framework of time-to-event analyses. PHS46 has demonstrated excellent performance in an independent test set of men from varied genetic ancestries. The model incorporates genetic data of 46 unique single nucleotide polymorphisms (SNPs), and was identified through a systematic search of genotyped European men. With an ever-increasing list of loci associated with prostate cancer in the literature, we sought to determine what effect, if any, the incorporation of additional SNPs would have on the performance of PHS46. To this end, we employed a machine-learning approach to select SNPs from a list that included the 46 used in PHS46, as well as over 100 SNPs identified in previous analyses as having genome-wide significance for association with prostate cancer. Of the 180 SNPs originally considered, 166 were selected for the final PHS model (PHS166).

Karunamuni RA, Huynh-Le MP, Fan CC *et al*. (2021). Additional SNPs improve risk stratification of a polygenic hazard score for prostate cancer. *Prostate Cancer and Prostatic Diseases*.

Using AI to design nanomedicine to tackle cancer stem cells



The Future and Emerging Technologies Programme (FETFX), supported by a European Innovation Council grant, aims to transform advanced scientific ideas into new technologies for the future. They organised, alongside the European Commission, the second annual Future Tech Week, which was held as a virtual event 21 - 25 September 2020. The event offered a snapshot of what's currently brewing in Europe's tech sphere and the science that creates tomorrow's technologies.

Sabine Hauert (Engineering Mathematics, pictured) was part of the EVO-NANO team that submitted a video entitled *Using AI to design nanomedicine to tackle cancer stem cells to the event.*

Watch the video

EVO-NANO are a consortium of seven partners with the shared goal of creating an entirely new nanoparticle design platform capable of autonomously evolving solutions for cancer treatment; they bring together expertise in computer science, artificial evolution, modelling, microfluidics, and medicine.

Patients with HPV-driven oropharyngeal cancer survive better

Patients with human papillomavirus (HPV)-driven oropharyngeal cancer (OPC) experience better survival than those with HPV-negative OPC. It is unclear whether this benefit varies by demographic characteristics and serologic response. Records from 1411 patients with OPC who had HPV serology data were analysed. Participants were followed for a median of 5.9 years, and Cox proportional hazards models were used to estimate hazard ratios (HRs). The association between HPV status and overall survival was analysed by age group, sex, smoking status, tumour site, HPV antibody levels, and HPV antibody pattern. Models were adjusted for age, sex, smoking status, and comorbidity.

There was no clear evidence for an interaction by sex, smoking status, or tumour site. Survival did not differ according to E6 antibody levels in those who were seropositive. All seropositivity patterns were associated with increased survival compared with a pattern of seronegativity for all antibodies. Patients who are positive for E1, E2, E6, and E7 may experience better survival. We concluded that HPV status confers a survival advantage across all groups which is more marked for younger patients. The HPV antibody pattern, but not the antibody level, may also affect survival.

Whitmarsh A, Pring M, Thomas SJ *et al*. (2021). Survival advantage in patients with human papillomavirus-driven oropharyngeal cancer and variation by demographic characteristics and serologic response: Findings from Head and Neck 5000. *Cancer*.

New Chair for Children's Cancer & Leukaemia Group

Prof of Molecular Oncology Karim Malik (Cellular and Molecular Medicine, pictured) was named at the new Chair of the Children's Cancer and Leukaemia Group (CCLG) Research Advisory Group (RAG) in February 2021. Karim was recognised as a hard-working member of RAG and has provided knowledgeable advice about the research proposals received by CCLG.

Despite the challenging circumstances caused by COVID-19, the charity funded 24 new projects in 2020, totalling nearly £3 million of new research. CCLG's Special Named Funds have helped raise £500,000 for six new research projects focused on specific children's cancers, including

Wilms' tumour, rhabdomyosarcoma, lymphoma and ependymoma.

Karim co-leads the Cancer Epigenetics Lab and his research group focuses on:

i) delineating cellular functions in development and cancer of protocadherins (recently shown to be epigenetically silenced in cancer),

ii) evaluating novel drugs for the treatment of neuroblastoma, and

iii) transcriptional regulation of, and by, WT1.

Children's Cancer and Leukaemia Group
the EXPERTS in CHILDHOOD CANCER

New Cancer Research UK Bristol superstore

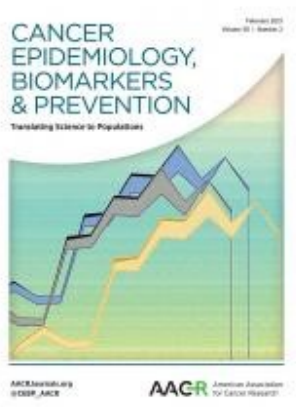
Richard Martin, Professor of Clinical Epidemiology in Bristol Medical School, has been studying lifestyle cancers for many years and the habits and behaviours that lead people to getting the disease. His team's mission is to help reduce the number of people who get cancer, working with large-scale population studies and sophisticated genetic profiling to dig deep into what can cause cancer to develop and progress.

In recognition of his work, Cancer Research UK invited Richard to open their first charity superstore located at Brislington Retail Park in Bristol on 15 April 2021.

The store sells selling furniture, electrical items, clothing and gifts and also boasts a Coffee Together café.

The role of gallstones in gallbladder cancer in India

Past history of gallstones is associated with increased risk of gallbladder cancer in observational studies. We conducted complementary observational and Mendelian randomization (MR) analyses to determine whether history of gallstones is causally related to development of gallbladder cancer in an Indian population. To investigate associations between history of gallstones and gallbladder cancer, we used questionnaire and imaging data from a gallbladder cancer case–control study conducted at Tata Memorial Hospital, Mumbai, Maharashtra, India (cases = 1,170; controls = 2,525). We then used 26 genetic variants identified in a genome-wide association study of 27,174 gallstone cases and 736,838 controls of European ancestry in an MR approach to assess causality. The association of these genetic variants with both gallstones and gallbladder cancer was examined in the gallbladder cancer case–control study. We found a strong observational association between gallstones and gallbladder cancer using self-reported history of gallstones and with objective measures of gallstone presence using imaging techniques. We found consistent causal estimates across all MR techniques, with ORs for gallbladder cancer in the range of 1.3–1.6. Our findings indicate a causal relationship between history of gallstones and increased risk of gallbladder cancer, albeit of a smaller magnitude than those found in observational analysis.



Mhatre S, Richmond RC, Chatterjee N *et al.* (2021). The Role of Gallstones in Gallbladder Cancer in India: A Mendelian Randomization Study. *Cancer Epidemiology, Biomarkers & Prevention*.

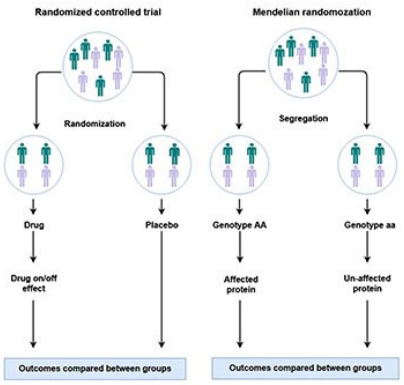
Genetic study of proteins for drug development

Working in collaboration with pharmaceutical companies, Bristol researchers have developed a comprehensive analysis pipeline using genetic prediction of protein levels to prioritise drug targets, and have quantified the potential of this approach for reducing the failure rate of drug development.

Genetic studies of proteins are in their infancy. The aim of this research was to establish if genetic prediction of protein target effects could predict drug trial success. The team worked with pharmaceutical companies to set up a multi-disciplinary collaboration to address this scientific question.

Using a set of genetic epidemiology approaches, including Mendelian randomization and genetic colocalization, the researchers built a causal network of 1002 plasma proteins on 225 human diseases. In doing so, they identified 111 putatively causal effects of 65 proteins on 52 diseases, covering a wide range of disease areas (including cancer). The results of this study are accessible via EpiGraphDB.

Zheng J, Haberland V, Baird D et al. (2020). Phenome-wide Mendelian randomization mapping the influence of the plasma proteome on complex diseases. *Nature Genetics*.



Comparison between randomised controlled trial and the genetic approach Mendelian randomization

Biochemical factors and prostate cancer incidence

Prostate cancer is the second most commonly diagnosed cancer in men worldwide after lung cancer and is a leading cause of cancer death. However, its well-established risk factors: age, ethnicity family history and other genetic factors, are not modifiable. There is evidence that higher circulating insulin-like growth factor-I (IGF-I) concentrations are related to higher overall prostate cancer risk, and obesity has been associated with a higher risk of aggressive disease. Moreover, men with low free testosterone concentrations may have a lower risk of overall prostate cancer. However, the aetiology of prostate cancer is not well understood, and there is a need to identify novel risk factors for the disease.

A range of cardiovascular, bone, joint, diabetes, renal and liver-related biomarkers were measured in baseline blood samples collected from 211,754 men and in a subsample 5 years later. After follow-up, 5763 prostate cancer cases and 331 prostate cancer deaths were ascertained. Prostate cancer incidence was positively associated with circulating vitamin D, urea and phosphate concentrations and inversely associated with glucose, total protein and aspartate aminotransferase. Phosphate and cystatin-C were the only biomarkers positively and inversely, respectively, associated with risk in analyses excluding the first 4 years of follow-up. There was little evidence of associations with prostate cancer death.

Perez-Cornago A, Fensom GK, Andrews C *et al.* (2020). Examination of potential novel biochemical factors in relation to prostate cancer incidence and mortality in UK Biobank. *British Journal of Cancer*.

B vitamins and digestive system cancers

Folate, vitamin B6 and vitamin B12 have important roles in DNA methylation, synthesis and repair and have been proposed to modify the risk of cancer, in particular digestive system cancers. Notwithstanding, the association between these B vitamins and digestive system cancers is not fully understood. We conducted a two-sample Mendelian randomisation study to assess the causality of these associations.

Two, one and 14 independent single nucleotide polymorphisms associated with serum folate, vitamin B6 and vitamin B12 at the genome-wide significance threshold were selected as genetic instruments.

Results showed that genetically predicted folate and vitamin B6 concentrations were not associated with overall cancer, overall digestive system cancer or oesophageal, gastric, colorectal or pancreatic cancer. Genetically predicted vitamin B12 concentrations were positively associated with overall digestive system cancer and colorectal cancer. Further evidence is needed to assess the safety of wide use of vitamin B12 supplementation with respect to colorectal cancer development.

Yuan S, Carter P, Vithayathil M *et al*. (2021). Genetically predicted circulating B vitamins in relation to digestive system cancers. *British Journal of Cancer*.

Young adult cancer risk behaviours originate in adolescence

An estimated 40% of cancer cases in the UK in 2015 were attributable to cancer risk behaviours. Tobacco smoking, alcohol consumption, obesity, and unprotected sexual intercourse are known causes of cancer and there is strong evidence that physical inactivity is associated with cancer. These cancer risk behaviours co-occur however little is known about how they pattern longitudinally across adolescence and early adulthood. Using data from ALSPAC, a prospective population-based UK birth cohort study, we explored patterns of adolescent cancer risk behaviours and their associations with cancer risk behaviours in early adulthood.

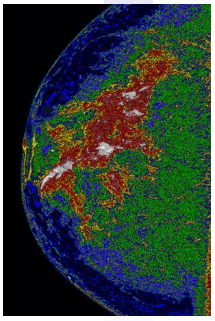
We found distinct groups of adolescents characterised by consistently high and consistently low engagement in cancer risk behaviours. After adjustment, adolescents in the top quartile had greater odds of all outcomes in early adulthood: nicotine dependency, daily smoking, obesity, high waist circumference, harmful drinking, and high waist-hip ratio, compared to the bottom quartile. In latent class analysis, adolescents characterised by consistently high-risk behaviours throughout adolescence were at higher risk of all cancer risk behaviours at age 24, except harmful drinking.

We conclude that Exposure to adolescent cancer risk behaviours greatly increased the odds of cancer risk behaviours in early adulthood. Interventions to reduce these behaviours should target multiple rather than single risk behaviours and should focus on adolescence.

Wright C, Heron J, Kipping R *et al*. (2021). Young adult cancer risk behaviours originate in adolescence: a longitudinal analysis using ALSPAC, a UK birth cohort study. *BMC Cancer*.

ANTHEM Feasibility Study

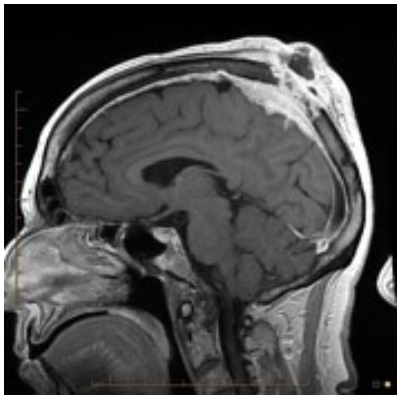
Approximately 40% of the 55 000 women diagnosed with breast cancer each year in the UK undergo mastectomy because they are considered unsuitable for standard breast-conserving surgery (BCS) due to tumour size or multiple tumour foci. Mastectomy can significantly impact women's quality of life, and only one in four women currently undergo immediate breast reconstruction (IBR). Level 2 oncoplastic breast-conserving surgery (OPBCS) combines removing the cancer with a range of plastic surgical volume replacement and volume displacement techniques that can extend the role of BCS and may allow some women not suitable for standard BCS to avoid mastectomy. High-quality research to determine whether OPBCS offers a safe and effective alternative to mastectomy±IBR is currently lacking. Preliminary work is needed to ensure a future large-scale study is feasible and well designed and addresses questions important to patients and the National Health Service. Mixed methods will be used to inform feasibility and design of a future large-scale study comparing the clinical effectiveness and cost-effectiveness of OPBCS and mastectomy±IBR. All centres offering OPBCS and mastectomy in the UK have been invited to participate.



Davies C *et al*. (2021). Protocol for a mixed-method study… *BMJ Open*.

The effect of cholesterol on head and neck cancer

Head and neck squamous cell carcinoma (HNSCC), which includes cancers of the oral cavity and oropharynx, is a cause of substantial global morbidity and mortality. Strategies to reduce disease burden include discovery of novel therapies and repurposing of existing drugs. Statins are commonly prescribed for lowering circulating cholesterol by inhibiting HMG-CoA reductase (HMGCR). Results from some observational studies suggest that statin use may reduce HNSCC risk. We appraised the relationship of genetically-proxied cholesterol-lowering drug targets and other circulating lipid traits with oral (OC) and oropharyngeal (OPC) cancer risk using two-sample Mendelian randomization (MR).



We found limited evidence for a role of cholesterol-lowering in OC and OPC risk, suggesting previous observational results may have been confounded. There was some evidence that genetically-proxied inhibition of PCSK9 increased risk, while lipid-lowering variants in LDLR, reduced risk of combined OC and OPC. This result suggests that the mechanisms of action of PCSK9 on OC and OPC risk may be independent of its cholesterol lowering effects; however, this was not supported uniformly across all sensitivity analyses and further replication of this finding is required.

Gormley M, Yarmolinsky J, Dudding T *et al*. (2021). Using genetic variants to evaluate the causal effect of cholesterol lowering on head and neck cancer risk: A Mendelian randomization study. *PLOS Genetics*.

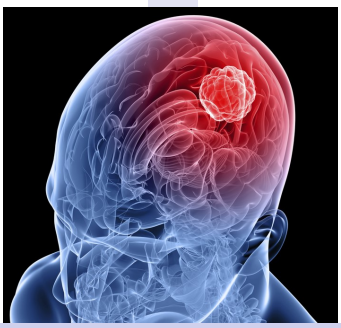
Experiences of radiotherapy for prostate cancer

This study aimed to investigate men's experiences of receiving external-beam radiotherapy (EBRT) with neoadjuvant Androgen Deprivation Therapy (ADT) for localised prostate cancer (LPCa) in the ProtecT trial. Men experienced bowel, sexual, and urinary side effects, mostly in the short term but some persisted and were bothersome. Most men downplayed the impacts, voicing expectations of age-related decline, and normalising these changes. There was some reticence to seek help, with men prioritising their relationships and overall health and well-being over returning to pre-treatment levels of function. Some unmet needs with regard to information about treatment schedules and side effects were reported, particularly among men with continuing functional symptoms. These findings reinforce the importance of providing universal clear, concise, and timely information and supportive resources in the short term, and more targeted and detailed information and care in the longer term to maintain and improve treatment experiences for men undergoing EBRT.

Sutton E, Lane JA, Davis M *et al*. (2021). Men's experiences of radiotherapy treatment for localized prostate cancer and its long-term treatment side effects: a longitudinal qualitative study. *Cancer Causes & Control*.

Survival of glioblastoma treated with temozolomide

Glioblastoma is an aggressive form of brain cancer. Approximately five of every 100 people with glioblastoma survives for five years past diagnosis. Glioblastomas that have a particular modification to their DNA (called methylation) in a particular region (the O^6-methylguanine–DNA methyltransferase (MGMT) promoter) respond better to treatment with chemotherapy using a drug called temozolomide. Although we know that modification of this DNA region is important, we don't know the best way to measure it.



In this Cochrane Review we aim to assess which way of measuring methylation of the MGMT promoter best predicts survival when people with glioblastoma are treated with temozolomide.

The primary objective of this review is to determine which technique (test) for assessing MGMT methylation status best predicts overall survival in people diagnosed with glioblastoma who are treated with temozolomide. We will consider each MGMT test as a separate prognostic factor.

The secondary objective will be to undertake a full integrated economic review to identify economic evaluations in relation to the different methods of assessing MGMT methylation status effect on overall survival. Furthermore, we will develop a simple cost-effectiveness decision model exploring the cost-effectiveness of alternative approaches to assessing MGMT methylation status.

McAleenan A, Howell A, Kernohan A *et al*. (2021). Prognostic value of test(s) for O^6-methylguanine–DNA methyltransferase (MGMT) promoter methylation for predicting overall survival in people with glioblastoma treated with temozolomide. *Cochrane Database of Systematic Reviews*.

Academy of Medical Sciences Fellowship

Professor Jane Blazeby has been elected to The Academy of Medical Sciences' respected and influential Fellowship.

Jane Blazeby FMedSci is Professor of Surgery at the University of Bristol and an Honorary Consultant Surgeon at University Hospitals Bristol and Weston NHS Foundation Trust. She studied Medicine at the University of Bristol and undertook higher surgical training in the South West of England. Jane has a long-standing interest in patient centred surgical care and standards of surgery. She has developed and validated an international portfolio of patient reported outcome measures which are widely used in clinical trials in surgical oncology. She collaborates with surgeons, methodologists, trialists and patient partners to design and deliver randomised controlled surgical trials and is working hard to establish evidence based surgical practice in the UK.

Prognostic factors for prostate cancer progression

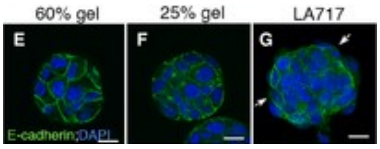
Prostate cancer prognosis and treatment decisions remain a challenging clinical area for clinicians and patients, particularly for men with localised disease at the time of diagnosis. In recent decades, prostate cancer detection rates have increased markedly, in part, as a result of the rising use of asymptomatic prostate specific antigen (PSA) testing; however, more intensive PSA-based detection of prostate cancer has not been convincingly directly correlated with reductions in prostate cancer mortality for all men, implying increasing over-detection of clinically insignificant tumours. Treatments for prostate cancer carry a significant risk of morbidity for men, underlining the importance of being able to identify which men with tumours confined to the prostate at diagnosis are at higher risk of prostate cancer progression and mortality.

The team undertook a retrospective cohort study using a longitudinal data set of prospectively collected electronic primary care medical records from general practices in England for the Clinical Practice Research Datalink. This data set was linked with cancer registry data from the National Cancer Research and Analysis Service and mortality data from the Office for National Statistics. 10,901 men with localised prostate cancer were followed up for a mean of 14 years. 2,331 men underwent systemic therapy and 3,450 died, including 1,250 from prostate cancer. Factors associated with an increased risk of prostate cancer mortality included age; high PSA; current or ex-smoker; ischaemic heart disease; high C reactive protein; high ferritin; low haemoglobin; high blood glucose and low albumin. Results identified several new potential prognostic factors and confirmed known ones. Further research is needed to develop and validate a prognostic model for prostate cancer progression.

Merriel SW, Ingle SM, May MT & Martin RM (2021). Retrospective cohort study evaluating clinical, biochemical and pharmacological prognostic factors for prostate cancer progression using primary care data. *BMJ Open*.

Cancer spheroid models

3D cultures of cancer cells in liquid without extracellular matrix (ECM) offer *in vitro* models for metastasising conditions such as those in vessels and effusion. However, liquid culturing is often hindered by cell adhesiveness, which causes large cell clumps. A liquid culture material, LA717, which prevents nonclonal cell adhesion and subsequent clumping, allows clonal growth of spheroids in an anchorage- independent manner. In this study the team examined such liquid culture cancer spheroids for the acquisition of apical–basal polarity, sensitivity to an Akt inhibitor (anticancer drug



MK-2206) and interaction with ECM. At the multicellular stage, liquid culture spheroids presented bleb-like protrusion on the surface, which was enhanced by the activation of the PI3K/Akt pathway and reduced by PI3K/Akt inhibitors. Liquid culture spheroids exhibited slow proliferation speed and low endogenous pAkt levels compared with gel-cultured spheroids and 2D-cultured cells, explaining the susceptibility to the Akt-inhibiting anticancer drug.

Abe-Fukasawa N, Watanabe R, Gen Y *et al*. (2021). A liquid culture cancer spheroid model reveals low PI3K/Akt pathway activity and low adhesiveness to the extracellular matrix. *FEBS Journal*.

Cabazitaxel chemotherapy for urinary bladder cancer

Neoadjuvant cisplatin-based combination chemotherapy improves survival in muscle-invasive bladder cancer. However, response rates and survival remain suboptimal. We evaluated the efficacy, safety, and tolerability of cisplatin plus cabazitaxel.

A phase II single-arm trial was designed and recruited eligible patients. Objective response was seen in 15 of 26 evaluable patients (57.7%) and more than one- third of patients achieved a pathologic complete response (9/26; 34.6%). Seventy-eight percent of the patients (21/27) completed all cycles of treatment, with only 6.7% of the reported adverse events being graded 3 or 4. There were 6 treatment-related serious adverse event reported, but no suspected unexpected serious adverse reactions. In the patients who achieved an objective response, the median progression-free survival and overall survival were not reached (median follow-up of 41.5 months). In contrast, the median progression-free survival (7.2 months) and overall survival (16.9 months) were significantly worse in patients who did not achieve an objective response.

Results from this study conclude that cabazitaxel plus cisplatin for neoadjuvant treatment of muscle-invasive bladder cancer can be considered a well-tolerated and effective regimen before definitive therapy with higher rates (57.7%) of objective response, comparing favourably to that with of cisplatin/gemcitabine (23%–26%). These results warrant further evaluation in a phase III study.

Challapalli A, Masson S, White P *et al*. (2021). A Single-arm Phase II Trial of Neoadjuvant Cabazitaxel and Cisplatin Chemotherapy for Muscle-Invasive Transitional Cell Carcinoma of the Urinary Bladder. *Clinical Genitourinary Cancer*.

Coffee consumption and breast cancer risk

Observational studies have reported either null or weak protective associations for coffee consumption and risk of breast cancer. We conducted a two-sample Mendelian randomization (MR) analysis to evaluate the relationship between coffee consumption and breast cancer risk using 33 single-nucleotide polymorphisms (SNPs) associated with coffee consumption from a genome-wide association (GWA) study on 212,119 female UK Biobank participants of White British ancestry. Risk estimates for breast cancer were retrieved from publicly available GWA summary statistics from the Breast Cancer Association Consortium on 122,977 cases [of which 69,501 were oestrogen receptor (ER)-positive, 21,468 ER-negative] and 105,974 controls of European ancestry. Random-effects inverse variance weighted MR analyses were performed along with several sensitivity analyses to assess the impact of potential MR assumption violations. One cup per day increase in genetically predicted coffee consumption in women was not associated with risk of total ER-positive and ER-negative breast cancer. Null associations were also found in the sensitivity analyses.

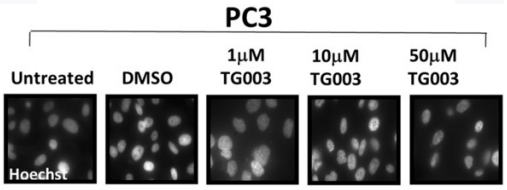
Ellingjord-Dale M *et al*. (2021). Coffee consumption and risk of breast cancer: A Mendelian randomization study. *PLOS One*.

CDC2-like kinases as a therapeutic in prostate cancer

The vast majority of human genes are alternatively spliced (> 94%), expressing splice isoforms that often exhibit antagonistic properties. Aberrant alternative splicing contributes to the pathogenesis and progression of cancer and plays an essential role in all hallmarks of cancer. Dysregulated alternative splicing has even been proposed as new a cancer hallmark, and is associated with the effectiveness of treatments and the development of drug resistance.

Dysregulation occurs because of mutations in splice sites or sites that regulate splicing, or because of the altered expression and activity of splice factors and of splice factor kinases that regulate splice factor activity.

Recently the CDC2-like kinases (CLKs) have attracted attention due to their increasing involvement in cancer. We measured the effect of the CLK inhibitor, the benzothiazole



TG003, on two prostate cancer cell lines. TG003 reduced cell proliferation and increased apoptosis in PC3 and DU145 cells. Conversely, the overexpression of CLK1 in PC3 cells prevented TG003 from reducing cell proliferation. TG003 slowed scratch closure and reduced cell migration and invasion in a transwell assay. TG003 decisively inhibited the growth of a PC3 cell line xenograft in nude mice. We performed a transcriptomic analysis of cells treated with TG003. We report widespread and consistent changes in alternative splicing of cancer-associated genes including CENPE, ESCO2, CKAP2, MELK, ASPH and CD164 in both HeLa and PC3 cells. Together these findings suggest that targeting CLKs will provide novel therapeutic opportunities in prostate cancer.

Uzor S, Porazinski SR, Li L *et al*. (2021). CDC2-like (CLK) protein kinase inhibition as a novel targeted therapeutic strategy in prostate cancer. *Scientific Reports*.

5-Aminosalicylic acid in colorectal tumorigenesis

Most colorectal cancers (CRC) arise sporadically from precursor lesions: colonic polyps. Polyp resection prevents progression to CRC. Risk of future polyps is proportional to the number and size of polyps detected at screening, allowing identification of high-risk individuals who may benefit from effective chemoprophylaxis. We aimed to investigate the potential of 5-aminosalicylic acid (5-ASA), a medication used in the treatment of ulcerative colitis, as a possible preventative agent for sporadic CRC. Human colorectal adenoma, transformed adenoma and carcinoma cell lines were treated with 5-ASA. The effect on growth in 2– and 3D culture, β-catenin transcriptional activity and on cancer stemness properties of the cells were investigated. 5-ASA was shown, *in vitro*, to inhibit the growth of adenoma cells and suppress β-catenin transcriptional activity. Downregulation of β-catenin was found to repress expression of stem cell marker LGR5 (leucine-rich G protein-coupled receptor-5) and functionally suppress stemness in human adenoma and carcinoma cells using 3D models of tumorigenesis.

Dixon SW, Collard TJ, Mortensson EMH *et al*. (2021). 5-Aminosalicylic acid inhibits stem cell function in human adenoma-derived cells: implications for chemoprophylaxis in colorectal tumorigenesis. *British Journal of Cancer*.

Lifetime smoking on breast and colorectal cancer risk

Breast and colorectal cancer are two of the most common cancers globally with a combined estimated number of 4 million new cases and 1.5 million deaths in 2018. Smoking is the most common cancer risk factor globally, with an estimated 18% of all cancers attributable to smoking.

We used Mendelian randomization (MR) to examine causal associations between smoking and risks of breast and colorectal cancer. Genome-Wide Association Study summary data were used to identify genetic variants associated with lifetime amount of smoking (n = 126 variants) and ever having smoked regularly (n = 112 variants). Using two-sample MR, we examined these variants in relation to incident breast and colorectal cancer. In inverse-variance

weighted models, a genetic predisposition to higher lifetime amount of smoking was positively associated with breast cancer risk. Similar associations were found for oestrogen receptor-positive and oestrogen receptor-negative tumours. Higher lifetime amount of smoking was positively associated with colorectal cancer, colon cancer and rectal cancer. Ever having smoked regularly was not associated with risks of breast or colorectal cancer.

These findings are consistent with prior observational evidence and support a causal role of higher lifetime smoking amount in the development of breast and colorectal cancer.

Dimou N, Yarmolinsky J, Bouras E *et al*. (2021). Causal Effects of Lifetime Smoking on Breast and Colorectal Cancer Risk: Mendelian Randomization Study. *Cancer Epidemiology, Biomarkers & Prevention*.

ELIZABETH BLACKWELL FUNDING

Nurturing Research. Improving Health.

EBI Global Public Health: workshops

A funding call to support workshops focusing on research into public health issues in Low- and Middle-Income Country (LMIC) settings.

Deadline: 10:00 Friday 21 May 2021

EBI Global Public Health: Round 3

A funding call for global public health research focused on low- and middle-income countries.

Deadline: 18:00 Friday 28 May 2021

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

Would you like to receive timely, tailored funding opps information?

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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. If you register for the site and log in, you'll be able to:

- **Set up automated funding opportunity email alerts** - **tailored according to your discipline and research interests**
- **Save searches and bookmarks** - store items of interest for future reference, download and email to colleagues
- **Sign up for higher education news bulletins**

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**.

National Cancer Institute (USA)

Exploratory grants in cancer epidemiology (R21 clinical trial optional)

Closing date: 8 June 2021 Award amount: USD275,000

This supports research on cancer epidemiology. The overarching goal is to provide support to promote the early and conceptual stages of research efforts on novel scientific ideas that have the potential to substantially advance population-based cancer research.

Cancer Research UK

Multidisciplinary project award

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

This supports collaborations between cancer researchers and scientists from engineering and physical science disciplines. The aim is to generate creative research ideas and explore their applicability in cancer research. Proposals across all engineering and physical science disciplines including physics, engineering, mathematical and computational modelling, chemical and molecular sciences, materials sci-

ence, molecular and tissue engineering and regenerative medicine are welcomed. The research themes for this award include:

- direct application of physics, engineering, chemical or mathematical concepts to address the underlying physical processes of cancer, including tumour initiation, growth and metastasis;
- development of new transformational approaches or the translation of technologies for direct applications in, or a clear path to, a direct application in the prevention, diagnosis or treatment of cancer.

Cancer Research UK
Early detection and diagnosis project award

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

This supports research projects that drive a transformational change in how and when early cancers and pre-cancerous states are diagnosed. Projects should aim to detect and diagnose consequential pre-cancerous changes and cancer at the earliest possible point at which an intervention might be made, reducing the burden of late-stage disease.

Pezcoller Foundation / American Association for Cancer Research
International award for cancer research

Closing date: 31 August 2021 Award amount:€75,000

This recognises a scientist who has made a major scientific discovery in basic cancer research or has made significant contributions to translational cancer research, and whose ongoing work holds promise for continued substantive contributions to progress in the field of cancer.

Cancer Research UK
Experimental medicine award

Closing date: 21 October 2021 Award amount: £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.

World Cancer Research Fund International
Regular grant programme

Closing date: 15 November 2021 (forecast) 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.

FEATURED PUBLICATION

Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction

David V Conti, Burcu F Darst, Lilit C Moss *et al*. (2021). *Nature Genetics*.

Prostate cancer is a highly heritable disease with large disparities in incidence rates across ancestry populations. We conducted a multi-ancestry meta-analysis of prostate cancer genome-wide association studies (107,247 cases and 127,006 controls) and identified 86 new genetic risk variants independently associated with prostate cancer risk, bringing the total to 269 known risk variants. The top genetic risk score (GRS) decile was associated with odds ratios that ranged from 5.06 (95% confidence interval (CI), 4.84–5.29) for men of European ancestry to 3.74 (95% CI, 3.36–4.17) for men of African ancestry. Men of African ancestry were estimated to have a mean GRS that was 2.18-times higher (95% CI, 2.14–2.22), and men of East Asian ancestry 0.73-times lower (95% CI, 0.71–0.76), than men of European ancestry. These findings support the role of germline variation contributing to population differences in prostate cancer risk, with the GRS offering an approach for personalized risk prediction.

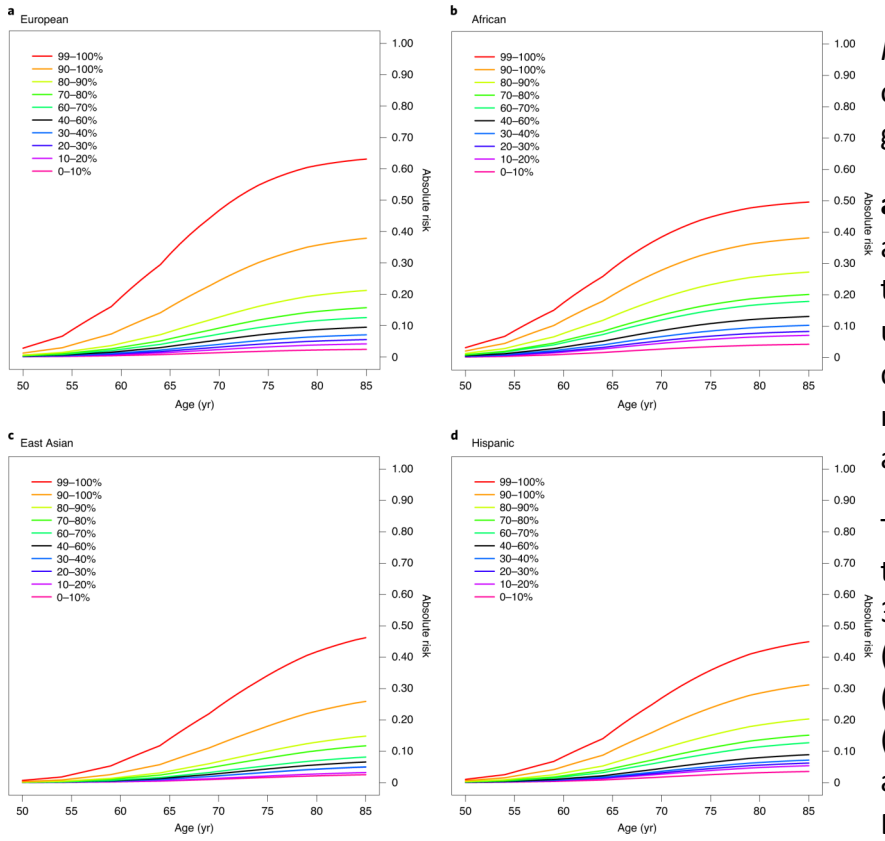

Image: Lifetime absolute risks of prostate cancer by GRS category and ancestry group.

a, European ancestry. **b**, African ancestry. **c**, East Asian ancestry. **d**, Hispanic. SEER data are used for mortality and incidence rates corresponding to non-Hispanic white, Black, Asian and Hispanic men.

The absolute risk for men in the top decile of the GRS reached 38% for men of both African (95% CI, 36–41%) and European (95% CI, 37–39%) ancestry, 31% (95% CI, 27–36%) for Hispanics and 26% (95% CI, 22–30%) for East Asians. Absolute risk estimates were only slightly reduced when using GRS estimates from men of European and African ancestry in the UK Biobank and CA UG replication studies, respectively. Men with a first-degree family history of prostate cancer had increased absolute risks for each GRS category, with 67% (95% CI, 59–76%) and 56% (95% CI, 52–60%) lifetime absolute risks estimated for men in the top 10% for men of African and European ancestry, respectively.

Cancer Network

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- Dr Axel Walther, *Senior Lecturer and Research Lead, Bristol Haematology & Oncology Centre*
- Prof Richard Martin, *Professor of Clinical Epidemiology*

Steering Group members:

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- Dr Grace Edmunds, *Clinical Research Fellow*
-

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- Dr Zoë Holland, *Research Development Manager*

- Dr Kathreena Kurian, *Reader in Brain Tumour Research and Consultant Clinical Neuropathologist*

- Prof Paul Martin, *Professor of Cell Biology*

- Prof Caroline Relton, *Professor of Epigenetic Epidemiology*

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

- Prof Ann Williams, *Professor of Experimental Oncology*

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- Dr Helen Winter, *Medical Oncologist*

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University of BRISTOL
Elizabeth Blackwell Institute for Health Research

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