Cancer Network Newsletter

May - June 2019

University of BRISTOL
Elizabeth Blackwell Institute for Health Research

Non-communicable disease prevention

The University of Bristol, in partnership with the Universities of Bath, West of England, Manchester, Reading and Cardiff and Bristol City Council and Greater Manchester Combined Authority, has been awarded £6.6 million by the UK Prevention Research Partnership (UKPRP) to tackle unhealthy urban planning and development linked to non-communicable diseases (NCDs) such as heart disease, obesity, poor mental health, cancer and diabetes.

The funding is part of a £25 million UKPRP investment awarded to eight projects that aim to address the bigger picture factors behind the prevention of NCDs which make up the vast majority of illnesses in the UK and account for an estimated 89% of all deaths.

The projects aim to deliver real changes that reduce the burden of these diseases on our health and social care systems and enable people to live longer, healthier lives. Many aspects of the world around us influence our health, from the communities in which we live, to the design of our cities and transport systems, the quality of our housing and education. There is strong evidence to show that wider factors such as these, often called 'upstream determinants', can have a great influence on how healthy our lives will be.

The projects cover a wide variety of issues, including; investigating the commercial determinants of health (i.e. the approaches used by commercial producers of tobacco, alcohol and food to promote products, influence policy and people's choices, which in turn impacts on our health as a population); school food systems and their effects on the quality of children's diets; improving the life chances of children in deprived areas in the UK; embedding health considerations in urban planning and decision-making processes; and developing new economic methods for judging the effectiveness and costs and benefits in policy areas such as economic growth and housing.

Read more

Inside this issue:

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EVENTS

High Dimensional and Bayesian Inference toward Quantifying Real-World Uncertainties
30 May 2019, 9.00 - 17.00, Hepple Lecture Theatre, Geographical Sciences

Towards a Socially Responsible Civic University: balancing the global and the local
30 May 2019, 16.00 - 18.00, Dr Rajesh Tandon (UNESCO Co-Chair of Community Based Research and Social Responsibility in Higher Education), The Winston Theatre, University of Bristol Students' Union, Queen's Road

"Effective Successful Happy Academic" workshops in qualitative research methods and academic workplace skills
3 - 4 June 2019, Engineers' House

The Half-Causation Method to Aid the Development of Patentable Inventions
5 June 2019, 13.00 - 14.00, Dr Mo Abolkheir (Dept of Philosophy, School of Arts, University of Bristol), C44 Biomedical Sciences Building

Global Child Health and Poverty seminar
6 June 2019, 12.30 - 14.00, venue TBC to delegates once registered

Launch: Great West | Celebrating innovation in the South West
6 June 2019, 18.00 - 22.00, Mercure Bristol Grand Hotel , Broad St

Introduction to Randomised Controlled Trials
10 - 14 June 2019, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS

Conversations That Count: Being a Reflexive Researcher
10 June 2019, 10.00 - 12.00, Room 2.26, 35 Berkeley Square

How to maximise patient recruitment and retention
10 June 2019, 12.00 - 13.30, Lucy Culliford (University of Bristol), Tutorial room 4, Education & Research Centre, Upper Maudlin Street, Bristol

Data-driven systems medicine workshop
11 - 12 June 2019, Cardiff University Brain Research Imaging Centre, Maindy Road, Cardiff, CF24 4HQ

Translation toolkit: Planning for your future - where to next? Hear from GSK and others about how they support ECRs
11 June 2019, 14.00 - 15.00, David Tew (GSK), F40, Biomedical Sciences Bldg

Statistics Clinic

LAUNCH: Great West

CUBRIC

From top: Rajesh Tandon, Mo Abolkheir, Lucy Culliford, David Tew

SEE ALL EVENTS ON THE CANCER RESEARCH NETWORK WEBSITE

EVENTS CON'T

12 June 2019, 14.00 - 15.30, SM3 Mathematics Building

Young women with breast cancer and Sylvia Lawler Prize meeting
17 June 2019, 10.00 - 19.20, Royal Society of Medicine, London

JOIN US FOR THE
Cancer Research Network: Translational Pathway half-day symposium
17 June 2019, 13.30 - 18.00
Lecture Theatre 2, Education and Research Centre, Upper Maudlin Street, Bristol BS2 8AE
Last few spaces left, **registration closes 7 June 2019**
REGISTER NOW
LIST OF SPEAKERS AND FURTHER INFORMATION

Enhancing Facilitation Skills for Patient and Public Involvement workshop
19 June 2019, 9.00 - 13.00, venue will be confirmed after registration. Facilitated by Rosie Davies (Research Fellow, People in Health West of England) and Cathy Rice (public contributor, People in Health West of England)

From top:
Rosie Davies
Cathy Rice

T3 Technical Talk Time Seminar series
19 June 2019, 14.00 - 15.00

Cell and Gene Therapy Catapult Seminar Day @ the University of Bristol
20 June 2019, 9.00 - 16.30, School of Chemistry, Cantock's Close

Data Visualisation Working Group
20 June 2019, 12.30 - 13.30, Hepple Lecture Theatre, Geographical Sciences

Open Presentation from NIHR Global Health Team
21 June 2019, 11.00 - 12.00, venue to be confirmed with delegates

Start Something: Launchpad
25 - 28 June 2019, Bristol

Treatment-emergent neuroendocrine prostate cancer: Clinical relevance and molecular pathogenesis
25 June 2019, 9.45 - 18.00, The Open University, Milton Keynes, MK7 6AA

Cardiff-Bristol clinical cancer meeting
19 September 2019, 10.00 - 14.00
Cardiff & Vale University Health Board (Heath Hospital), Cardiff, CF14 4XW
The Universities of Cardiff and Bristol are holding a joint symposium with the purpose of highlighting potential areas of clinical collaboration. Topics to be covered include phase I trials, other clinical trials research, imaging, radiotherapy, screening, population genetics.
REGISTER NOW

SEE ALL EVENTS ON THE CANCER RESEARCH NETWORK WEBSITE

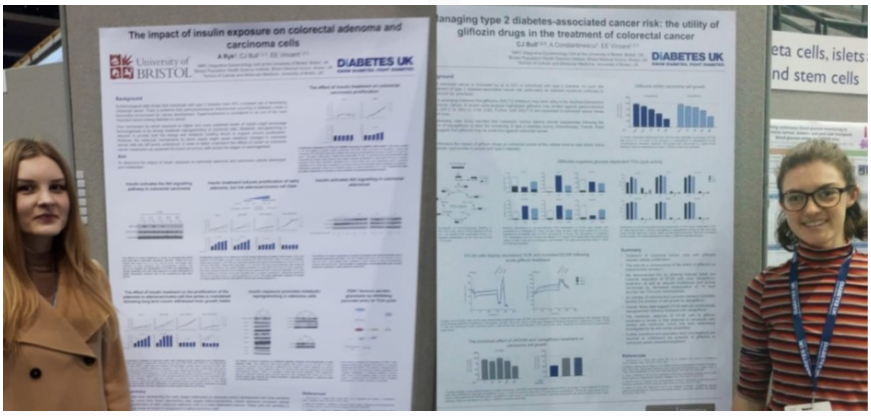
NEWS

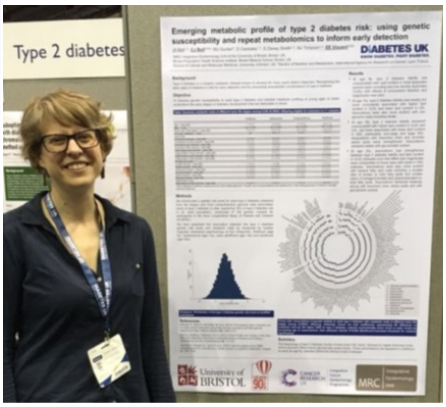
Diabetes UK Professional Conference

Dr Emma Vincent, Caroline Bull and Aleksandra Ryk attended the Diabetes UK Professional Conference in Liverpool from 6 to 8 March 2019.

The members of the Vincent team presented three posters, including Caroline's *Managing type 2 diabetes-associated cancer risk: the utility of gliflozin drugs in the treatment of colorectal cancer*, and Aleksandra's *The impact of insulin exposure on colo-rectal adenoma and carcinoma cells*.

Emma gave an oral presentation on *Emerging metabolic profile of type 2 diabetes risk: using genetic susceptibility and repeat metabolomics to inform early detection*. The meeting aligned well with her RD Lawrence Fellowship, which was awarded to investigate the impact of cancer on people living with type 2 diabetes.





Boost to Bristol's research in Africa

A £1 million gift from the The Perivoli Trust will create new roles and opportunities for Bristol researchers to tackle key challenges and pioneer innovative solutions for the most pressing concerns in Africa. A new Perivoli Chair in Africa Research and Partnerships will develop and expand the University's portfolio of interdisciplinary research in partnership with universities, international agencies, charities, governments and organisations across Africa.

The gift will additionally fund opportunities for Vice-Chancellor Fellowships, PhD scholarships and ultimately lead to the creation of a new Centre for Africa Research and Partnerships to achieve real and impactful change in the Trust's priority areas of research: education, health and wellbeing, sustainable agriculture, resilience and governance, and migration and mobility.

The University has over 50 active research projects working with African partners, co-created with regional communities to bring real and local impact. Working with its partners in the Worldwide Universities Network (WUN) and international agencies, Bristol leads projects on migration data, policy and development and health outcomes of migration events.

A delegation from Bristol visit the University of Nairobi for the WUN Global Africa Group workshop in Nov 2018

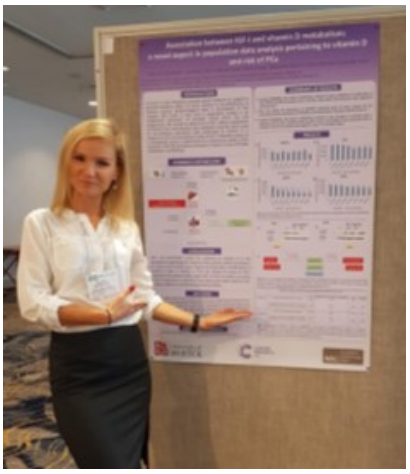
External engagements: Part 1

Dr Emma Vincent (Cellular and Molecular Medicine and Bristol Medical School: Population Health Sciences) presented her Diabetes UK-funded research on adiposity and colorectal cancer at the **Magnetoencephalography Research conference** (MEG UK) organised by Cardiff University on 15-17 April 2019.

Dr Claire Perks (Bristol Medical School: Translational Health Sciences) chaired the **Gordon Research Conference on IGF and Insulin System in Physiology and Disease** hosted in Ventura, California, 10-15 March 2019. Research Associate Kalina Biernacka (pictured) gave both oral and poster presentations at the conference.

The conference focused on a showcase of innovative research in the insulin and insulin-like growth factor field and their fundamental role in normal physiology and in diseases particularly related to ageing, cancer and metabolic disorders.

My presentation was entitled Association between IGF-I and vitamin D metabolism: a novel aspect in population data analysis pertaining to vitamin D and risk of prostate cancer*, where I showed data indicating that IGF-I can potentially modify the response of prostate cancer cell lines to vitamin D by regulating the enzymes that regulate the interconversion of vitamin D between its active and inactive states. Based on these data, stratification of vitamin D data in relation to prostate cancer risk relative to levels of IGF-I indicated that patients with higher IGF-I in the circulation would be to less responsive to vitamin D than those with lower levels of IGF-I, where vitamin D could have a beneficial effect*.



Funding successes

To Tom Wilson (Cellular & Molecular Medicine), an **Elizabeth Blackwell Institute** Clinical Primer for *Roles of Rho GTPase kinase targets in prostate cancer invasion*. Primers are designed to give early career clinicians the chance to experience a research environment for the first time.

To Profs Paul Martin (Biochemistry) and Steve Mann (Chemistry), a **Wellcome Trust iTP** award to investigate the feasibility of loading leukocytes with miR223 sponges via protocells to enhance their cancer killing potential, £79,000.

To Dr Jaap Velthuis (Physics) from **Vivamos Ltd**, for *Enhancing the value of MAPS for radiotherapy verification* from 11 Nov 2018 for two years.

To Dr Caroline Wright (Bristol Medical School: Population Health Sciences), a **Cancer Research UK** Cancer Policy Research Centre (CPRC) Innovation grant. The 12-month £40,000 grant runts until February 2020. The grant will: 1) Develop a valid and reliable algorithm (targeted accuracy of 80%) to determine inaccurate risk perception information about the use of e-cigs for smoking cessation viewed by adult smokers on the internet using Twitter and Google searches; 2) Explore the impact of exposure to online misinformation regarding e-cigarettes on smokers' knowledge, beliefs, attitudes, intentions to quit smoking tobacco & use of e-cigarettes.

Technicians make it happen—Green Lab Accreditation

The University of Bristol's Biomedical Sciences Building, which houses the Schools of Biochemistry; Cellular and Molecular Medicine; and Physiology, Pharmacology and Neuroscience, has gained 100% Green Lab Accreditation status. This was awarded in collaboration with NUS's Green Impact scheme and achieved through a series of rigorous, green-initiatives.

University laboratories require large amounts of energy and resources, on average consuming 5-10 times more energy than other academic spaces. Occupying only 6% of University space, laboratories account for 40% of energy, water and waste.

Befitting of a city well-known for its green-credentials, over 170 laboratories within the University's Biomedical Sciences Building have made changes to ensure that the world-leading teaching and research is done with utmost efficiency and minimal waste, resulting in a combined cost saving of over £85,000 worth of energy over the past two years. Steps taken include the replacement of energy-inefficient laboratory equipment such as ultralow freezers, drying cabinets and biosafety cabinets have saved £22,000, or 120 tonnes of CO_2.

Building on this success the University is now participating in a national pilot of the Laboratory Efficiency Assessment Framework (LEAF).

Cancer Research UK Business Beats Cancer

Business Beats Cancer brings together business leaders across the UK to fight cancer one city at a time. Board members are the ambassadors for Cancer Research UK in their cities and membership to boards is exclusive, but growing.

Business Beats Cancer board members work with their business networks to host annual fundraising events. Business Beats Cancer Bristol are hosting a launch event on 6 June 2019 at the Avon Gorge Hotel and are looking for local business representatives to attend and help raise money to further research right here in Bristol.

Please do raise awareness of this event with your industrial colleagues.

Supporting Cancer Research and attending the fundraising Gala Dinner is really important to us as the event will not only raise valued funds but will also raise awareness into the major research being carried out by Cancer Research UK in Bristol. The city is a major hub for research into cancer, with Cancer Research UK coordinating a £4.1m 5-year programme focusing on new ways to predict cancer, as well as ways to prevent it. We are proud to be supporting this prestigious event.

Vanessa Moon
Director of Moon Consulting

Business Beats Cancer Bristol Board Members

Equality, Diversity and Inclusion (EDI)

The Elizabeth Blackwell Institute has appointed a new EDI Champion, **Fiona McPhail**, who took up her post in February 2019. Fiona's main focus will be on health and life sciences research communities and will be working very closely with the Health and Life Sciences Faculty EDI leads to ensure work complements and aligns with Faculty priorities. Writing a blog on International Women's Day (21 March 2019), Fiona remarked "As a sector, Higher Education has been grappling with how we enable all groups to enter and thrive, striving to become institutions which are fair for all and where everyone can achieve according to their ability. We have travelled a long way, with sector wide initiatives providing a platform for change and a structured and assessed methodology for analysing outcomes. We know, however, that despite our efforts, we are not yet there and there is more for us to do."

Read the full article here

External engagements: Part 2

PhD student Ryan Langdon (Bristol Medical School) presented a poster at the **American Association for Cancer Research (AACR) Annual Meeting** held in Atlanta, Georgia 29 March-3 April 2019. His poster was entitled *Identifying epigenetic biomarkers in a clinical cohort of individuals with oropharyngeal cancer*.

On 7-8 March 2019 PhD student James Yarmolinsky (Integrative Cancer Epidemiology Programme) attended the **Radical Approaches to Cancer Prevention International Symposium** hosted by the Cancer Research UK Cambridge Institute. The programme included talks on a wide range of topics including: using new technology to reduce and prevent disease, training the immune system, preventing cancer through medical intervention, and preventing cancer through life-style and policy. James gave an oral presentation entitled *HMGCR, NPC1L1, and PCSK9 genetic variation and risk of ovarian cancer*.

Dr Rebecca Richmond (Vice Chancellor's Fellow) attended the **Society for Research on Nicotine and Tobacco (SRNT) conference** in San Francisco with several members of the Tobacco and Alcohol Research Group (Dr Robyn Wootton, Dr Olivia Maynard, PhD student Jasmine Khouja and Prof Marcus Munafò, all Psychological Science). Rebecca was awarded with an SRNT travel award to present her work on e-cigarette use and epigenetic changes which has identified DNA methylation profiles specific to e-cigarette use and distinct from cigarette smoking.

Prof Jeff Holly (Bristol Medical School: Translational Health Sciences) was an invited speaker at the **4th Joint Global Symposium on Obesity** at the International Congress of Endocrinology iat the Cape Town International Convention Centre, South Africa, on 2 December 2018. His talk was entitled *Obesity gives you cancer and we know why*.

Economic health evaluation

Dr Sabina Sanghera (Bristol Medical School: Population Health Sciences) is a Lecturer in Health Economics and part of the Health Economics at Bristol group. Sabina holds an NIHR Postdoctoral Fellowship (2018-2022) to determine how best to measure and value quality of life in economic evaluations when health fluctuates.

As quality of life data inform cost-effectiveness decisions and it is not clear how patients with fluctuating health complete quality of life questionnaires, the first step of the project was to interview patients with fluctuating symptoms.

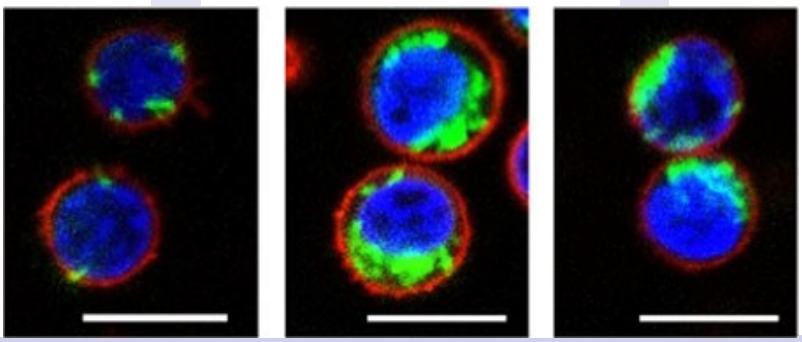
In her first year, Sabina has been busy interviewing patients undergoing chemotherapy for cancer to explore whether these patients with constantly fluctuating symptoms adhere to recall periods, construct an average or recall the worst point of the chemotherapy cycle when completing EQ-5D-5L ('health today'), SF-12 ('past four weeks') and EORTC-QLQ-C30 ('past week').

Look out for the results and implications of using these questionnaires to calculate quality-adjusted life years, as Sabina starts to publish these findings.

CD4+ T-cell response to TCR stimulation

Metabolic pathways that regulate T-cell function show promise as therapeutic targets in diverse diseases. Here, we show that at rest cultured human effector memory and central memory CD4+ T-cells have elevated levels of glycolysis and oxidative phosphorylation (OXPHOS), in comparison to naïve T-cells. Despite having low resting metabolic rates, naïve T-cells respond to TCR stimulation with robust and rapid increases in glycolysis and OXPHOS. This early metabolic switch requires Akt activity to support increased rates of glycolysis and STAT5 activity for amino acid biosynthesis and TCA cycle anaplerosis. Importantly, both STAT5 inhibition and disruption of TCA cycle anaplerosis are associated with reduced IL-2 production, demonstrating the functional importance of this early metabolic program. Our results define STAT5 as a key node in modulating the early metabolic program following activation in naive CD4+ T-cells and in turn provide greater understanding of how cellular metabolism shapes T-cell responses.

Jones N, Vincent E *et al*. (2019). Akt and STAT5 mediate naïve human CD4+ T-cell early metabolic response to TCR stimulation. *Nature Communications*. 10:2042.



Representative images of NV, EM and CM T-cells stained with DRAQ5 (nucleus), cell mask orange (plasma membrane) and MitoTracker green (mitochondria) scale bar = 10 µm

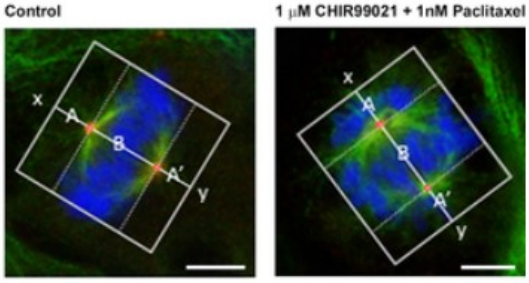
Lycopene, green tea and prostate cancer

Lycopene and green tea consumption have been observationally associated with reduced prostate cancer risk, but the underlying mechanisms have not been fully elucidated. We investigated the effect of factorial randomisation to a 6-month lycopene and green tea dietary advice or supplementation intervention on 159 serum metabolite measures in men with raised PSA levels (but prostate cancer-free), analysed by intention-to-treat. The causal effects of metabolites modified by the intervention on prostate cancer risk were then assessed by Mendelian randomisation (MR), using statistics from cancer cases and controls. The systemic effects of lycopene and green tea supplementation on serum metabolic profile were comparable to the effects of the respective dietary advice interventions. Metabolites which were altered in response to lycopene supplementation were acetate, valine, pyruvate, and docosahexaenoic acid. Valine and diacylglycerol were lower in the lycopene dietary advice group. A genetically instrumented SD increase in pyruvate increased the odds of prostate cancer by 1.29. An intervention to increase lycopene intake altered the serum metabolome of men at risk of prostate cancer. Lycopene lowered levels of pyruvate, which MR suggests may be causally related to reduced prostate cancer risk.

Beynon RA, Richmond RC *et al*. (2018). Investigating the effects of lycopene and green tea on the metabolome of men at risk of prostate cancer: The ProDiet randomised controlled trial. *IJC*.

Tumor growth suppression in non-small cell lung cancer

Glycogen synthase kinase-3 (GSK3) is over-expressed and hyperactivated in non-small cell lung carcinoma (NSCLC) and plays a role in ensuring the correct alignment of chromosomes on the metaphase plate during mitosis through regulation of microtubule stability. This makes the enzyme an attractive target for cancer therapy. We examined the effects of a selective cell-permeant GSK3 inhibitor (CHIR99021), used alone or in combination with paclitaxel, using an *in vitro* cell growth assay, a quantitative chromosome alignment assay, and a tumor xenograft model. CHIR99021 inhibits the growth of human H1975 and H1299 NSCLC cell lines in a synergistic manner with paclitaxel. CHIR99021 and paclitaxel promoted a synergistic defect in chromosomal alignment when compared to each compound administered as monotherapy. Furthermore, we corroborated our *in vitro* findings in a mouse tumour xenograft model. Our results demonstrate that a GSK3 inhibitor and paclitaxel act synergistically to inhibit the growth of NSCLC cells *in vitro* and *in vivo* via a mechanism that may involve converging modes of action on microtubule spindle stability and thus chromosomal alignment during metaphase. Our findings provide novel support for the use of the GSK3 inhibitor, CHIR99021, alongside taxol-based chemotherapy in the treatment of human lung cancer.

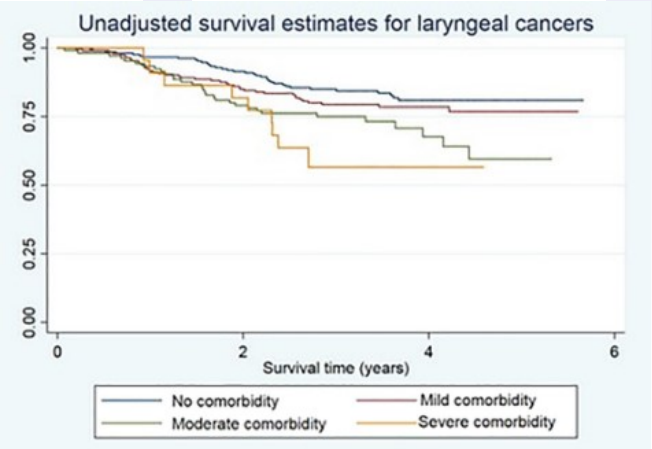


O'Flaherty L, Shnyder SD *et al*. (2019). Tumor growth suppression using a combination of taxol-based therapy and GSK3 inhibition in non-small cell lung cancer. *PLOS One*.

Comorbidity in head and neck cancer

People with head and neck cancer have higher comorbidity levels but it remains unclear if pre-treatment comorbidity is an independent prognosticator in head and neck cancer.

Survival analyses were performed using data from participants in a UK multicentre cohort study with cancers of the oral cavity (n = 668), oropharynx (n = 1074), and larynx (n= 530). Survival analyses were incrementally adjusted for age, sex, marital status, income, education, stage, alcohol, and smoking.

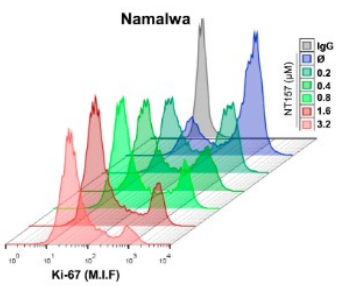


After adjusting for demographic, clinical, and behavioural confounders, higher baseline comorbidity was associated with reduced overall survival. Our findings suggest that comorbidity is an independent prognosticator for overall survival in head and neck cancer. Comorbid illnesses should be considered in the assessment and treatment planning of people with head and neck cancer.

Schimansky S, Lang S *et al*. (2019). Association between comorbidity and survival in head and neck cancer: Results from Head and Neck 5000. *Head & Neck*. 41(4), pp. 1053-1062.

Targeting IGF1R/IRS1 in acute lymphoblastic leukemia

IGF1R/IRS1 signalling is activated in acute lymphoblastic leukemia (ALL) and can be targeted by the pharmacological inhibitors NT157 (IGF1R-IRS1/2 inhibitor) and OSI-906 (IGF1R/IR inhibitor). Here we investigate the cellular and molecular effects of NT157 and OSI-906 in ALL cells. NT157 and OSI-906 treatment reduced viability, proliferation and cell cycle progression in ALL cell lines. Similarly, in primary samples of patients with ALL, both OSI-906 and NT157 reduced viability, but only NT157 induced apoptosis. NT157 and OSI-906 did not show cytotoxicity in primary samples from healthy donor. NT157 and OSI-906 significantly decreased Jurkat cell migration, but did not modulate Namalwa migration. Consistent with the more potent effect of NT157 on cells, NT157 significantly modulated expression of 25 genes related to the MAPK signalling pathway in Jurkat cells, including oncogenes and tumour suppressor genes. Both compounds inhibited mTOR and p70S6K activity, but only NT157 inhibited AKT and 4-EBP1 activation. In summary, in ALL cells, NT157 has cytotoxic activity, whereas OSI-906 is cytostatic. NT157 has a stronger effect on ALL cells, and thus the direct inhibition of IRS1 may be a potential therapeutic target in ALL.



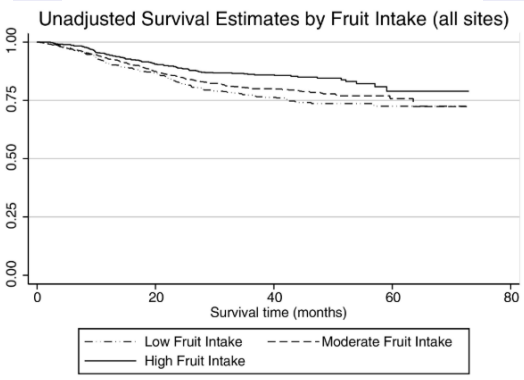
Alves, AP, Fernandes JC… Ridley AJ *et al*. (2019). IGF1R/IRS1 targeting has cytotoxic activity and inhibits PI3K/AKT/mTOR and MAPK signaling in acute lymphoblastic leukemia cells. *Cancer Letters*. 456, pp59-68.

NT157 and OSI-906 reduce cell proliferation and delay cell cycle progression in Namalwa cell lines. Ki-67 mean fluorescence intensity was determined by flow cytometry after incubation treated with NT157.

Dietary behaviours and survival with head and neck cancer

The association between diet and head and neck cancer (HNC) survival is unclear. Cox proportional hazard models measured the association between fruit, vegetable, and deep-fried food intake and HNC overall survival adjusting for clinical, social and lifestyle variables including smoking, alcohol, and HPV status.

Fruit and vegetable intake and improved survival were associated in minimally adjusted analyses. Following adjustment for smoking and alcohol consumption, the association with survival disappeared for fruit and attenuated for vegetables. We observed no association between survival and deep-fried food intake in minimally adjusted or fully adjusted analyses. We conclude that vegetable intake and HNC survival are modestly associated, with some confounding by tobacco and alcohol consumption.



Lang S *et al*. (2019). Dietary behaviors and survival in people with head and neck cancer: Results from Head and Neck 5000. *Head and Neck*. Early view published online 30 January 2019.

Inhibition of orthotopic xenograft tumour growth

The overall survival for patients with primary glioblastoma is very poor. Glioblastoma contains a subpopulation of glioma stem cells (GSC) that are responsible for tumour initiation, treatment resistance and recurrence. PPARα is a transcription factor involved in the control of lipid, carbohydrate and amino acid metabolism and is overexpressed in GSC compared to foetal neural stem cells. To investigate the role of PPARα in GSC, we knocked down its expression using lentiviral transduction with short hairpin RNA (shRNA). Transduced GSC were tagged with luciferase and stereotactically xenografted into the striatum of NOD-SCID mice. Imaging showed that knockdown (KD) of PPARα reduced the tumourigenicity of GSC *in vivo*. PPARα-expressing control GSC xenografts formed invasive histological phenocopies of human glioblastoma, whereas PPARα KD GSC xenografts failed to establish viable intracranial tumours. PPARα KD GSC showed significantly reduced proliferative capacity and clonogenic potential *in vitro* with an increase in cellular senescence. In addition, PPARα KD resulted in significant downregulation of the stem cell factors c-Myc, nestin and SOX2. This was accompanied by downregulation of the PPARα-target genes and key regulators of fatty acid oxygenation ACOX1 and CPT1A, with no compensatory increase in glycolytic flux. These data establish the aberrant overexpression of PPARα in GSC and demonstrate that this expression functions as an important regulator of tumourigenesis. We conclude that targeting GSC PPARα expression may be a therapeutically beneficial strategy with translational potential as an adjuvant treatment.

Haynes HR, Scott HL *et al*. (2019). shRNA-mediated PPARα knockdown in human glioma stem cells reduces in vitro proliferation and inhibits orthotopic xenograft tumour growth. *The Journal of Pathology*. 247(4), pp422-434.

Collaborating with the nuclear medicine community

The South West Nuclear Hub (the Hub), funded by a HEFCE Catalyst Fund grant, facilitates the University of Bristol's leading role in co-ordinating and growing regional nuclear energy activities. The Hub is an umbrella for civil nuclear energy related research, innovation and teaching activities at Bristol.

Launched in September 2016, it acts as a focal point for nuclear energy research and teaching at Bristol, providing a common collaboration space for academics across the University. Externally, it draws together academic, industrial and government institutions to provide an efficient interface for research and development capability across the south west region.

Via the Hub, UoB has developed a nuclear energy research, innovation and teaching strategy which includes ambitious plans for growth both in terms of activity and new facilities. Since 2015 the Hub has been home to a unique interdisciplinary MSc programme in Nuclear Science and Engineering, a research-focused postgraduate programme with significant industry input.

Our objectives include:

- Providing a link between Higher Education, Nuclear Industry and Government sectors
- Creating a single door for the nuclear industry to access and form partnerships in academic research and teaching in the region
- Joining capability, activity and resource
- Fostering an integrated mixture of multidisciplinary students, staff and experts
- Increasing the number and quality of people trained in nuclear energy and related fields
- Increasing industrial investment in research and teaching
- Shaping the direction of regional and national nuclear energy-related research and teaching to ensure it best meets industry needs
- Establishing a joint knowledge base between academia and industry
- Facilitating the transfer of relevant skills and knowledge
- Delivering innovative underpinning science, engineering solutions and technologies that have a positive impact on the economy and society

Nuclear medicine

The Hub's academic community is able to offer competencies and expertise to the medical community. Focused mainly around equipment development, our researchers have innovative technologies, which could be tailored for the needs of various medical applications.

In particular Dr **John Day** from the Interface Analysis Centre (IAC) had some of his work going to clinical trials, including:

- **Development of probes for cancer detection**
- **Use of Raman spectroscopy for lymphoma detection**
- **Kidney perfusion monitoring after transfusion using fibre optics**

Others, such as Dr **Jaap Velthuis** (Physics) can offer:

- **Cameras-driven methodologies to monitor and adjust the dosimetry in real time**
- **Independent monitoring of beams used to treat tumours in order to adjust in real time localisation and dosimetry of these beams**

If you have an idea or project that aspects of nuclear medicine could contribute to, contact enquiries@southwestnuclearhub.ac.uk

SOUTH WEST NUCLEAR HUB

Data science capabilities

The University of Bristol and LV= General Insurance (LV=GI) have created a new partnership with the aim of working together to make advancements in the field of data science by sharing knowledge, skills and opportunities. As part of the partnership, LV=GI will establish a team of data scientists and engineers who will be based at the University, working closely with the Faculties of Engineering and Social Sciences & Law, and the Jean Golding Institute (JGI) for Data Science and Data Intensive Research. The teams will carry out research and development projects to better understand the possibilities presented by machine learning and AI in the insurance sector. Collaborating with the University's social scientists, the teams will work to better understand the societal challenges and opportunities of digital technologies.

Vitamin D and prostate cancer

Evidence from studies on prostate cancer progression have identified vitamin D to be a potentially important nutrient. However, the World Cancer Research Fund and American Institute for Cancer Research have reported the quality of this evidence to be limited and warrant further investigation. We put together a protocol on how we will perform a systematic review of the literature in human and animal studies. We will search the electronic databases MEDLINE, EMBASE, PubMed, and BIOSIS Citation Index without restrictions on year of publication or language. We will extract data from observational and experimental studies examining two inter-linked pathways in the relationship between vitamin D and prostate cancer progression: (1) vitamin D and testosterone, and (2) testosterone and prostate cancer progression. We focus on testosterone as its actions form a potentially novel intermediate mechanism that was identified via our online literature mining tools. The outcomes of interest include incidence or prevalence of prostate cancer, measures of prostate cancer progression (including biochemical recurrence, local, or distal metastases), and prostate cancer-specific mortality. We will assess study quality and the level of certainty of the evidence. We will analyse data where possible.

To our knowledge, this will be the first systematic synthesis of the evidence underpinning the vitamin D-testosterone-prostate cancer mechanistic pathway. The results of the review may inform future research, intervention trials, and public health messages.

Robles LA, Dawe K *et al*. (2019). Does testosterone mediate the relationship between vitamin D and prostate cancer? A systematic review and meta-analysis protocol. *Systemic Reviews*. 8(1), p52.

Systemic metabolism, its regulators, and cancer

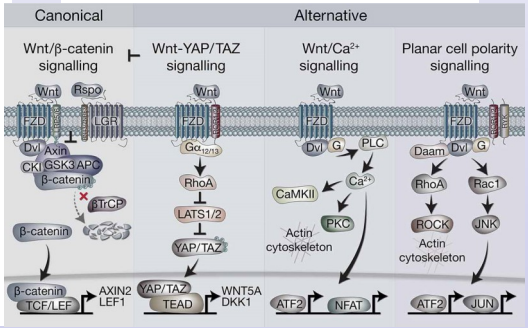
There is a resurgence of interest in cancer metabolism, primarily in its resetting within malignant cells. Metabolism within cells has always been a tightly regulated process; central to these regulators is the insulin/insulin-like growth factor (IGF) system that has integrated the control of tissue growth with metabolic status. Oncological interest in the main systemic metabolic regulators subsided when pharmaceutical strategies designed to treat cancers failed in the clinic; but, during that period, an explosion of new information from genetics revealed the complexity and heterogeneity of advanced cancers and helped explain the problems of managing cancer at this stage. Now evidence implies that the setting of the internal environment determines whether cancers progress to advanced disease and metabolic status is an important component of this. We are in the midst of an epidemic of metabolic disorders and there is much research into strategies for controlling metabolism; integrating these suggests new possibilities for cancer prevention.

Holly JMP *et al*. (2019). Systemic metabolism, its regulators, and Cancer: Past mistakes and future potential. *Frontiers in Endocrinology*.

Neuroblastoma and Wnt Signaling

The neural crest (NC) comprises a multipotent cell population which will specify diverse cells and tissues, including craniofacial cartilage and bones, melanocytes, the adrenal medulla and the peripheral nervous system. These cell fates are known to be determined by gene regulatory networks (GRNs) acting at various stages of NC development, such as induction, specification, and migration. Although transcription factor hierarchies and some of their interplay with morphogenetic signalling pathways have been characterised, the full complexity of activities required for regulated development remains uncharted. Deregulation of these pathways may contribute to tumorigenesis, as in the case of neuroblastoma, a frequently lethal embryonic cancer thought to arise from the sympathoadrenal lineage of the NC. We utilise the next generation sequencing data from neuroblastoma cells and tumours to evaluate the possible influences of Wnt signalling on NC GRNs and on neuroblastoma cell lineages. We propose that Wnt signalling is a major determinant of regulatory networks that underlie mesenchymal/neural crest cell (NCC)-like cell identities through PRRX1 and YAP/TAZ transcription factors. Furthermore, Wnt may also cooperate with Hedgehog signalling in driving proneural differentiation programmes along the adrenergic (ADRN) lineage. Elucidation of Signalling Regulatory Networks can augment and complement GRNs in characterising cell identities, which may in turn contribute to the design of improved therapeutics tailored to primary and relapsing neuroblastoma.

Szemes M, Greenhough A and Malik K (2019). Wnt Signaling Is a Major Determinant of Neuroblastoma Cell Lineages. *Frontiers in Molecular Neuroscience*.



Overview of canonical and alternative Wnt signaling pathways

Environmental exposures and ALL

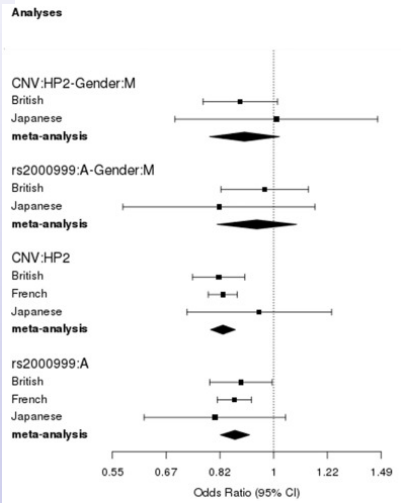
The aetiology of childhood acute lymphoblastic leukaemia (ALL) is unclear. Genetic abnormalities have been identified in a number of cases, but alone are not sufficient for leukaemic transformation. Various environmental exposures have been suggested to alter risk of childhood ALL. DNA methylation patterns can be influenced by environmental exposures, and are reported to be altered in ALL, suggesting a potential mediating mechanism between environment and ALL disease risk. We investigated the overlap between exposure-associated and disease-associated methylation change. Genome-wide DNA methylation changes in response to possible ALL-risk exposures (e.g. radiation exposure, alcohol intake) were investigated in a sub-population of the ALSPAC cohort using an epigenome-wide association study, and compared to a list of ALL disease-associated methylation changes compiled from published data. Probability tests suggested that the number of directionally concordant gene methylation changes observed in ALL disease and in response to exposures were not due to chance.

Timms JA *et al*. (2019). Exploring a potential mechanistic role of DNA methylation in the relationship between in utero and post-natal environmental exposures and risk of childhood acute lymphoblastic leukaemia. *International Journal of Cancer*.

Genetic determinants of circulating haptoglobin

Haptoglobin (Hp) is a major plasma acute-phase glycoprotein. The main biological function of Hp is to bind free haemoglobin (Hb) to prevent the loss of iron and subsequent kidney damage following intravascular hemolysis; it may also have immunomodulatory properties. In humans Hp can have different structures - HP1 and HP2 - and variants may influence the susceptibility and/or outcome in several diseases, for example diabetes mellittus, atherosclerosis and cardiovascular disease, malignancies and infections. The different structures differ in their ability to clear Hb and may have may have other functional differences relating to protection from Hb-induced oxidative stress (an imbalance of anti- and pro-oxidative reactions in favor of the pro-oxidant, thus limiting the capacity of a biological system to detoxify the reactive intermediates or to repair the resulting damage).

A single nucleotide polymorphism, rs2000999, has also been associated with serum Hp level. In a meta-analysis of three studies from England, France and Japan, with a combined sample size of 1210 participants, we show that rs2000999's effect on circulating Hp level is independent of HP1 and HP2. The combined use of rs2000999 and HP1 and HP2 can be an important genetic epidemiological tool to discriminate between the two potential mechanisms underlying differences between HP1 and HP2.



Kazmi N et al. (2019). Genetic determinants of circulating haptoglobin concentration. *Clinica Chimica Acta*. 494, pp138-142.

ELIZABETH BLACKWELL FUNDING

EBI Research for Mental Health in Young People Challenge scheme
Funding available for challenge-led research projects addressing mental health in young people, with particular emphasis on University of Bristol students.

Closing date: 11 June 2019

EBI Translational Acceleration and Knowledge Transfer (TRACK)
This scheme provides funding to support health related translational projects.

Closing date: 13 June 2019

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.).

The deadline for applications is 30 April and 31 October each year.

EBI Bridging Funds for Research Fellows
This scheme is designed to support a small number of academic staff at the University of Bristol who currently hold an externally funded research fellowship. Applications accepted on a rolling basis.

The Elizabeth Blackwell Institute for Health Research is officially a member of **Equality, Diversity and Inclusion in Science and Health**, or EDIS, an initiative set up by the Wellcome Trust, the Crick Institute and GSK.

FUNDING OPPORTUNITIES

Would you like to receive timely, tailored funding opps information?
Do you want to know what funding opportunities come up in your research area?
Get tailored funding alerts?

Research Professional provides access to an extensive database of funding opportunities, and can send out tailored alerts based on keywords that you input, ensuring that the funding alerts you receive are the ones you want to hear about. UoB staff and students have **FREE** online access to the database from any device – once you've registered then you can view upcoming funding opportunities from home or away, not just while on the University network.

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**, an easy process that will take just a few minutes to set up through the use of keywords
- **Save searches and bookmarks** - store items of interest for future reference, download and email to colleagues
- **Sign up for higher education news bulletins** – want to hear about what is going on in the broader HE environment? Latest news on the REF, setting up of UKRI etc? Sign up for the 8am playbook or the Research Fortnight news publications and stay up to date with the latest news.

Alternatively, a full calendar of funding opportunities for neuroscience research has already been set up and is available online. Subscribing to the calendar will place the entries in your own calendar, which will automatically update according to pre-specified search criteria. 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 Faculty Research Directors and/or School Research Directors, and **are available on the Research Development website**.

American Association for Cancer Research and Cancer Research UK
AACR-CRUK transatlantic fellowships

Closing date: 25-Jul-19 Award amount: £300,000

These enable US and UK postdoctoral researchers to develop their independent career in the UK and US, respectively. Applications may be from any area of CRUK's remit except clinical trials.

National Cancer Institute
Physical sciences-oncology network – physical sciences-oncology projects

Closing date: 30-Jul-19 Award amount: USD 2.5 million

These foster the convergence of physical sciences approaches and perspectives with cancer research to advance the understanding of cancer biology and oncology by forming transdisciplinary teams of physical scientists, cancer biologists and physician scientists.

Cancer Research UK
Multidisciplinary project award

Closing date: 01-Aug-19 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 science, molecular and tissue engineering and regenerative medicine are welcomed.

Cancer Research UK
Career development fellowship

Closing date: 20-Aug-19 Award amount: £ unspecified

This enables scientists without a salaried independent position to set up their own independent research group in any area of CRUK's funding remit, with the exception of drug discovery and clinical trials. Postdoctoral and early-career researchers may apply.

Cancer Research UK
Programme Foundation Awards

Closing date: 22-Aug-19 Award amount: £1.5 million

These enable cancer researchers with eight to 14 years' experience post-PhD to establish or further develop their independent research group. Research proposals should address the following areas: basic biological research relating to cancer; preclinical studies that will generate biological data to underpin therapeutic development; biomarkers; imaging; radiotherapy; the application of engineering and physical sciences to cancer.

Cancer Research UK
Pioneer Award

Closing date: 03-Sep-19 Award amount: £200,000

This supports innovative, higher-risk ideas that could revolutionise the understanding of cancer. Early-stage ideas from any discipline are welcomed, including: molecular and cellular biology; optimising treatments and diagnostics; device and software development; behavioural and population studies.

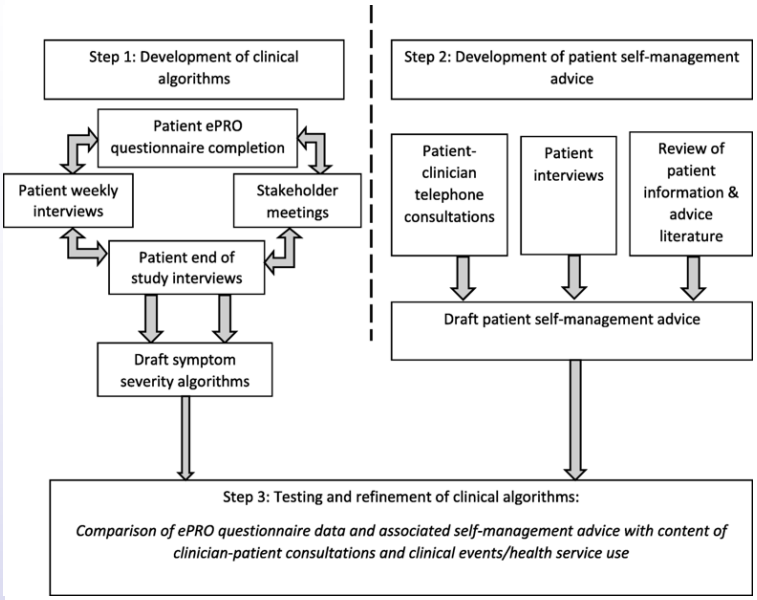
FEATURED PUBLICATION

Developing a real-time electronic symptom monitoring system for patients after discharge following cancer-related surgery

Avery KNL, Richards HS, Portal A, Reed T, Harding R, Carter R, Bamforth L, Absolom K, Francischetto EO'C, Velikova G & Blazeby JM (2019). *BMC Cancer*. 19:463

Patients undergoing major cancer surgery frequently require post-acute care for complications and adverse effects. Enhanced recovery after surgery programmes mean that patients are increasingly discharged home earlier. Symptom/complication detection post-discharge is sub-optimal. Systematic patient monitoring post-discharge following surgery may be optimally achieved through routine electronic patient-reported outcome (ePRO) data capture. ePRO systems that employ clinical algorithms to guide management of patients and automatically alert clinicians of clinically-concerning symptoms can improve patient outcomes and decrease hospital admissions. ePRO systems that provide individually-tailored self-management advice and integrate live ePRO data into electronic health records (EHR) may also advance personalised health and patient-centred care. This study aims to develop a hospital EHR-integrated ePRO system to improve detection and management of complications post-discharge following cancer-related surgery.

The ePRO system was developed in two phases: (1) Development of a web-based ePRO symptom-report from validated European Organisation for Research and Treatment of Cancer (EORTC) questionnaires, clinical opinion and patient interviews, followed by hospital EHR integration; (2) Development of clinical algorithms triggering symptom severity-dependent patient advice and clinician alerts from: (i) prospectively-collected patient-completed ePRO symptom-report data; (ii) stakeholder meetings; (iii) patient interviews. Patient advice was developed from: (i) clinician-patient telephone consultations and patient interviews; (ii) review of hospital patient information leaflets (PIL) and patient support websites.



Telephone consultations, patient interviews and review of PILs and patient support websites identified 4 themes to inform self-management advice. Comparisons between ePRO symptom-report data, telephone consultations and clinical events/outcomes further refined clinical algorithms. A hospital EHR-integrated ePRO system that alerts clinicians and provides patient self-management advice has been developed to improve the detection and management of problems and complications after discharge following surgery. An ongoing pilot study will inform a multicentre randomised trial to evaluate the effectiveness of the ePRO system compared to usual care.

Phase 2: Development and testing of clinical algorithms to guide patient management by symptom severity

Cancer Network

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