



**In this issue:** Cost-effectiveness of whole-exome and whole-genome sequencing • Collaboration with Oxford School of Public Health • Workshop on economic modelling of Alzheimer's disease • Global income distribution Spotlight on Matthew Little • Latest staff news, seminars, presentations and publications

## Are whole-exome and whole-genome sequencing approaches cost-effective?

**Project team:** Katharina Schwarze, James Buchanan, Sarah Wordsworth

The first human genome sequence was produced in 2003, costing between \$500 million and \$1 billion. For many years, the cost of sequencing an entire genome remained prohibitively expensive for routine clinical use, but since 2008, when next-generation sequencing approaches entered the research setting, costs have fallen. These approaches allow either the whole genome (via whole genome sequencing (WGS)) or parts of it (via whole-exome sequencing (WES)) to be sequenced faster and more comprehensively than ever before, making the clinical application of sequencing more feasible. Demand is now increasing for evidence on the costs and health outcomes associated with these technologies to ensure that they are not merely an expensive add-on to patient care.

HERC researchers recently undertook a systematic review to summarise the evidence in the health economic literature on the use of WES and WGS in a clinical setting. This review, published in *Genetics in Medicine*, identified 36 studies published between 2005-2017, and found that the cost of a single test ranged from £382-£3,592 per patient for WES, and from £1,312-£17,243 per patient for WGS. There was no evidence that the cost of WES was falling over time, and only limited evidence that the cost of WGS was decreasing, contrary to the widely held belief that sequencing costs are falling rapidly in clinical settings.

The most commonly utilised outcome measure was diagnostic yield, with few studies using outcome measures such as survival or quality of life. Furthermore, in only a few individual patients was the provision of an accurate diagnosis from WES/WGS followed through to identify changes in clinical investigations and treatment. Only eight publications were full economic evaluations, and of these, only five produced evidence that WES or WGS might be cost-effective.

The results of our review indicated that the current health economic evidence base to support the more widespread use of WES and WGS in clinical practice is very limited. We hope that future studies at HERC will contribute to this evidence base.

For more information: **HERC**



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# HERC's collaboration with the Oxford School of Public Health

**Placement coordinator:** Filipa Landeiro

Since December 2013, HERC has been offering placements to Public Health Registrars and to Foundation Doctors on their public health rotations as part of a collaboration between HERC researcher Filipa Landeiro and the Oxford School of Public Health. So far, HERC has hosted 25 Foundation Doctors and seven Public Health Registrars who have worked on projects on a wide variety of conditions: hip fractures, diabetes, stroke, chronic kidney disease, cardiovascular disease, ischaemia, child anxiety, social isolation and loneliness, delayed discharges, osteoarthritis, dementia and vertebral fractures. The medical doctors have contributed by undertaking primary data collection and

analysis (including analysis of big datasets such as Clinical Practice Research Datalink), systematic reviews, audits, cost-effectiveness analyses and economic modelling studies. These projects have resulted in many publications, and this work has also been presented at multiple international conferences. Some of these projects are described below. We are committed to continuing to provide medical doctors with insights into health economics during their training.

For more information: **HERC**



## Ellen Nuttall-Musson, Paige Barrows and Sihao Zhao

Ellen and Paige spent four months at HERC in 2016 during their second year of training as Foundation Doctors. During that time they worked with Filipa, José Leal and Alastair Gray on two systematic literature reviews; one on interventions aimed at reducing social isolation and the other on interventions aimed at alleviating loneliness. The protocol of these reviews has been published in *BMJ Open* (see link below) and Sihao, a Foundation Doctor on her public health rotation, is currently helping to finalise the two manuscripts for publication. In addition, Ellen worked on a model which aimed to determine how interventions to alleviate social isolation could help reduce the number of days of delayed discharges for older hip fracture patients.

Link to publication: **HERC**



## Emily Dobell and Kate Nichol

Emily, a Public Health Registrar, and Kate, a second year Foundation Doctor on a public health rotation, undertook placements at HERC in 2015. During this time, they worked with Ramón Luengo-Fernández on the health economic aspects of studies run by the Centre for the Prevention of Stroke and Dementia (CPSD), primarily the Oxford Vascular Study. As part of their work they collected data on the use of health services among patients who had experienced limb and visceral ischaemia. This work led to a publication in the *European Journal of Vascular and Endovascular Surgery* (see link below). They also carried out an audit into the adequacy of capacity assessments for patients with cognitive impairments on the Surgical Assessment Unit at the John Radcliffe Hospital under the supervision of Associate Professor Sarah Pendlebury (CPSD). These results were presented by both Emily and Kate at the 12th European Union Geriatric Medicine Society Congress in Lisbon. Finally, they collected data on medical fitness for discharge for hip fracture patients enrolled in the Fracture Free study alongside Filipa.

Link to publication: **HERC**



## Amarnath Marthi and Christopher Rooney

Amar and Chris spent four months of their foundation training in public health in 2014-15 working with HERC researcher Bobby Mihaylova, and William Herrington and Richard Haynes at the Clinical Trial Service Unit, investigating the association between Fibroblast Growth Factor-23 (FGF23) level and cardiovascular risk. They conducted a systematic review of prospective studies and, following standardisation, a meta-analysis of associations. This study has just been published in the *Journal of the American Society of Nephrology*. In addition, Amar and Chris worked on the Fracture Free study with Filipa, interviewing patients who had been admitted to the John Radcliffe Hospital with a hip fracture and collecting additional data from the patients' medical records, such as ICD-10 and procedure codes.

For more information: **HERC**

## Workshop on economic modelling of Alzheimer's disease

**Project team:** Filipa Landeiro, Alastair Gray

In February 2018 the "Real world Outcomes across the Alzheimer's Disease spectrum for better care: Multi-modal data Access Platform" (ROADMAP) Health Economics team convened a workshop in Paris entitled "Modelling the economic value of Alzheimer's disease interventions: how far have we come, and what next?". This provided an opportunity to discuss the specifications of an economic model on Alzheimer's disease (AD) with invited experts and representatives from Health Technology Assessment organisations.

After an introduction from Alastair, Anders Wimo and Bengt Winblad (Karolinska Institute), Colin Green (University of Exeter) and Peter Neumann (Tufts Medical Center and Tufts University) presented their research on modelling of AD.

ROADMAP members discussed the proposed structure of a future economic model before Filipa presented the results of two systematic literature reviews which will inform future modelling. Finally, mortality in AD, capturing uncertainty, and issues relating to data collection were



discussed. The workshop findings will form the basis of a paper on specifications for an economic model in AD.

# How polarised is the global income distribution?

**Project lead:** Laurence Roope

Inequality and globalisation have become prominent political themes in recent years. As the world has become more interconnected, there has been increasing interest not only in domestic inequality, but also in the global distribution of income. Although inequality has increased in many countries in recent decades, many studies have found that global inequality has decreased – at least according to relative measures such as the Gini coefficient.

A recent HERC study in collaboration with the United Nations University World Institute for Development Economics Research (UNU-WIDER), published in *Economics Letters*, has provided the first estimates of the extent to which the global income distribution is bipolarised. Bipolarisation, though related to inequality, is a distinct concept. It essentially captures the presence or absence of a middle class – often regarded as being important to a healthy and stable society. Many previous studies have investigated bipolarisation within individual countries. We used country-level quantile share data from the World Income Inequality Database (managed by UNU-WIDER) to construct global income distributions for six years (1975, 1985, 1995, 2000, 2005, 2010), then estimated bipolarisation using both ‘relative’ and ‘absolute’ measures. Relative measures focus on proportionate

differences in income, while absolute measures focus on absolute differences. For example, if everyone’s income doubles, relative bipolarisation remains unchanged but absolute bipolarisation increases.

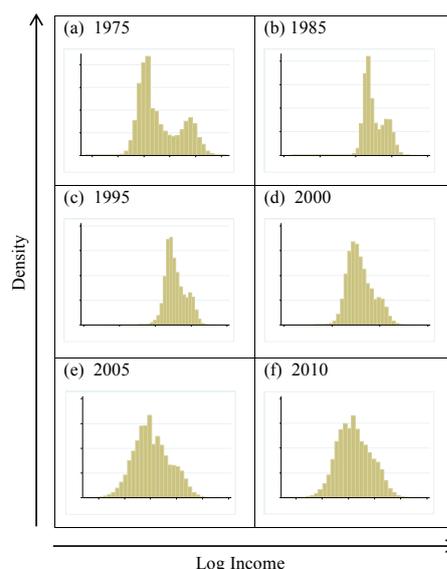
We found that the global (log) income distribution in 1975 was a bi-modal normal distribution (see Panel (a) in the figure). Over the decades this bi-modality became less pronounced until, by 2010 (Panel (f)), the distributions were approximately normal. Consistent with this trend, we found that bipolarisation has decreased steadily and substantially according to relative measures. However, it has increased according to absolute measures.

Our results are consistent with a combination of decreased income gaps between countries (causing polarisation to have declined in relative terms), and high growth (causing polarisation to have increased in absolute terms). While policymakers would conclude that polarisation has declined, for many people the increased absolute income differences may be more salient.

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For more information:

“ While policymakers would conclude that polarisation has declined, for many people the increased absolute income differences may be more salient ”



Global Log Income Histograms 1975–2010

## Spotlight on MATTHEW LITTLE



I joined HERC as a Researcher in April 2017 to conduct an economic evaluation as part of the NIHR funded Laminar Airflow in Severe Asthma for Exacerbation Reduction (LASER) trial. LASER investigated whether the nocturnal use of a new machine that reduces the number of allergy particles in the air is effective in reducing the frequency of severe asthma attacks in patients with severe allergic asthma.

I am now working on the analysis of the British Heart Foundation/ Medical Research Council funded Arterial Revascularisation Trial (ART) and the NIHR funded All Adenomas study (AA). The ART study is the largest randomised comparison of the use of single and bilateral internal mammary arteries during coronary artery bypass graft surgery ever conducted, with patients being followed for up to 10 years after

surgery. The AA study will provide evidence to support an update of the guidelines for monitoring people with any type of bowel polyp. I am also investigating the potential cost implications of these interventions for the NHS.

Prior to joining HERC, I was completing a PhD in the Health Economics Group at Newcastle University. My PhD looked at the relationship between financial stability and individual health: I used British household longitudinal data to analyse how deviations between ex-ante financial expectations and their ex-post realisations are associated with individual health, and investigated how financial expectation data could improve models of individual health investment.

My short time at HERC has already allowed me to be involved in important studies in their respective field and I am very happy to be a part of them.

## Staff News – Welcome to:



**Liz Morrell** joined HERC as a Senior Researcher in February 2018, from the Centre for the Advancement of Sustainable Medical Innovation (CASMI). Her work at CASMI focused on the health economics of cancer drugs, exploring the impact of technology appraisal processes on patient access to drugs, and the value that society places on treating cancer relative to other conditions. Liz is working with Sarah Wordsworth and colleagues, initially on a series of discrete choice experiments exploring clinician and public attitudes to antibiotics and antimicrobial resistance.



**Charlotte Colam** is a foundation doctor on a 4-month rotation in HERC. She will be working with Filipa Landeiro and Alastair Gray on the ROADMAP project on the specifications for an economic model for Alzheimer's disease.



**Sihao Zhao** is a 2nd year foundation doctor on a 4-month rotation in HERC. She will be working with Filipa Landeiro and José Leal on the Fracture Free Study estimating the healthcare costs of hip fractures.

Additionally, Sihao will also be working with Filipa Landeiro on a systematic review of interventions aimed at alleviating social isolation in older people.

## Congratulations to:



**Seamus Kent** on successfully defending his DPhil entitled "Hospital use and costs in relation to body mass index in over 1 million middle-aged and older women in England" in January 2018.



**Matthew Little** who also successfully defended his PhD entitled "Essays on the Relationship between Financial Expectations and Individual Health" at the University of Newcastle in March 2018.



**Mandy Fruin** who received a Merit Award in April 2018 for her outstanding contribution to HERC through a period of relocation and time without an administrative manager in 2017.

**Brett Doble**, **Seamus Kent** and **Liz Stokes** who were promoted to Senior Researchers in April 2018.



## HERC Seminars

Convenor: **Brett Doble**

HERC runs a series of seminars with invited speakers from the health economics community who talk on a wide range of applied and methodological topics.

Details of forthcoming talks can be found on the HERC website: <http://www.herc.ox.ac.uk>. To be added to our mailing list for future seminars, email us at [herc@dph.ox.ac.uk](mailto:herc@dph.ox.ac.uk)

In February, **Dr Hareth Al-Janabi**, Institute of Applied Health Research, University of Birmingham visited to present his work on: *Carer and family effects in economic evaluation: an overview of recent research*.

In March, **Dr Monica Hernandez Alava**, Reader in Health Econometrics, HEDS, ScHARR, University of Sheffield came to HERC to present: *EQ-5D-3L vs EQ-5D-5L: what are the consequences for cost-effectiveness in the UK?*

In April, **Professor Martin Gulliford**, from the Department of Primary Care & Public Health Sciences, King's College London gave a seminar on: *Using electronic health records in health economic modelling studies*.

## Presentations by members of HERC

**ROADMAP Workshop at the International Pharmacoeconomic Conference on Alzheimer's Disease**

Paris, France, February 2018

**Alastair Gray**

*Presentation of the ROADMAP project*

**Filipa Landeiro**

*Resources used and costs incurred by people with dementia and their caregivers*

*Quality of life of people with dementia*

**NiHR Health Protection Research Unit in Gastrointestinal Infections: Annual Scientific Meeting**

Norwich, March 2018

**Mara Violato**

*Family income and exposure to norovirus in childhood: findings from the UK Millennium Cohort Study*

*Congratulations to Mara who was awarded the 'Best Plain English Poster' prize*

**University of Cantabria**  
Santander, Spain, March 2018

**Filipa Landeiro**

*The challenges of collecting patient level data for observational studies*

*The impact of social isolation of older patients on delayed hospital discharges*

**European Causal Inference Meeting**

Florence, Italy, April 2018

**Joel Smith & Alastair Gray**

*From Average Treatment Effects to the Identification of Treatment Responders*

## Conference registration now open: Resource Allocation in Personalised Medicine

HERC will be co-hosting a conference with the Centre for Personalised Medicine and the Ethox Centre, University of Oxford on the 19th June 2018. The title of this conference is *Resource Allocation in Personalised Medicine: Evaluation, Translation & Ethics*. Confirmed speakers include **Dr Tom Fowler** (Deputy Chief Scientist, Director of Public Health, Genomics England), **Ellen Graham** (Deputy Director – Genomics, NHS England), **Dr Dean Regier** (School of Population & Public Health, University of British Columbia), **Professor Katherine Payne** (Professor of Health Economics, University of Manchester), **Professor Christian Munthe** (Professor of Practical Philosophy, University of Gothenburg) and **Dr Jayne Spink** (Chief Executive, Genetic Alliance UK). For further information, and to register, please click on the link below.

<http://www.well.ox.ac.uk/cpm/resource-allocation-in-personalised-medicine-conference>



## Publications

1. Beard DJ, Rees JL, et al. [includes **Rombach I, Gray A**]. *Arthroscopic subacromial decompression for subacromial shoulder pain (CSAW): a multicentre, pragmatic, parallel group, placebo-controlled, three-group, randomised surgical trial*. *Lancet*. 2018. 391:329–38. doi:10.1016/S0140-6736(17)32457-1
2. Benedetto U, Altman DG, et al. [includes **Gray AM**]. *Incidence and clinical implications of intraoperative BITA grafts conversion. Insights from the Arterial Revascularization Trial (ART)*. *Journal of Thoracic and Cardiovascular Surgery*. 2018. doi:10.1016/j.jtcvs.2018.02.012
3. Burns RM, Wolstenholme J, et al. *Economic analysis of oral dexamethasone for symptom relief of sore throat: the UK TOAST study*. *BMJ Open*. 2018. 8:e019184. doi:10.1136/bmjopen-2017-019184
4. Dakin H, Abel L, et al. [includes **Burns R**]. *Review and critical appraisal of studies mapping from quality of life or clinical measures to EQ-5D: an online database and application of the MAPS statement*. *Health and Quality of Life Outcomes*. 2018. 16(1):31. doi:10.1186/s12955-018-0857-3
5. Dakin HA, Gray A. *Decision-making for healthcare resource allocation: Joint versus separate decisions on interacting intervention*. *Medical Decision Making*. 2018. 38:476–486. doi:10.1177/0272989X18758018
6. Dritsaki M, Rivero-Arias O, et al. [includes **Gray A**]. *What do we know about managing Dupuytren's Disease cost-effectively? BMC Musculoskeletal Disorders*. 2018. 19:34. doi:10.1186/s12891-018-1949-2
7. Landeiro F, Walsh K, et al. [includes **Ghinai I, Mughal S, Nye E, Wace H, Wolstenholme J, Gray AM**]. *Measuring quality of life of people with predementia and dementia and their caregivers: a systematic review protocol*. *BMJ Open*. 2018. 8:3. doi:10.1136/bmjopen-2017-019082
8. Luengo-Fernandez R, Howard DPJ, et al. [includes **Nichol K, Dobell E**]. *Hospital and institutionalisation care costs after limb and visceral ischaemia benchmarked against*

- stroke: long-term results of a population-based cohort study*. *European Journal of Vascular and Endovascular Surgery*. 2018. doi:10.1016/j.ejvs.2018.03.007
9. Murphy J, Pritchard MG, Cheng LY, Janarthanan R, Leal J. *Cost-effectiveness of enhanced recovery in hip and knee replacement: a systematic review protocol*. *BMJ Open*. 2018. 8:e019740. doi:10.1136/bmjopen-2017-019740
10. Noonan K, Burns R, Violato M. *Family income, maternal psychological distress and child socio-emotional behaviour: longitudinal findings from the UK Millennium Cohort Study*. *SSM Population Health*. 2018. 4:280–290. doi:10.1016/j.ssmph.2018.03.002
11. Pegington M, Adams JE, et al. [includes **Wolstenholme J**]. *Recruitment to the "Breast-Activity and Healthy Eating after Diagnosis" (B-AHEAD) Randomized Controlled Trial*. *Integr Cancer Ther*. 2018. 17:131–137. doi:10.1177/1534735416687850
12. Price CP, Wolstenholme J, et al. *Translational health economics: The key to accountable adoption of in vitro diagnostic technologies*. *Health Serv Manage Res*. 2018. 31:43–50. doi:10.1177/0951484817736727
13. Schwarze K, Buchanan J, et al. [includes **Wordsworth S**]. *Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature*. *Genetic Medicine*. 2018. doi:10.1038/gim.2017.247
14. Watson EK, Shinkins B, et al. [includes **Burns RM, Wolstenholme J**]. *Supporting prostate cancer survivors in primary care: Findings from a pilot trial of a nurse-led psycho-educational intervention (PROSPECTIV)*. *Eur J Oncol Nurs*. 2018. 32:73–81. doi:10.1016/j.ejon.2017.12.002
15. Wolstenholme JL, Bargo D, et al. *Preference-based measures to obtain health state utility values for use in economic evaluations with child-based populations: a review and UK-based focus group assessment of patient and parent choices*. *Quality of Life Research*. 2018. doi:10.1007/s1136-018-1831-6