Exploring the role of genetically determined BMI in infancy, childhood and early adulthood on colorectal cancer development in later life

International 100K Cohort Consortium

Global Genomic Medicine Collaborative

IHCC 4th International Cohorts Summit

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CANCER BIOLOGY & THERAPEUTICS LAB

UCD DUBLIN

University College Dublin
Ireland's Global University

Background & Aims

Genetic propensity to childhood and adult obesity

?

↑ **Excess energy**

- **Obesity**
- hyperinsulinemia
- insulin resistance
- dyslipidemia
- metabolic syndrome

↑ **Oxidative stress**

↑ **Inflammation**

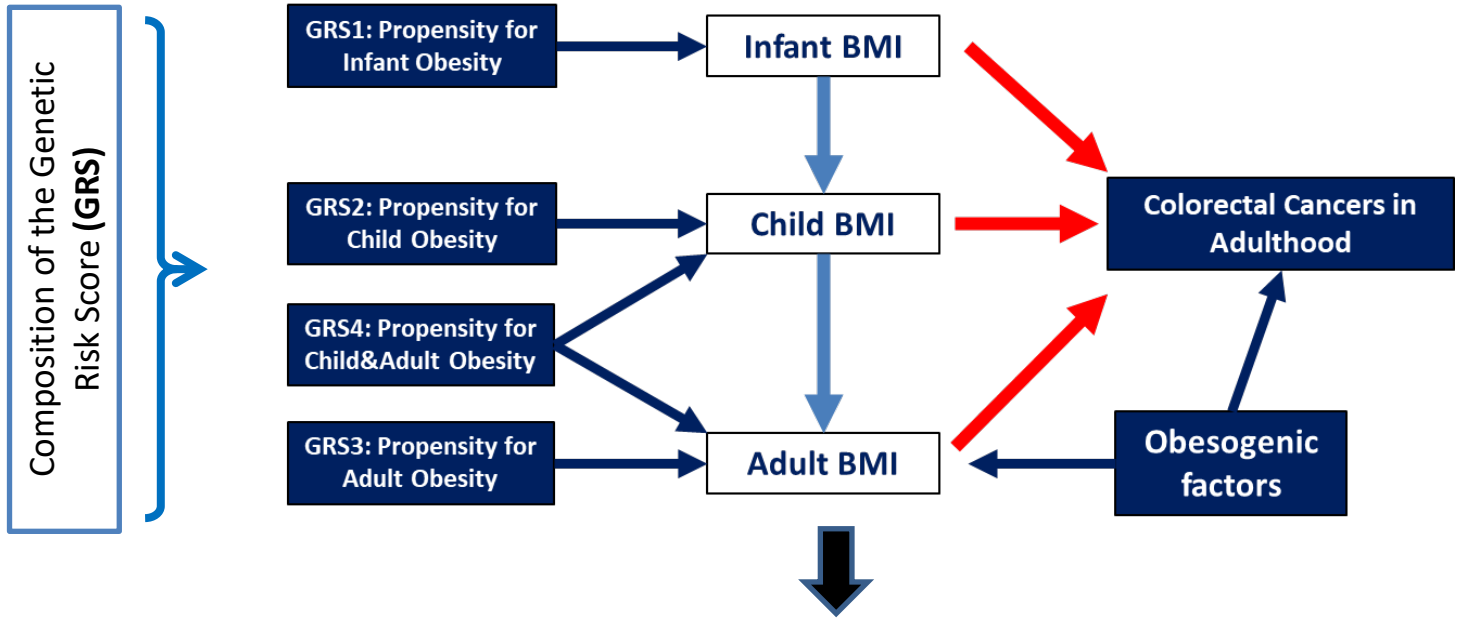
↑ **Proliferative stimulus**

Higher risk of developing **colorectal cancer**

- We hypothesize that varying obesogenic inherited predisposition in early- and later-life stages infers different metabolic processes that may underlie adiposity and differentially impact risk of CRC and possibly earlier-onset disease

- **AIMS**: To investigate how the propensity and temporality of genetic predisposition towards common obesity across distinct life stages may differentially impact risk of adulthood CRC

Project Analytical Strategy



- The GRS will be calculated from the sum of risk alleles corresponding to obesity phenotypes - weighted by the effect size estimate of the corresponding GWAS on the phenotype
- Cause specific risks for the GRS-cancer associations will be estimated using logistic regression models or Cox proportional hazard, as appropriate

Obesity Variables for Stratified Analyses / Adjustment:

- Early life obesity assessed by birth weight (UKBB only)
- Adult obesity assessed by: (1) WHO BMI categories, (2) duration of obesity during adult life, (3) Cross categorization of weight/waist-circumference (UKBB, GECCO, EPIC)

Dietary, Lifestyle Variables Stratified Analyses / Adjustment (UKBB, GECCO, EPIC):

- Healthy Lifestyle (HLI) and Mediterranean Diet (MDS) Scores
- Physical activity, alcohol intake, alcohol drinking pattern, smoking patterns
- By Sex (men/women), by age group at study enrolment and at diagnosis (<40, 40 to <60, ≥60 years old)

Polygenic Risk Score

a weighted sum of the number of risk alleles

$$PRS = \beta_1 SNP_1 + \ldots + \beta_m SNP_m$$

- β, the effect size estimated by different approaches
- m, the number of SNPs included in the polygenic risk score

Additional exploratory analyses:

- By levels of pre-diagnostic circulating CRP, C-peptide, and by calculated metabolic syndrome (MetS) score (EPIC, UKBB where possible)

Project Timelines (1st May 2021- 31st October 2022)

Time	Month 1-6	Month 7-12	Month 13-18
Recruitment			
1 Postdoctoral fellow at UCD and IARC			
Objectives			
1. Construct different life stage Genetic Risk Scores to associate with colorectal cancer development [all cohorts]:			
Preparation of UKBB, EPIC, and GECCO datasets, extraction of existing relevant data *(for objectives 1, 2)*			
Construction of life-course 'obesity predisposition' SNP-based Genetic Risk Scores (GRS 1 to 4 from infant to adulthood obesity)			
Assessment of GRS values for BMI and CRC development risk (all cohorts)			
2. Determine whether the assessed CRC risks are modified by body size at different life stages, exposure to obesogenic factors in adult life, or by sex [all cohorts] *(exploratory analyses)*			
3. Assess association of the GRSs with BMI-trajectories and age categories of CRC onset			
4. Assess association between the GRSs and important mechanisms of obesity-mediated CRC development, i.e., metabolic dysfunction and inflammation, using existing biomarker measures [EPIC & UKBB] (*exploratory analyses*)			
Review and update of work plans / Project meetings			
Write up & Publish a high-impact manuscript & other dissemination activities to key stakeholders			

Project Progress: Data Access

any other cohorts who wish to join are very welcome – please contact me! (david.hughes@ucd.ie)

- Access to GECCO and UKBB data (Neil Murphy, IARC) ✓
  - Neil will discuss with GECCO as to whether we can also have direct access to individual level data or whether we need to make a new application

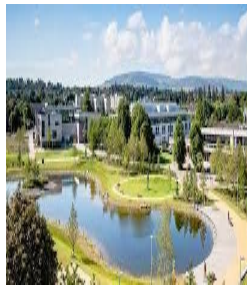
- Access to EPIC data (Mazda Jenab, IARC) ✓
  - except we need permission for the EPIC CRC biochemical data
  - anyway, we will apply to the IARC Ethics Committee in June for the entire project

biobank uk

FRED HUTCH CURES START HERE

epic European Prospective Investigation of Cancer

Project Postdoc Recruitment



- Postdoc post (1 year) OPEN until June 2nd
  - https://www.ucd.ie/workatucd/jobs/
  - Reference 013227

- Dr Nikolaos Papadimitriou (under supervision of Dr Neil Murphy and Dr Mazda Jenab)
  - has experience in genetic epidemiology and MR analyses
  - He will contribute to constructing the GRS and assessing the GRS-CRC risk associations

Project development: PhD study

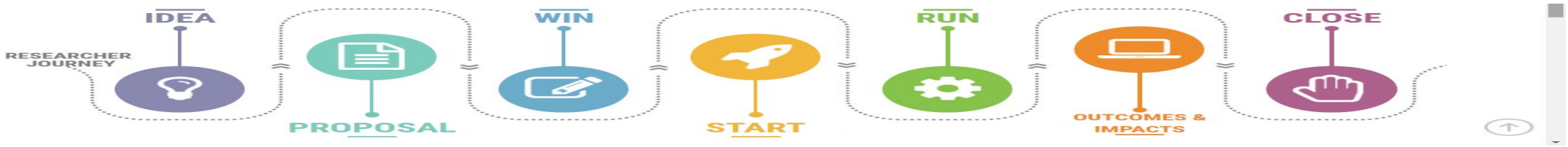
- https://genomicsdatascience.ie/

- Extensions of this project (to other cancers & survival outcomes) will be offered to the accepted students for this September's intake (they choose the projects!)

Some points from the grant timespan & registration process

- Grant funding negotiation process between G2MC and the relevant institutes was protracted
  - seemed to stem from being a new funder and no previous contact with the institutes
  - some misunderstanding of each side waiting on the other to clarify relatively simple agreement points (such as on confusion with IHCC membership stipulation)
  - probably a telecon with the funding body and the institution admin would be good at the start of the process
  - obviously will improve as the consortium, its funders and the institutes becomes more familiar with each other

- Two years is probably a better project span
  - for reasons such as in many European counties for example have generally stricter hiring regulations for research staff than North America
  - for example, in UCD we must only offer contracts to Post-docs in full year durations, so 1 year, or 2 years, but not 18 months



Acknowledgements

IARC-EPIC, LYON, FRANCE

Mazda Jenab

Neil Murphy

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Nikolaos Papadimitriou

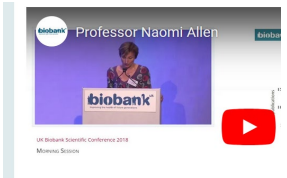



& all EPIC-associated colleagues

& all subjects participating in the EPIC study

MD ANDERSON,HOUSTON, TX, USA

Veronika Fedirko

https://www.ukbiobank.ac.uk/researchers/

UKBB and GECCO cohorts

Rory Collins (UKBB); Ulrike Peters (GECCO)

& all associated colleagues

& all subjects participating in these studies