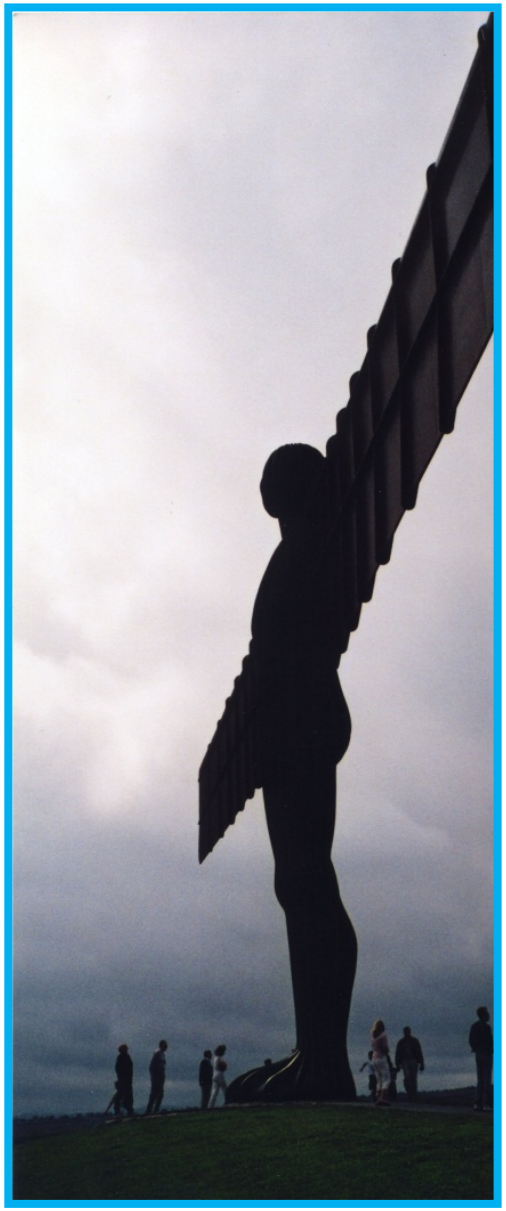
The future of nutrigenomics



John Mathers

Human Nutrition Research Centre

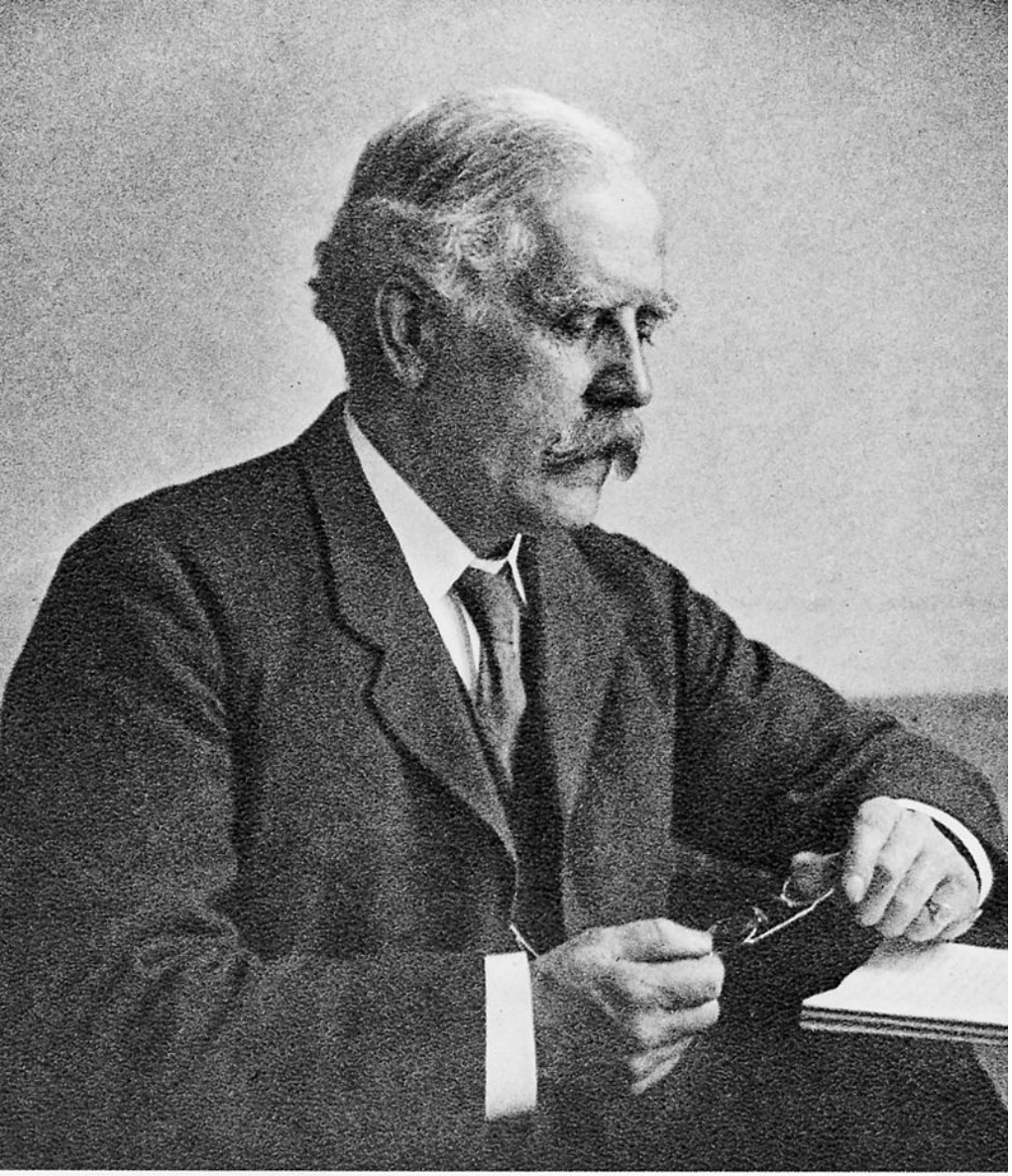
Institute of Cellular Medicine

Newcastle University

UK

Newcastle University

Human Nutrition Research Centre



1857-1936

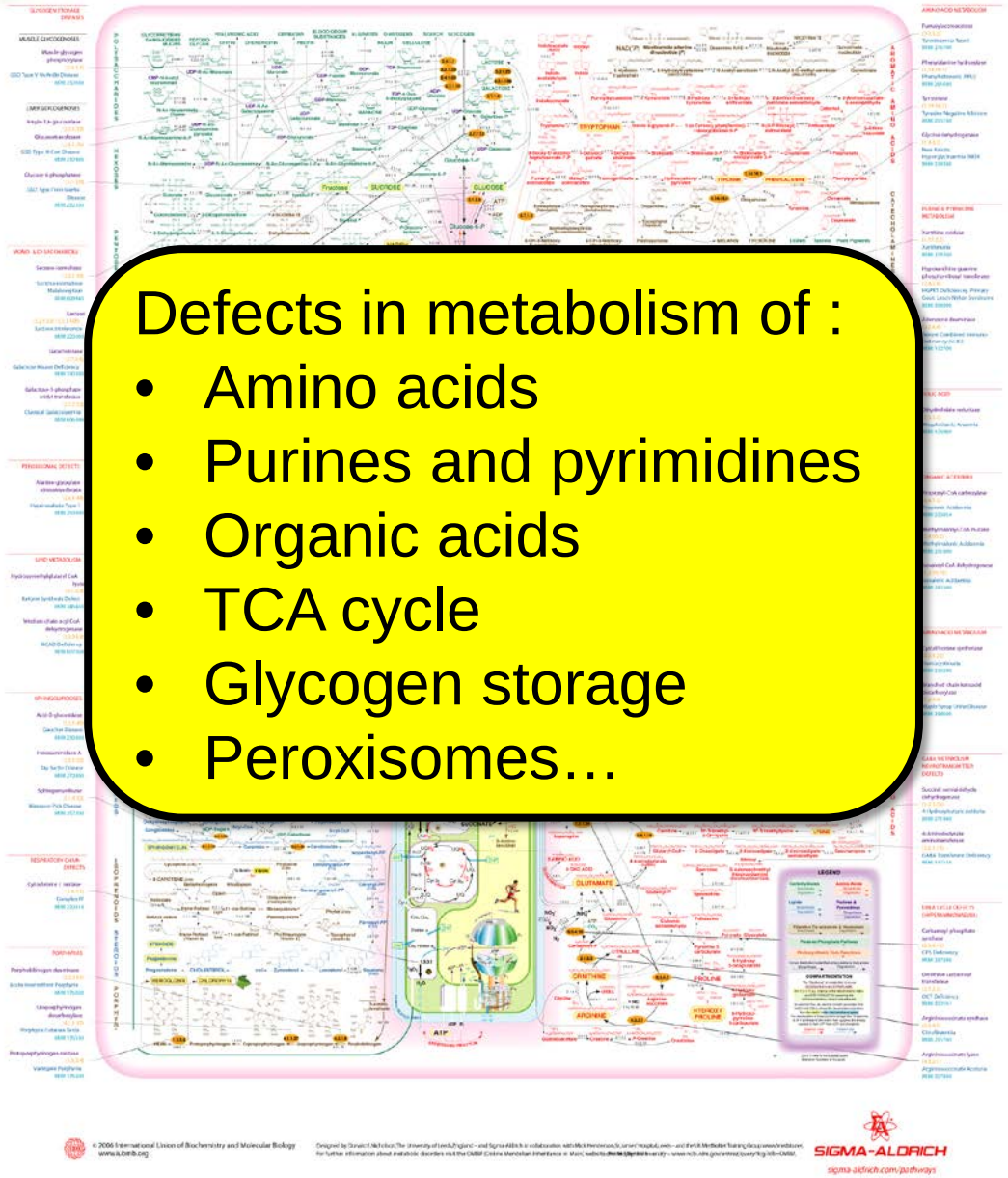
A.E. Garrod,

Alkaptonuria

- Black urine disease or black bone disease
- Common in offspring of 1st cousin marriages
- Defect in metabolism of phenylalanine and tyrosine
- Caused by mutations in *HGO* which encodes homogentisate 1,2-dioxygenase

Garrod AE (1902) *The Lancet* December 13

Inborn Errors of Metabolism



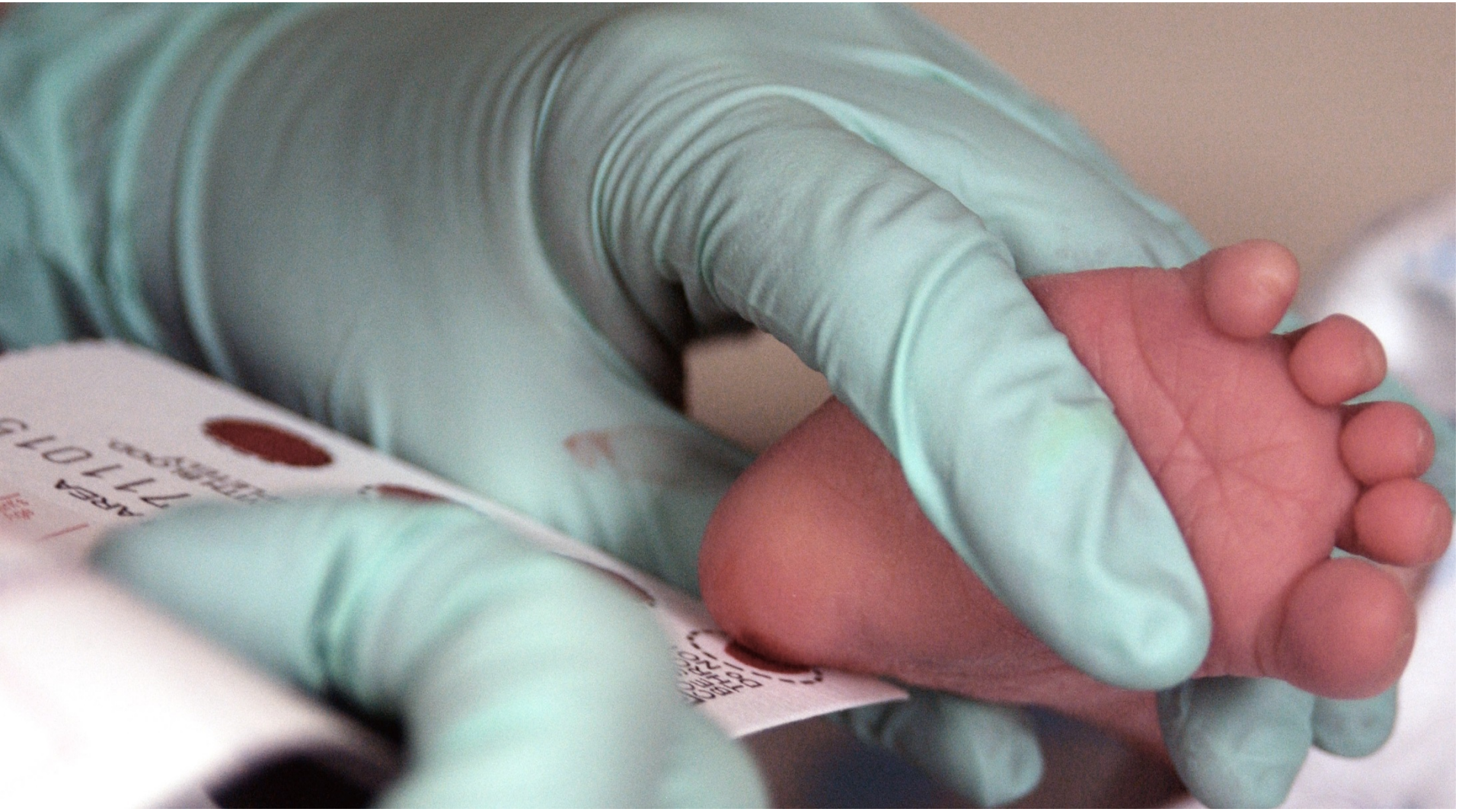
>40 Inborn Errors of Metabolism

Individually rare but collectively common – about 1 in 1500 births

http://www.iubmb-nicholson.org/inborn_errors.html

Phenylketonuria

Heel prick for Guthrie test

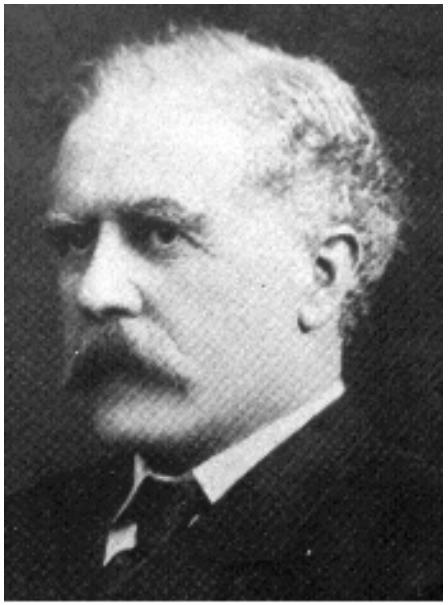


The importance of inter – individual variability in metabolism

"… If it be a correct inference …that the individuals of a species do not conform to an absolutely rigid standard of metabolism, but differ slightly in their chemistry…

Such slight peculiarities of metabolism… will readily be masked by ***the influences of diet*** *and of disease…*

The ***phenomena of obesity*** *and the various tints of hair, skin and eyes point in the same direction…"*



Sir Archibald Garrod, around 1910.

Garrod AE (1902) *The Lancet* December 13

Inter-individual variation in metabolic responses to nutritional challenge

DIETARY FACTORS THAT INFLUENCE THE DEXTROSE TOLERANCE TEST

A PRELIMINARY STUDY *

J. SHIRLEY SWEENEY, M.D.

DALLAS, TEX.

The dextrose tolerance test is now being extensively employed as a diagnostic procedure. It is most beneficially used in the differentiation of mild diabetes mellitus and renal diabetes. It is also being used, and is believed to be of diagnostic value, in many pathologic conditions, such as encephalitis, malignant tumor, pituitary and thyroid dysfunctions and nephritis.[1]

Banting & Best 1921-22

Sweeney JS (1927) *Arch. Int. Med.* **40**, 818-830

First paper at Nutrition Society in UK

Genetic determination of nutritional requirements

By J. A. Roper,* *Department of Genetics, University of Glasgow*

Introduction

A clear understanding of the genetic control of nutritional requirements came only after the fruitful union of biochemistry, genetics and microbiology. However, to present any account of the genetics of nutrition without a brief discussion of earlier fundamental work is to lose perspective.

The physician Garrod (1902, 1923), working on rare inherited metabolic disorders of man, such as alkaptonuria and cystinuria, was the first to show that genes act

* Present address: Department of Genetics, The University, Sheffield.

Conclusion

The application of genetical ideas and techniques to the nutrition of micro-organisms has brought a clearer understanding of the relationship of genotype and nutritional requirement. It has opened a new approach and a new way of thought to a large aspect of genotype–environment interaction. Further advances will lead to

Roper JA (1960) *Proc. Nutr. Soc.* **19,** 39-45

First map of human genome
26 June 2000

"…the most important, most wondrous map ever produced by humankind..."

FOR YOUR INFORMATION

The new frontier of nutrition science: Nutrigenomics

If you were to sum up the future of nutritional science into a single word, chances are it would be *nutrigenomics*. At least, that's the area of study that Dr. Nancy Fogg-Johnson firmly believes will revolutionize how nutrition and diet will be viewed by the general population.

"Nutrigenomics is the understanding of the effects of nutrients in molecular level processes in the body as well as the variable effects of nutrients and non-nutritive dietary phytochemicals have on each individual person," explains Fogg-Johnson, who has a PhD in nutrition and biochemistry, and has written and lectured extensively on the topic.

In an article titled "Nutrigenomics: The next wave in nutrition research," Fogg-Johnson and her co-author Alex Merolli, outline their prediction for how nutrigenomics will be the "next technological and commercial frontier emerging from genomics":

databases of genetic information will uncover genes that may interact with diet to influence disease.

While such scientific advances are obviously still in their early development stages, dietitians are already pondering their role in the field of nutrigenomics.

"It will be key for the dietitian and nutrition professionals to guide and counsel their patients on how these products and information will fit into their lifestyle. Consumer understanding is an important component of this. RDs should help their clients realize they will still enjoy eating food and that we are not talking about a Spartan diet here! Research shows that if food doesn't taste good, consumers simply won't buy it."

Once these products hit grocery store shelves, they could potentially appear in a variety of forms, according to Fogg-Johnson, from supplement pills to ready-to-eat breakfast cereals, to margarine and salad dressing.

can refer to, in order to gauge when this new technology will be available?

The article written by Fogg-Johnson quotes Dave Evans, president and CEO, Wellgen, Inc., a startup company commercializing Rutgers University technology, with a response to the question of 'when':

"In less than 10 years, you'll be able to go to a lab and complete a set of genetic tests to identify your personal disease susceptibilities. When you leave you'll be armed with a list of foods to eat and foods to avoid and a recommendation of dietary supplements to help prevent your diseases."

Dr. Jose M. Ordovas, of the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston, MA, echoes Evans' prediction that dietary supplements will be used in the prevention of diseases, though he doesn't speculate on when that technology will be developed.Instead, he emphasized

Peregrin T (2001) *J. Am. Diet. Assoc.* **10,** 1306

3 July 2003
NuGO is born!

From: Ommen, Dr.Ir. B. van [mailto:vanOmmen@voeding.tno.nl]
Sent: 03 July 2003 09:02
To: dolara@ds.unifi.it; enzing@stb.tno.nl; joost@mail.dife.de; jaap.keijer@wur.nl; John Mathers <john.mathers@newcastle.ac.uk>; h.mcardle@rowett.ac.uk; hmroche@tcd.ie; Stierum, Dr. R.H. <Stierum@voeding.tno.nl>
Subject: NuGO accepted

Dear all,

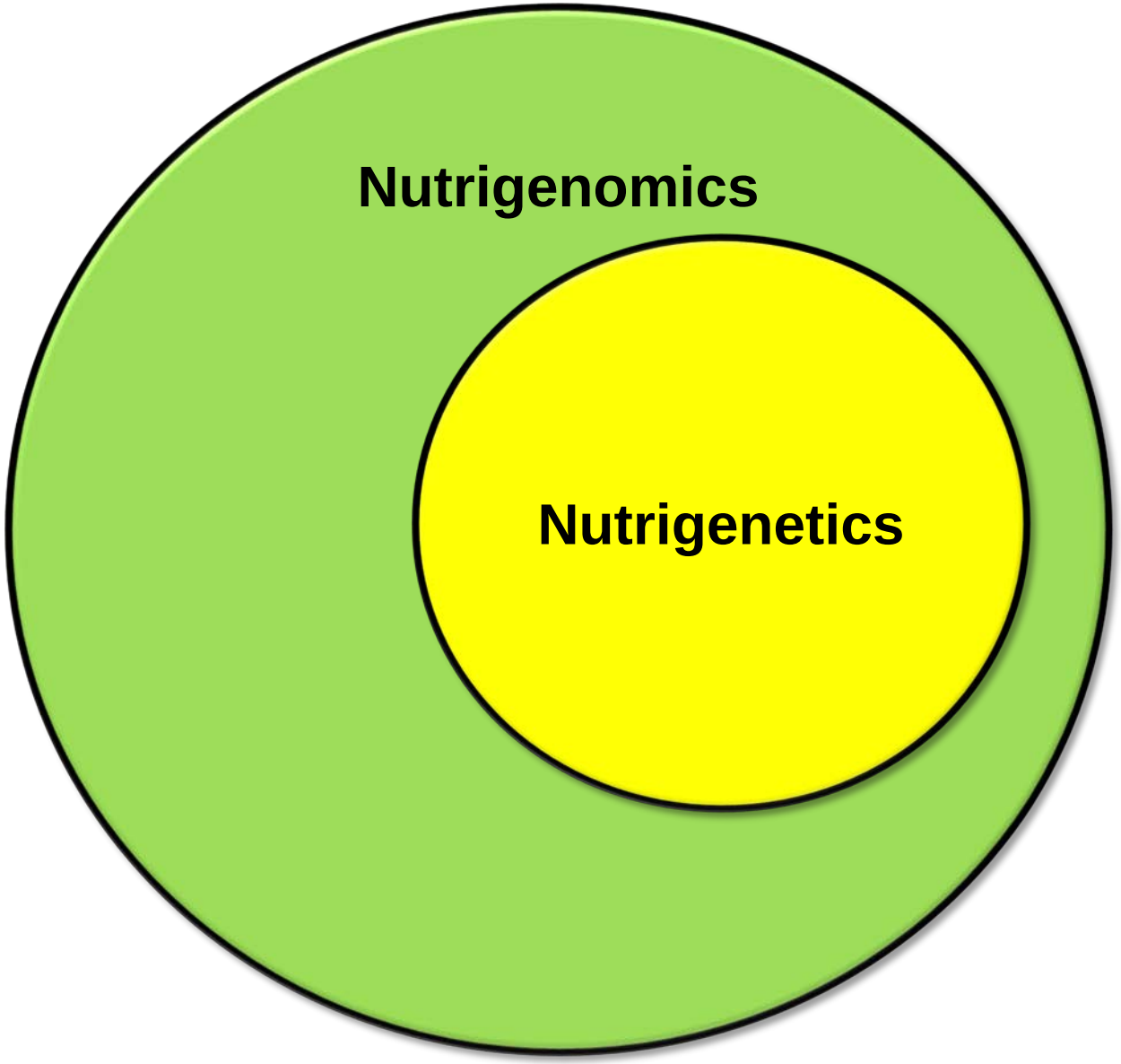
Although no official news yet, I have received very reliable and detailed news on the reviewing of the NuGO proposal. The proposal ended on the 6th place in the list of 12 "to be invited for discussion" priority 5 new instruments. We scored 22.5 out of 25 points, with 5/5 on relevance, 4.5/5 potential impact, 4/5 excellence of partners, 4.5/5 integration and 4.5/5 management. Official news will come next week, discussions to start in August.

So: good news! As soon as I get the report, I will let you know.

Greetings, Ben

NuGO
NUTRIGENOMICS ORGANISATION

Nutrigenomics

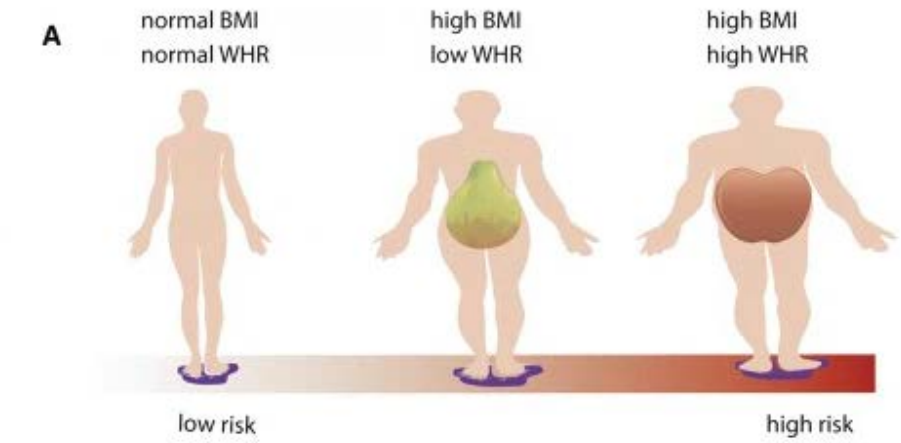


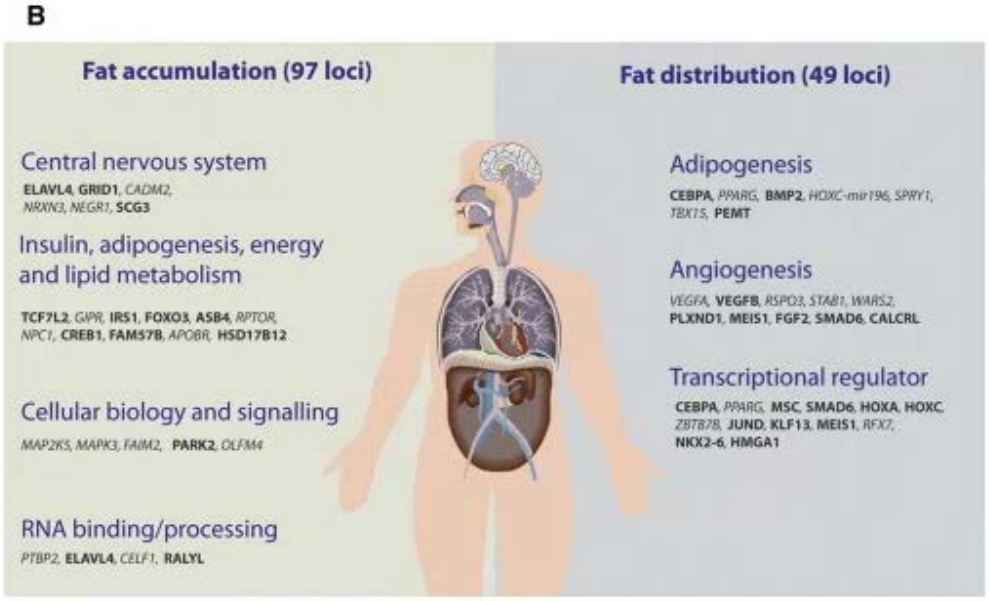
NuGO
NUTRIGENOMICS ORGANISATION

NuGO

Nutrigenetics:
Impact of genotypic variation

Genetic contribution to body fatness





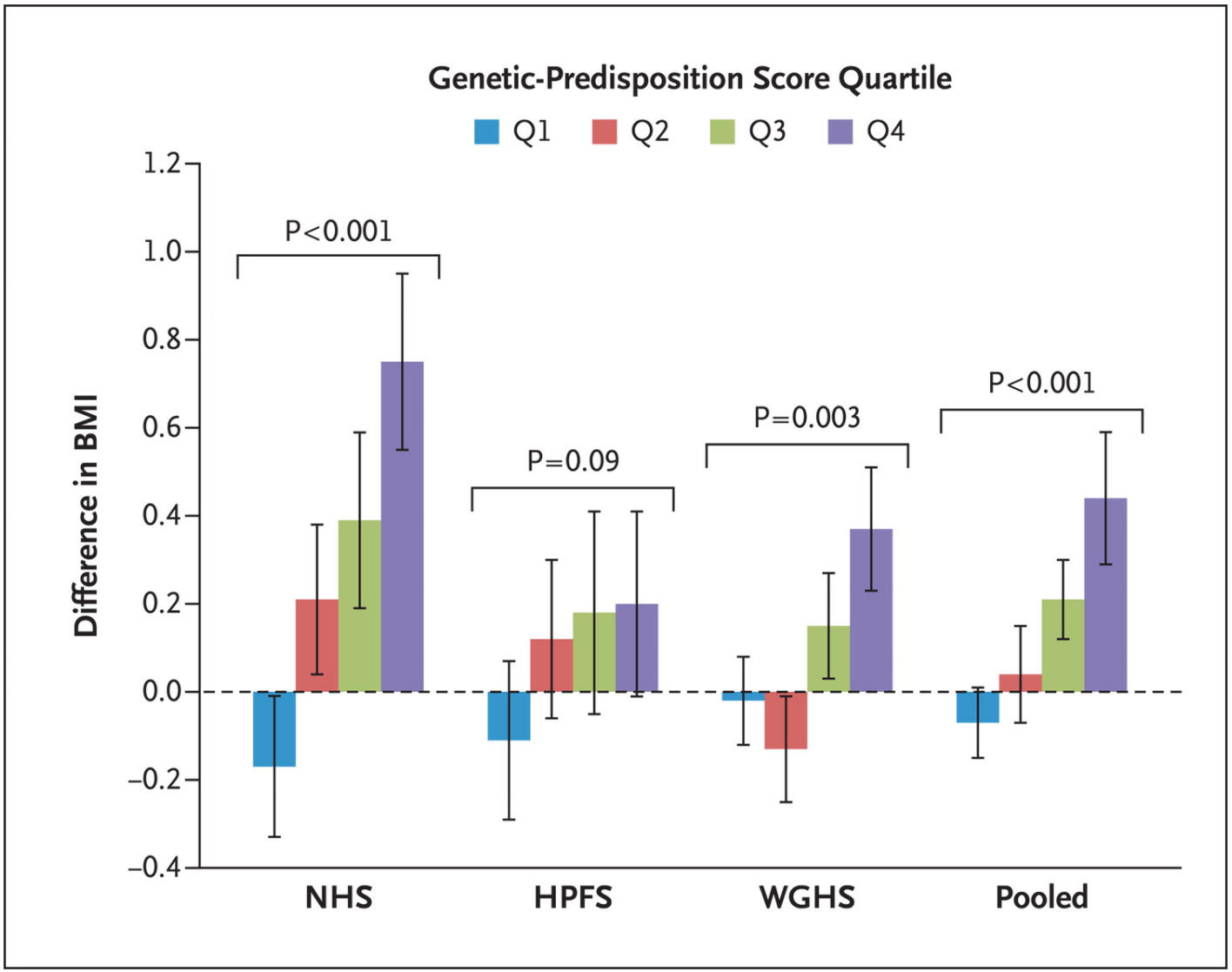
- 97 variants explain 2.7% of variation in BMI

Genetic risk scores

Shungin D *et al.* (2015) *Nature* **518,** 187-196
Locke AE *et al.* (2015) *Nature* **518,** 197-206

Fu J *et al.* (2015) *Cell Metabolism* 21, 507-508

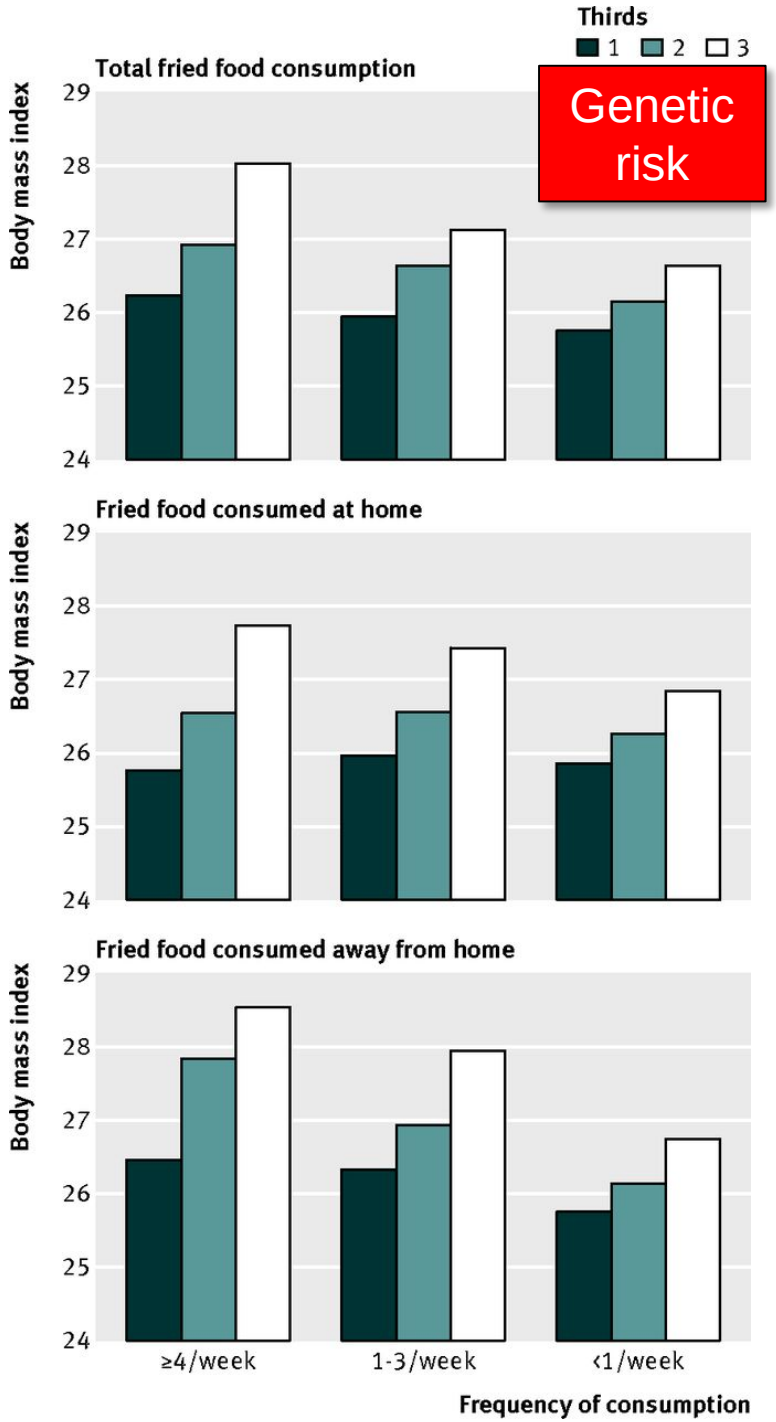
Genetic risk amplifies adiposity effect of sugar-sweetened beverages



Difference in BMI per serving of sugar-sweetened beverage per Day

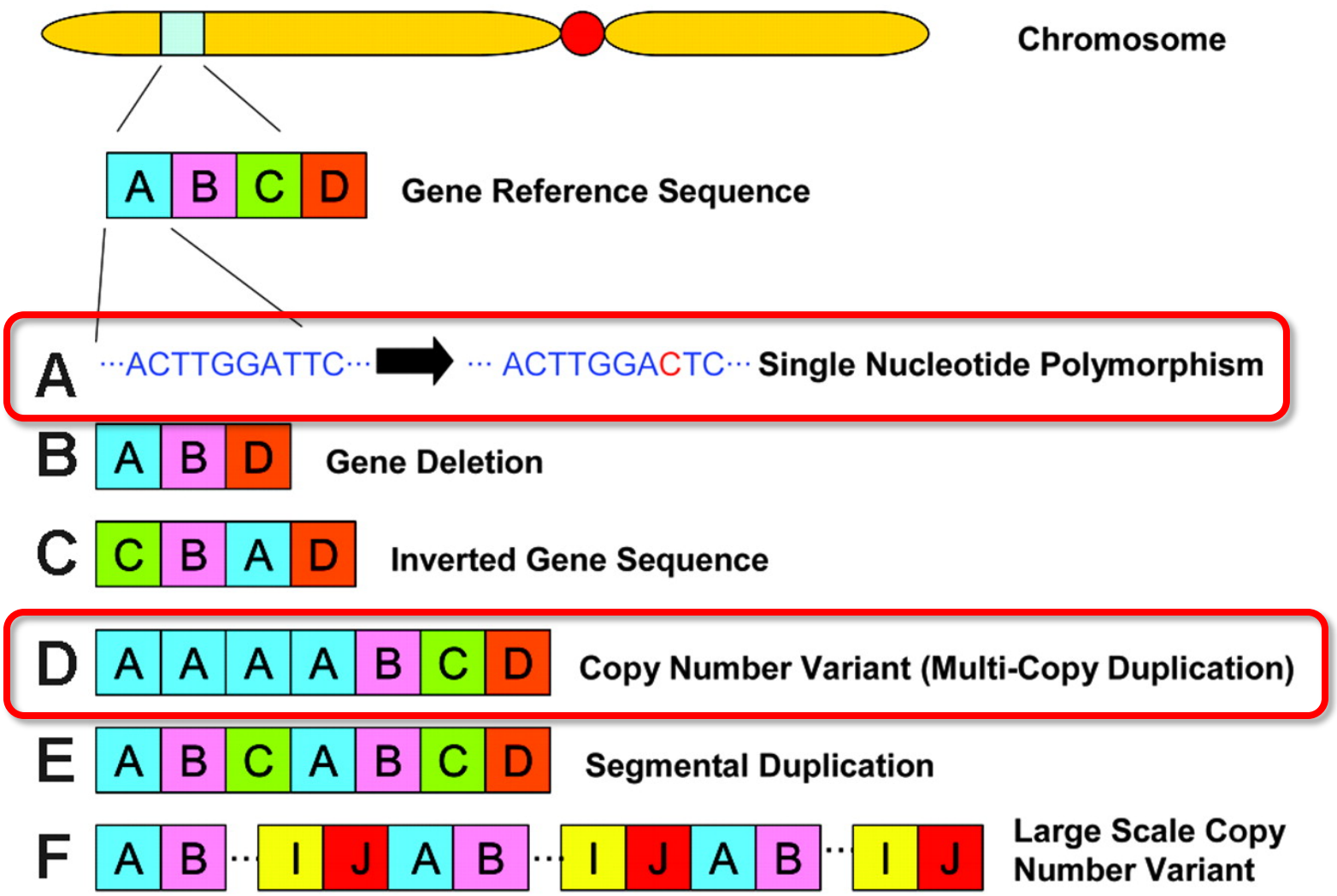
Qi Q *et al.* (2012) *New Eng. J. Med.* **367**,1387-1396

Genetic risk amplifies adiposity effect of fried foods



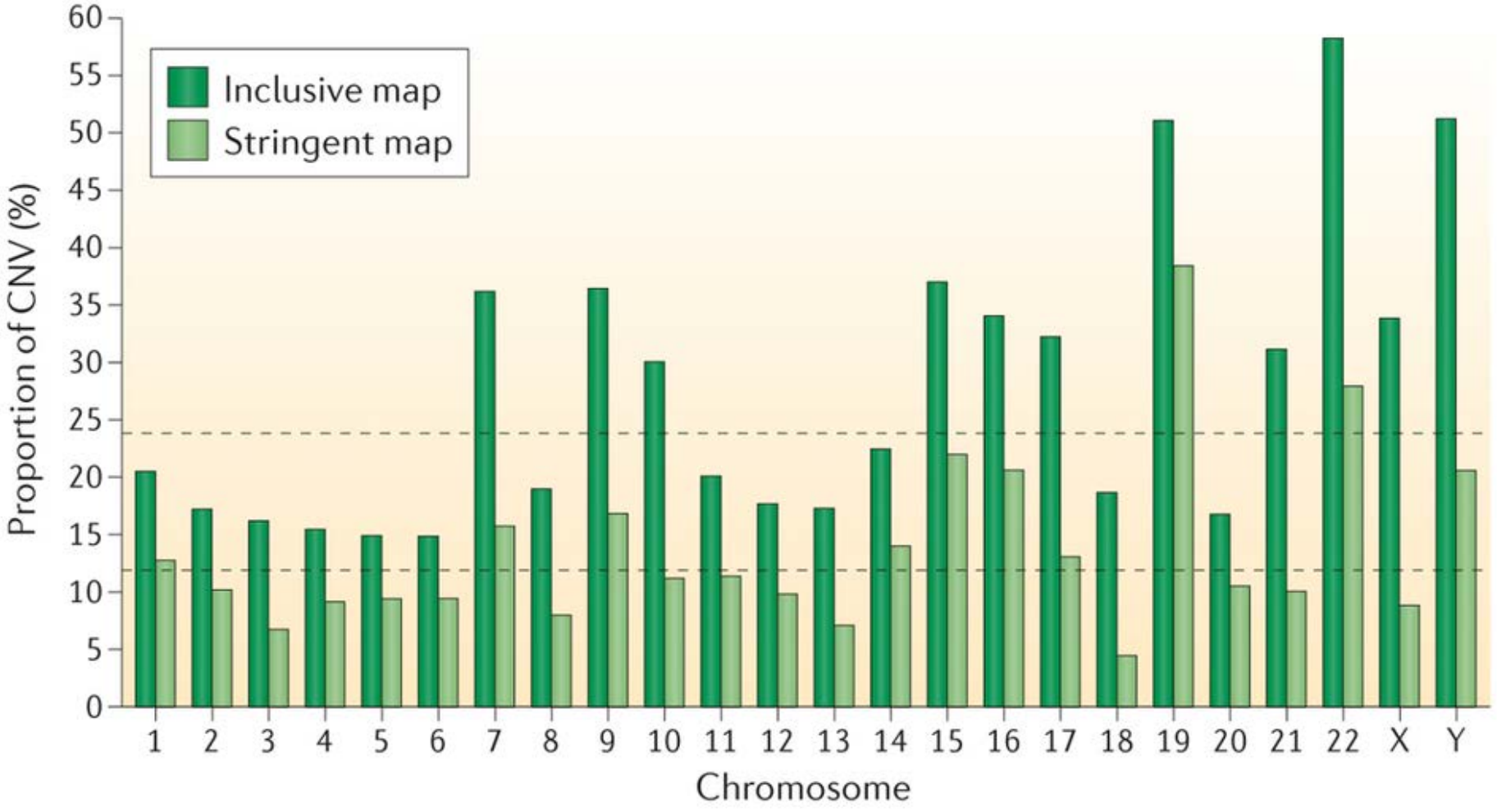
Qi Q *et al.* (2014) *BMJ* **348;** g1610

Genomic structural variation



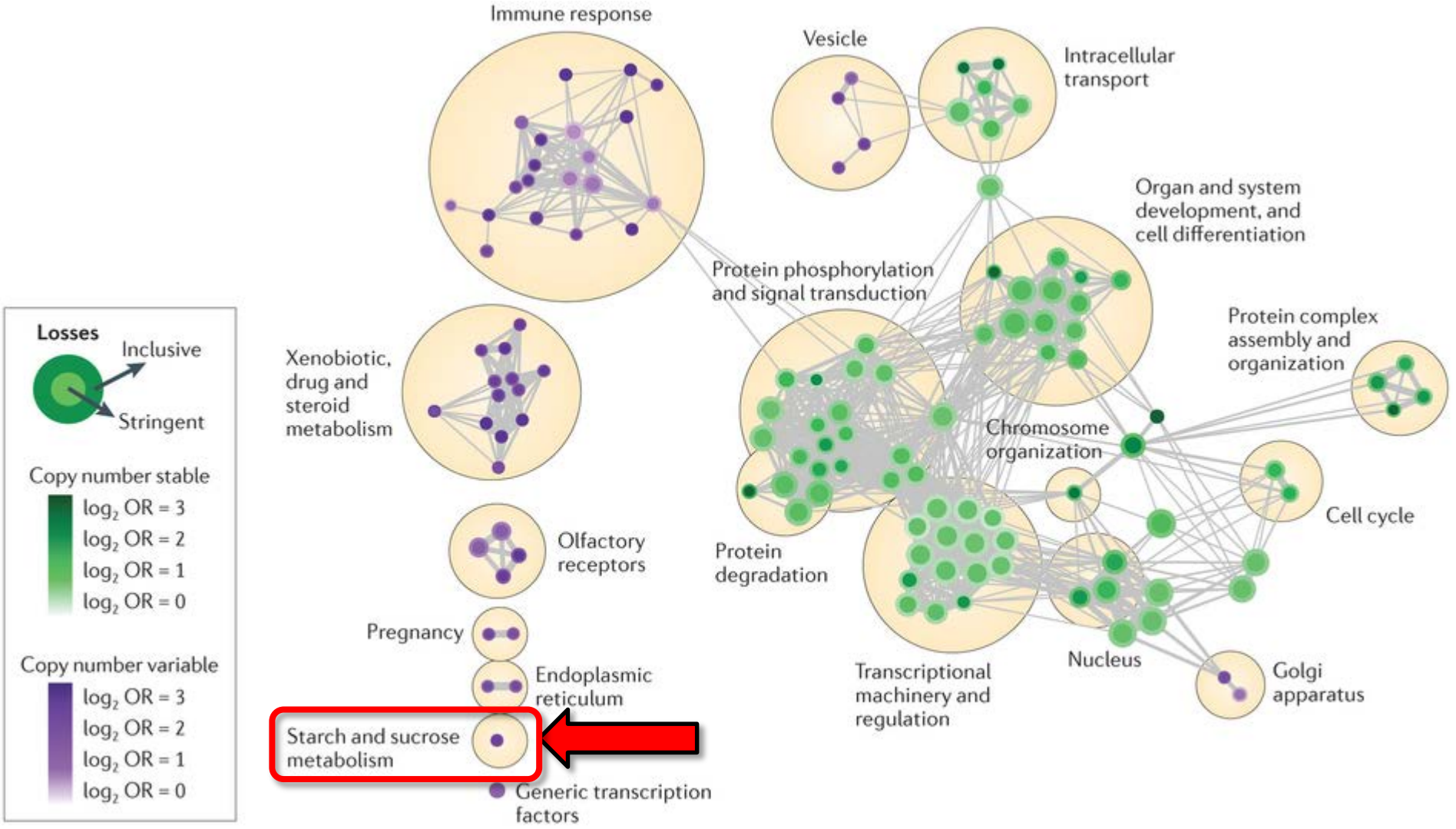
Mullally A & Ritz J (2007) *Blood* **109,** 1355-1362

Copy number variants are common!



Zarrei M *et al.* (2015) *Nature Reviews Genetics* **16,** 172-183

CNVs affect multiple cellular processes

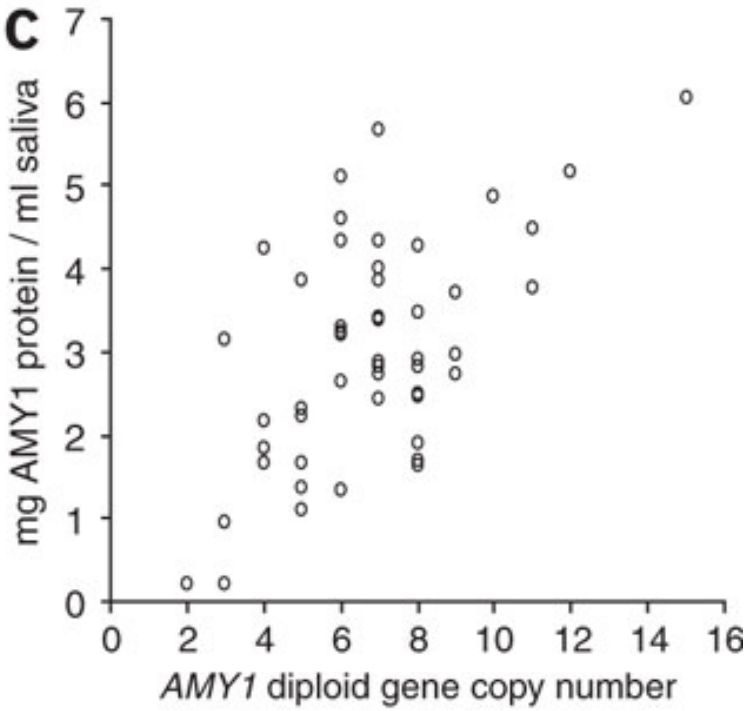


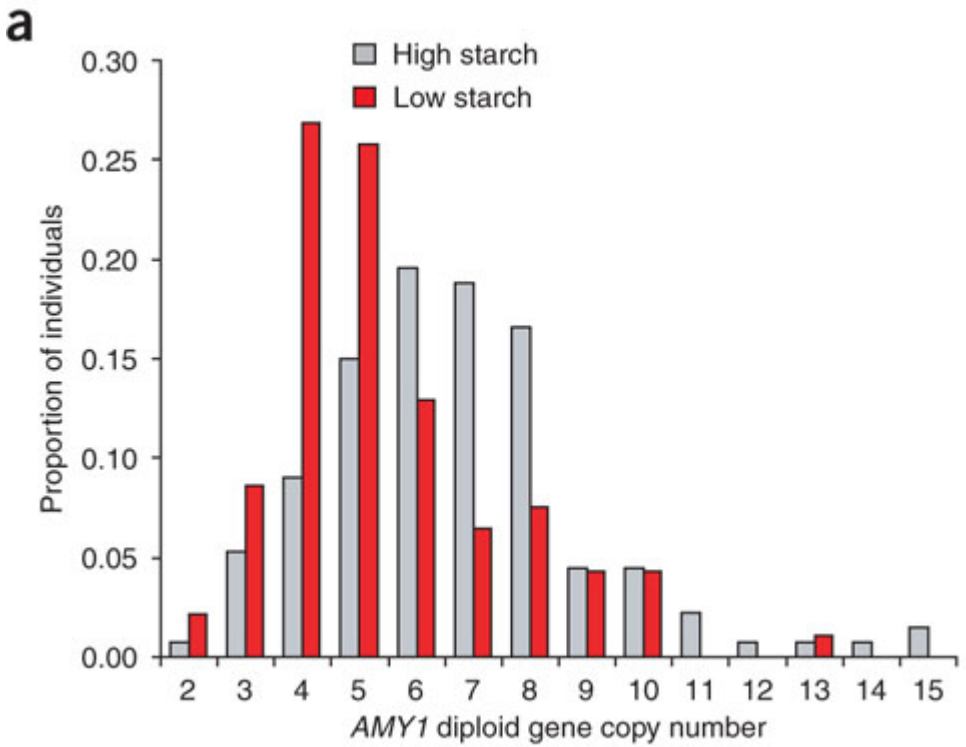
Zarrei M *et al.* (2015) *Nature Reviews Genetics* **16,** 172-183

Nature Reviews | Genetics

Starch, saliva and iodine

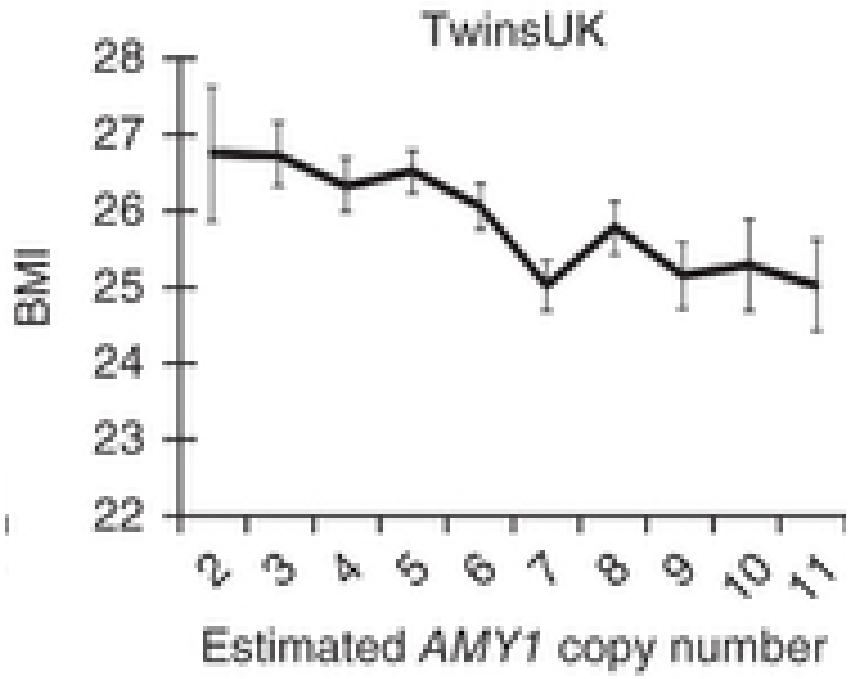
CNVs in salivary amylase gene appear to be functionally important

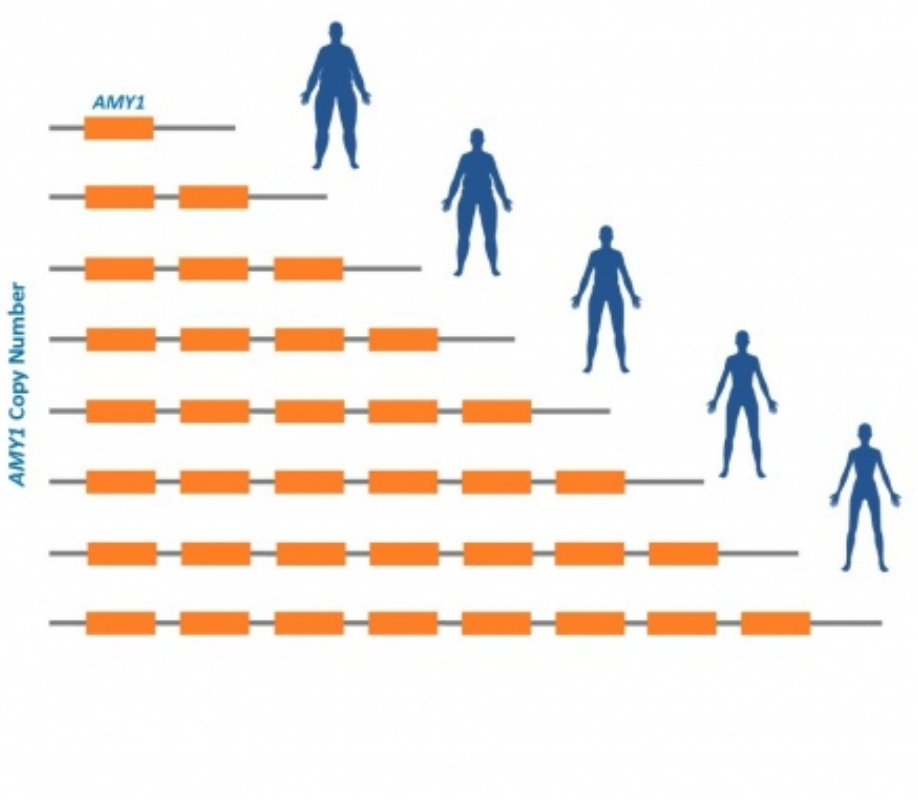




Perry GH *et al.* (2007) *Nature Genetics* **39,** 1256-1260

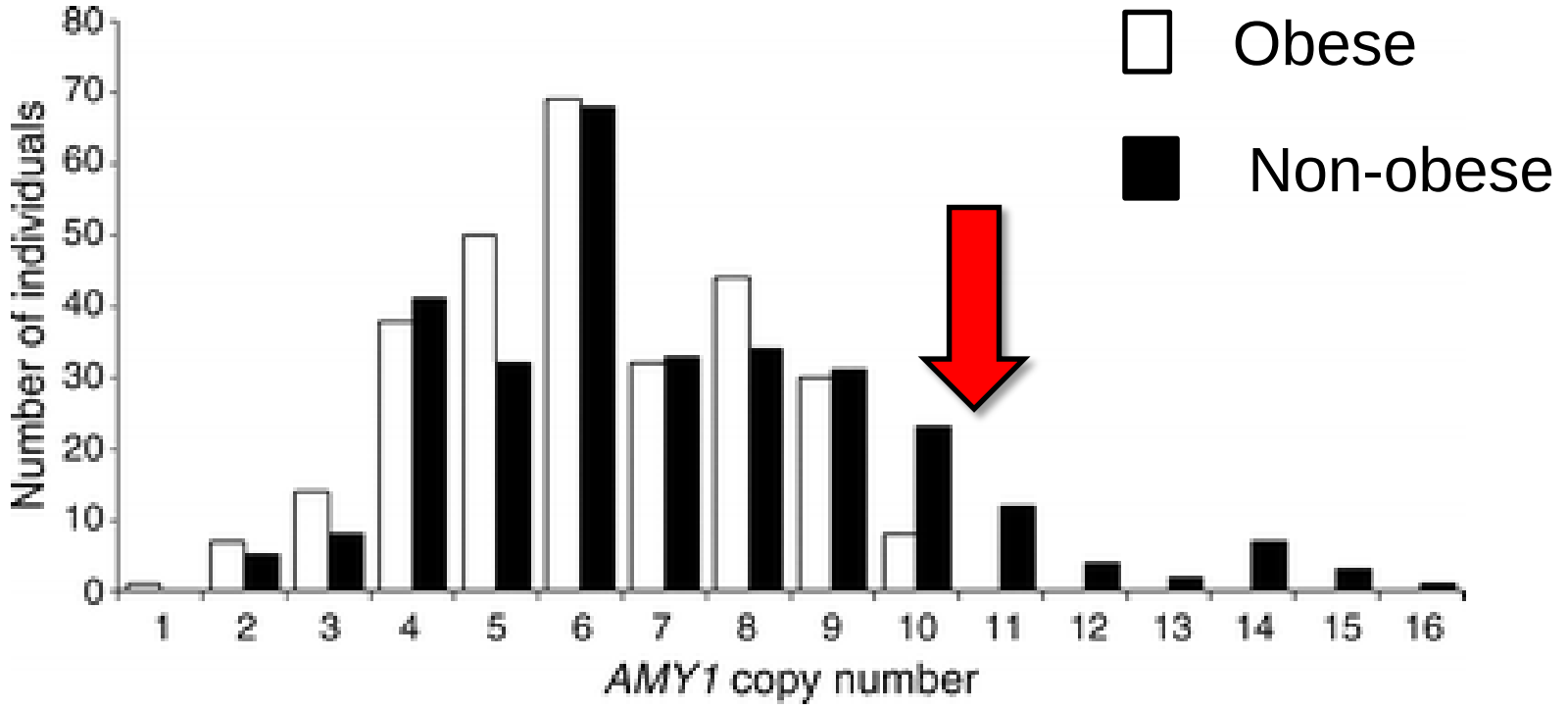
Low copy number for salivary amylase gene associated with obesity





Falchi M *et al.* (2014) *Nature Genetics* **46**, 492-497

Low salivary amylase copy number associated with obesity in Mexican children



Mejia-Benitez MA *et al.* (2015) *Diabetologia* **58,** 290-294

At least 84 CNVs associated with BMI

Peterson *et al. BMC Genomics* 2014, **15**:368
http://www.biomedcentral.com/1471-2164/15/368

BMC Genomics

RESEARCH ARTICLE Open Access

On the association of common and rare genetic variation influencing body mass index: a combined SNP and CNV analysis

Roseann E Peterson[1*], Hermine H Maes[2], Peng Lin[3], John R Kramer[4], Victor M Hesselbrock[5], Lance O Bauer[5], John I Nurnberger Jr[6], Howard J Edenberg[7], Danielle M Dick[8] and Bradley T Webb[9]

- ❑ Many are rare
- ❑ Small effect sizes

Nutrigenomics: Understanding mechanisms

Example: integrated transcriptomics and proteomics-based study

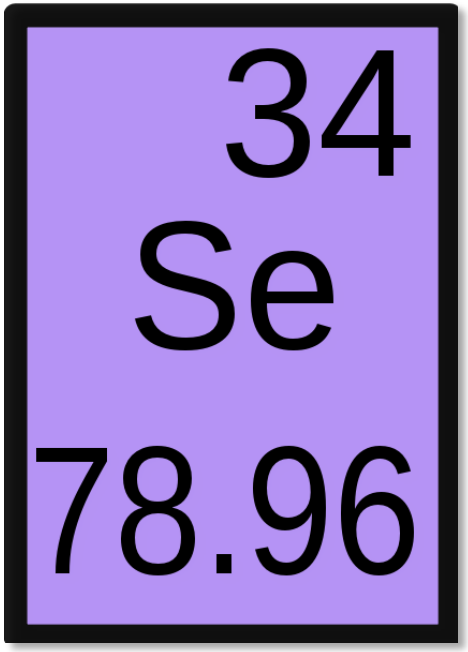
Research question: What is impact of suboptimal selenium status on colorectal epithelium?

Participants: Healthy adults from BORICC Study with suboptimal or optimal plasma Se status

Biological functions of selenium:

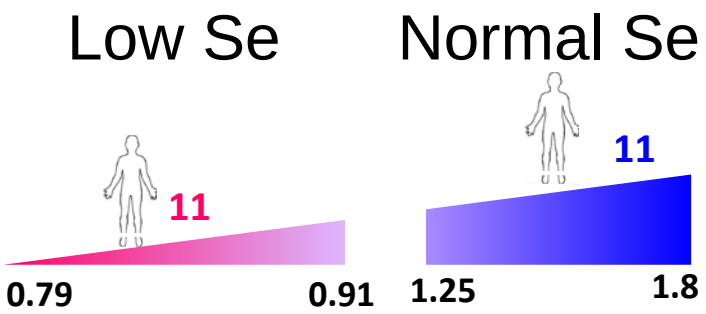
Essential trace element and cofactor for:

- ❑ glutathione peroxidases
- ❑ thioredoxin reductase
- ❑ thyroid hormone deiodinases



Méplan C *et al.* (2016) *FASEB J* **30,** 2812-2815

Study overview



22 Rectal biopsies

Microarray (illumina) **Proteomics 2D-Gel**

254 genes **26 proteins**

↓ inflammatory & immune signalling
NFκB inhibition

IPA

Cancer (80% genes)
Tissue morphology
Cellular movement

Cytoskeletal proteins
Ca^{2+}-signalling factors
Cytoskeleton remodelling

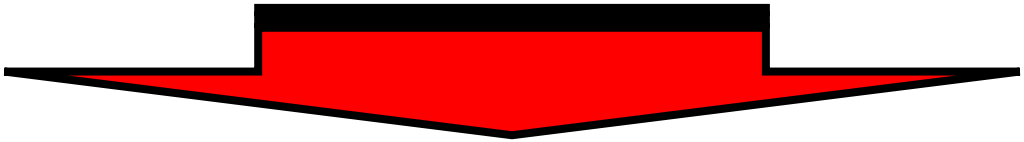
Méplan C *et al.* (2016) *FASEB J* **30,** 2812-2815

Effects of suboptimal Se status on gut epithelium

Healthy epithelium: NFκB coordinates cytokine production, immune cell response, response to gut microflora and balance between survival and apoptotic factors

Suboptimal Se:

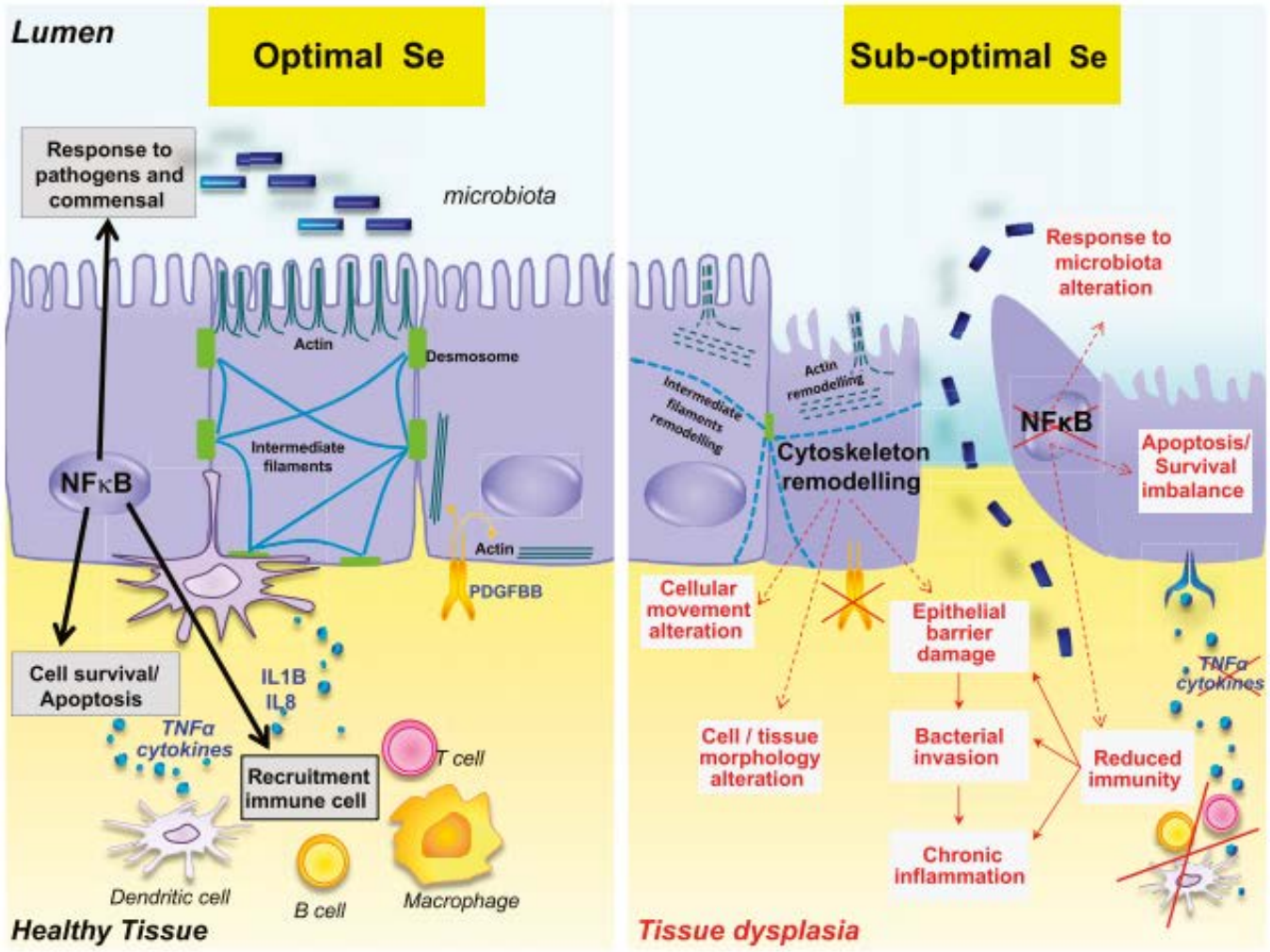
- ↓ inflammatory and immune signalling
- inhibition of NFκB and cytoskeleton remodelling
- changes in cell morphology and movement



↓ capacity to respond to inflammatory and oxidative stresses, thus could favour CRC development

Méplan C *et al.* (2016) *FASEB J* **30,** 2812-2815

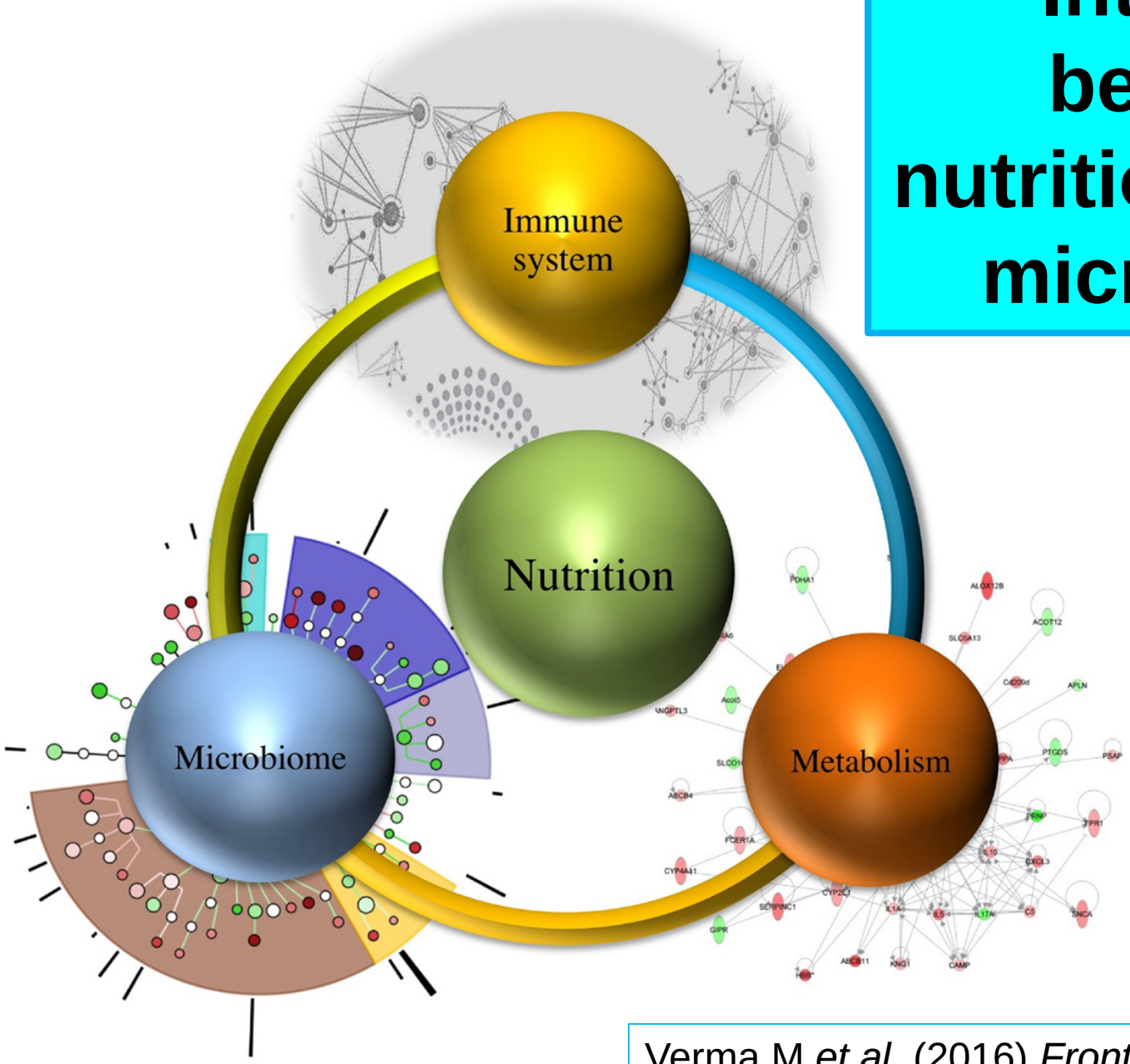
Model of effects of sub-optimal Se status on colorectal function



Méplan C *et al.* (2016) *FASEB J* **30,** 2812-2815

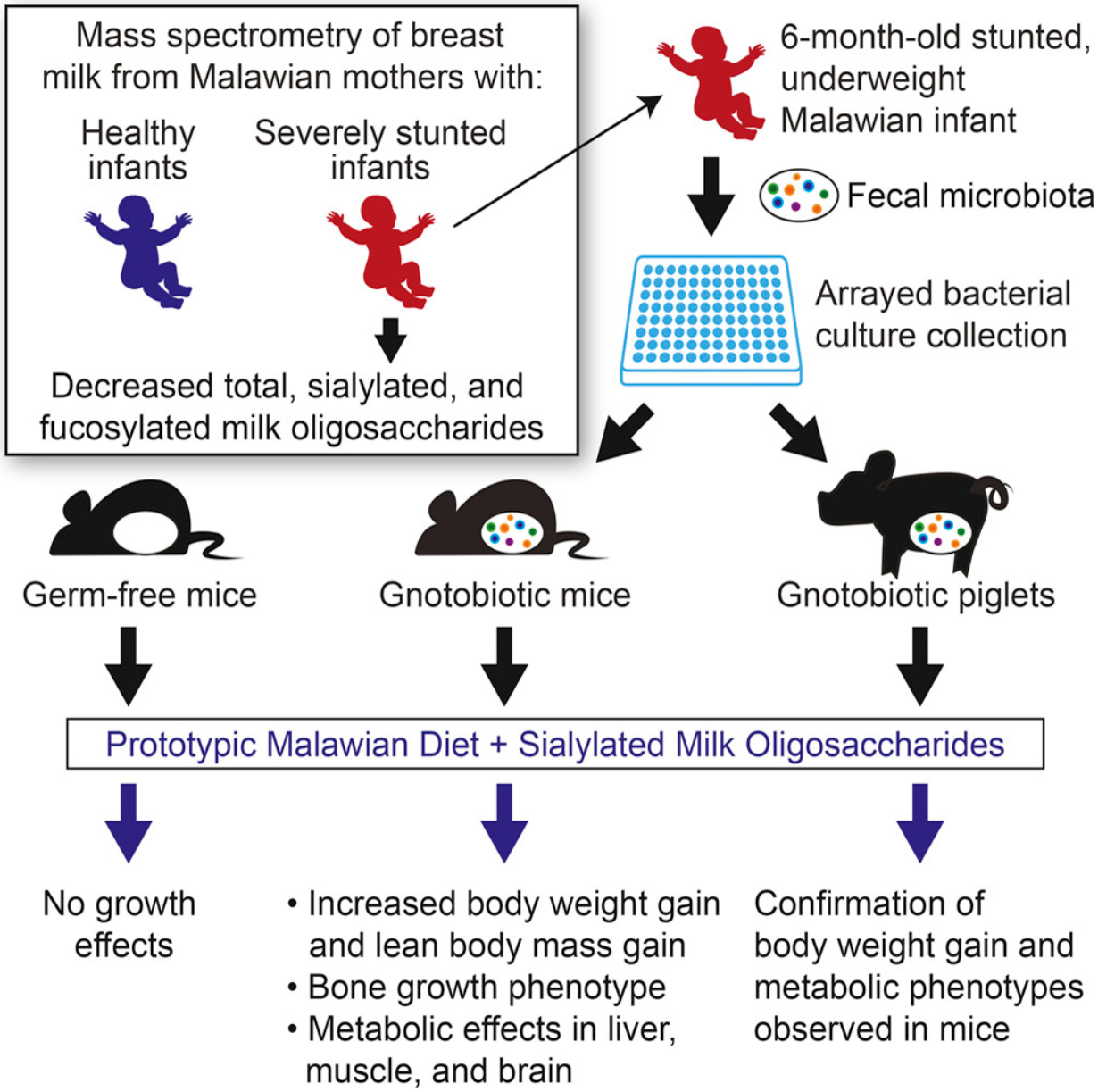
Newcastle University
Human Nutrition Research Centre

Interplay between nutrition and the microbiome



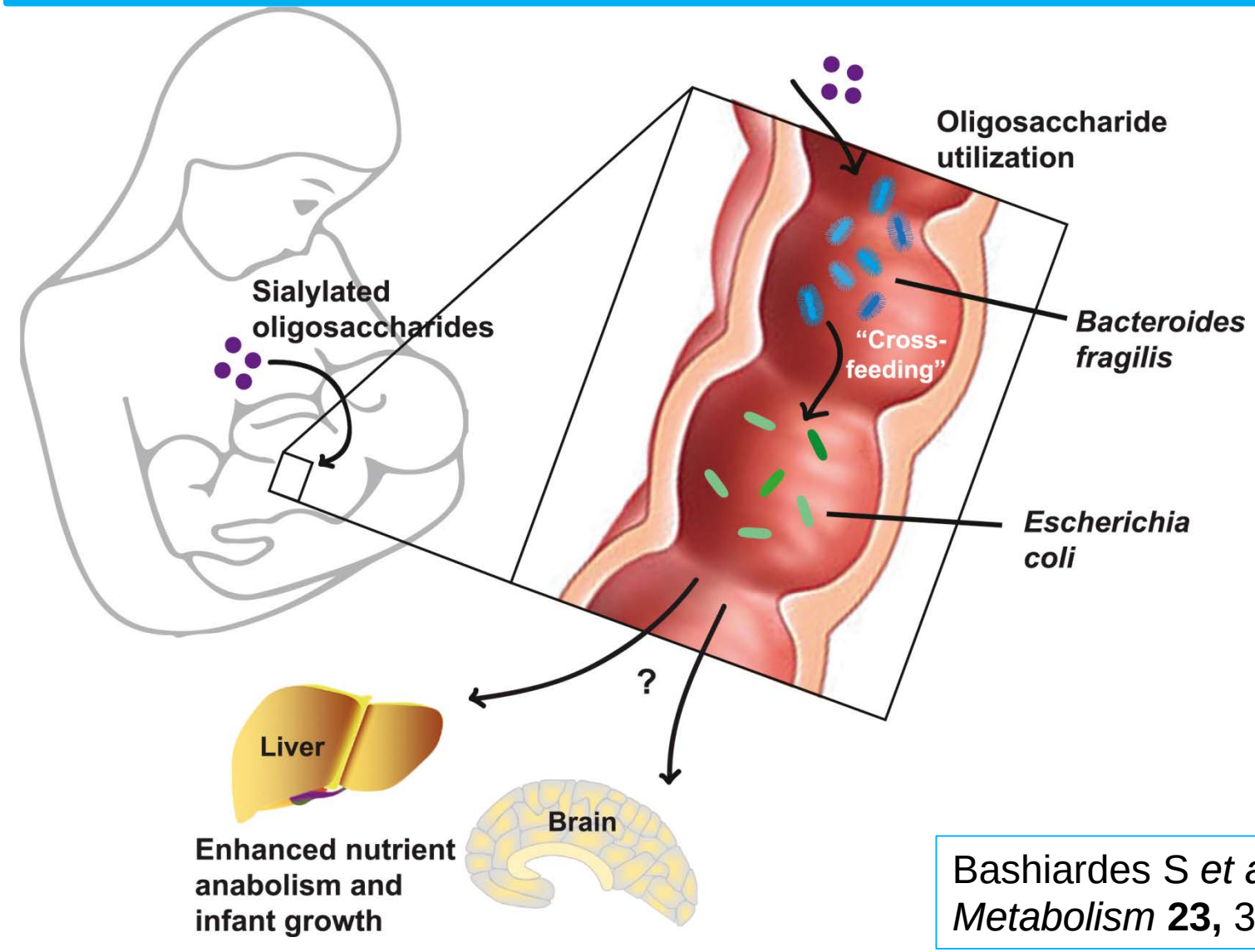
Verma M *et al.* (2016) *Frontiers in Nutrition* **3:**5

Modelling impact of malnutrition on gut microbiota



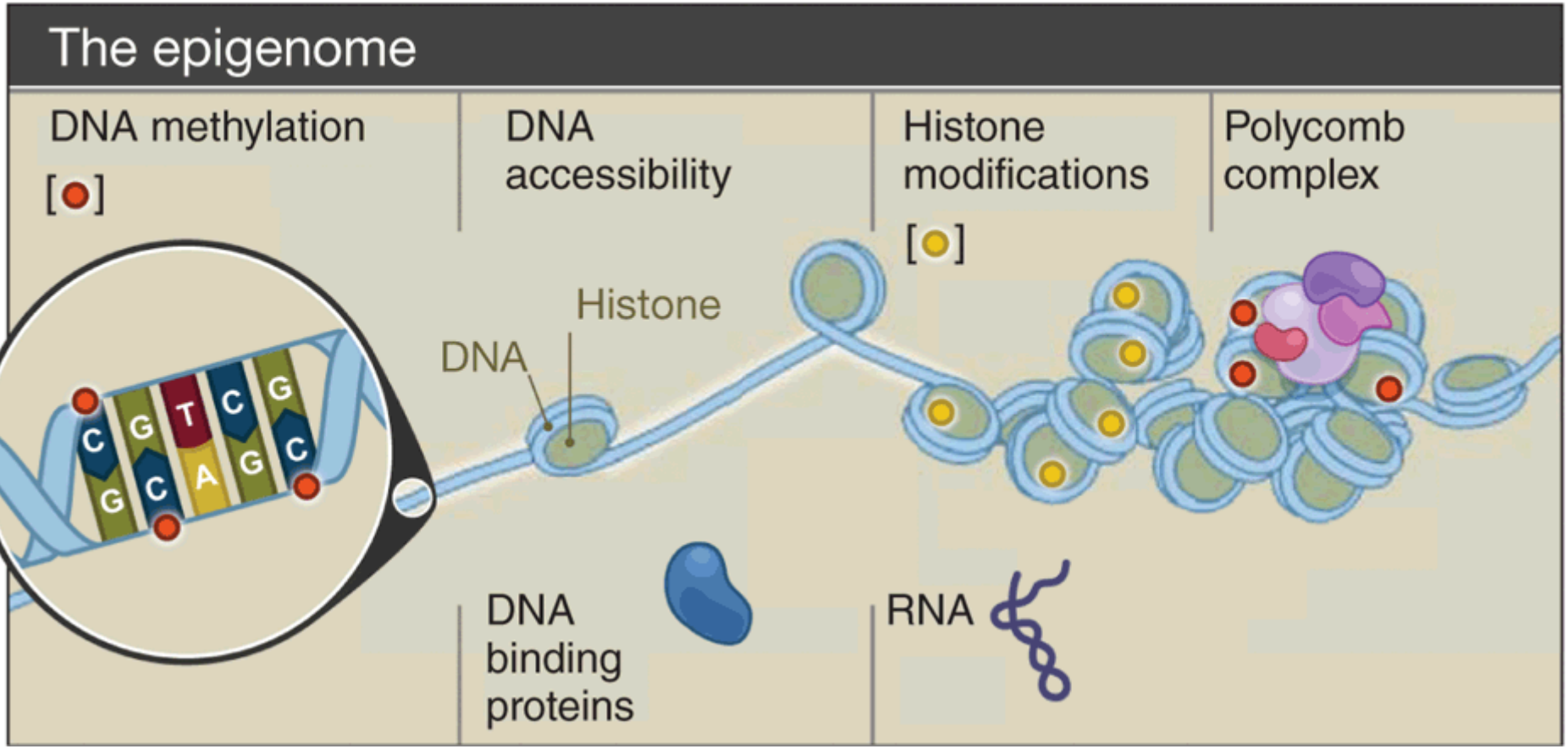
Charbonneau MR *et al.* (2016) *Cell* **164,** 859-871

Breastmilk oligosaccharides “feed” gut microbiota



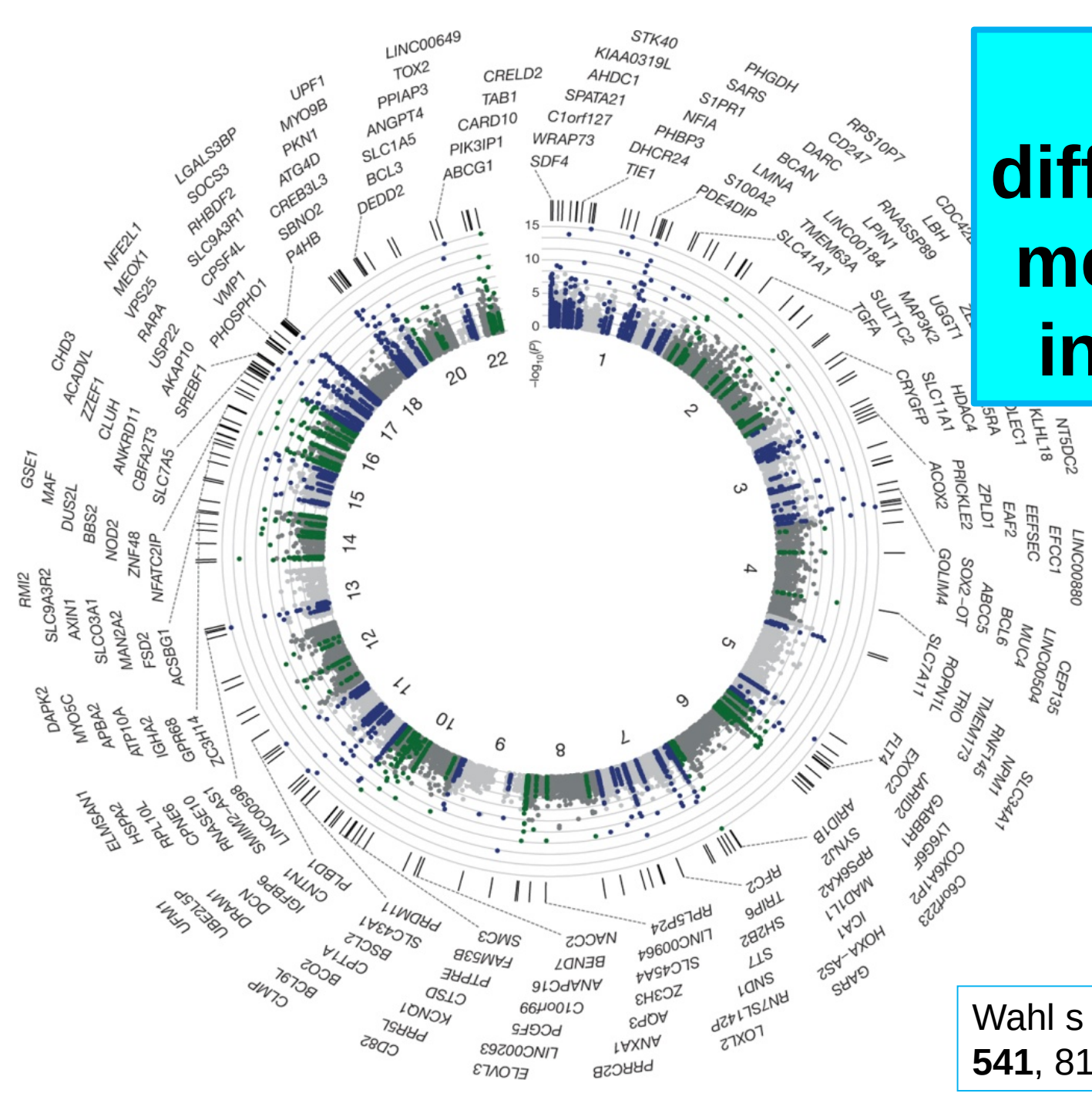
Bashiardes S *et al.* (2016) *Cell Metabolism* **23,** 393-394

Nutrition and epigenomics



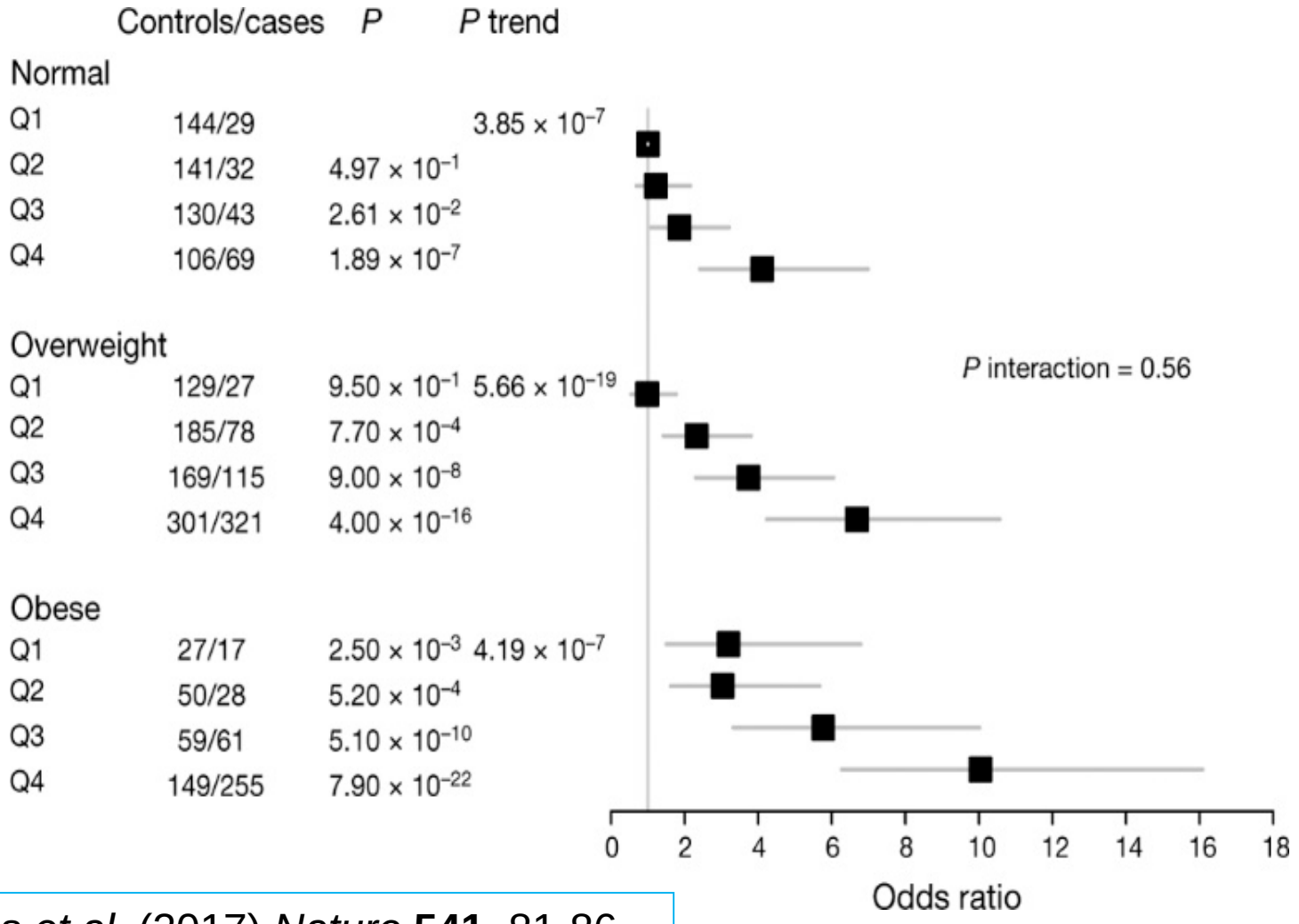
Bernstein BE et al. (2010) *Nature Biotechnol.* **28,** 1045-1048

Genes differentially methylated in obesity



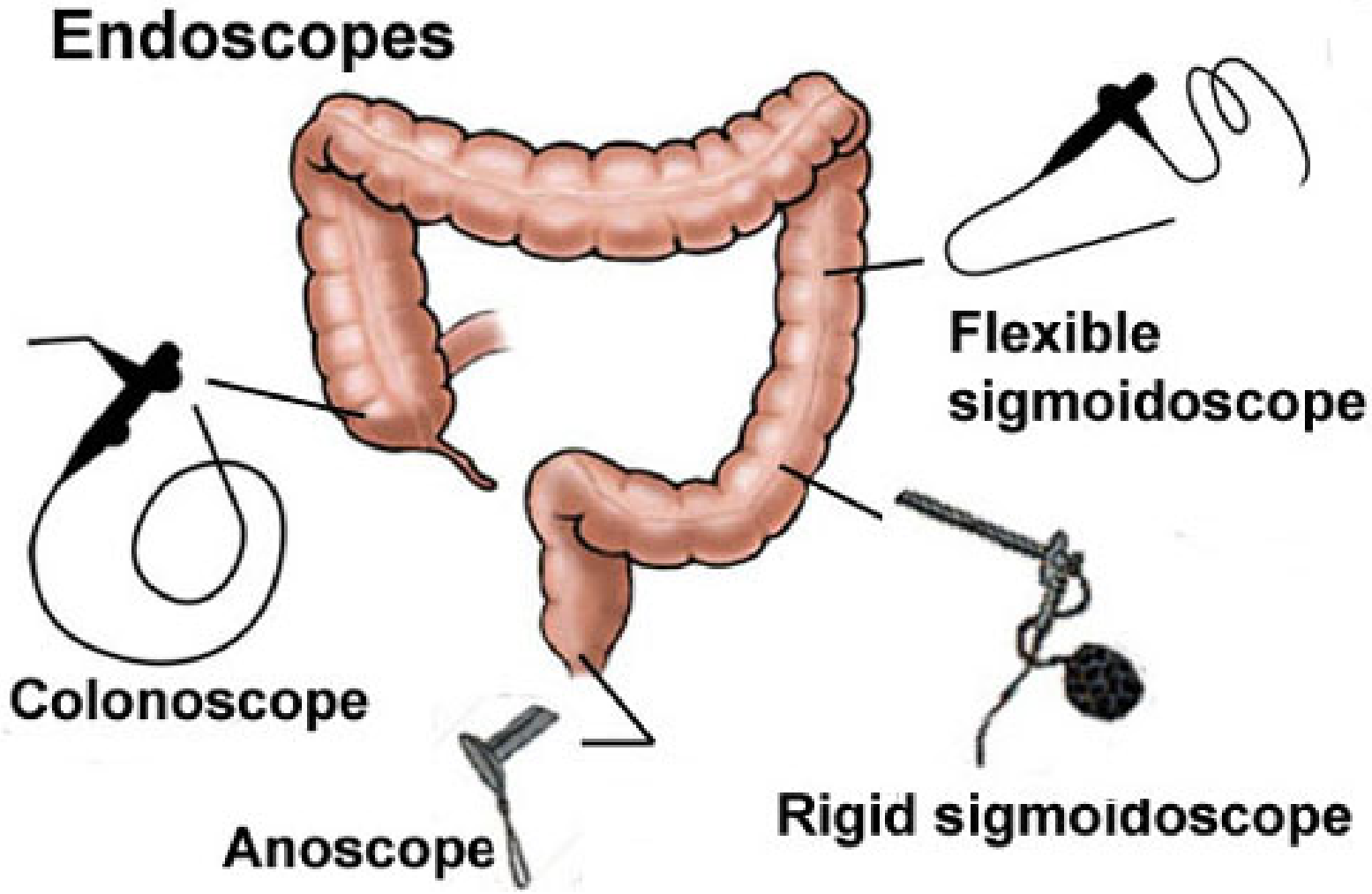
Wahl s *et al.* (2017) *Nature* **541**, 81-86

Methylation risk score and type 2 diabetes in Indian Asians

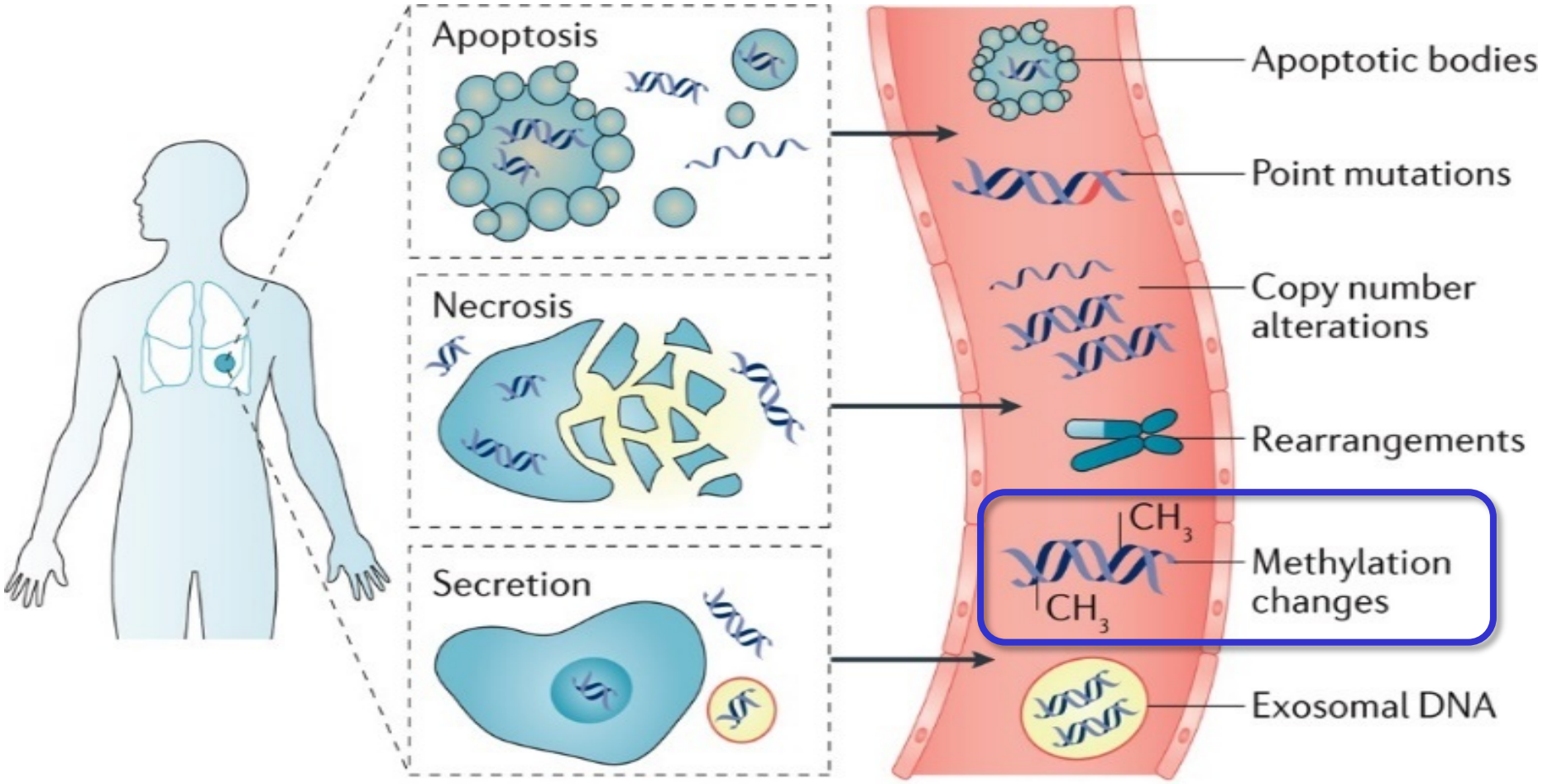


Wahl s *et al.* (2017) *Nature* **541**, 81-86

Epigenetic (DNA methylation) patterns are cell-type specific

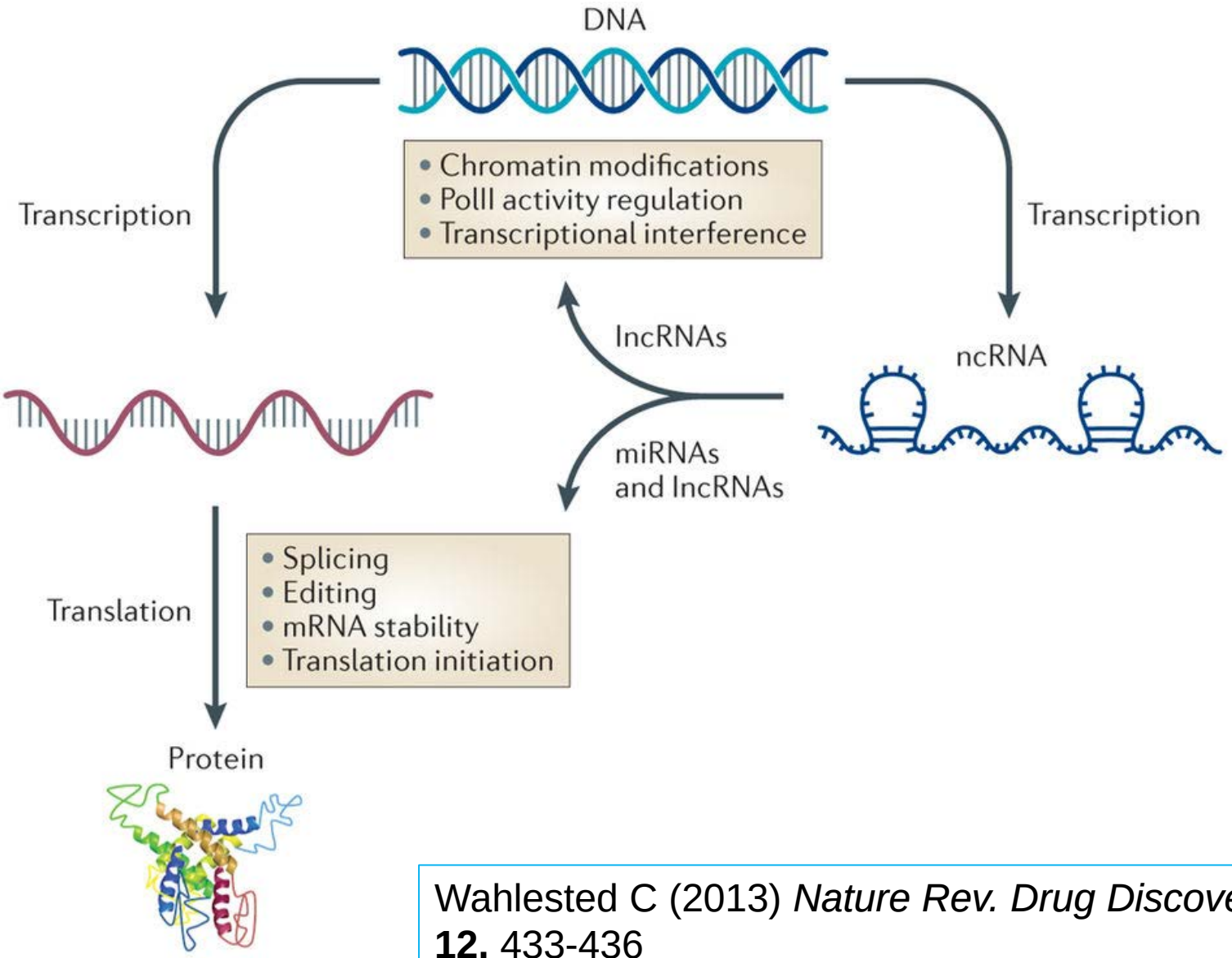


Potential utility of cell-free DNA



Wan JCM et al. (2017) *Nature Rev. Cancer* **17,** 223-238

Regulation by non-coding RNAs



Wahlested C (2013) *Nature Rev. Drug Discovery* **12,** 433-436

Most of us work for the taxpayer

The taxpayer - that's someone who works for the federal government but doesn't have to take the civil service examination.

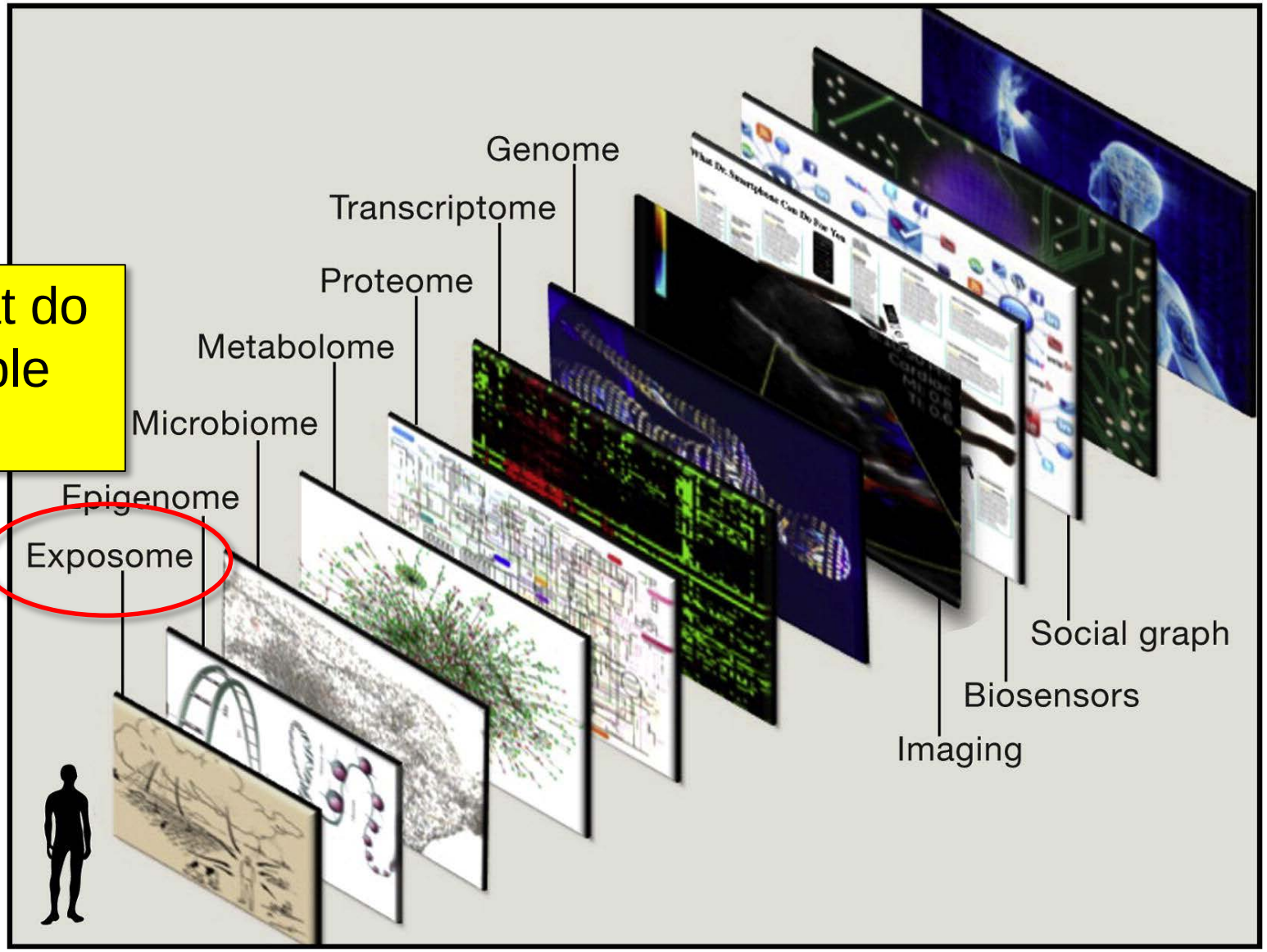
(Ronald Reagan)

izquotes.com

Nutrigenomics:
Applications to improve public health

Measuring dietary intake

Combining data across multiple levels



Adapted from Topol EJ (2014) *Cell* **157,** 241-253

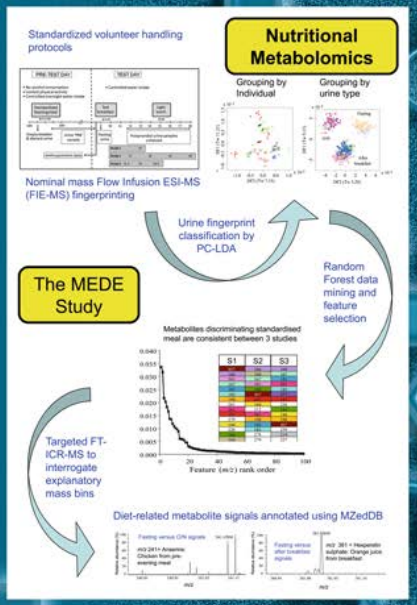
Using metabolomics approaches to discover novel biomarkers of food intake

Newcastle University

Prifysgol Aberystwyth University

Favé G *et al.* (2011)
Metabolomics 7, 469-484

METABOLOMICS
Volume 7 • Number 4
December 2011

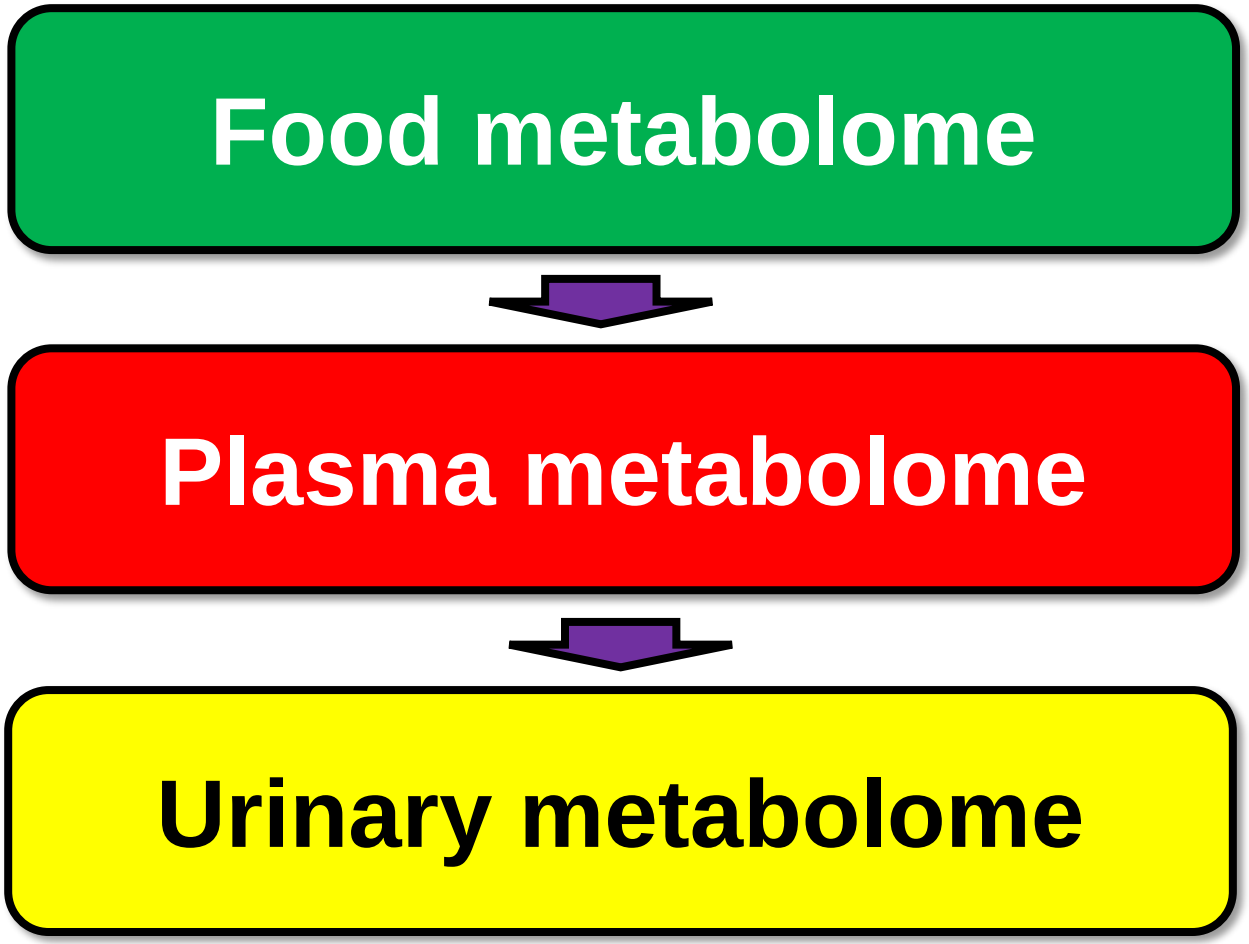


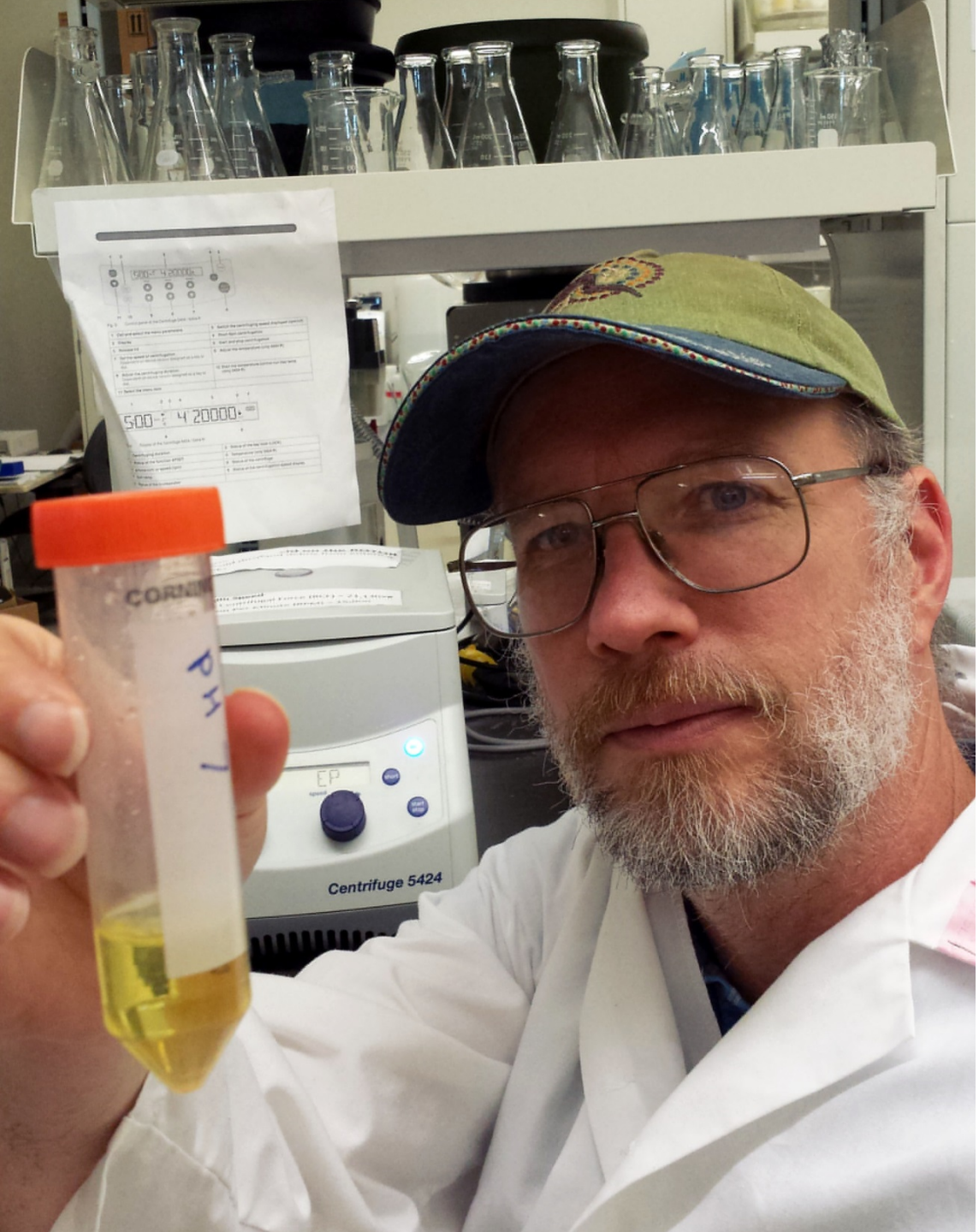
The Official Journal of
The Metabolomics Society

Springer
11306 • ISSN 1573-3882
7(4) 457–624 (2011)

Available online
www.springerlink.com

Rationale for a metabolomics approach for discovery of novel biomarkers of food intake



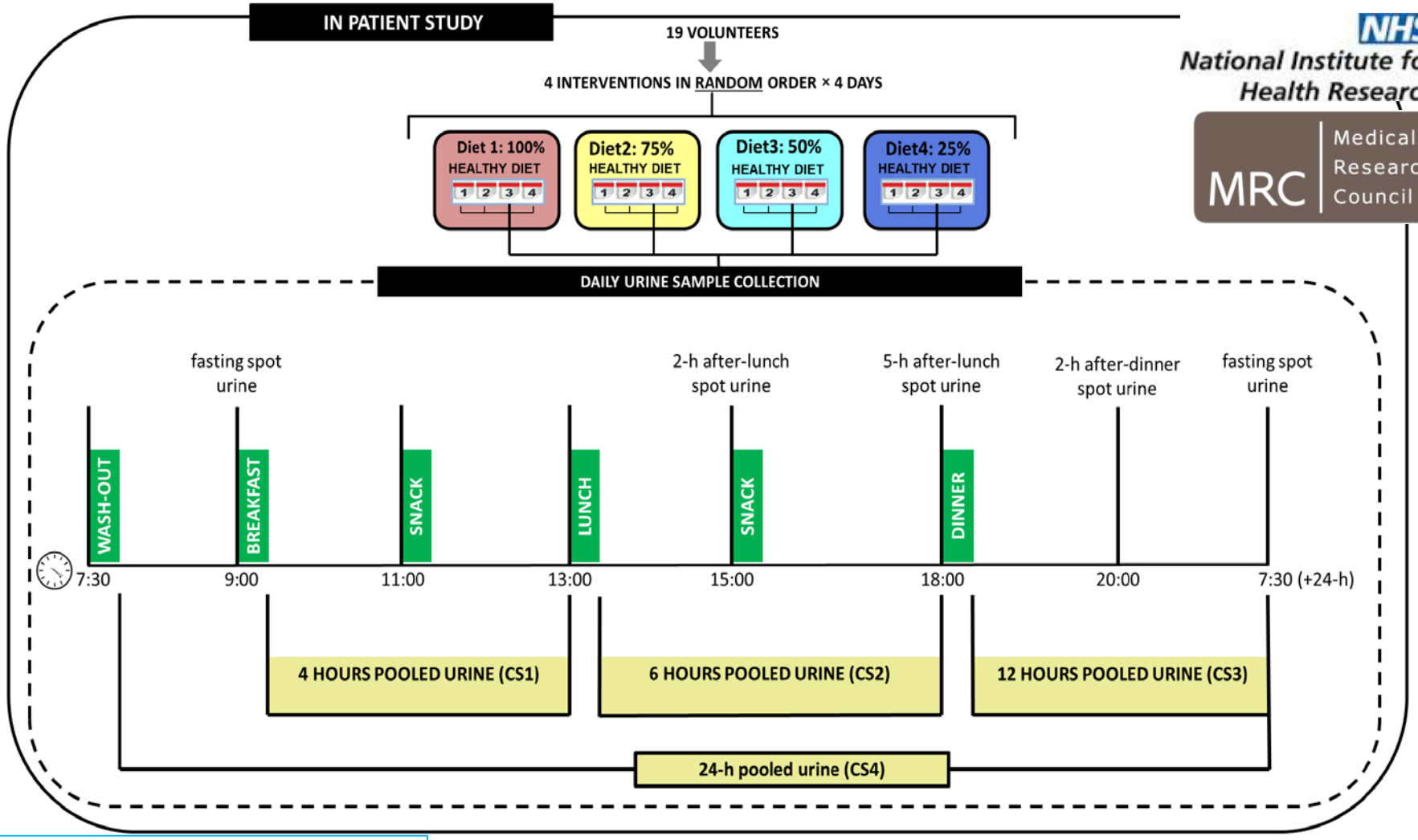


FOODBALL

The Food Biomarker Alliance

Challenge: Can we develop biomarkers for dietary patterns?

Study design



NHS National Institute for Health Research

MRC Medical Research Council

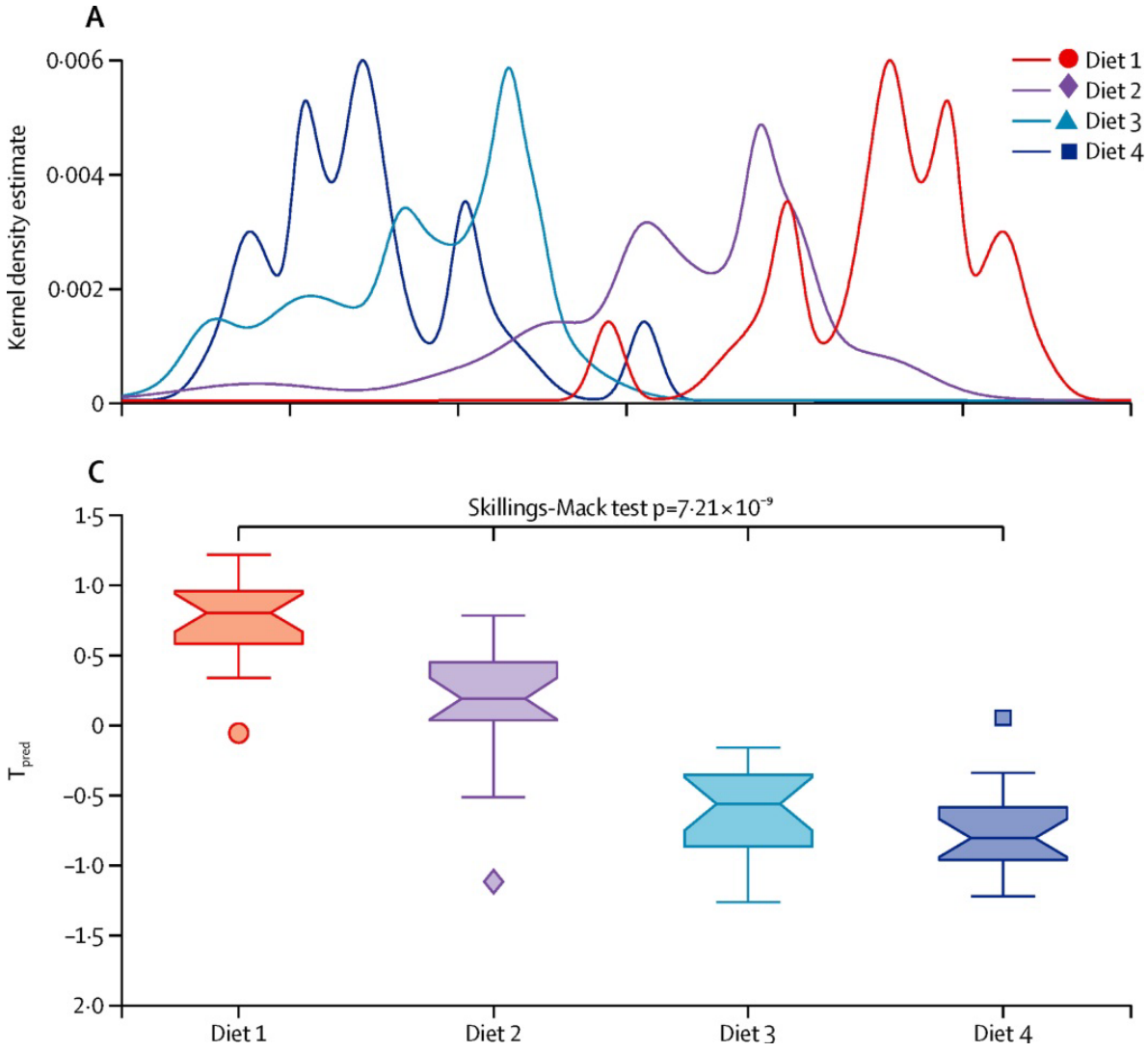
Garcia-Perez I *et al.* (2017) *Lancet Diabetes Endocrinol.* **5,** 185-195

Imperial College London

Prifysgol Aberystwyth University

Newcastle University

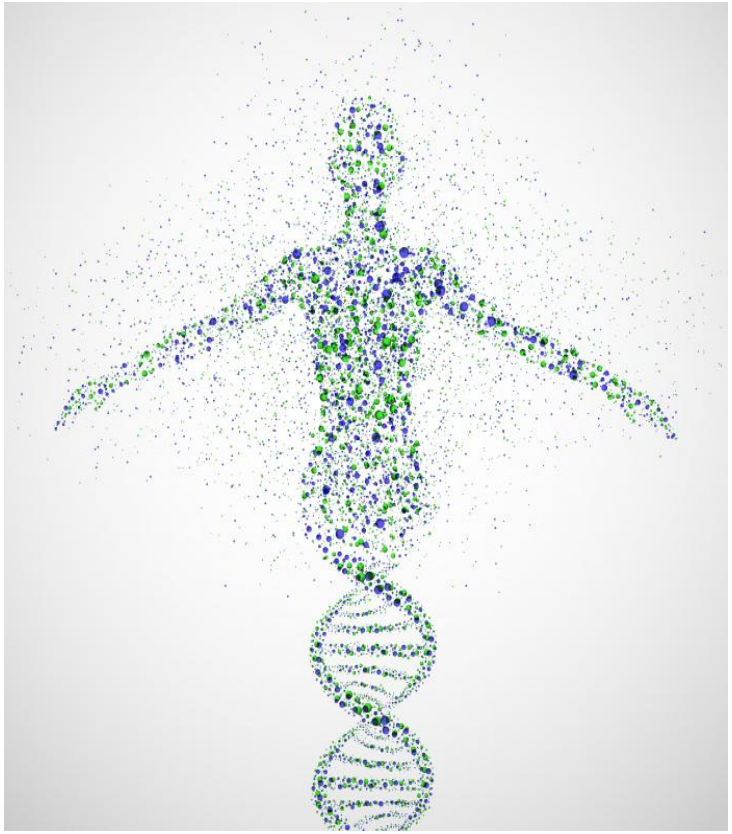
Diet “healthiness” is reflected in urinary metabolite patterns



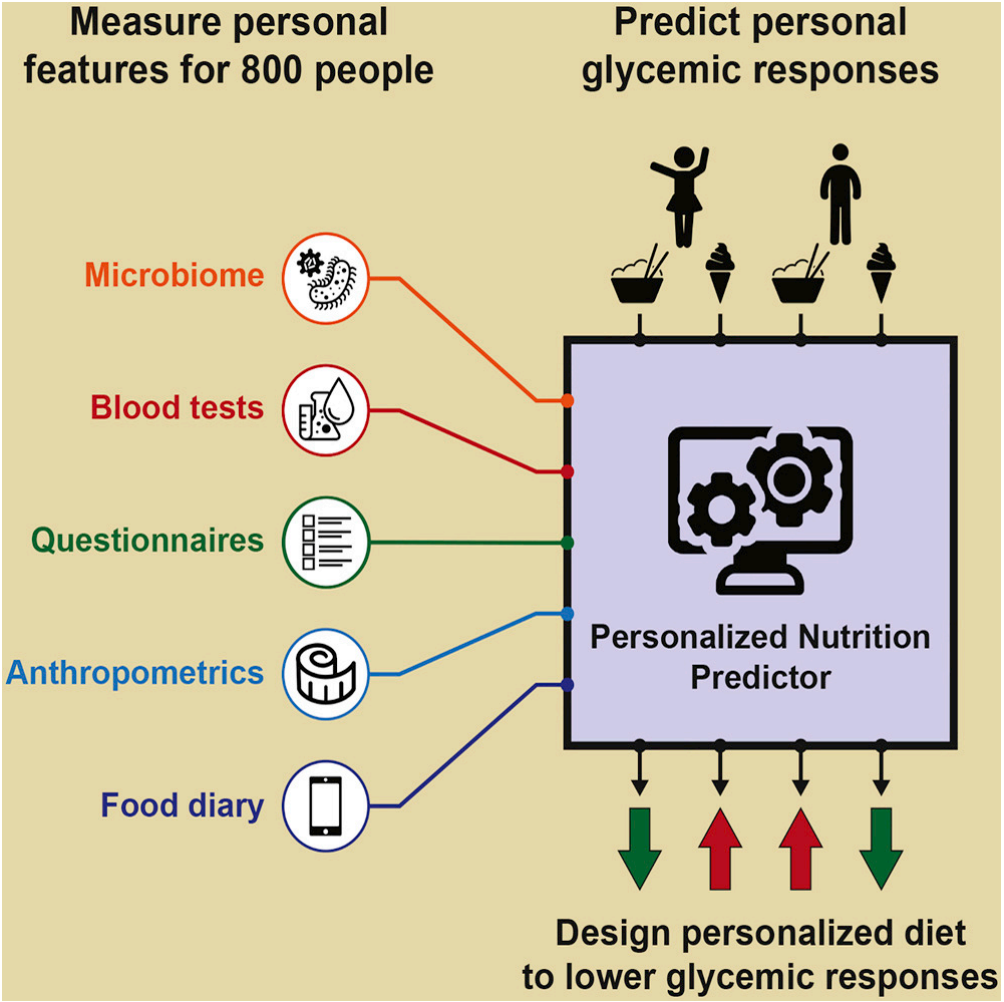
Validated in INTERMAP UK (n=225) and a Danish healthy-eating cohort (n=66)

Garcia-Perez I *et al.* (2017) *Lancet Diabetes Endocrinol.* **5,** 185-195

Application of nutrigenomics: Personalised Nutrition

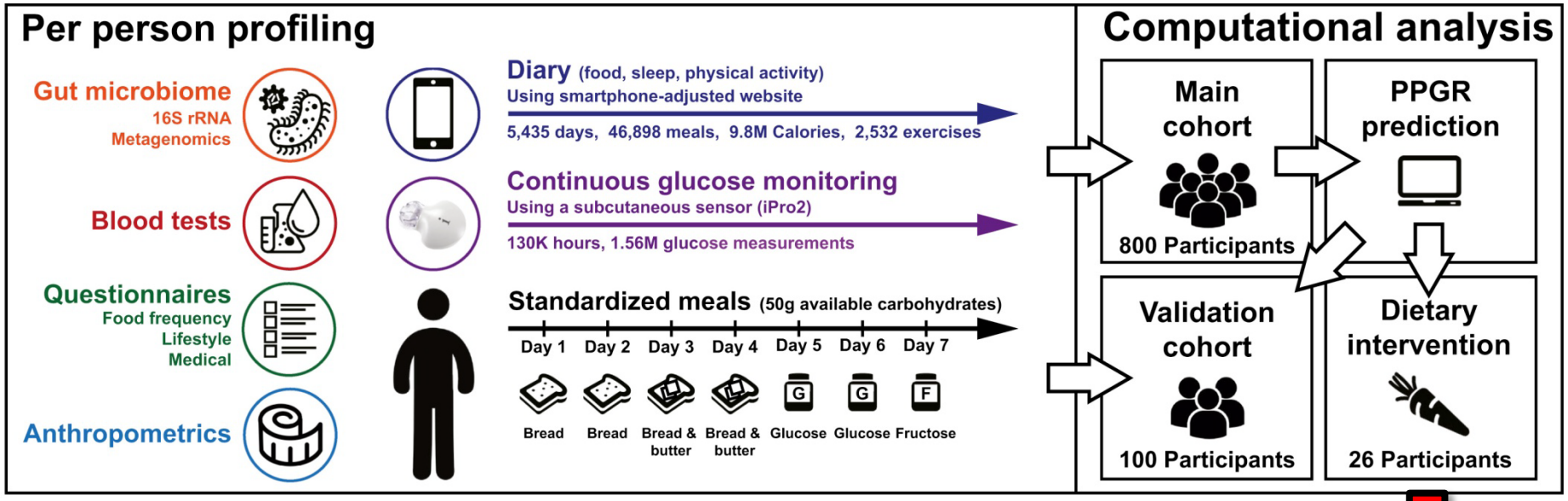


Personalised Nutrition by Prediction of Glycaemic Responses



Zeevi D *et al.* (2015) *Cell* **163,** 1079-1094

Overview of study



Prescribe "good" and "bad" diets

Good prediction of glycaemic responses over 7 days

Zeevi D *et al.* (2015) *Cell* **163,** 1079-1094

RCT in >1600 people across 7 European countries

A "Proof of Principle" study of Personalised Nutrition across Europe: The Food4Me intervention study

Celis-Morales C *et al.* (2017) *International Journal of Epidemiology* **46,** 578-588

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration. (Contract n°265494)

Take home messages

Personalised nutrition works

No added advantage of phenotypic or genetic information

Internet-based delivery is effective

Celis-Morales C *et al.* (2017) *International Journal of Epidemiology* **46,** 578-588

What next for personalised nutrition?

Unanswered questions:

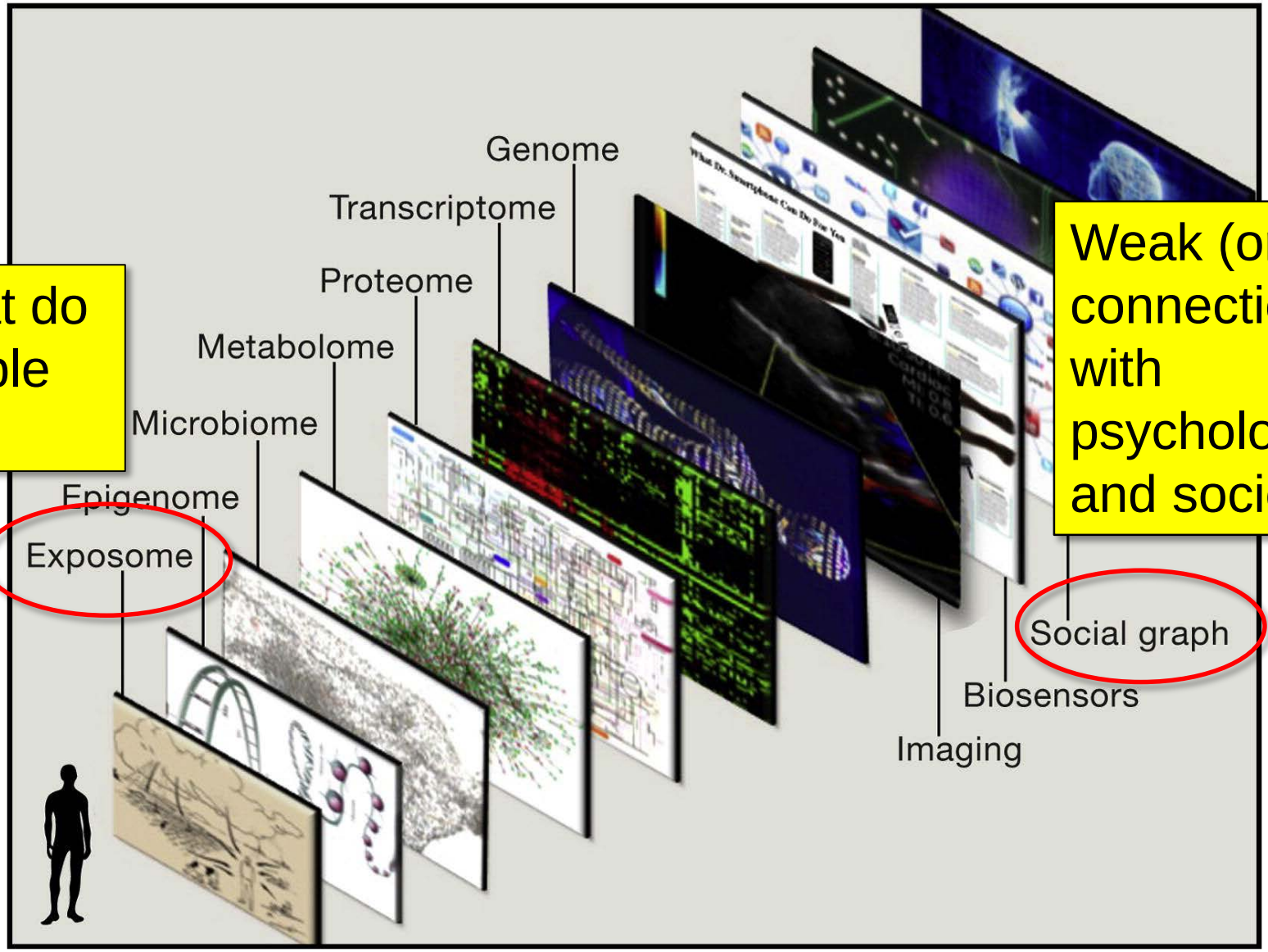
- What is personalised nutrition for?
  - Health-related goals?
  - Other personal goals?

- What are the key characteristics on which to base personalisation?

- Will personalised nutrition improve health outcomes?

- **Will personalised nutrition narrow (or exacerbate) health inequalities?**

Combining data across multiple levels



What do people eat?

Weak (or no) connections with psychology and sociology

Adapted from Topol EJ (2014) *Cell* **157,** 241-253

New opportunities for nutrigenomics

Better models make better science

Developments in stem cell biology

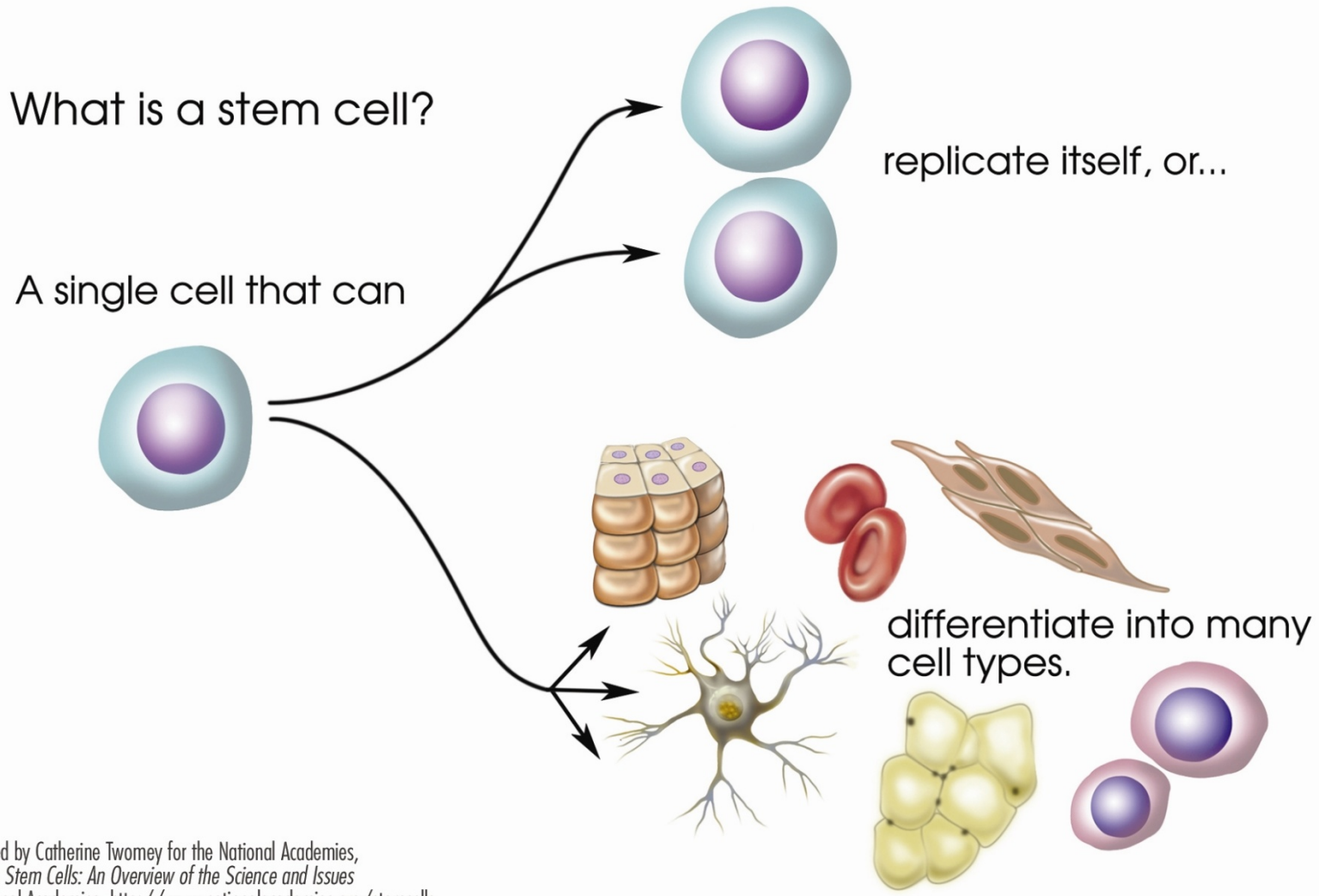
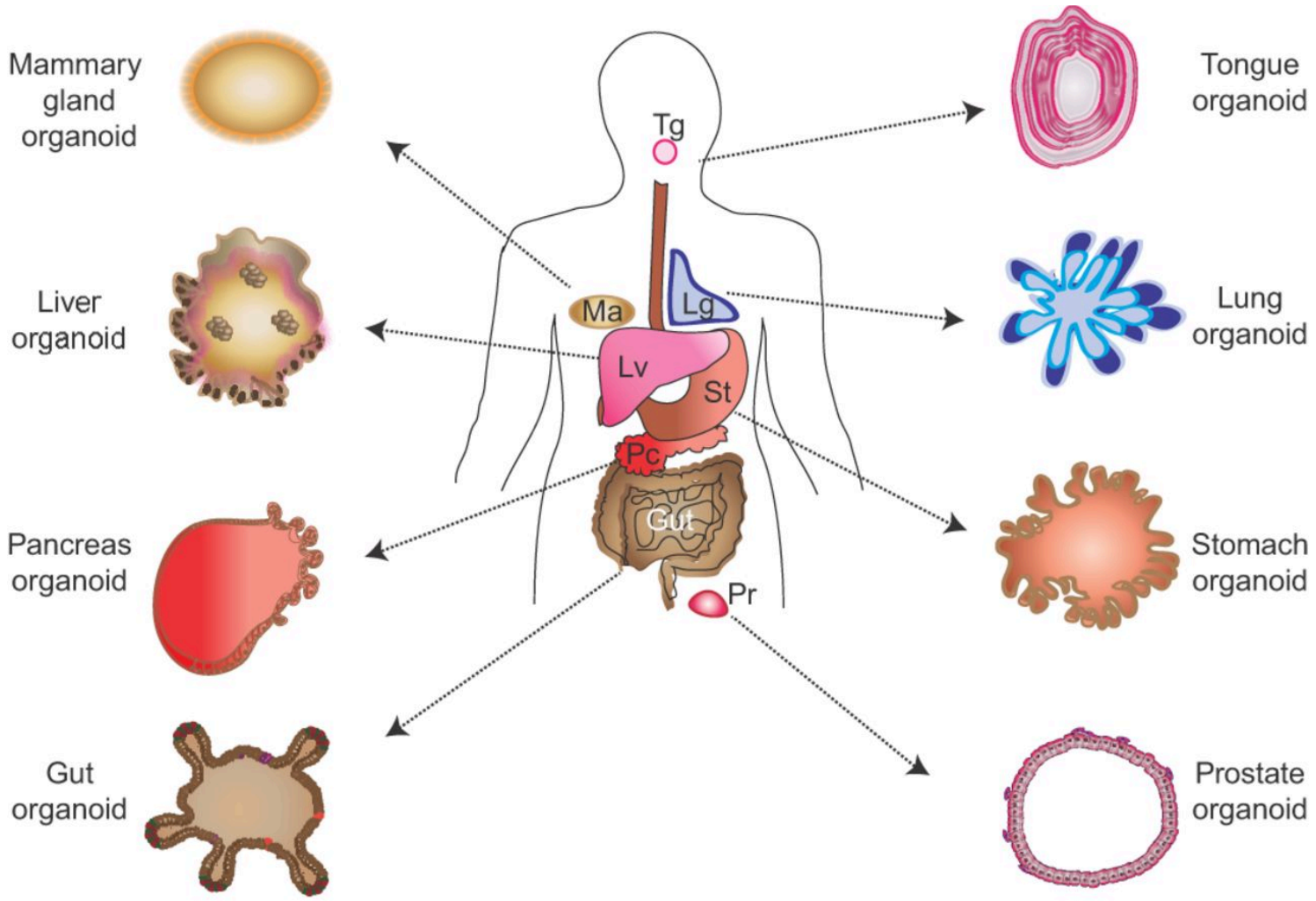


Image prepared by Catherine Twomey for the National Academies,
Understanding Stem Cells: An Overview of the Science and Issues
from the National Academies, http://www.nationalacademies.org/stemcells.
Academic noncommercial use is permitted.

Organoids from adult stem cells



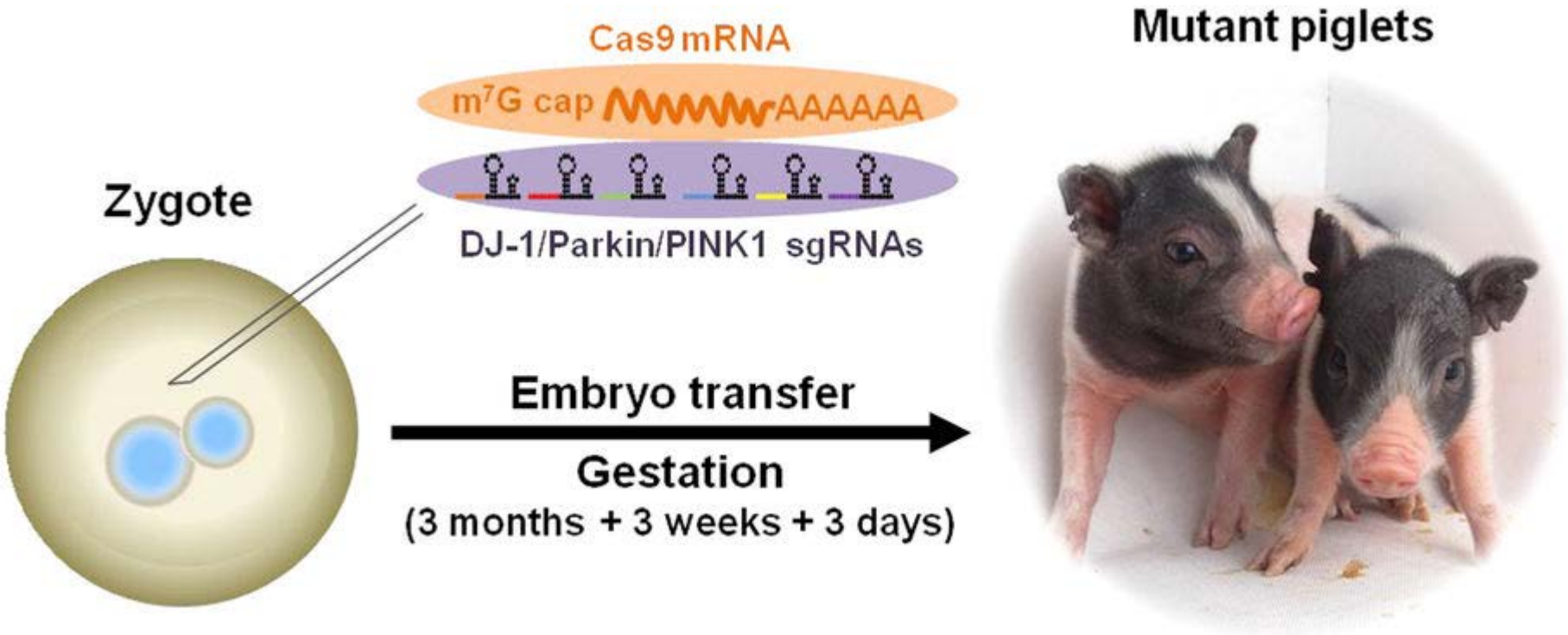
Huch M & Koo B-K (2015) *Development* **142,** 3113-3125

Development

Genome editing
From basic science to translation

Cyranoski D (2015) *Nature* **526,** 18

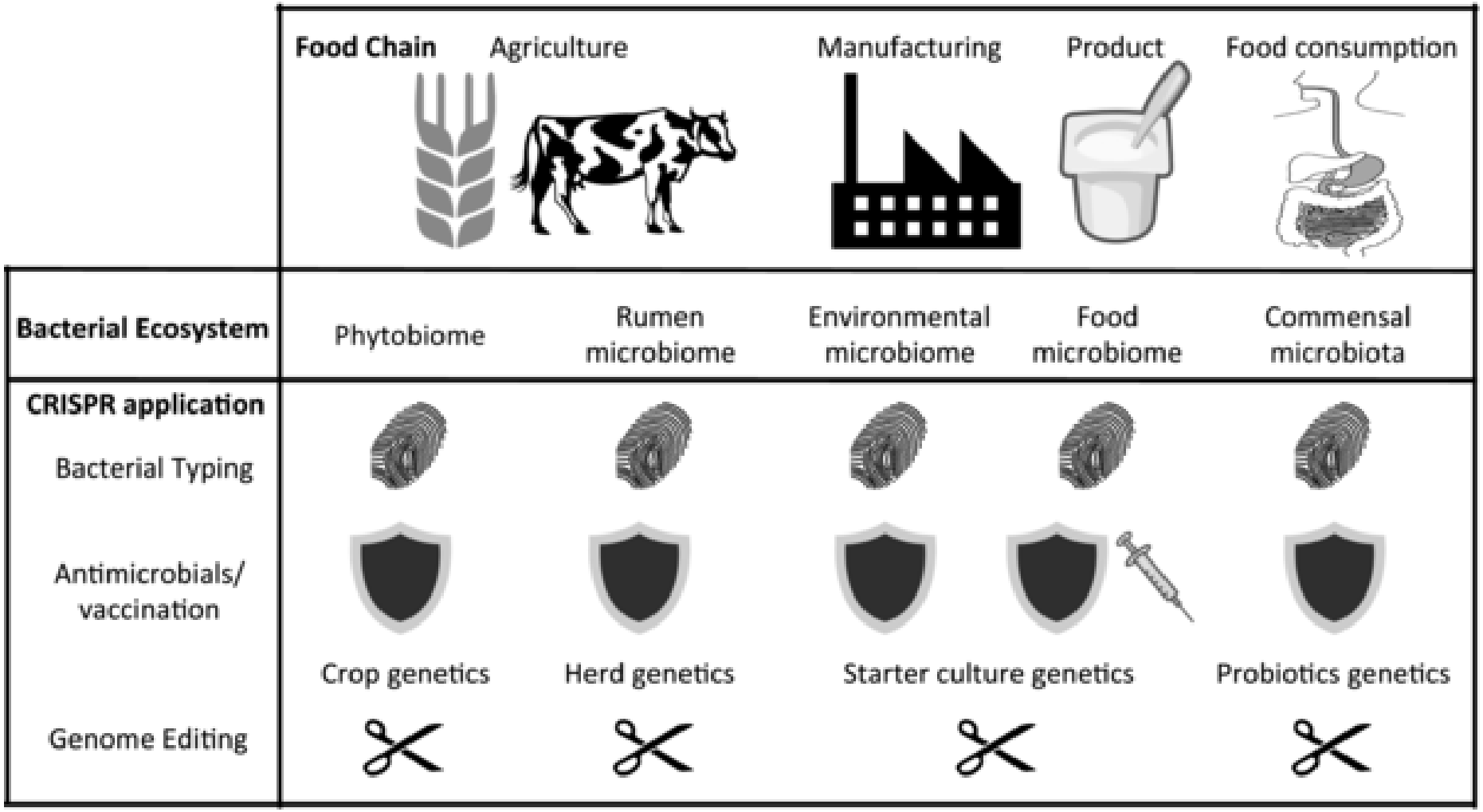
Using CRISPR-Cas to develop model of Parkinson's Disease



Wang X *et al.* (2016)
Scientific Reports **6**: 20620

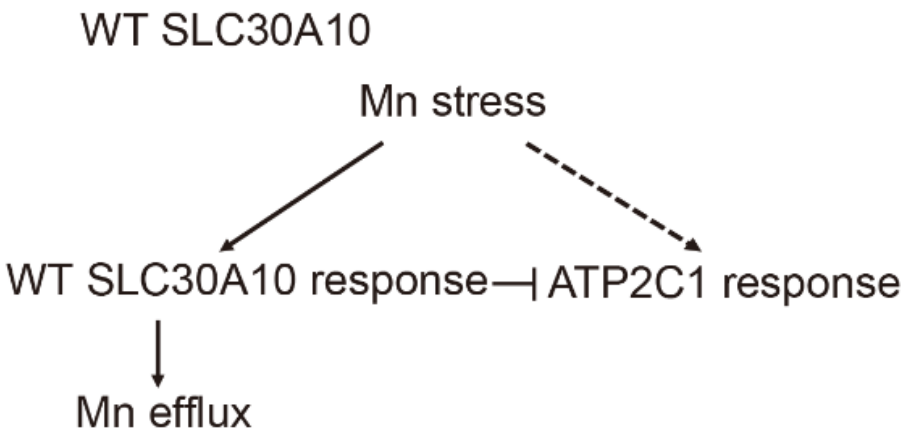
SCIENTIFIC REPORTS

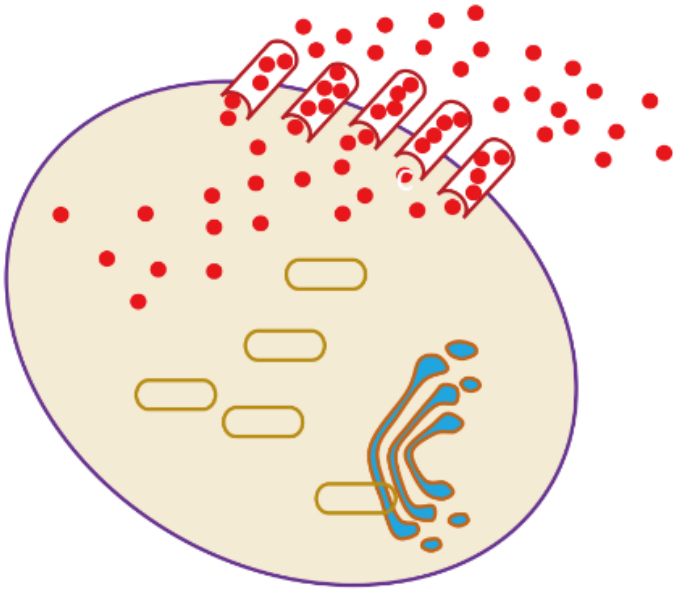
Gene editing in the future food industry



Selle K & Barrangou R (2015) *Food Science* **80,** R2367-R2372

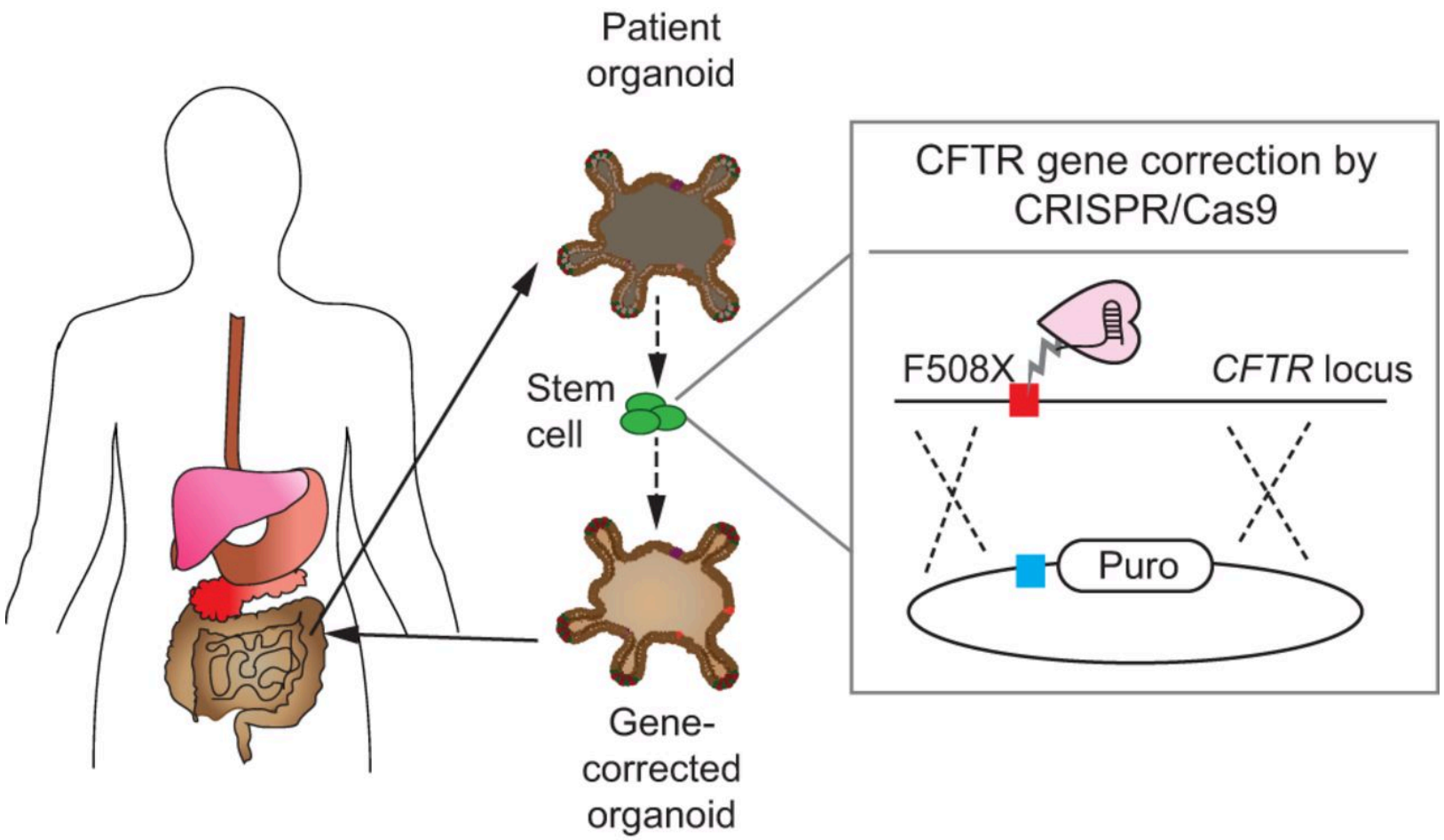
Gene editing using CRISPR in zebrafish to investigate manganese homeostasis





Xia Z *et al.* (2017) *PloS Genetics* **13:** e1006892

Using genome editing to repair gene defect in cystic fibrosis



Schwank G *et al.* (2013) *Cell Stem Cell* **13,** 663-658
Huch M & Koo B-K (2015) *Development* **142,** 3113-3125

Development

LEAH NASH/NYT/REDUX/EYEVINE

Targeted mutation in *MYBPC3* which causes hypertropic cardiomyopathy: major cause of sudden death in young athletes

Reproductive biologist Shoukhrat Mitalipov and his team used genome editing to correct a gene that causes a potentially fatal heart condition in humans.

BIOTECHNOLOGY

CRISPR fixes embryo error

Gene-editing experiment in human embryos pushes scientific and ethical boundaries.

Ledford H (2017) Nature **548,** 13-14

Schneller *et al. BMC Medicine* (2017) 15:43
DOI 10.1186/s12916-017-0798-4

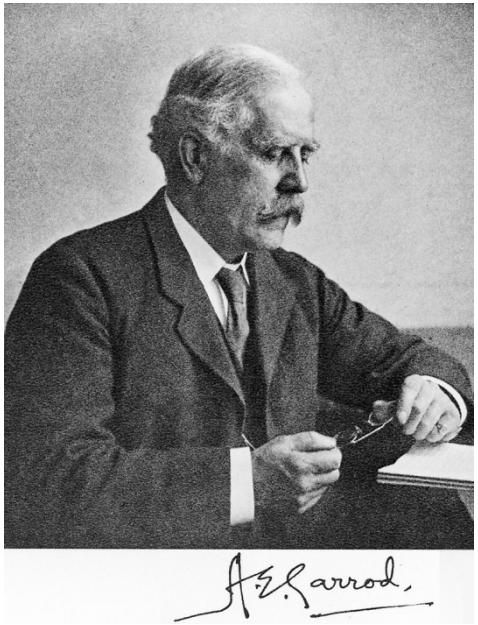
BMC Medicine

REVIEW Open Access

Genome editing for inborn errors of metabolism: advancing towards the clinic

Jessica L. Schneller[1,2], Ciaran M. Lee[3], Gang Bao[3] and Charles P. Venditti[2*]

?

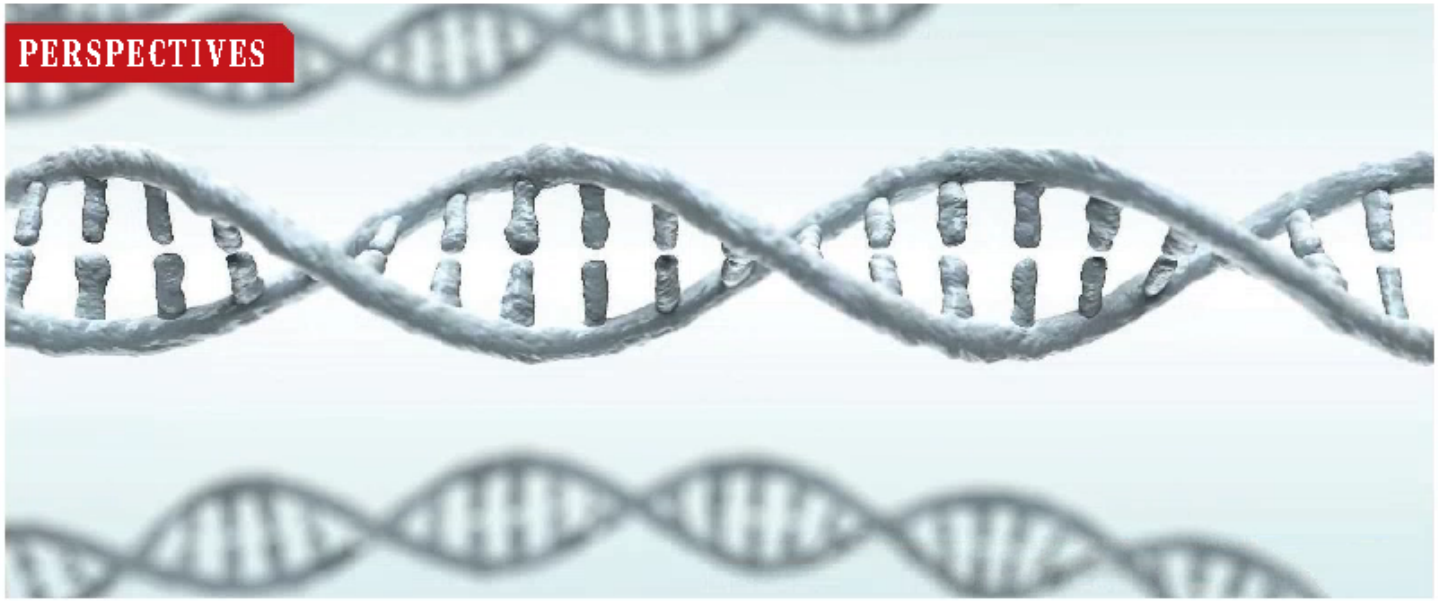


?

Ethical considerations

INSIGHTS

PERSPECTIVES



BIOTECHNOLOGY

A prudent path forward for genomic engineering and germline gene modification

A framework for open discourse on the use of CRISPR-Cas9 technology to manipulate the human genome is urgently needed

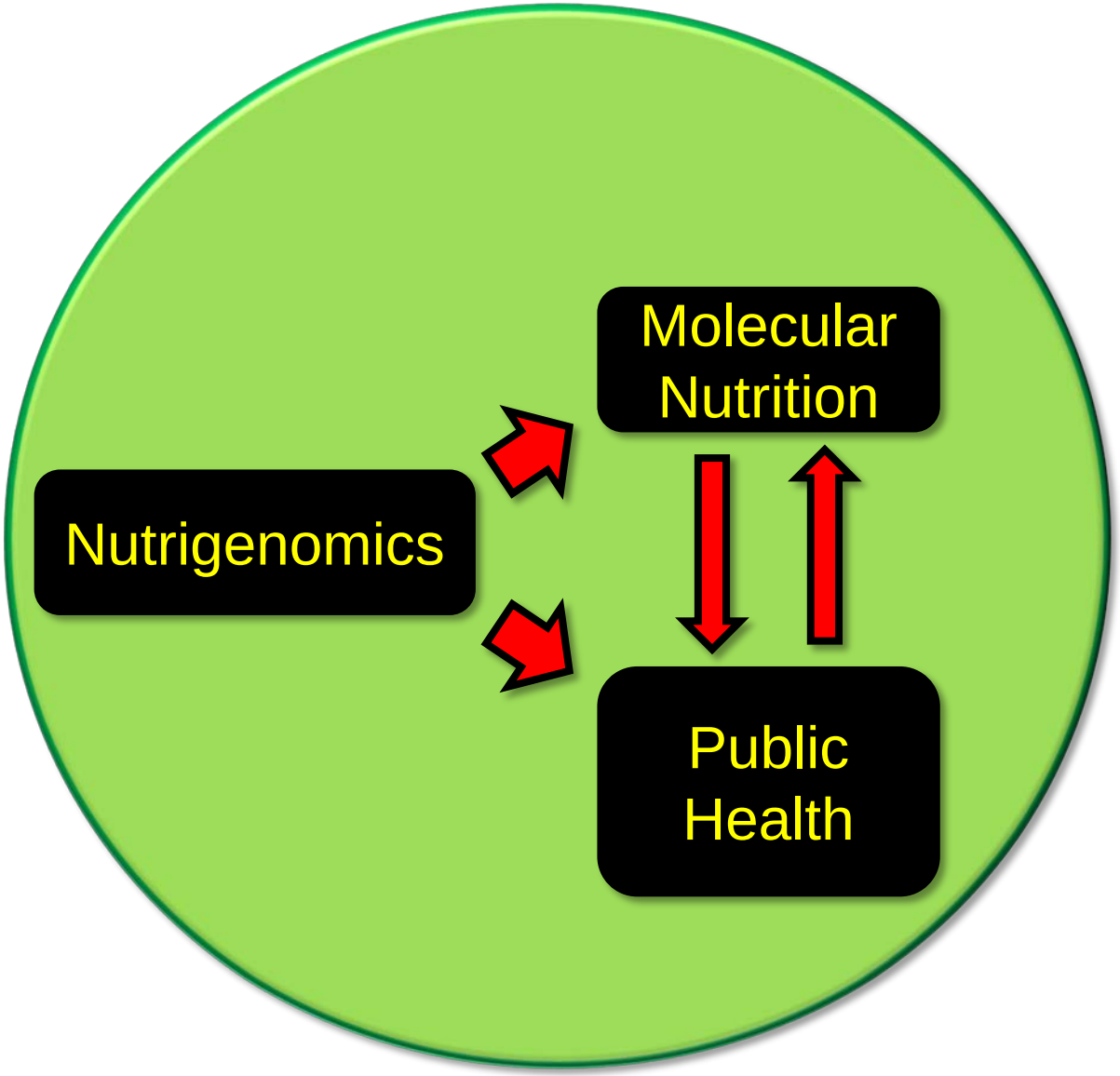
By David Baltimore,[1] Paul Berg,[2] Michael Botchan,[3,4] Dana Carroll,[5]

ture developments. The meeting identified immediate steps to take toward ensuring

CURRENT APPLICATIONS. The simplicity of the CRISPR-Cas9 system allows any re-

Baltimore D *et al.* (2015) *Science* **348,** 36-38

The future of nutrigenomics?



Summary

- ✓ **You** will make the future of nutrigenomics
- ✓ Be ambitious – tackle the big questions
- ✓ Design better hypothesis-testing studies
- ✓ Innovate – use novel approaches/ technologies
- ✓ Collaborate, especially with other disciplines

NuGO

Newcastle University

Human Nutrition Research Centre