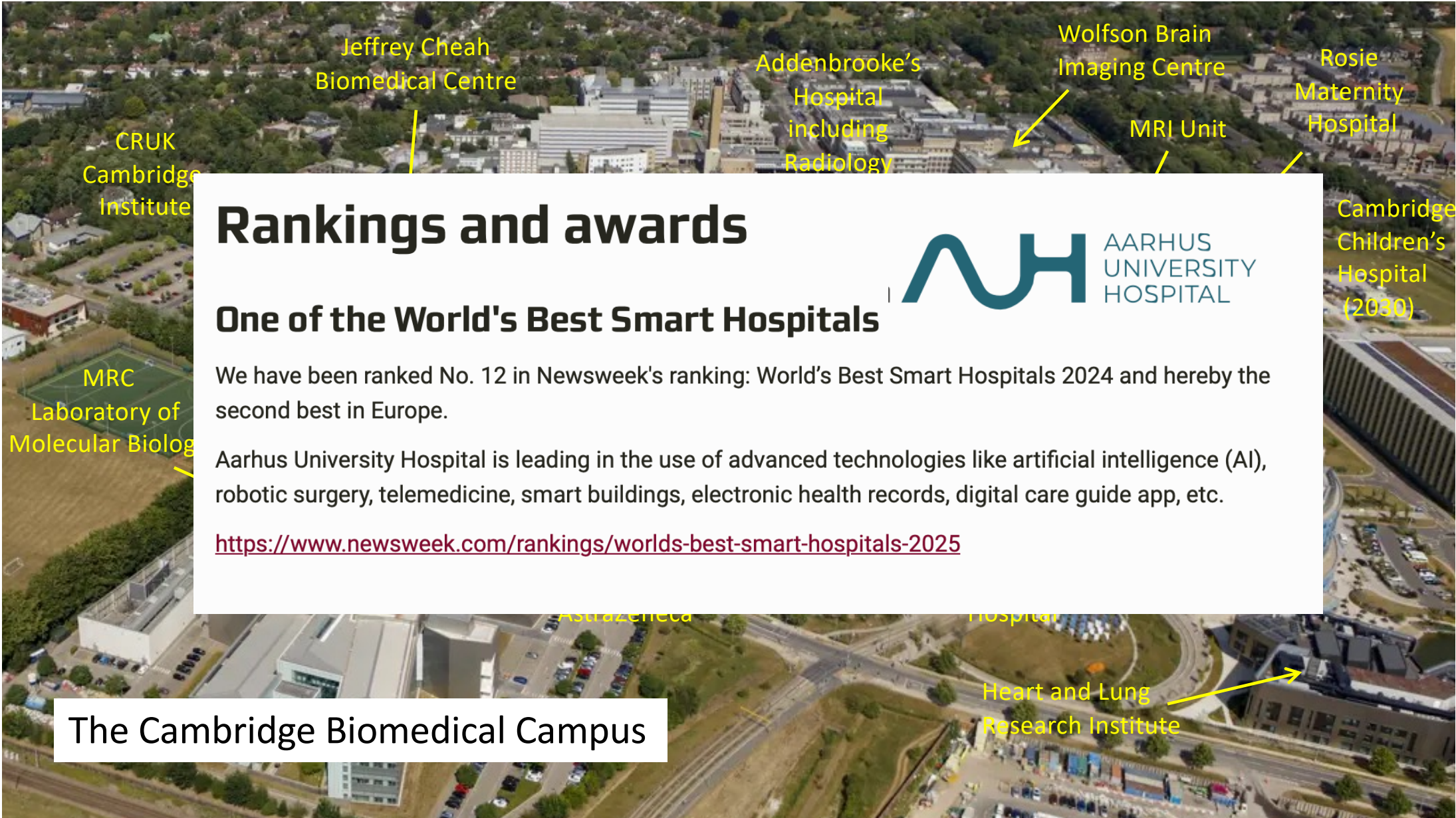


Considerations for Human Experiments

Ferdia Gallagher

Department of Radiology, University of Cambridge
Training Course on Hyperpolarized ^{13}C & ^{129}Xe MRI:
moving to clinical use, Aarhus 7th October 2026



CRUK Cambridge Institute

Jeffrey Cheah Biomedical Centre

Addenbrooke's Hospital including Radiology

Wolfson Brain Imaging Centre

MRI Unit

Rosie Maternity Hospital

Cambridge Children's Hospital (2030)

Rankings and awards

One of the World's Best Smart Hospitals



We have been ranked No. 12 in Newsweek's ranking: World's Best Smart Hospitals 2024 and hereby the second best in Europe.

Aarhus University Hospital is leading in the use of advanced technologies like artificial intelligence (AI), robotic surgery, telemedicine, smart buildings, electronic health records, digital care guide app, etc.

<https://www.newsweek.com/rankings/worlds-best-smart-hospitals-2025>

The Cambridge Biomedical Campus

AstraZeneca

Heart and Lung Research Institute

1766

Imaging in Cambridge

Preclinical Imaging

MRI
PET/CT
Ultrasound
PHIP polariser
Multiphoton microscopy
Photoacoustic Imaging
Bioluminescent

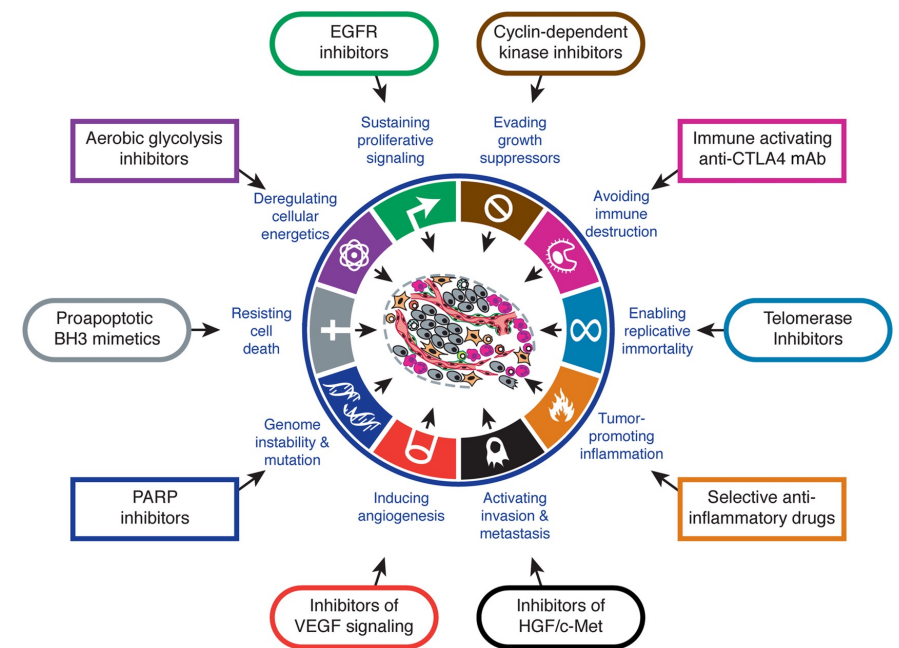


Clinical Imaging

MRI (7T, 3T 1.5T)
PET/MRI
Hyperpolarised carbon-13
Xenon Polariser
PET/CT, SPECT/CT
CT
Ultrasound
Photoacoustic Imaging
Radiopharmacy Unit
Radiochemistry Unit

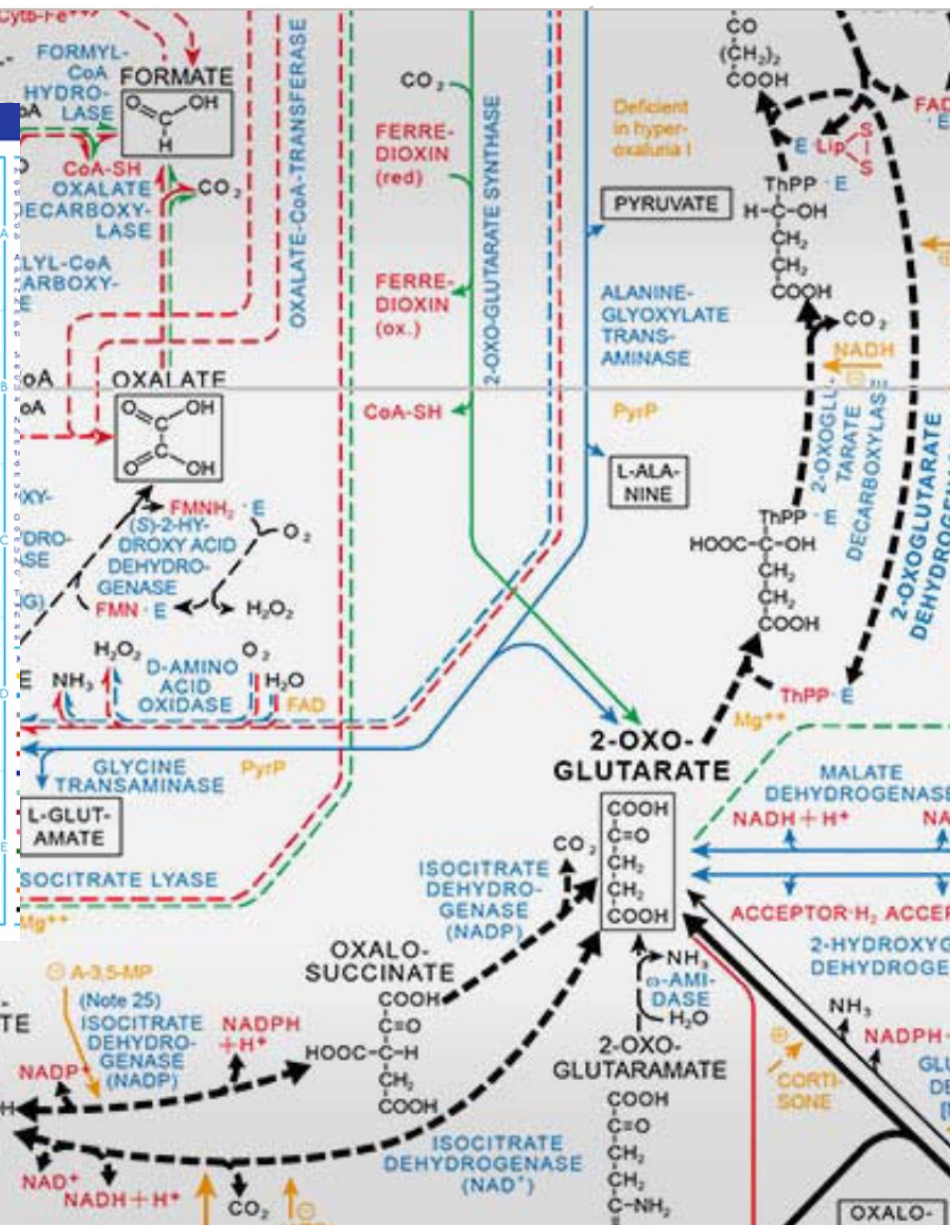
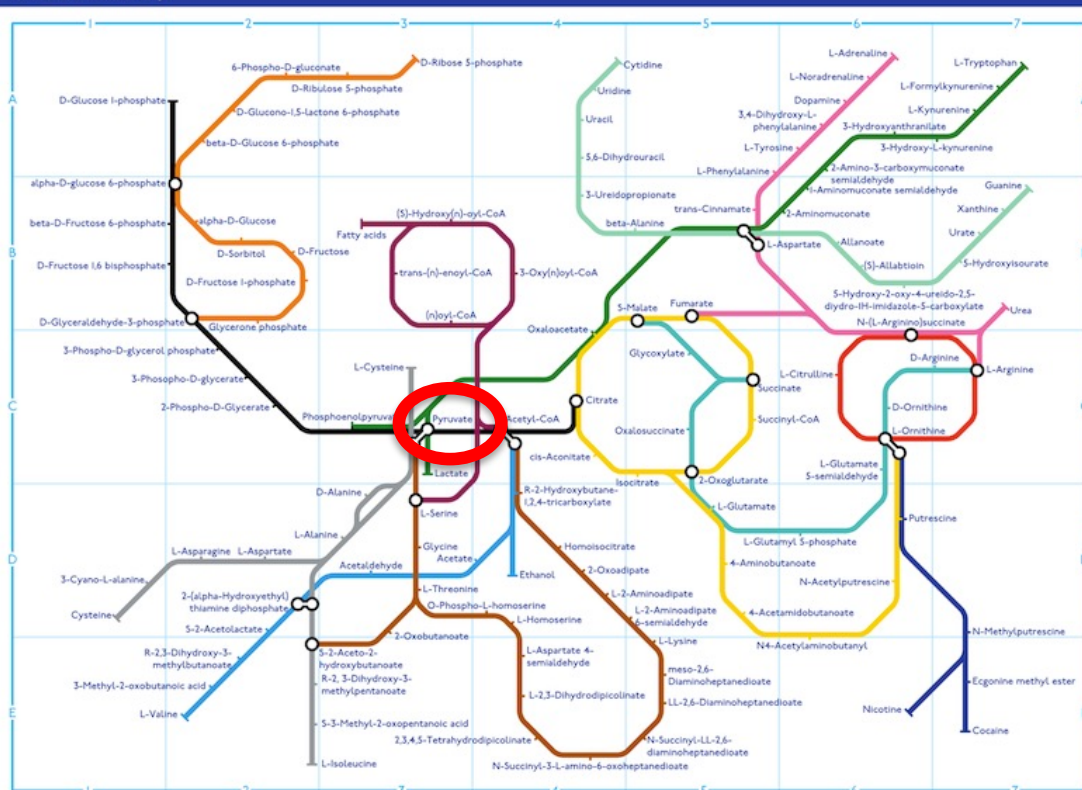
Imaging of tumour metabolism

- Cancer hallmark: alternations in metabolism
- Tumours are acidic
- Tumour suppressors & oncogenes affect metabolism
- Metabolism can be modified for treatment
- Mutations in some mitochondrial enzymes are tumorigenic



Hanahan and Weinberg
Cell 2011;144:646-674

Metabolism map



METABOLISM

roche.com

popsci.com

Metabolism central to health and disease

OPLABS

[Shop Full Range](#) [Our Mission](#) [Customer Support](#) [The Research Edit](#) [COA Database](#)

WARNING: We only sell from this website. Never via Messaging or Social

Home / Shop

Default sorting Showing 1-40 of 69 results

£20.23 with offer

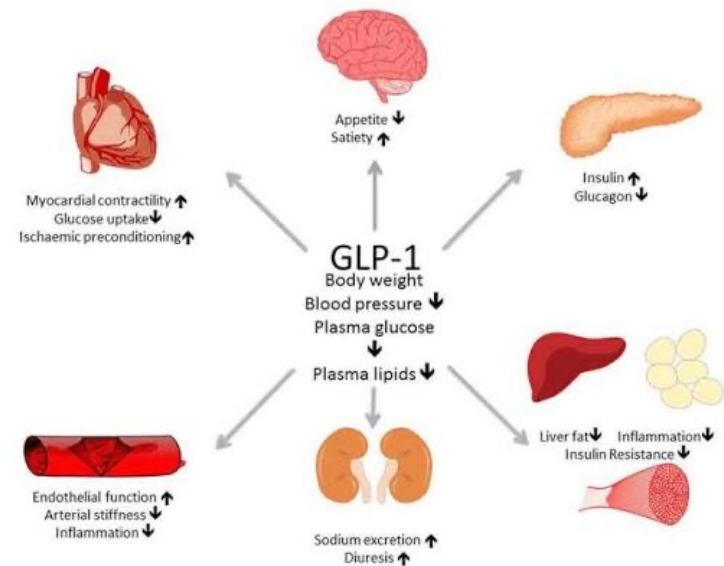
5-Amino-1MQ 10mg

£31.47 with offer

ACE-031 1mg

£20.97 with offer

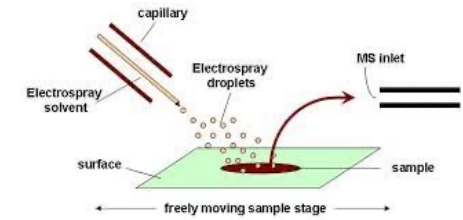
Adamax 5mg



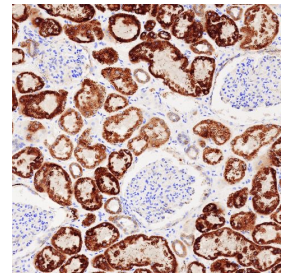
Invasive imaging of metabolism



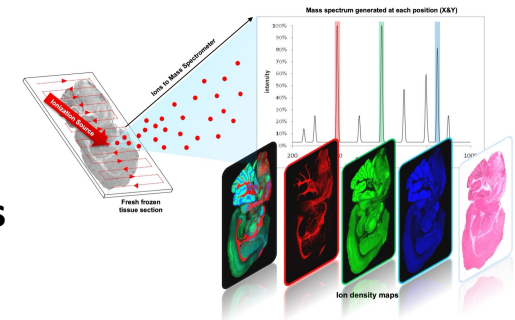
Liquid chromatography
Mass spectrometry



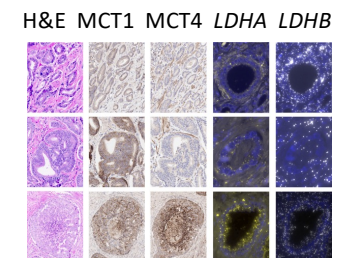
Immunohistochemistry
Spatial Proteomics



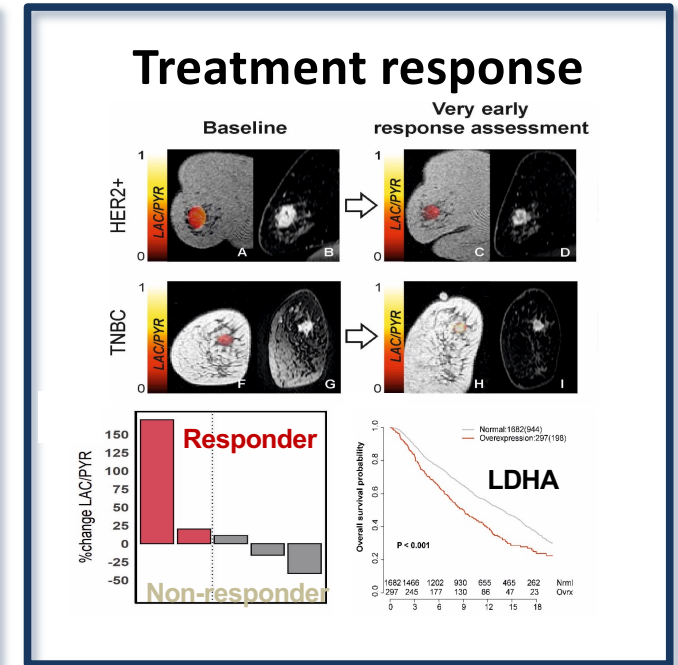
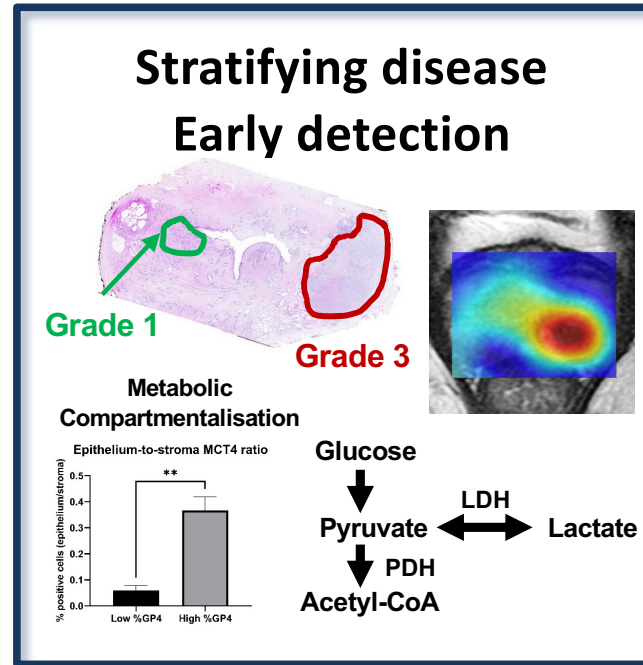
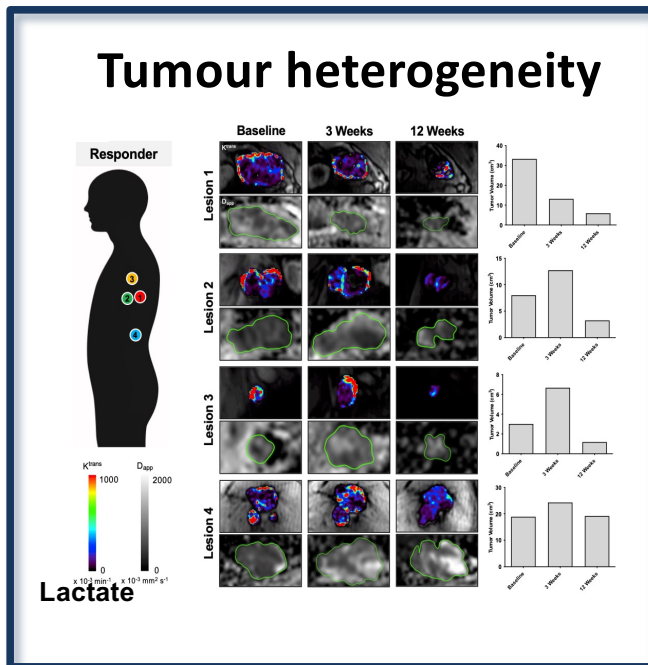
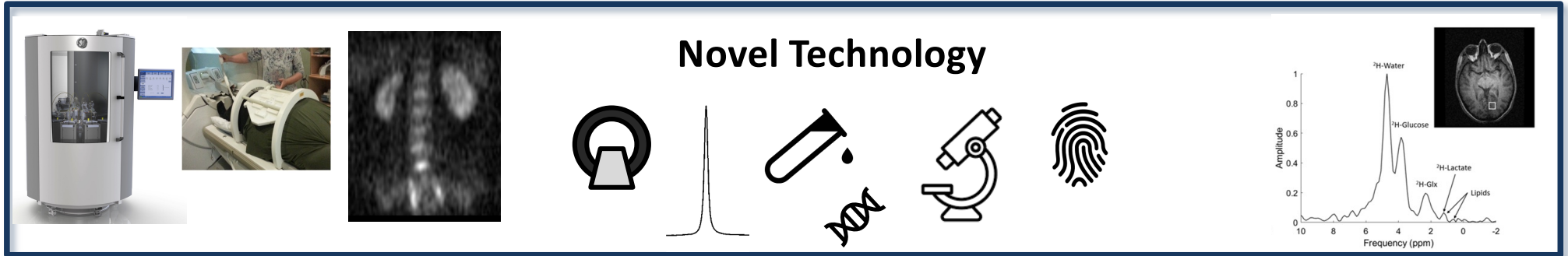
Spatial
Metabolomics



Spatial
Transcriptomics



Integrating metabolic imaging into the clinic across scales



Innovation: a frozen valley of death?

Research

Adoption

Discovery Concept Technology Transfer Development Product Commercialisation

Harvard Glacier Alaska



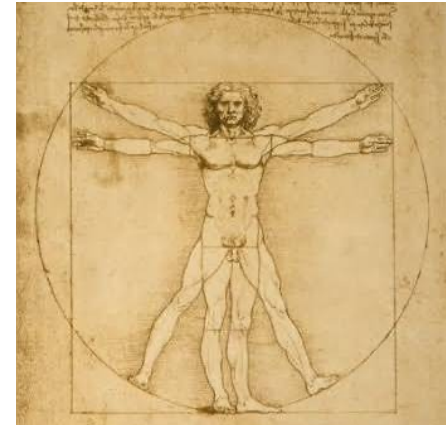
Translation



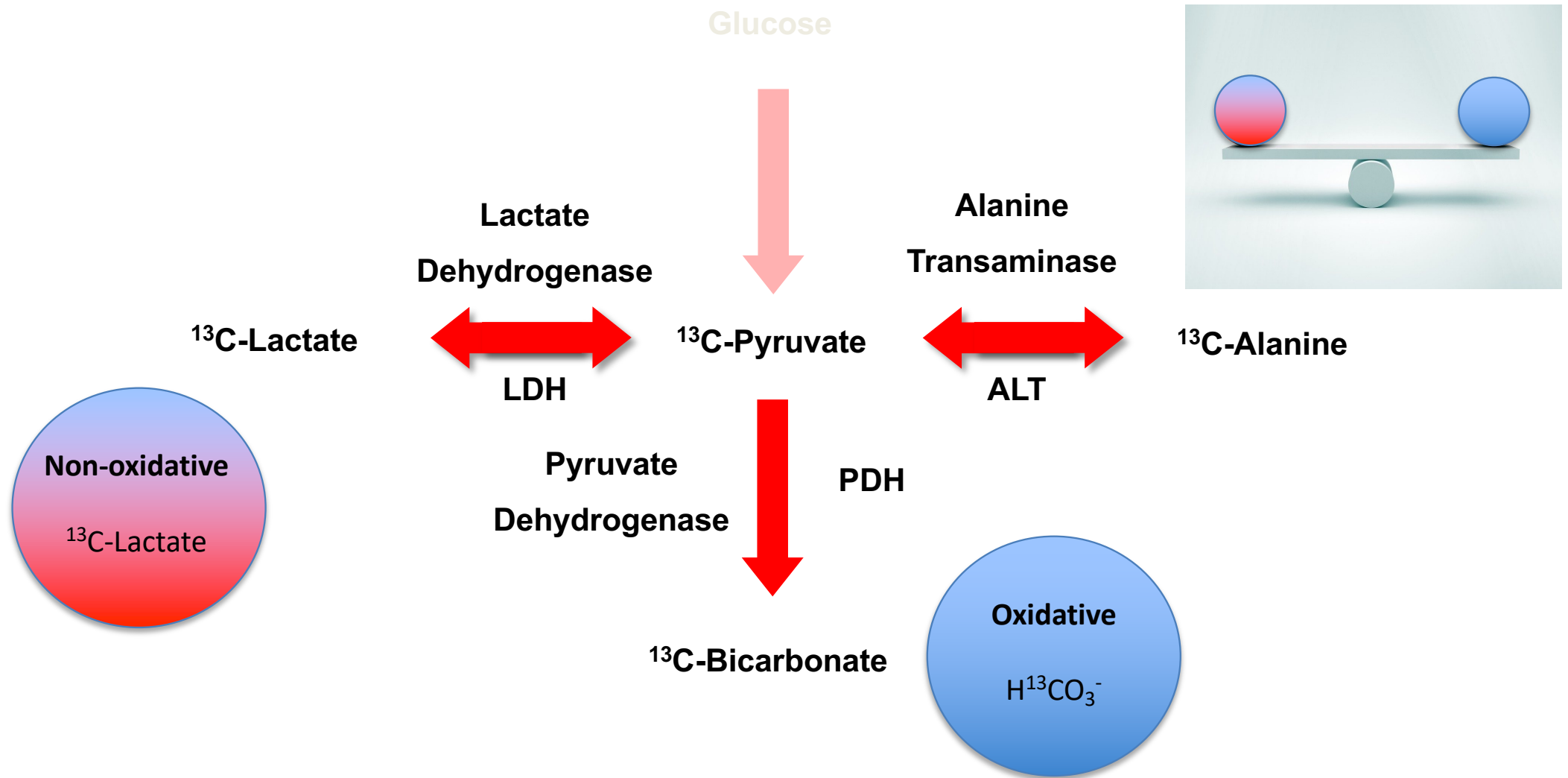
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≠



Hyperpolarised Carbon-13 MRI



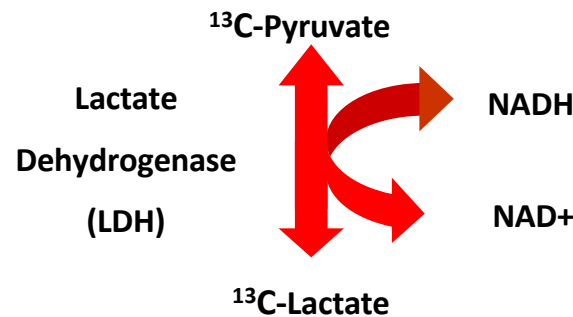
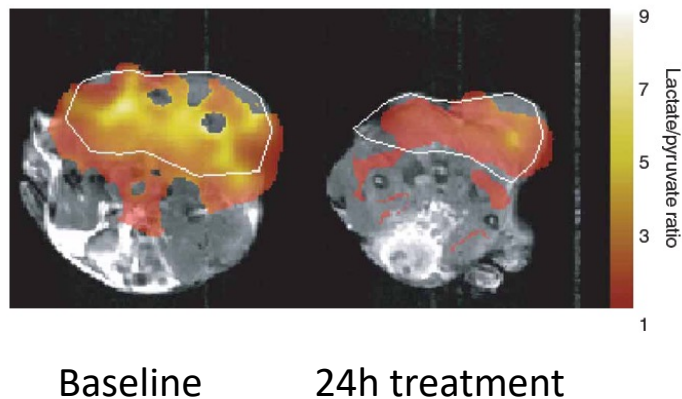
Early treatment response

TECHNICAL REPORTS

nature
medicine

Detecting tumor response to treatment using hyperpolarized ^{13}C magnetic resonance imaging and spectroscopy

Sam E Day^{1,5}, Mikko I Kettunen^{1,5}, Ferdia A Gallagher^{1,2}, De-En Hu¹, Mathilde Lerche³, Jan Wolber⁴, Klaes Golman³, Jan Henrik Ardenkjaer-Larsen⁴ & Kevin M Brindle¹



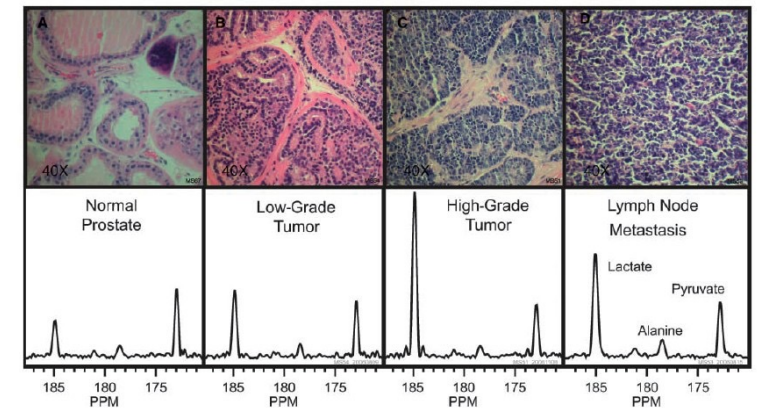
Tumour grading

Research Article

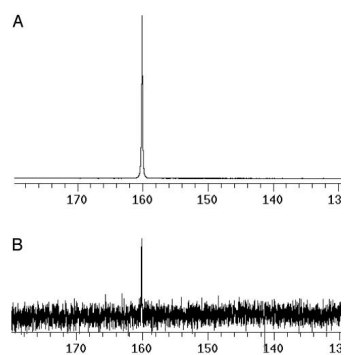
Hyperpolarized ^{13}C Lactate, Pyruvate, and Alanine: Noninvasive Biomarkers for Prostate Cancer Detection and Grading

Mark J. Albers,^{1,2} Robert Bok,² Albert P. Chen,² Charles H. Cunningham,³ Matt L. Zierhut,^{1,2} Vickie Yi Zhang,² Susan J. Kohler,⁴ James Tropp,⁵ Ralph E. Hurd,⁵ Yi-Fen Yen,⁵ Sarah J. Nelson,^{1,2} Daniel B. Vigneron,^{1,2} and John Kurhanewicz^{1,2}

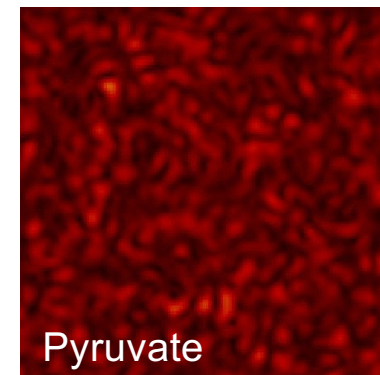
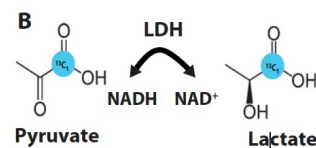
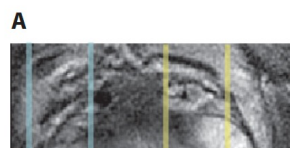
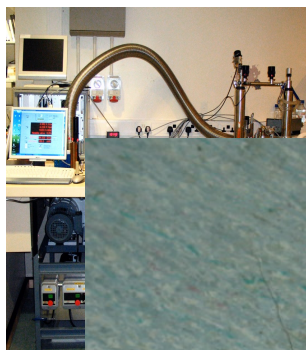
¹Department of Bioengineering, University of California San Francisco and University of California Berkeley; ²Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, California; ³Sunny Brook Health Sciences Centre, Toronto, Ontario, Canada; ⁴Union College, Schenectady, New York; and ⁵GE Healthcare, Menlo Park, California



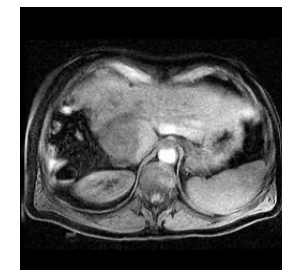
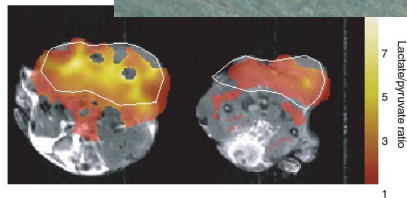
Hyperpolarisation: translation to humans



2003



2016



The path towards clinical utility for hyperpolarized ^{13}C -MRI

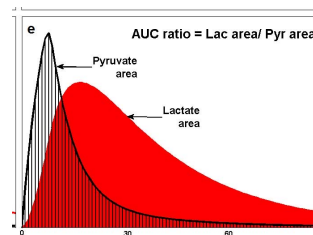
Molecules



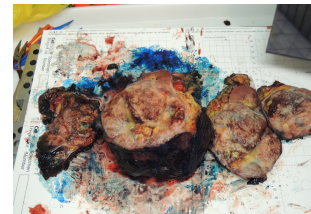
Acquisition



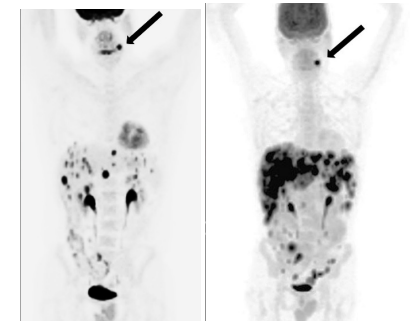
Modelling
analysis



Biological
Validation



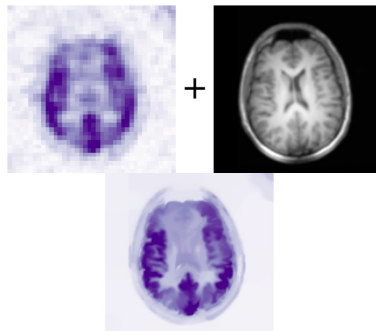
Technique
comparison



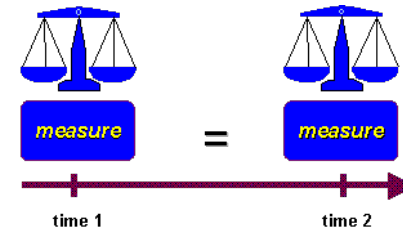
^{13}C -Pharmacy



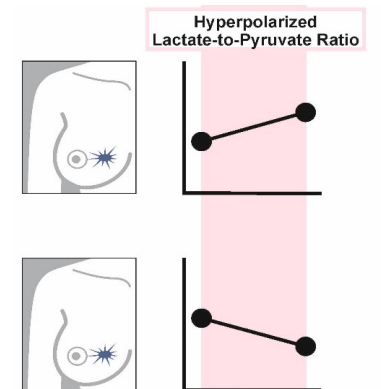
Hardware



Denoising
Segmentation
Resolution



Technical
validation



Clinical application
and validation

Regulatory Issues

- **Good Clinical Practice (GCP)**
 - International **quality standard**, which governments transpose into regulations for clinical trial
 - International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (**ICH**)
 - Courses
 - Certification (usually 3y)
- **Regulatory Authorities:**
 - Food and Drug Administration (FDA)
 - Medicines and Healthcare Products Regulatory Agency (MHRA)
 - Federal Institute for Drugs and Medical Devices (BfArM)
 - Danish Medicines Agency (DKMA)
 - European Medicines Agency (EMA)
- **Medicines vs Medical Devices**
- **Clinical Trial of an Investigational Medicinal Product** (IMP, CTIMP or IND in US)
- **Physiological Study**
- **MHRA Algorithm**

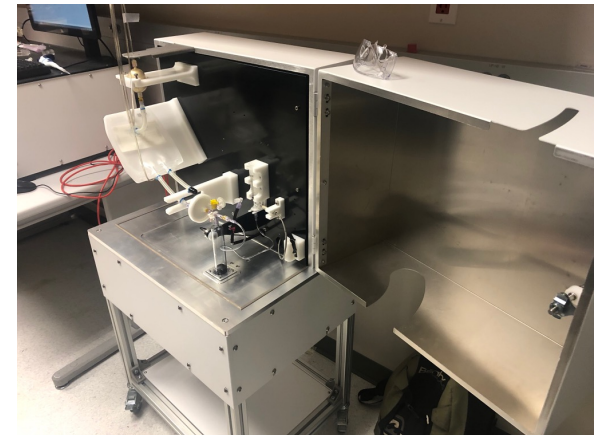
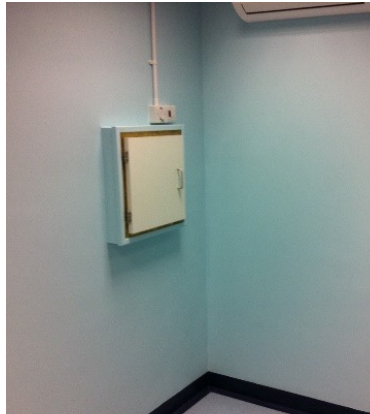
IS IT A CLINICAL TRIAL OF A MEDICINAL PRODUCT?

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions, contact the MHRA clinical trials unit.

A	B	C	D	E
A CLINICAL TRIAL OF A MEDICINAL PRODUCT?				A NON-INTERVENTIONAL CLINICAL TRIAL?
Is it a medicinal product (IMP)? ⁱ	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	How are you looking for those effects?
If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a MP. If you answer yes to <u>any</u> of the questions below go to column B.	If you answer yes to the question below in column B the activity is not a clinical trial on a MP. If you answer no to this question below go to column C.	If you answer no to <u>all</u> the questions in column C the activity is not a clinical trial under the scope of SI 1031. If you answer yes to <u>any</u> of the questions below go to column D.	If you answer no to <u>all</u> the questions in column D the activity is not a clinical trial under the scope of SI 1031. If you answer yes to <u>any</u> of the questions below go to column E.	If you answer yes to all these questions the activity is a non-interventional trial which is outside the scope of SI 1031. If your answers in columns A,B,C & D brought you to column E and you answer no to any of these questions the activity is a clinical trial within the scope of the Directive.
A.1 Is it a substanceⁱⁱ or combination of substances presented as having properties for treating or preventing disease in human beings? A.2 Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose? A.3 Is it an active substance in a pharmaceutical form?	B.1 Are you only administering any of the following substances? • Human whole bloodⁱⁱⁱ; • Human blood cells; • Human plasma; • Tissues except a somatic cell therapy medicinal product^{iv}; • A food product (including dietary supplements) not presented as a medicine; • A cosmetic product^v; • A medical device	C.1 To discover or verify/compare its clinical effects? C.2 To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics? C.3 To identify or verify/compare its adverse reactions? C.4 To study or verify/compare its absorption, distribution, metabolism or excretion?	D.1 To ascertain or verify/compare the efficacy^{vii} of the medicine? D.2 To ascertain or verify/compare the safety of the medicine?	E.1 Is this a study of one or more medicinal products, which have a marketing authorisation in the UK? E.2 Are the products prescribed in the usual manner in accordance with the terms of that authorisation? E.3 Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol^{viii}? E.4 Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study? E.5 Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice? E.6 Will epidemiological methods be used for the analysis of the data arising from the study?

Regulatory Issues

- **Manufacture**
 - Where this happens is key
 - pH changes are usually not regarded as manufacture
- **Good Manufacturing Practice**
 - GMP: **traceable, safe, pure, effective**
proper **design, monitoring** and **control** of the manufacturing processes, facilities and product
 - Clinical grade: suitable for clinical (therapeutic) use
- **Quality Control vs Quality Assurance**
 - QC: process of ensuring products meet **expectations**
 - QA: set of processes used to **measure** and **assure** the quality of a product
- **Release**
 - May involve a qualified person (QP)
- **Exemptions**
 - Injection under Section 9 of the Medicine Act 1968 (exemptions for doctors)
- **Befriend a pharmacist**



Process in Cambridge

For non-CTIMP e.g. Physiological Studies

- Filling of fluid paths/pharmacy kits as raw material
- Frozen and stored (3 months stability)
- Environmental monitoring assessment from laminar flow hood
- Pharmacist signs off (QA check)
- Mixed in SpinLab is the point of manufacture
- QC checks before injection into patients including pH
- Sterility + endotoxin samples taken and analysed retrospectively
- Injection under Section 9 of the Medicine Act 1968 (Exemptions for doctors) i.e. doctor takes responsibility to administer the product

QC and release

Pyruvate concentration	220 to 280 mM
pH	5.9 to 9.0
EPA concentration	$\leq 3.0 \mu\text{M}$
Temperature	25.0 to 39.0 °C
Time from start to dissolution	Any
Volume	$\geq 40 \text{ mL}$ (for volumes less than 40mL the decision to inject is left to the discretion of the clinical lead)
Hyperpolarization	$\geq 15 \%$ (for polarization less than 15% the decision to inject is left to the discretion of the clinical lead)

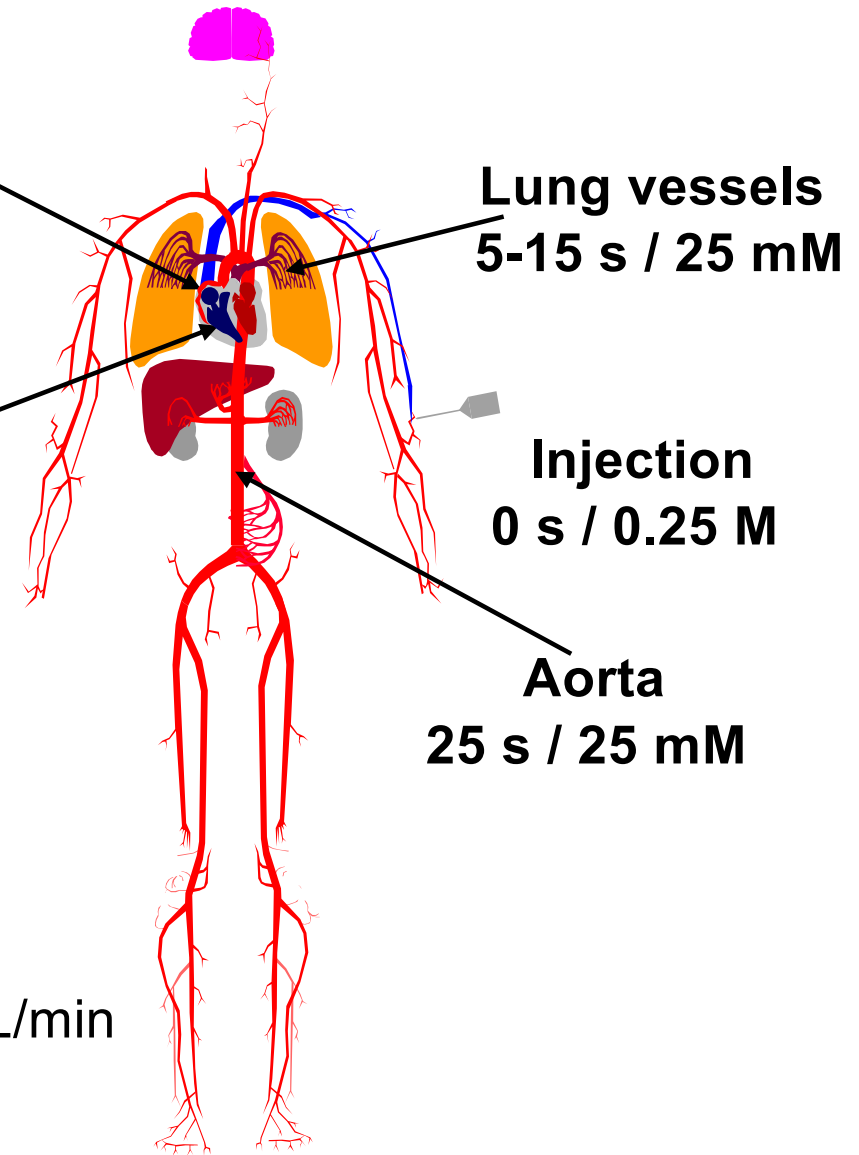
Patient issues



Coronary artery
15-20 s / 25 mM

Heart chambers
3-4 s / 25 mM

Cardiac output 6 L/min
Injection at 5 ml/s



Study Design and Approvals

After/while funding is acquired:

Study Set up:

- Title: MISSION
- Hypothesis
- Background
- Primary/Secondary objectives
- Study Design: flow chart
- Sample size/statistics
- Inclusion/exclusion criteria
- Serious Adverse Events (SAEs)

Review:

- Research & Development office (R&D)
- Research Ethics Committee
- Health Research Authority
- Local Approvals
- Site Initiation Visit

MISSION-Prostate
Version 2.0, 30 October 2019
IRAS Project ID: 196902



Cambridge University Hospitals 
NHS Foundation Trust

Title: A physiological study comparing hyperpolarised carbon-13 labelled pyruvate (^{13}C -pyruvate) metabolism and sodium MRI in prostate cancer and normal prostate tissue

Short Title: MISSION-Prostate (Molecular Imaging and Spectroscopy with Stable Isotopes in Oncology and Neurology – Imaging metabolism in **prostate**)

Department of Radiology
Box 218, Level 5
Addenbrooke's Hospital
Hills Road
Cambridge CB2 2QQ
Tel: 01223 336890

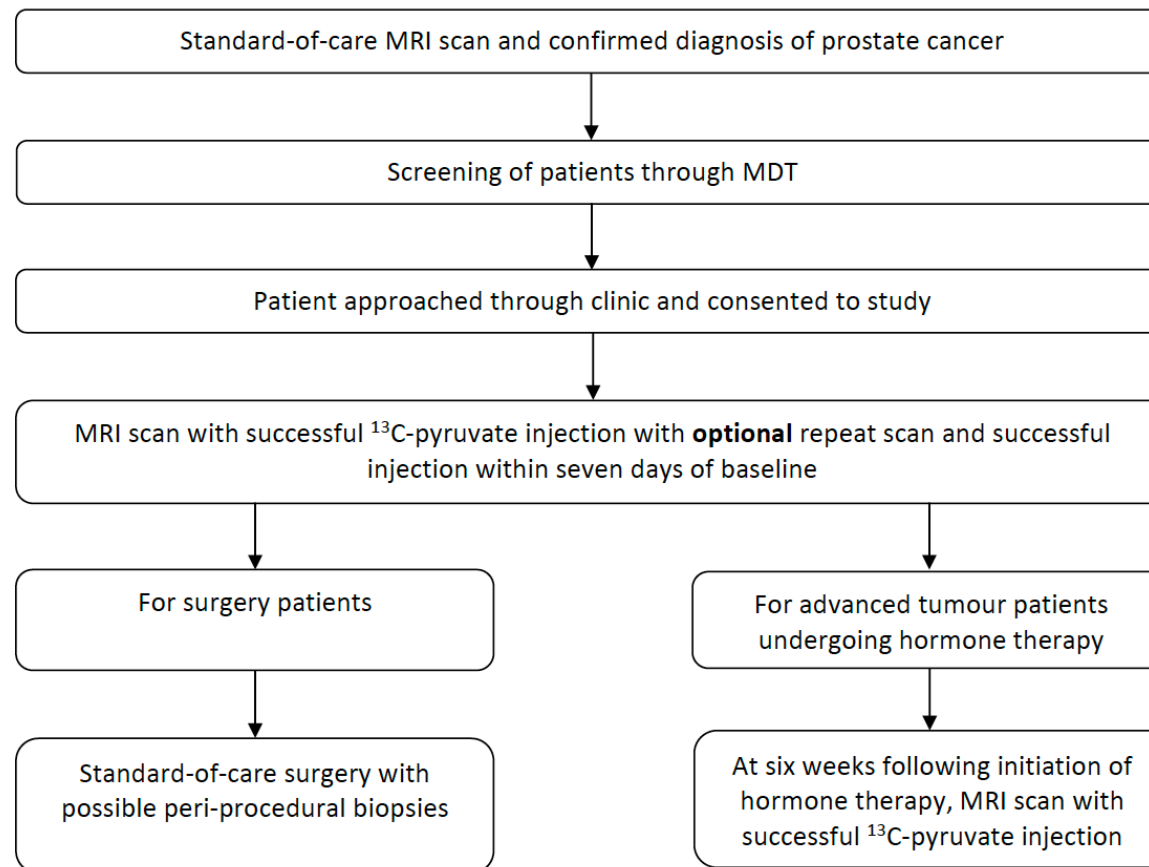


**Health Research
Authority**

Study Flow Chart

3. [Study Flow Chart](#)

For surgery and hormone therapy patients



Top tips

- Make sure your objective is clear
- Befriend a statistician: power the study
- **Make as flexible as possible:**
 - Up to X participants
 - Timing: Y-Z days
 - Order of studies
 - Optional elements
- Keep consent as wide as possible
- **Involve your clinical colleagues**
- Anonymisation
- Data storage and archiving
- **Collect as much data as possible**
 - Clinical
 - Imaging
 - Liquid biomarkers
 - Annotated/curated data
 - Tissue: frozen and FFPE

John Eng, MD

Index terms:
Radiology and radiologists, research
Statistical analysis

Published online
10.1148/radiol.2272012051
Radiology 2003; 227:309–313

¹ From the Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University, 600 N Wolfe St, Central Radiology Viewing Area, Rm 117, Baltimore, MD 21287. Received December 17, 2001; revision requested January 29, 2002; revision received March 7; accepted March 13. Address correspondence to the author (e-mail: jeng@jhmi.edu).
© RSNA, 2003

Sample Size Estimation: How Many Individuals Should Be Studied?¹

The number of individuals to include in a research study, the sample size of the study, is an important consideration in the design of many clinical studies. This article reviews the basic factors that determine an appropriate sample size and provides methods for its calculation in some simple, yet common, cases. Sample size is closely tied to statistical power, which is the ability of a study to enable detection of a statistically significant difference when there truly is one. A trade-off exists between a feasible sample size and adequate statistical power. Strategies for reducing the necessary sample size while maintaining a reasonable power will also be discussed.

© RSNA, 2003

Annals of Oncology Advance Access published August 12, 2015

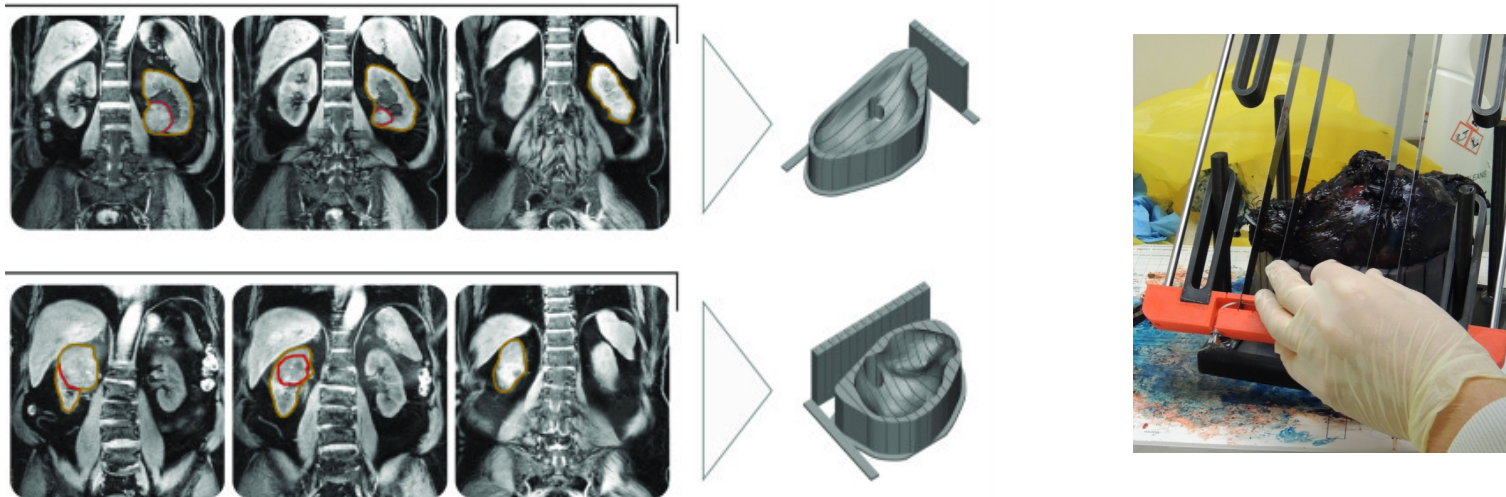
original article

Annals of Oncology 00: 1–6, 2015
doi:10.1093/annonc/mdv289

Prospective study evaluating the relative sensitivity of ¹⁸F-NaF PET/CT for detecting skeletal metastases from renal cell carcinoma in comparison to multidetector CT and ^{99m}Tc-MDP bone scintigraphy, using an adaptive trial design

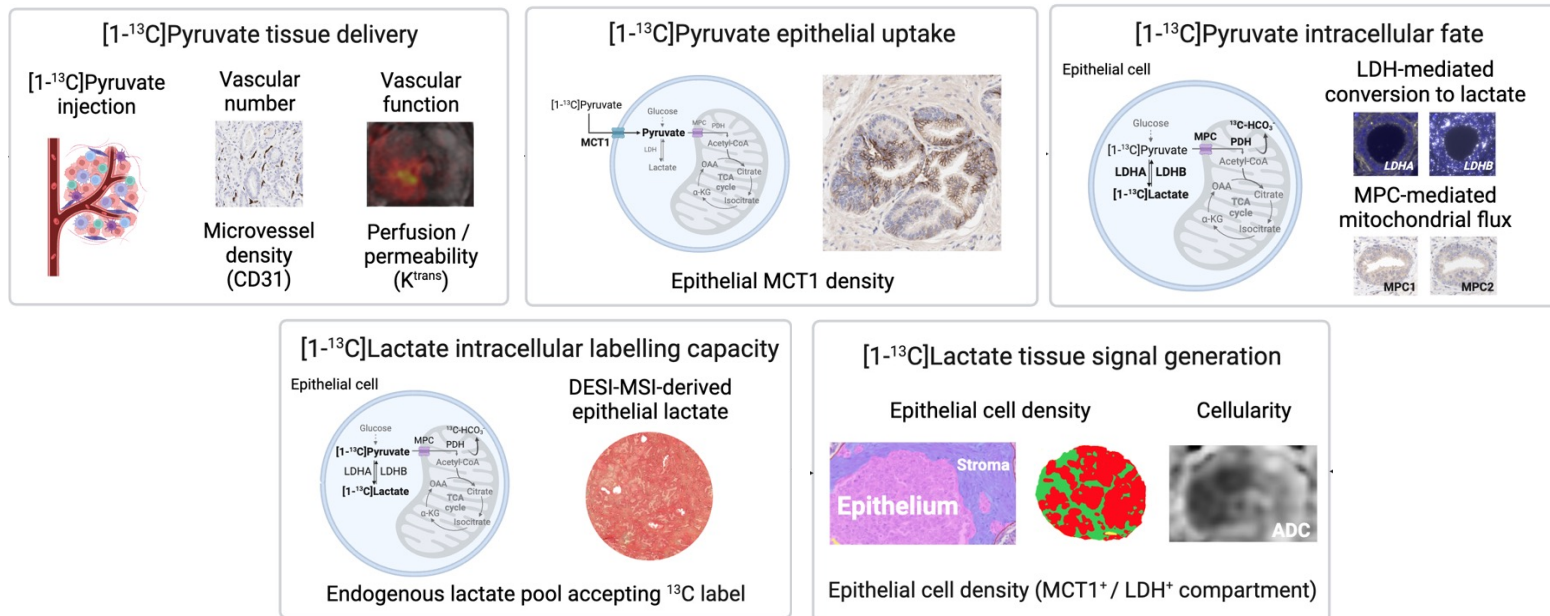
E. L. Gerety¹, E. M. Lawrence², J. Wason³, H. Yan², S. Hillborne², J. Buscombe⁴, H. K. Cheow^{1,4}, A. S. Shaw¹, N. Bird⁵, K. Fife⁶, S. Heard⁴, D. J. Lomas^{1,2}, A. Matakidou^{6,7}, D. Soloviev⁷, T. Eisen^{6,8,†} & F. A. Gallagher^{1,2,†*}

Biological validation: integrating imaging and pathology

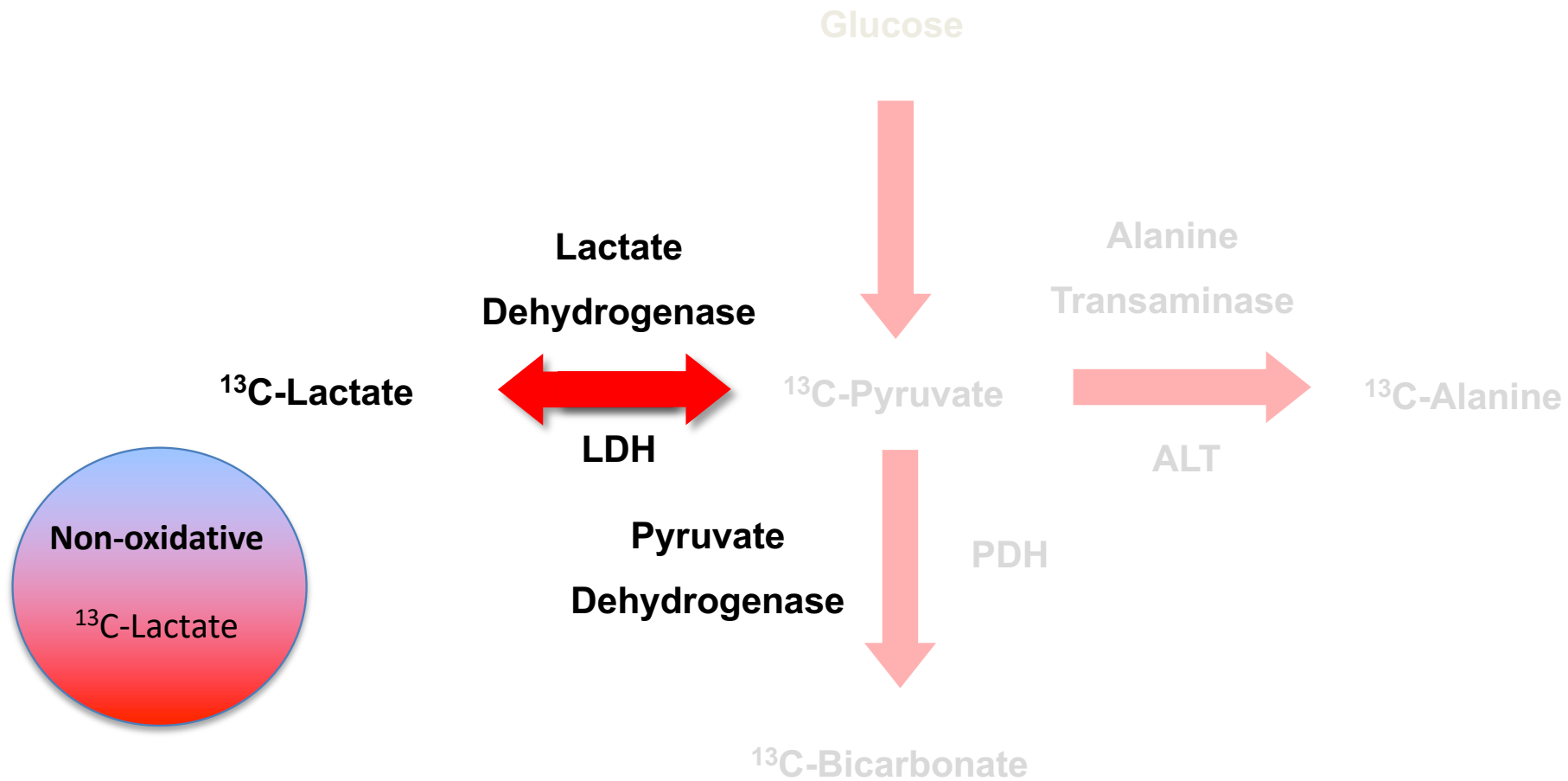


Crispin-Ortuzar M et al *JCO CCI* 2020 4:736

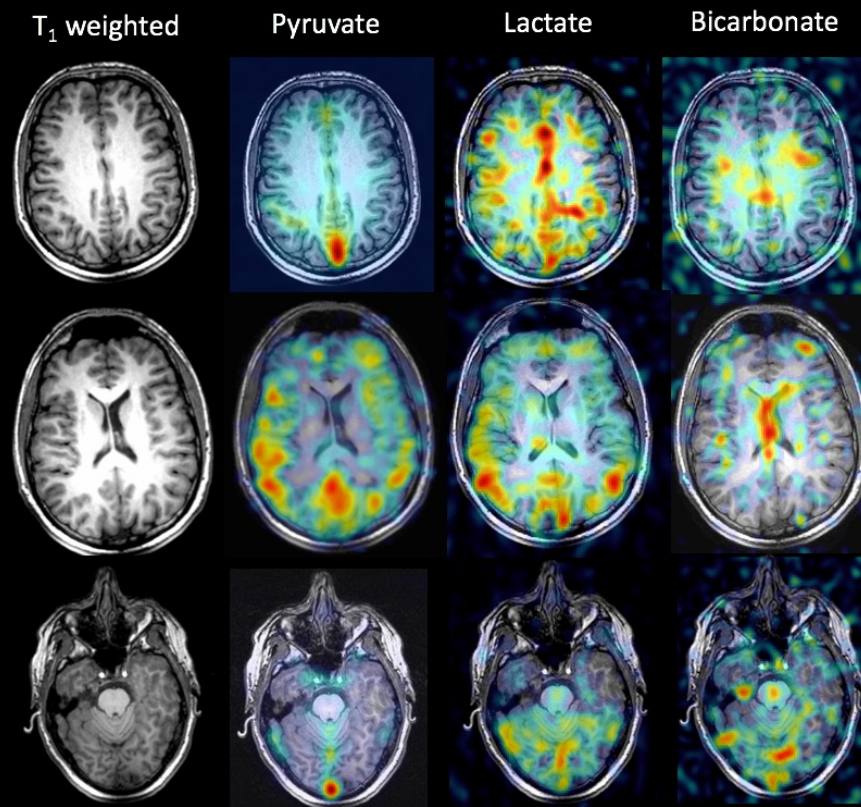
Biological drivers of signal of hyperpolarised signal



Hyperpolarised Carbon-13 MRI



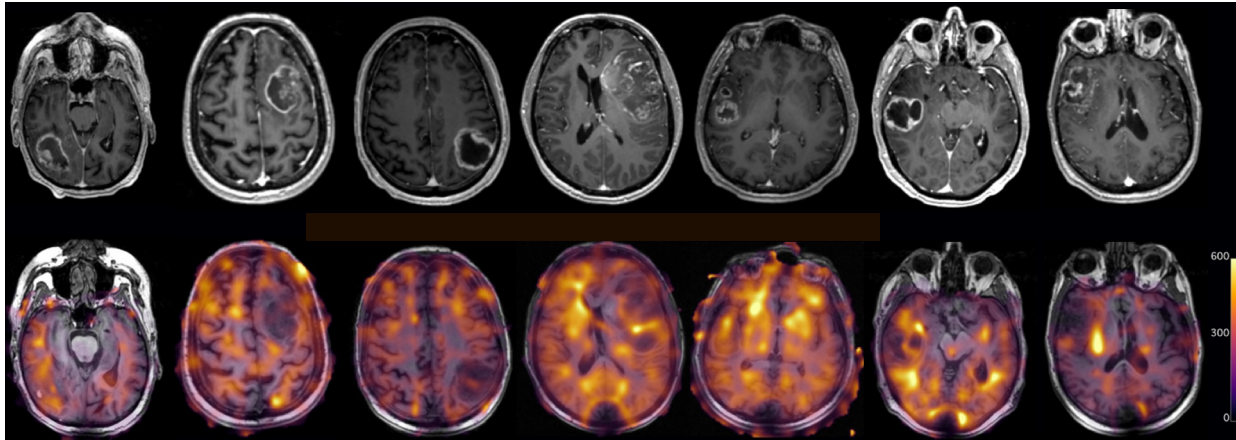
Normal brain metabolism



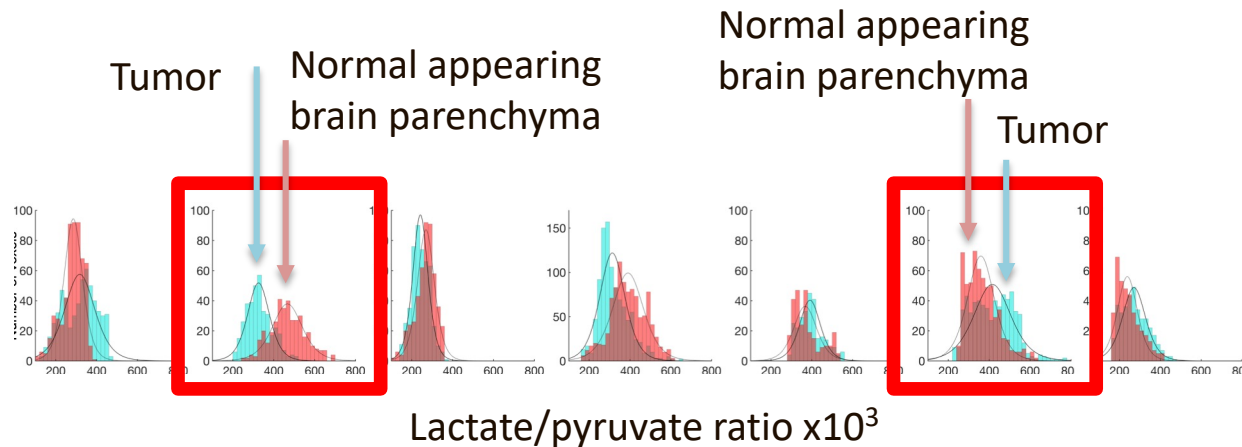
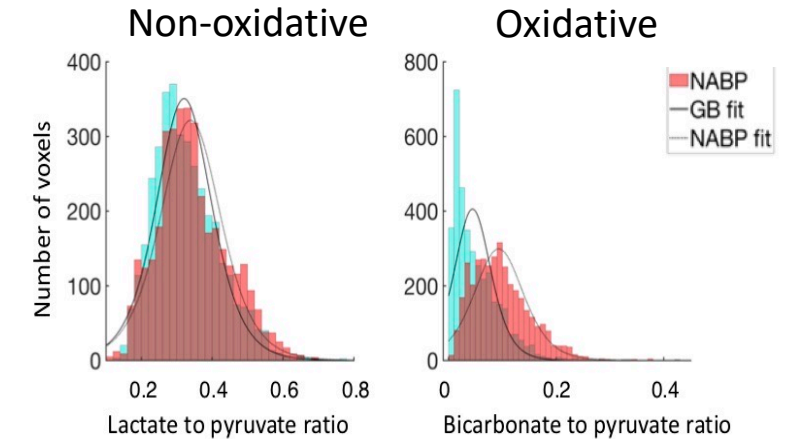
Grist Neuroimage 2019; 89:171-179.

Metabolic heterogeneity in glioblastoma

T1 post gadolinium



Lactate/pyruvate ratio

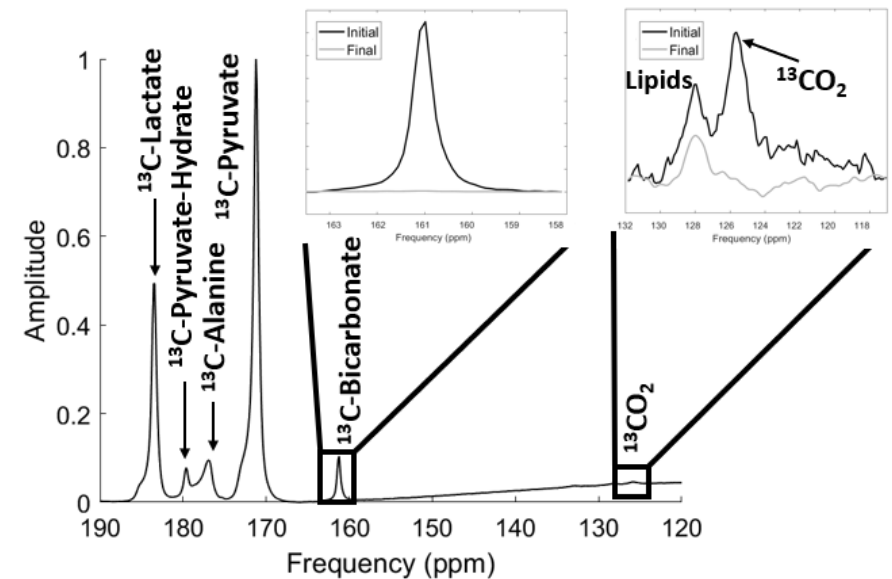
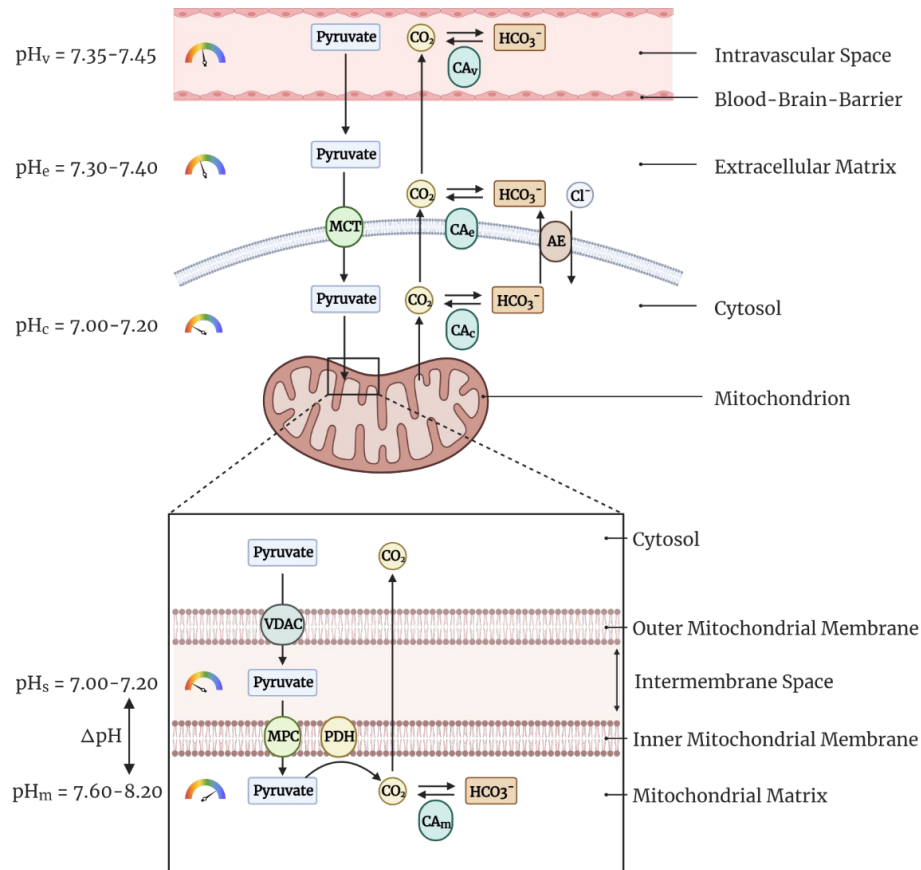


Lactate/pyruvate ratio $\times 10^3$

Zaccagna et al. *Radiol Imaging Cancer* 2022;4(4):e210076

- Intratumoral and interpatient heterogeneity
- Bicarbonate/pyruvate ratio reduced in all tumors compared to normal appearing brain
- Increased glycolytic and oxidative metabolism distant from tumour, compared to volunteers

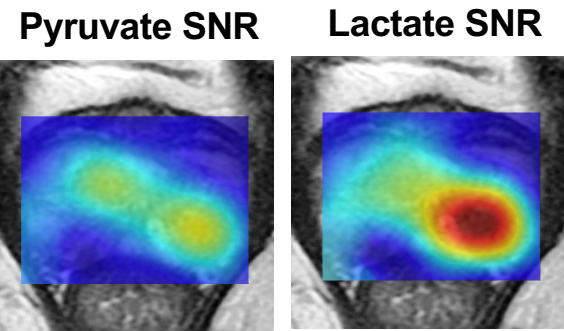
Human brain pH measured with pyruvate



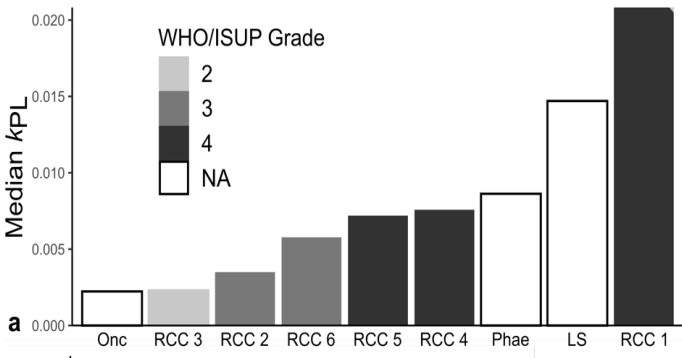
pH: 7.40 ± 0.02 (n=7)

Extracellular/vascular weighted pH

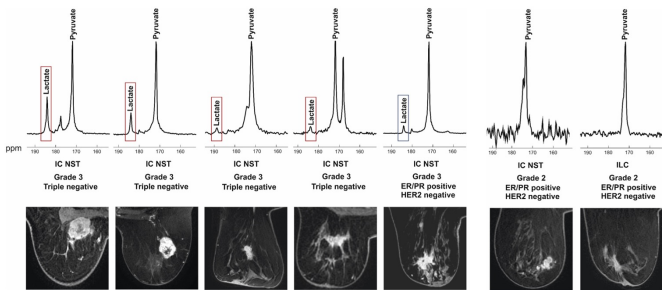
Imaging tumour aggressiveness



Renal



Stephan Ursprung *et al. Cancers*. 2022; 14(2):335.

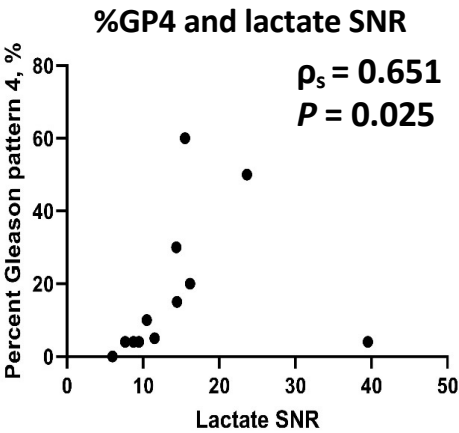


Breast

LAC/PYR	G3		G2		p
	Triple negative breast cancer (TNBC)		ER/PR+		
	IC NST		IC NST	ILC	
	mean ± SD		mean ± SD		
	0.21 (± 0.17)		0.01 (± 0.01)		

Gallagher & Woitek et al. 2020 *PNAS* 117(4):2092

Prostate

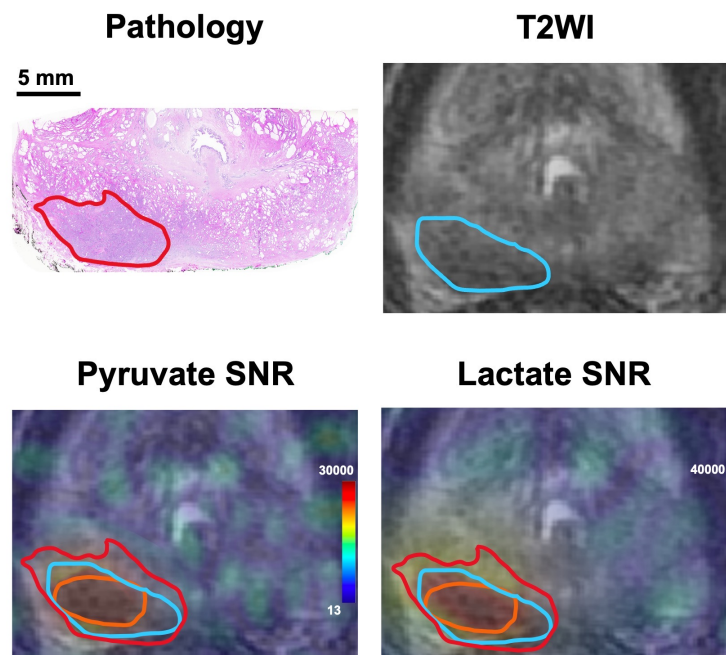


Nikita Sushentsev, Tristan Barrett *et al.*
Nat Commun. 2022; 13(1):466

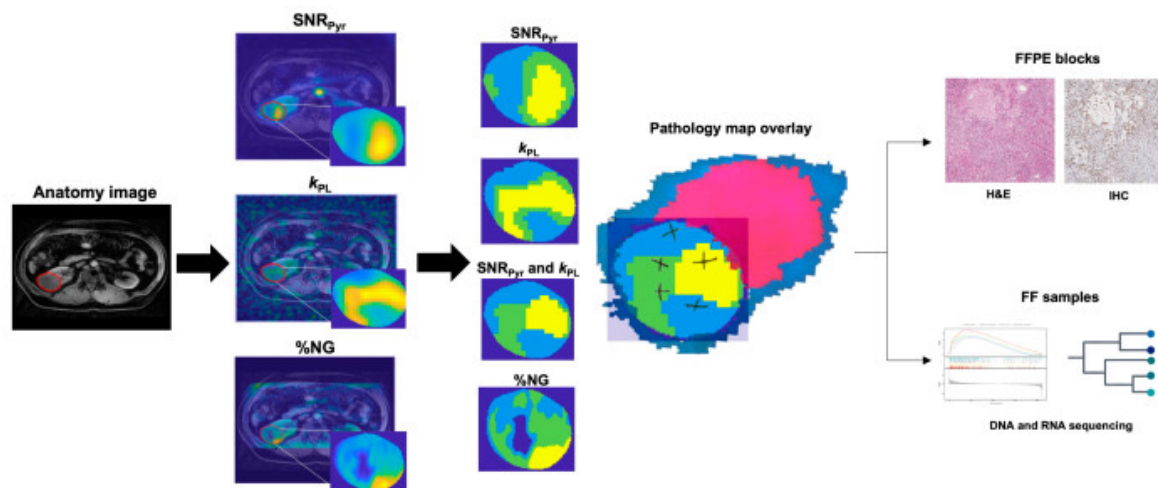
Metabolic imaging can identify aggressive tumours

Target biopsies to areas of increased metabolism

Prostate Cancer

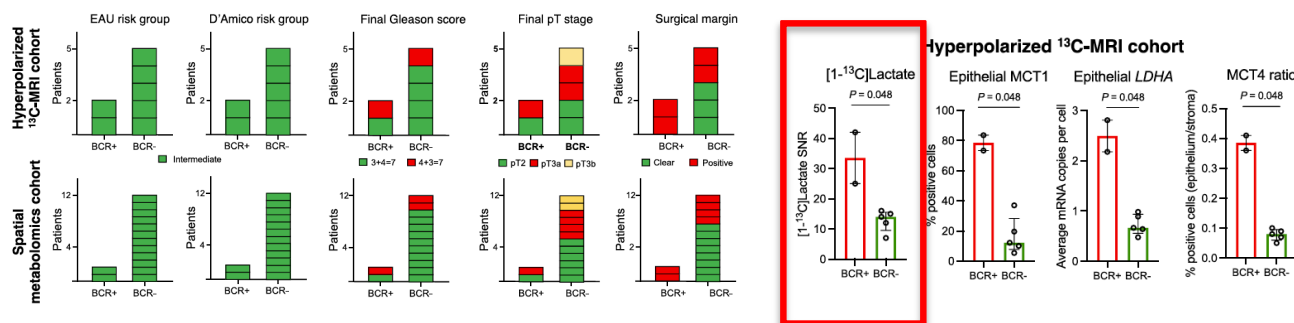
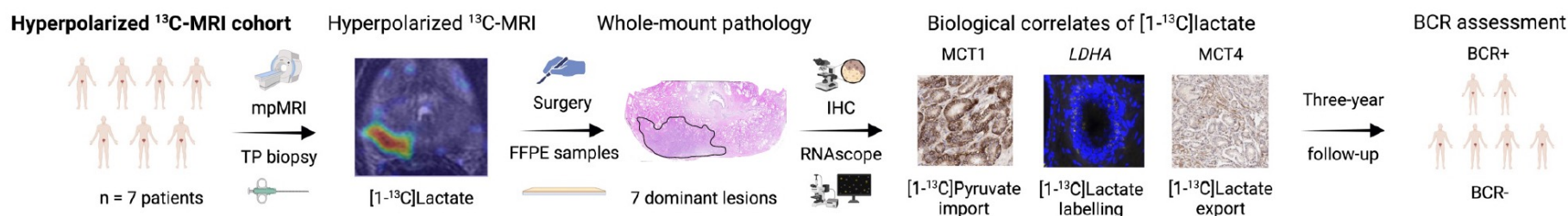


Clear Cell Renal Cell Carcinoma



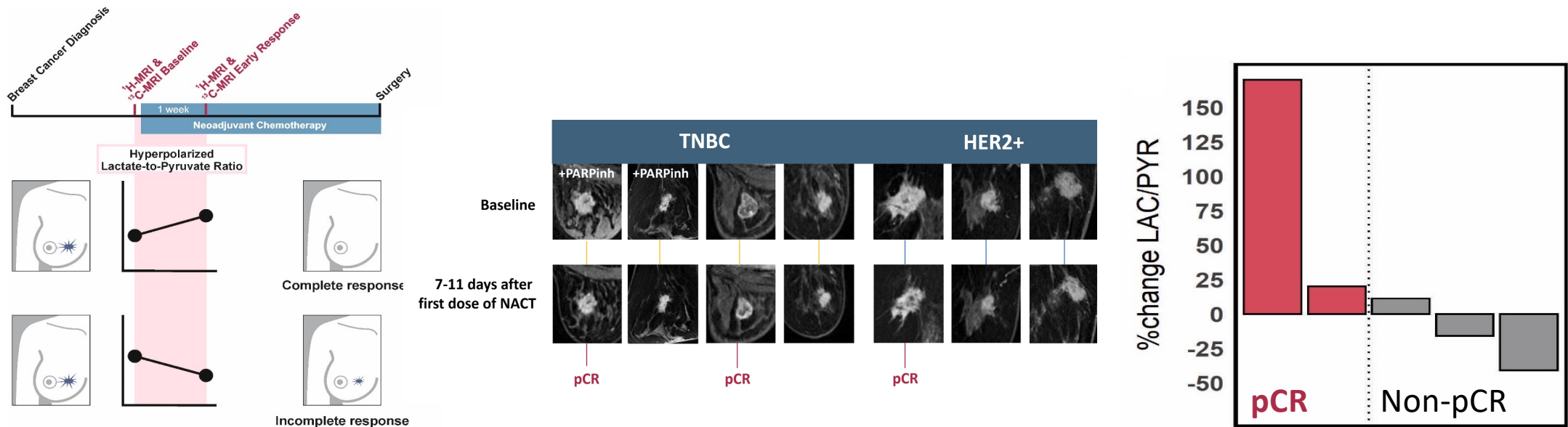
Metabolic imaging can guide biopsies to tissue of greatest biological interest

Predicting biochemical recurrence in prostate cancer



Increased lactate before prostatectomy correlates with later biochemical recurrence

Early response to neoadjuvant chemotherapy



Very early increase in lactates correlate with pathological response to standard therapy

Woitek R et al. *Cancer Res.* 2021 Dec 1;81(23):6004-6017.

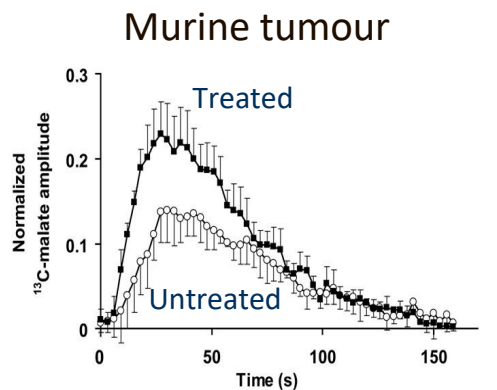
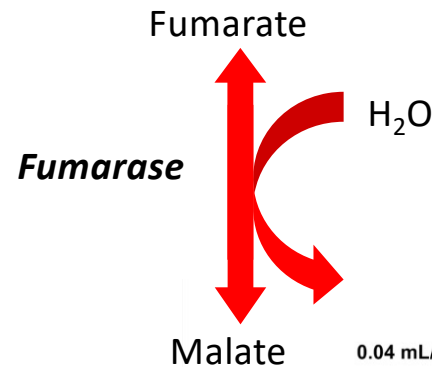
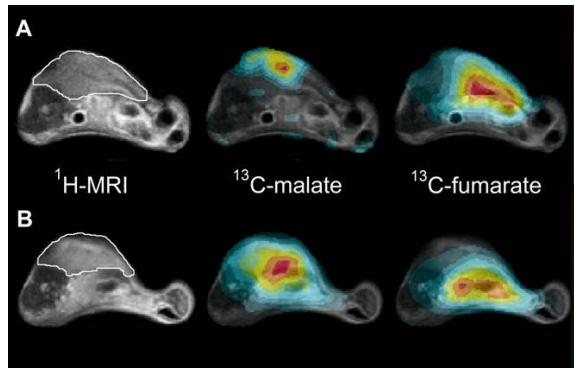
Emerging Hyperpolarised Probes

- Probing new biology
- Translate recipes for human dose levels
- Toxicity
 - Probes not tracers
 - Small animal studies
 - Large animal studies
 - Volunteer studies outside of the magnet?
 - Volunteer imaging in the MR?
 - Patient imaging

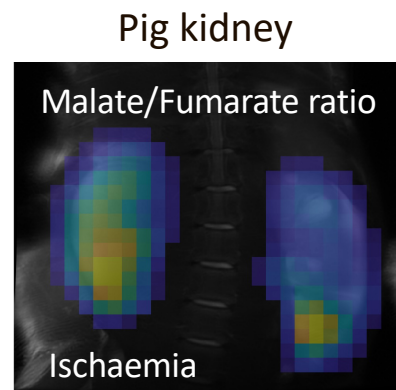


Molecule	Biological mechanism
2- ¹³ C Pyruvate	Citric acid cycle
Urea	Perfusion
Fumarate	Necrosis
Acetate	Fatty acid synthesis
Bicarbonate	Extracellular pH
Lactate	Glycolysis
α –ketoglutarate	Multiple reactions

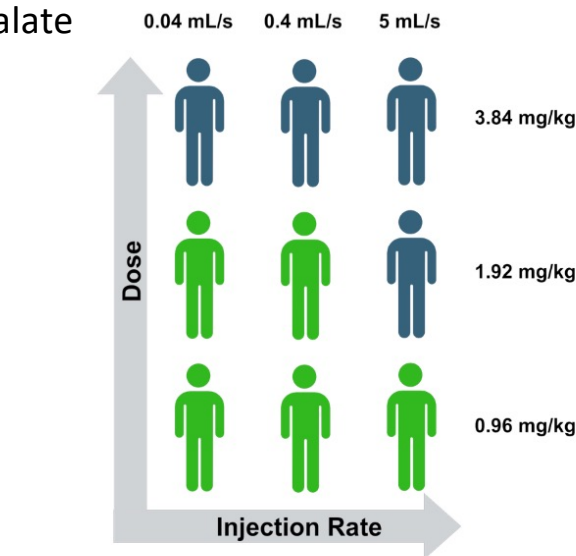
[1,4-¹³C₂]Fumarate to detect necrosis



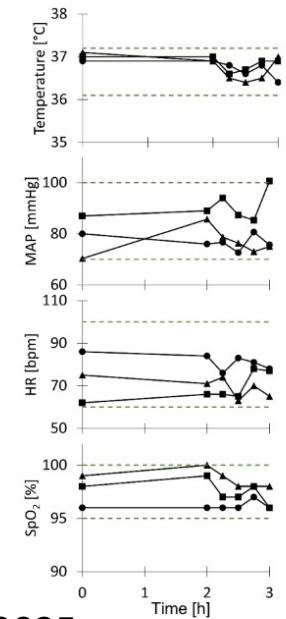
Gallagher F *et al.*
PNAS 106(47):19801, 2009



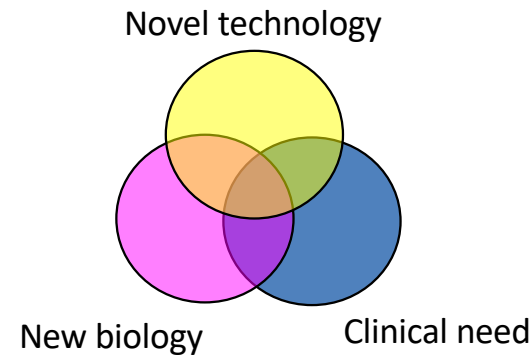
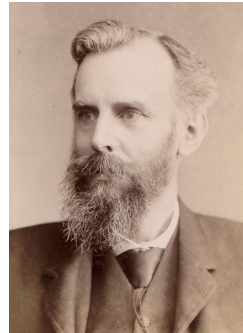
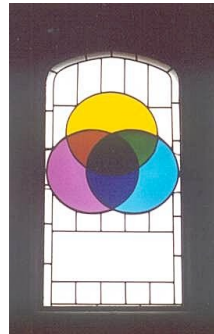
Chris Laustsen *et al.*
Aarhus University



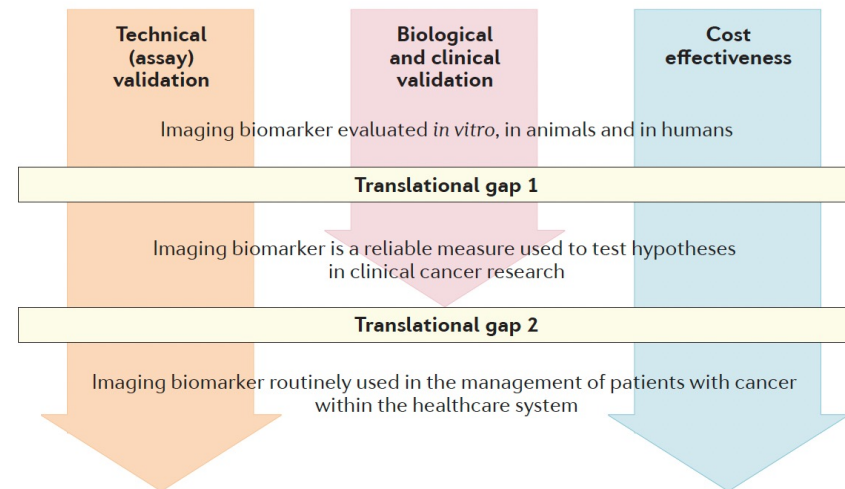
Birchall J *et al.* MRM 94(3):1202-1217, 2025



Translating novel imaging methods into healthcare



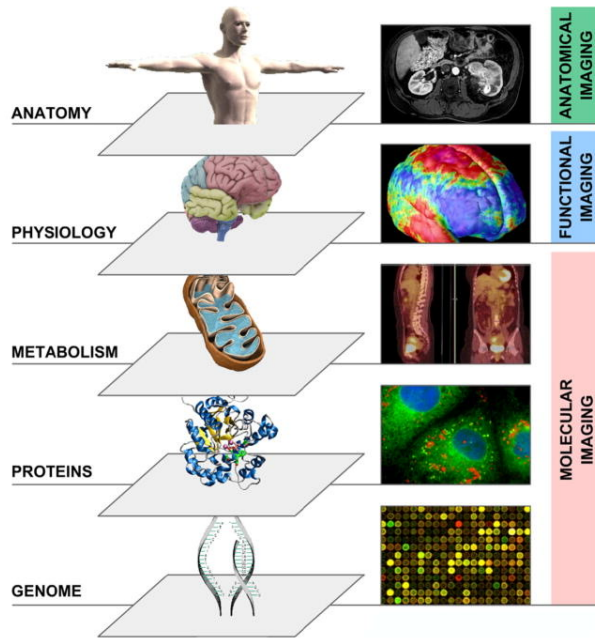
- Biological validation
- Technical validation
- Methods need to be simple
- Train staff
- Educate clinical colleagues
- Enable multisite studies
- Health economic assessment



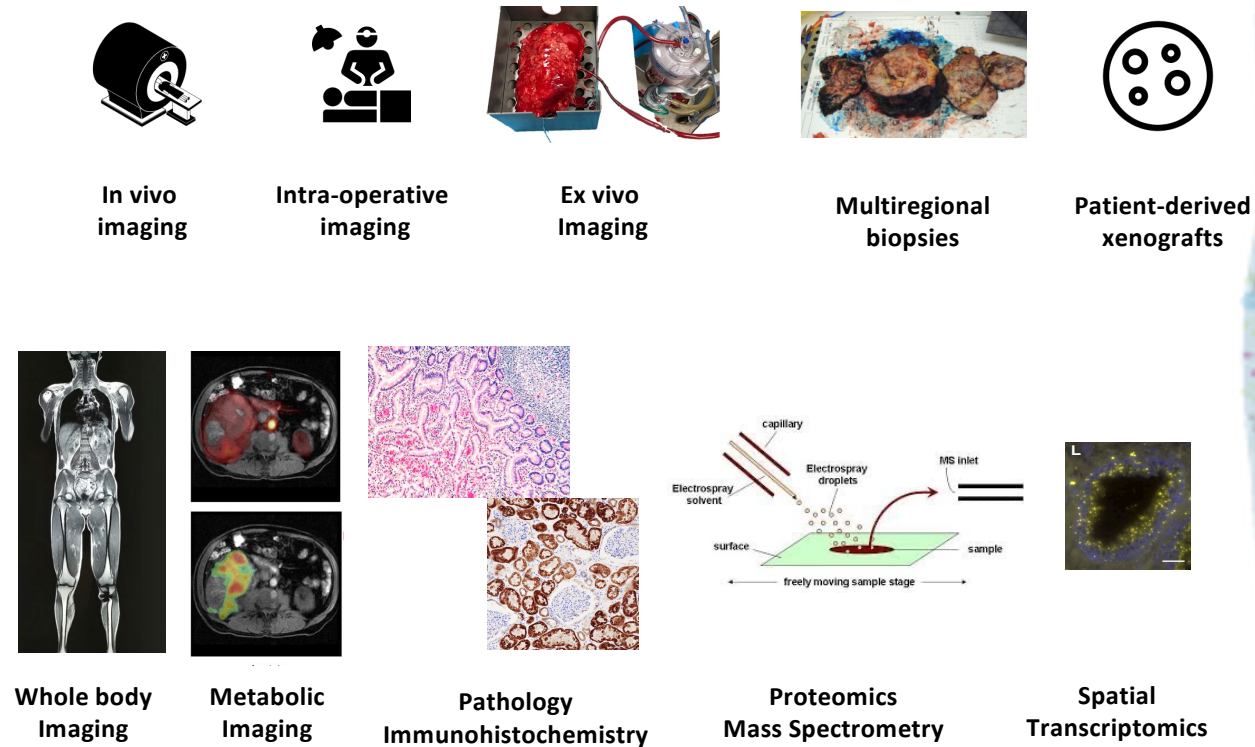
O'Connor et al.
Nat Rev Clin Oncol 2017

Multiscale, Multimodal, Multi-omic imaging

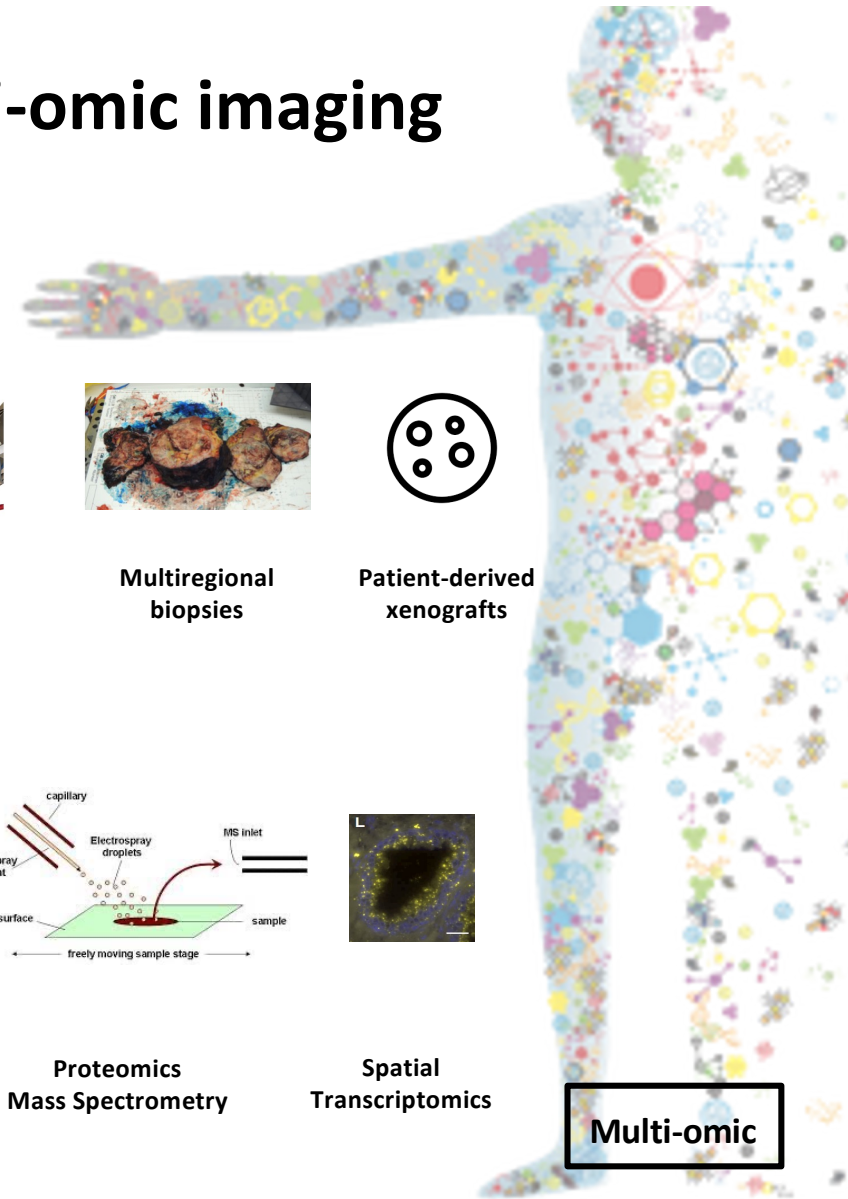
Multiscale



Multimodal



Multi-omic



Potential clinical roles for metabolic MRI in oncology

- Tumour stratification based on metabolism
- Assessing metabolic heterogeneity
- Targeting biopsies
- Early treatment response monitoring
- Guiding radiotherapy
- Longitudinal imaging
- Imaging patients most at risk of irradiation
- Complementary to circulating biomarkers

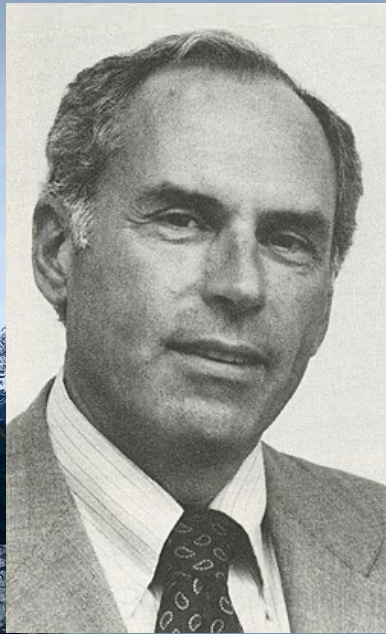


Perspective is important:
predicting the future is difficult!

1.5 miles

A wide-angle photograph of a massive glacier flowing from snow-capped mountains into a body of water. The glacier's surface is textured with dark rocks and ice. A white horizontal arrow with a right-pointing arrowhead is overlaid on the image, spanning the width of the glacier. The text "1.5 miles" is centered above the arrow. The sky is overcast and grey.

Innovation: predicting the future is difficult!



Amara's Law:

"We tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run"



Geoff Hinton:

2016

"People should stop training radiologists now - it's just completely obvious within 5 years deep learning is going to do better than radiologists"

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