Oxford Biomedical Research Centre
Enabling translational research through partnership

National Institute for Health Research
Office for Clinical Research Infrastructure

NIHR Statistical Group
Imaging in Translation Research Meeting

Challenges in the design and analysis of studies evaluating imaging modalities

Pembroke College, Oxford, OX1 1DW
Tuesday 1st October 2013
10:00 – 16:00

nihr-stats@kcl.ac.uk

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NIHR Statistical Group: Imaging in Translation Research Meeting

SESSION 1 CHAIR: Professor Doug Altman

10:30 - 10:35	**Introduction and welcome** *Professor Doug Altman, University of Oxford*
10:35 - 10:45	**Translational research and the NIHR** *Mark Samuels, Managing Director, NOCRI*
10:45 - 11:15	**What is translational research and why is it important?** *Professor Keith Channon, Director, NIHR Oxford BRC*
11.15 – 11.45	**Imaging technology evaluation for NICE: a physicists perspective** *Professor Steven Keevil, King's College London*
11:45 – 12.15	**Statistical considerations: studies evaluating imaging modalities** *Professor Doug Altman*
12:15 - 12:30	**Questions & discussion**

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NHS National Institute for Health Research

Translational Research and the NIHR

Mr Mark Samuels
NIHR Office for Clinical Research Infrastructure (NOCRI)
Mark.samuels@nihr.ac.uk

NOCRI

NIHR Office for Clinical Research Infrastructure

NHS National Institute for Health Research

Why is the Government committed to research in the NHS?

- To improve health outcomes through advances in research
- To improve quality of care by NHS participation in the research process
- To strengthen our international competitive position in science
- To drive economic growth through investment by life science industries

NOCRI

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NHS National Institute for Health Research

Research and Growth: Strategy for UK Life Sciences

“Life science - and the UK’s role in it - is at a crossroads.

Behind us lies a great history of discovery, from the unraveling of DNA to MRI scanning and genetic sequencing.

We can be proud of our past, but this government is acutely aware that we cannot be complacent about the future.”

David Cameron

December 2011

Research and Growth: Strategy for UK Life Sciences

"The old 'big pharma' model is becoming more difficult to maintain.

In its place is a new focus on translational medicine - more early stage clinical trials with patients, more external innovation, more collaboration."

"This is an ambitious strategy to:

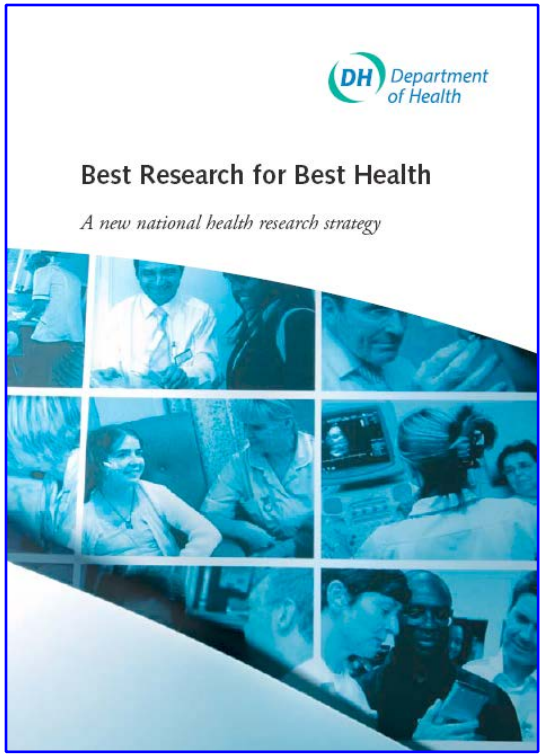
•open up universities and business to more collaboration;

•invest in the best ideas at an early stage;

•remove regulatory barriers;

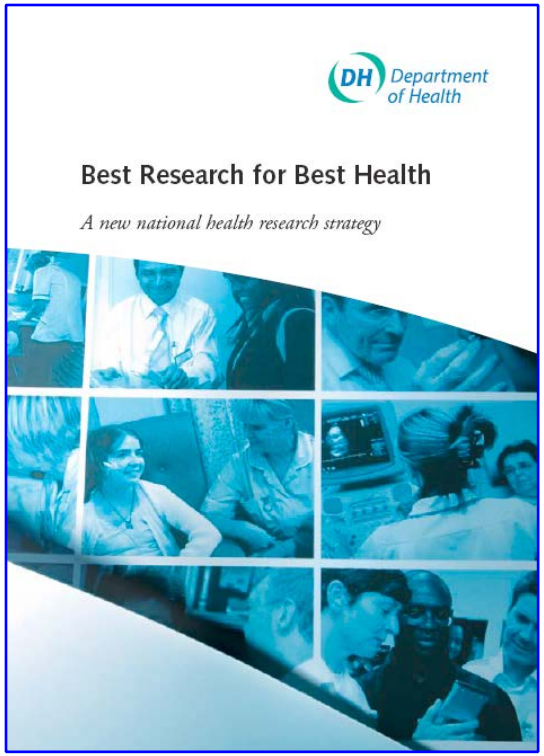
•open up the NHS to new innovations and new clinical trials."

National Institute for Health Research



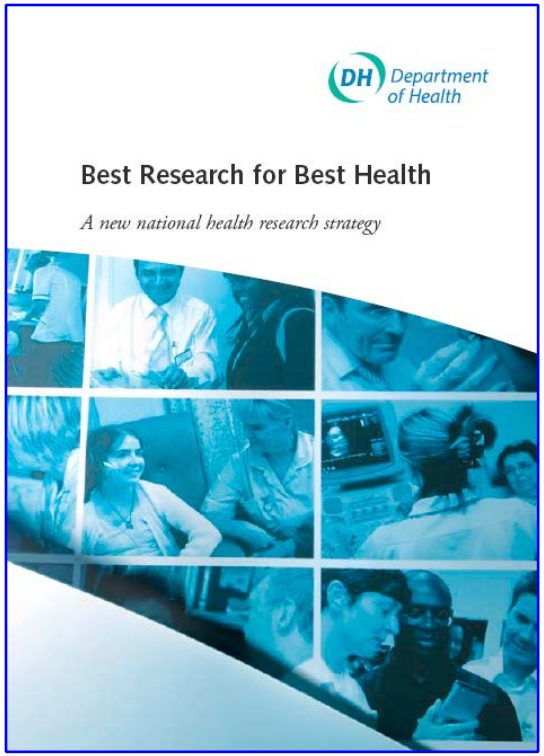
NIHR established on 1st April 2006 to deliver the strategy set out *in Best Research for Best Health*

Vision



To improve the health and wealth of the nation through research

Aim



To create a health research system in which the NHS supports:

- outstanding individuals
- working in world-class facilities
- conducting leading-edge research
- focused on the needs of patients and the public

Strategic priorities

- Transform research in the NHS
- Increase the volume of applied health research, and opportunities to participate in it, for the benefit of patients and the public
- Promote and protect the interests of patients and the public in health research
- Drive faster translation of basic science discoveries into tangible benefits for patients
- Develop and support the people who conduct and contribute to applied health research
- Maximise the research potential of the NHS to contribute to the economic growth of the country through the life science industries

Structure of the NIHR

- Distributed organisation
- Focused on the needs of patients
- Clear but flexible structure
- Maximum devolved decision-making
- Maximum local accountability

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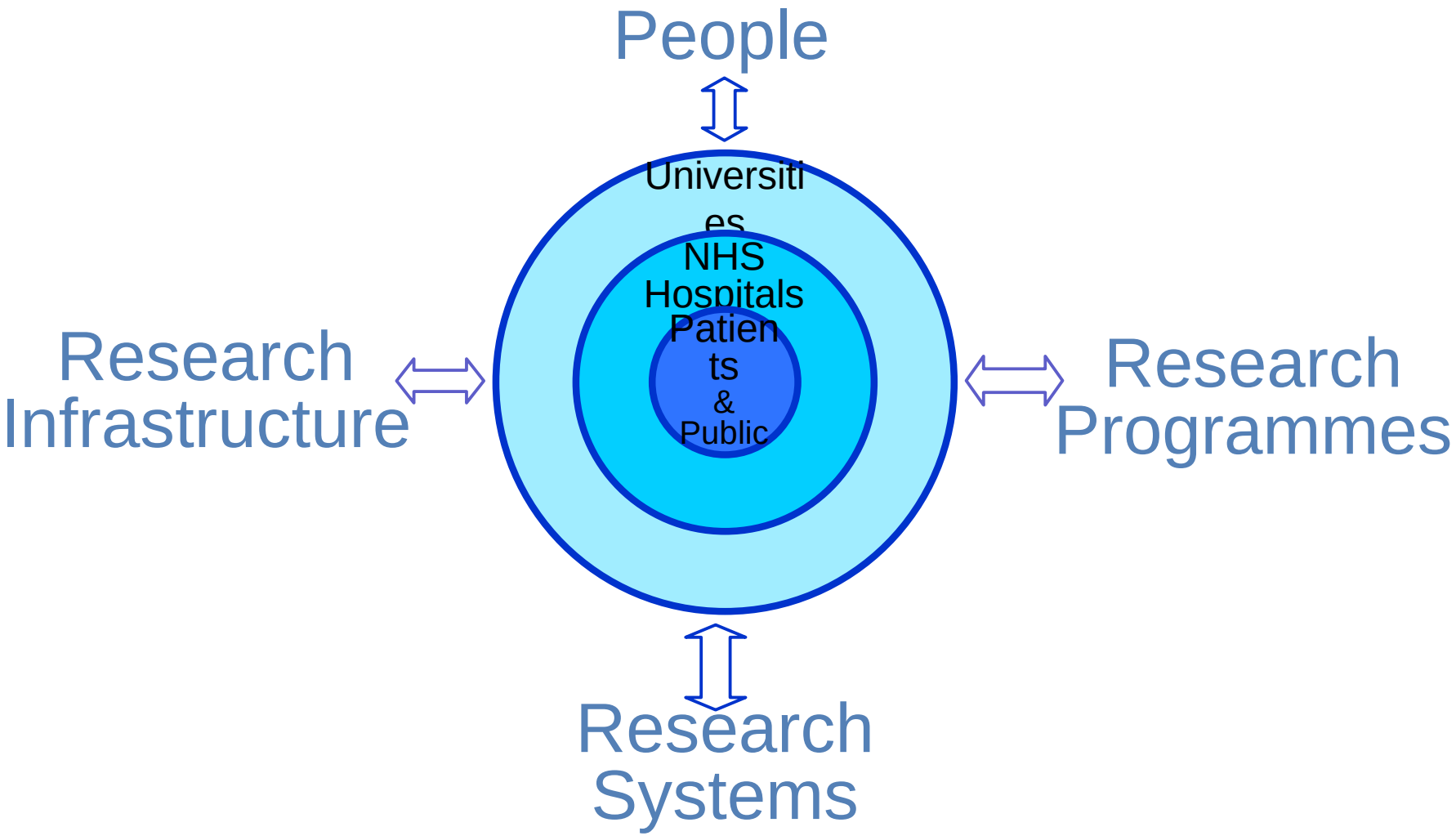
The NIHR Health Research System



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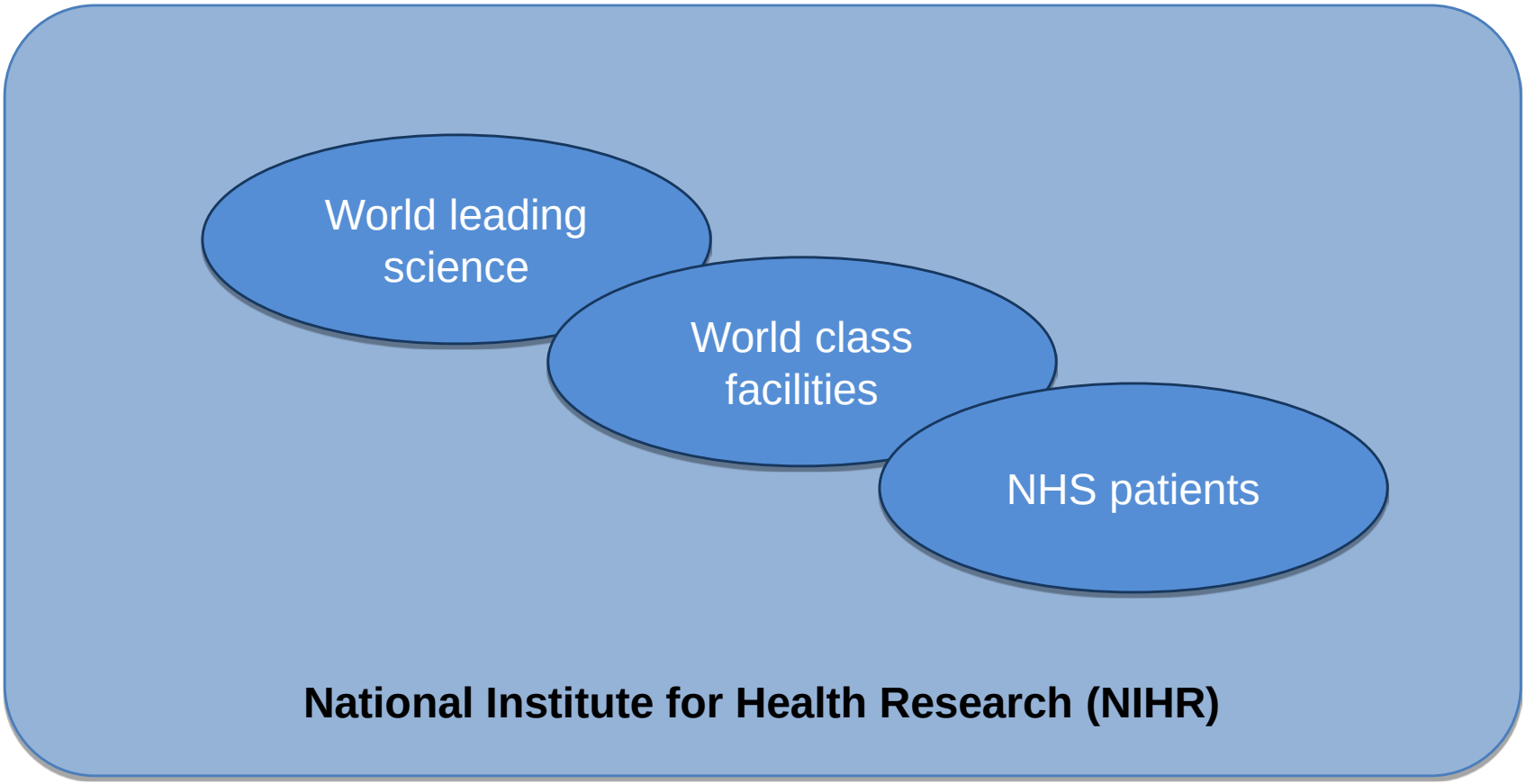
What can the UK offer to research partners?



NOCRI
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NHS National Institute for Health Research

NIHR Research Infrastructure

NIHR Biomedical Research Centres

NIHR Biomedical Research Units

NIHR Clinical Research Facilities

Experimental Cancer Medicine Centres

Healthcare Technology Co-operatives

Diagnostic Evidence Cooperatives

NIHR Clinical Research Network

> £0.5 billion p.a. investment in relevant infrastructure to support clinical research at all points in the development pipeline

NOCRI

NIHR Office for Clinical Research Infrastructure

NHS National Institute for Health Research

NIHR Clinical Research Network

	A single point of contact and entry for all Network research services
	Study and protocol feasibility from key opinion leaders and active commercial researchers
	Access to a streamlined system for obtaining NHS permission for R&D approvals
	Support with study start-up processes, including costing and contract negotiations using standard templates
	Dedicated and trained Research Network staff and support services to ensure study delivery at site level
	Performance management of the adopted study in partnership with a company
	Research Network 'badging' of adopted trials to attract both investigators and patients

NOCRI
NIHR Office for Clinical Research Infrastructure

NHS
National Institute for Health Research

Scale of opportunity for research partners

Access *via a single point of entry* to world class science in world leading institutions and patients across the NHS

NOCRI supports industry through:

- **sign-posting**
- **introductions**
- **establishing collaborations**
- **managing relationships**

NOCRI

NIHR Office for Clinical Research Infrastructure

NHS National Institute for Health Research

Contact NOCRI at:

nocri@nihr.ac.uk

www.nocri.nihr.ac.uk

KING'S HEALTH PARTNERS

An Academic Health Sciences Centre for London

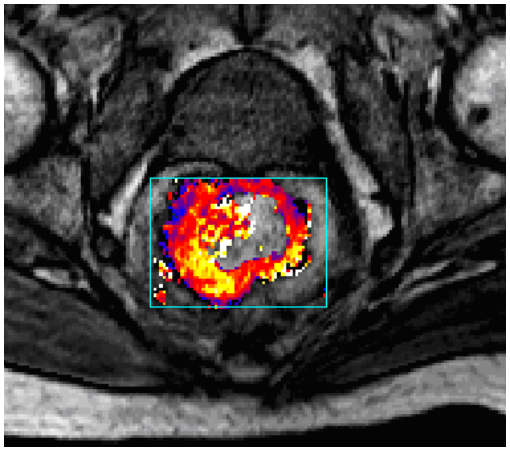
Pioneering better health for all

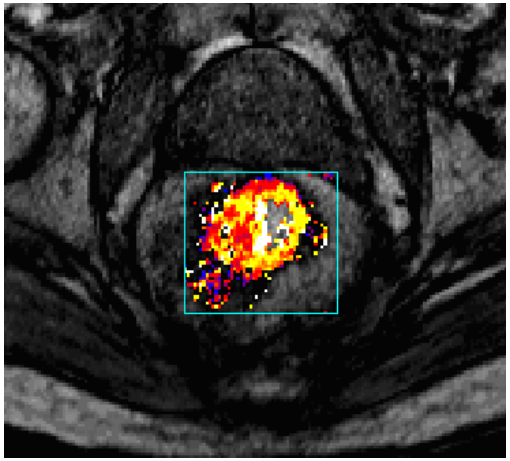
Imaging technology evaluation for NICE: a physicist's perspective

Professor Stephen Keevil, Joint Director,
KITEC: King's Imaging Technology Evaluation Centre

Introduction

- Imaging is no longer a purely diagnostic technique: it is increasingly important in treatment planning, guidance and assessment
- Imaging biomarkers have the potential to characterise individual patients, enabling personalised medicine
  - Improved quality of care through better patient selection
  - Reduced costs through identifying non-beneficial treatments
- Imaging makes increasing demands on capital and revenue budgets
  - Rapid development requires rapid adoption
  - But the evidence base is often poor
- Needs an integrated approach involving manufacturers, technical experts and clinical end users





A long time ago, in a galaxy far, far away…

GCAT

FAXIL

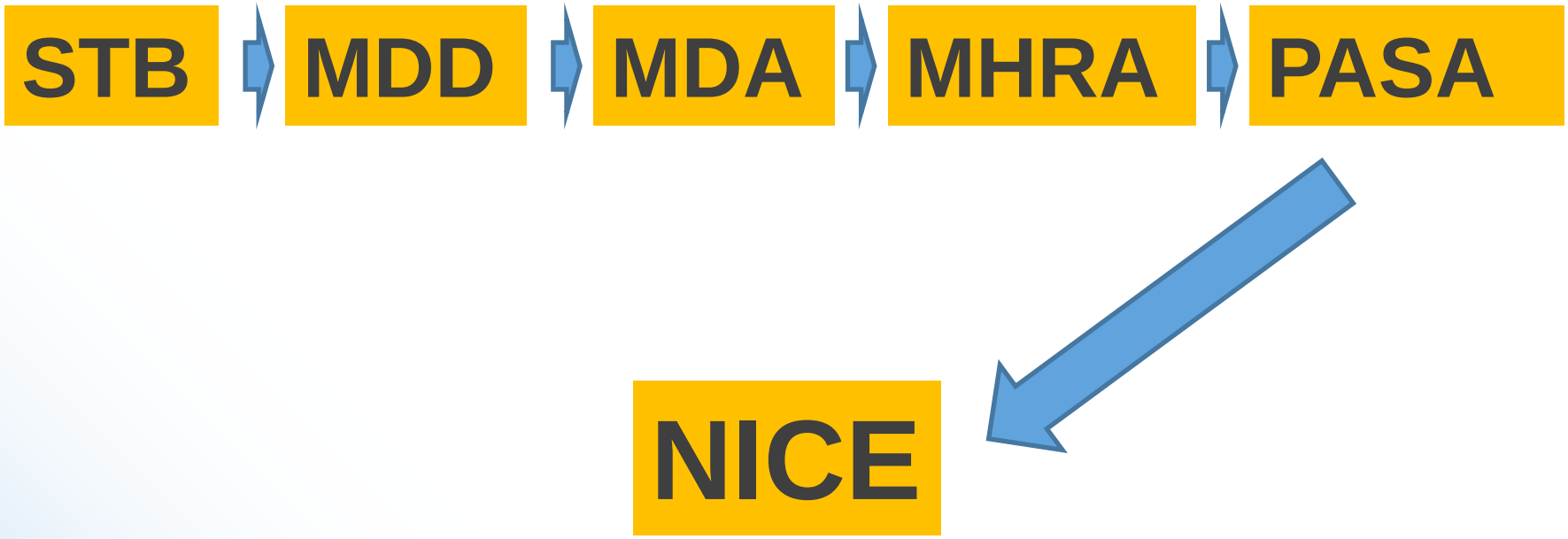
ImPACT

UEEP

PACSnet

KCARE

A long time ago, in a galaxy far, far away…



Coming up to date…

FAXIL

NICE is seeking to commission four external assessment centres (EACs) to provide a service to support the Evaluation Pathway and its related NICE programmes (see section 2.2). The envisaged four centres will each provide a comprehensive range of services as set out at section 4, but are required to have the following technical subspecialisation, with the associated knowledge and expertise:

- Medical devices (two centres)
- Imaging technologies (one centre)
- In vitro diagnostic tests (one centre).

KCARE

Areas of work

- Assessment reports
- Facilitating collaborative research into clinical and cost utility
- Specification, compilation and analysis of databases and registers
- Systematic reviews and meta-analysis
- Technical evaluation to advise on effective use

- Much broader than previous assessment centres: requires a multidisciplinary approach
- An idea task for an Academic Health Science Centre!

The tender...

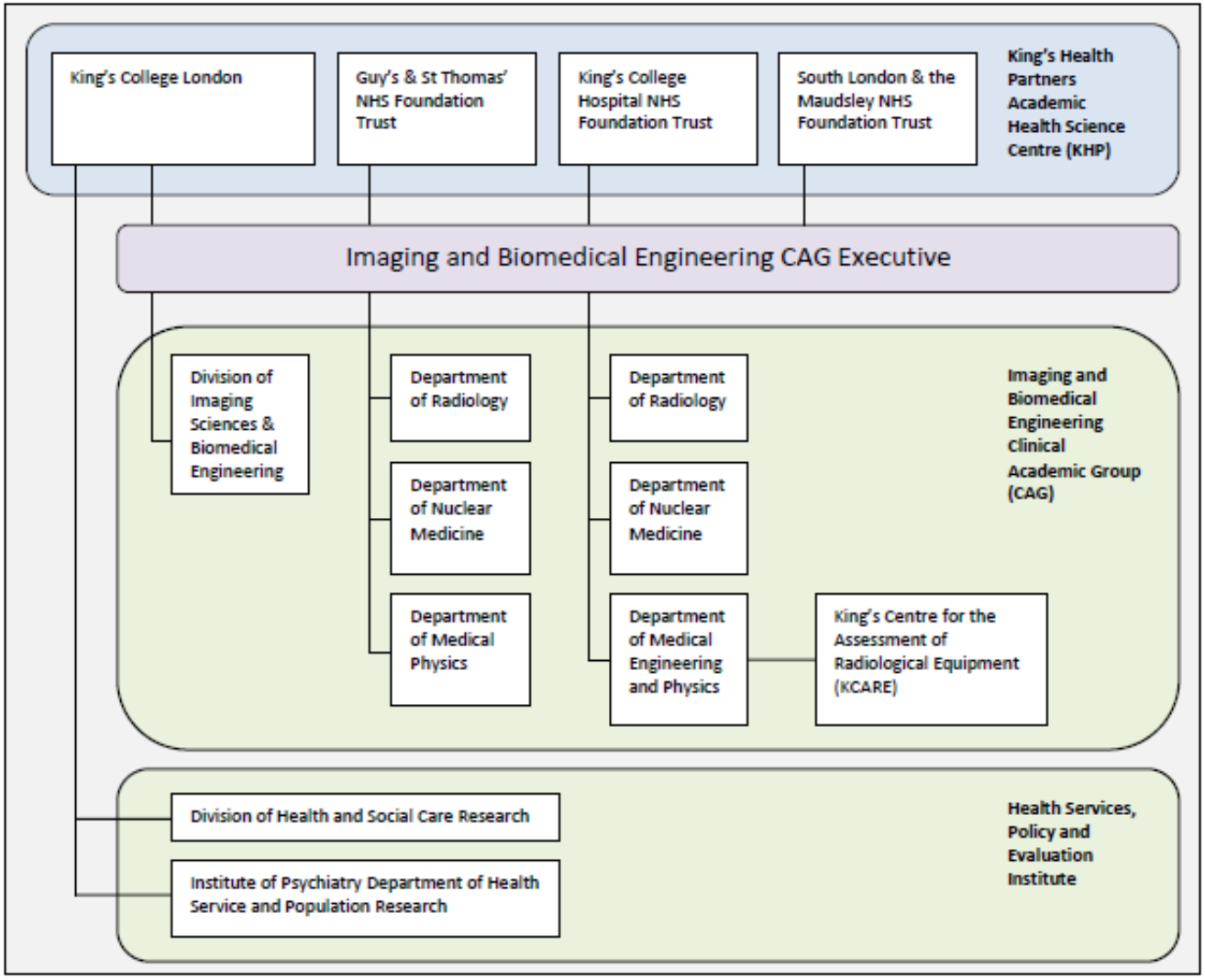
King's Health Partners Tender for NICE External Assessment Centre Four – Imaging Technologies

Executive Summary

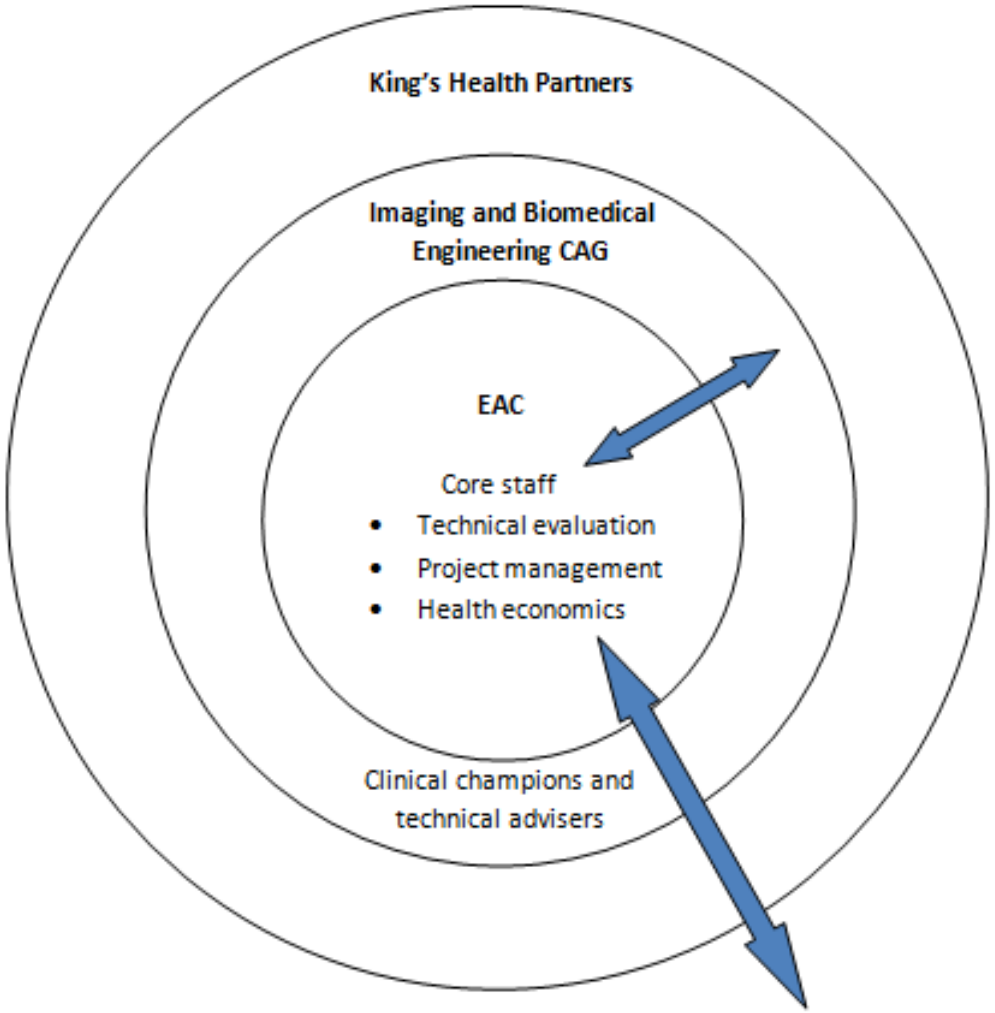
Background and context

Imaging continues to place high demands on hospital and health system capital and revenue budgets due to high equipment costs, rapid technological change and the need to recruit, train and retain highly skilled staff. Over the last few decades, advances in medical imaging have provided new measures for characterizing individual patients, resulting in the growing application of imaging in a variety of care pathways. Furthermore, the role of imaging has significantly changed from being purely diagnostic towards becoming a tool for image-guided surgical and therapeutic intervention. Today, imaging is increasingly used to assess the effects of treatment and to predict outcome. These imaging biomarkers are potentially of high importance in the development of new treatments (e.g. drugs, medical devices) and the selection of appropriate treatments for individual patients (personalised medicine). Personalisation of treatment has the potential to improve the quality of care by refining patient selection and characterisation and delivering better clinical outcomes. It will hopefully also lead to substantial cost reduction by identifying treatments that have little or no benefit for individual patients. But it is important that new applications of imaging are evidence-based and cost-effective. At present, new imaging technology is often adopted

Relationship between the partners



The broader picture

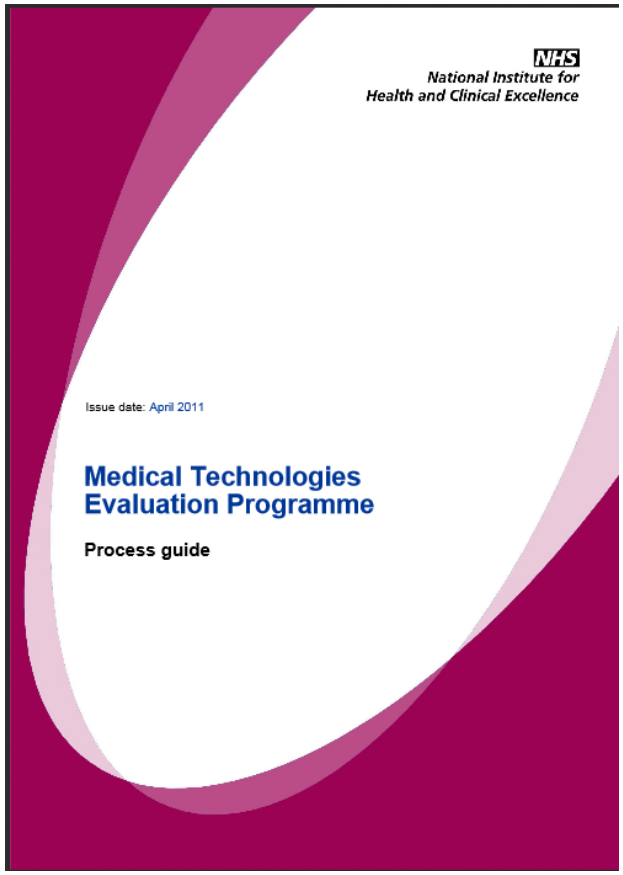


Outcome

- Tender submitted 9th December 2010
- Final round presentations scheduled for 22nd December 2010, postponed (on 21st December!) due to snow
- January 2011- March 2012 negotiations!
- Contract awarded March 2012
- So 2 years of 3 year term remaining
- Work slow to ramp up, very busy since Christmas 2012

NICE Medical Technologies Evaluation Programme (MTEP)

- To promote faster uptake of new medical technologies in the NHS
- To encourage collaborative research, in both industry and the NHS, to generate evidence on the clinical utility and/or healthcare system benefits of selected technologies



MTEP eligibility criteria

- Technology is a medical device (defined in EU Directive 93/42/EEC, as amended)
- Technology is new or innovative technology
- Technology has a CE mark, or this is expected within 12 months
- Technology is available in the NHS, or manufacturer plans to launch it in the NHS

MTEP selection

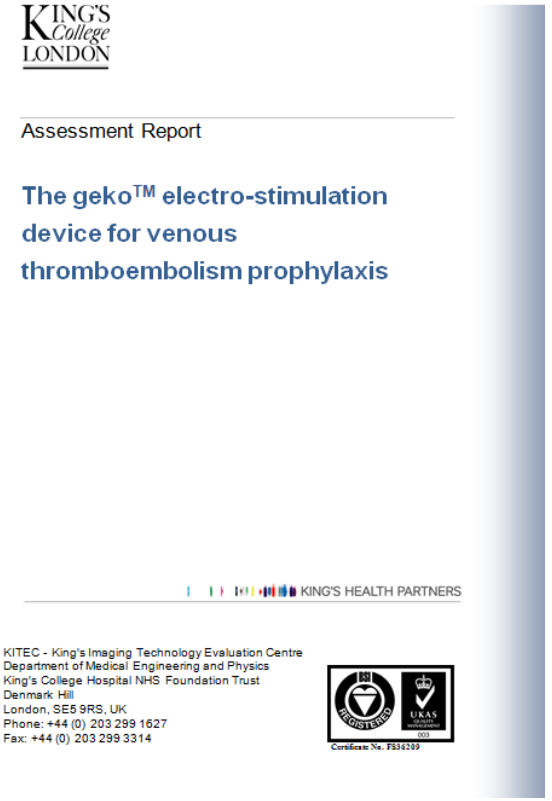
- Technology notified by manufacturer / sponsor
- NICE consults with Expert Advisers
- Medical Technologies Advisory Committee selects suitable technologies
  - September MTAC: 2/6 technologies selected
  - Reasons for rejection: inadequate clinical evidence, inadequate economic evidence, not unique…
- Routed to MTEP if technology:
  - is likely to be cost saving or cost neutral
  - can be evaluated as a single technology
  - can be evaluated on a short timescale
- Or can be routed to other programmes

MTEP assessment

- Project allocated to an External Assessment Centre (EAC)
- NICE prepares and consults on scope, defining disease(s), patients and technology covered by the assessment, outcomes, relevant comparators
- Manufacturer submission of clinical evidence (2 weeks)
- Manufacturer submission of economic evidence (6 weeks)
- EAC assessment report submitted (10 weeks)
- EAC presents at MTAC meeting. MTAC produces draft recommendations (c15 weeks)
- Final guidance issued following consultation (c32 weeks)

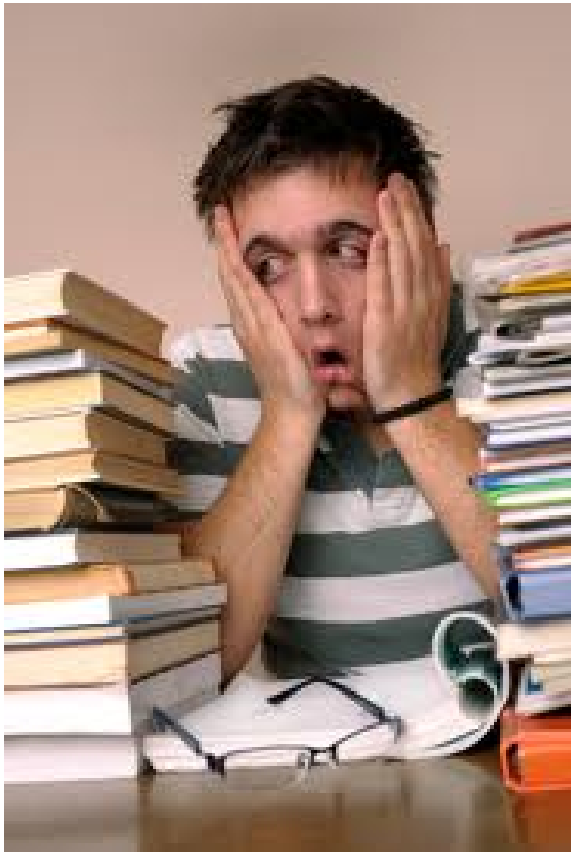
Contents of assessment report

- c100 pages
- c100 person-days of work
- Critique of clinical evidence: search strategy, study selection
- Critique of study methodology and sponsor's analysis and synthesis
- Additional work on clinical evidence
- Critique of economic evidence: search strategy, study selection
- Critique of cost model
- Additional work on economic evidence



Workload

- Assessment report: 2 (neither imaging related!)
- Initial product assessment: 62
- Research facilitation: 4
- Establishment of registers: 1
- Technical advice / horizon scanning: 4
- Expressions of interest: 8
- Miscellaneous: 3



Comments: nature of allocated work

- Very few imaging devices are coming through the programme
  - New or novel ‘single technologies’ that reduce costs are rare
  - Incremental development by several companies in parallel: about methods, not manufacturers
  - The Diagnostics Assessment Programme (DAP) can consider (1) multiple technologies, (2) cost-effectiveness
  - There is little evidence of impact of imaging on patient outcomes
- We are being used as a generic assessment centre and a source of specialist advice on imaging

Comments: process and timescales

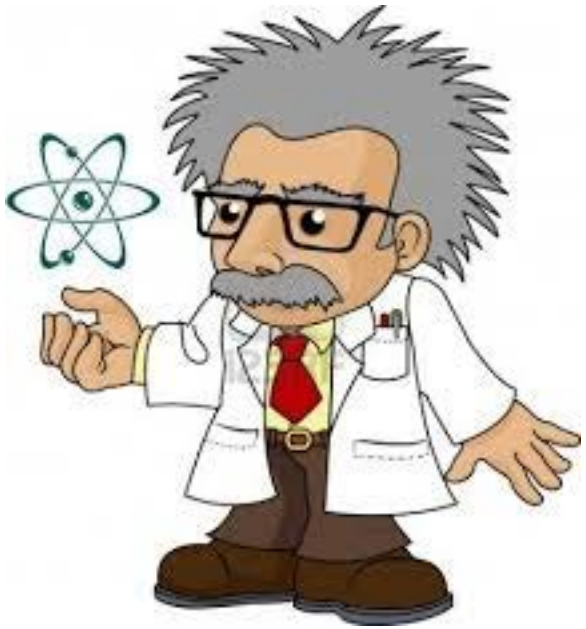
- Workload is unpredictable, new projects can be assigned at any time
- Timescales are extremely demanding, particularly if additional work is needed
- There is limited scope for extensions
- Variation of project plans requires discussion and approval by NICE
- All EACs are required to respond to all calls for expression of interest
- EoIs are assessed according to rigid criteria: it is possible to ‘know too much’!

Comments: quality of evidence and submissions

- Products are often quite new, with little published evidence available
- Manufacturers are often SMEs, with limited resources/expertise for systematic review and analysis
- Significant additional work can be required from the EAC
- NICE has a relatively low threshold for evidence
  - RCTs not expected
  - Considerable reliance on expert opinion
- Products have already been filtered by MTAC: a positive outcome is desired at this stage

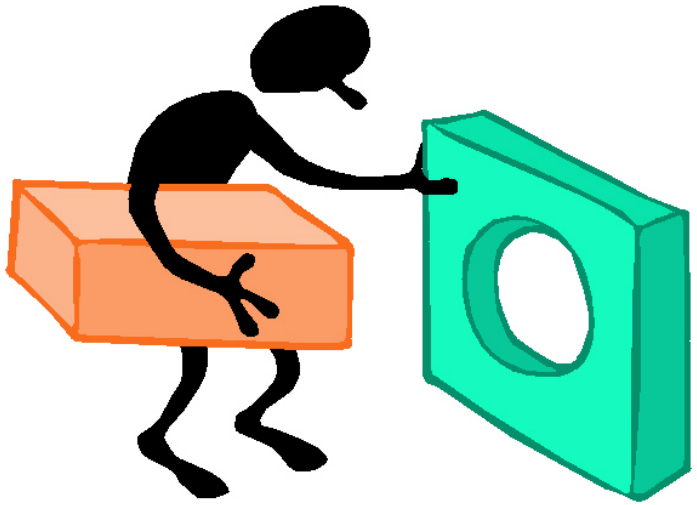
Comments: expert advisers

- Expert advisers need to be ratified by professional bodies before they can be formally consulted, which can introduce delay
- Consultation with expert advisers is formal and documented
- We cannot use local experts as expert advisers if we also want to involve them in production of the report



Comments: practical difficulties

- Only 2 years left when the contract was signed: difficult to recruit good people to fixed term contracts
- Work can be complex, requiring significant senior level input
- Difficult to coordinate work of four different teams across three campuses
- Difficulties at NHS-university interface: finance, HR, IT…



The future

- It’s been challenging but interesting; we’re keen to continue
- We and NICE have learned a lot from the process
- Current contract expires March 2014
- New call for tenders was expected in late June
- At the time of writing, we are still waiting…

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NIHR Statistical Group: Imaging in Translation Research Meeting

SESSION 2 CHAIR: Professor Janet Peacock

13:15 – 13:30 **Challenges for the statistician in designing studies in imaging**
Professor Janet Peacock, King's College London

13:30 – 13:45 **Challenges of functional & structural MRI in a clinical trial**
Dr Thomas Nichols, University of Warwick

13:45 – 14:00 **CASE STUDY 1: T1 mapping - bringing imaging biomarker into clinical practice**
Dr James Moon, NIHR University College London and UCLH BRC

14:00 – 14:15 **CASE STUDY 2: Tracking eye gaze during radiologist interpretation of endoluminal 3D CT Colonography**
Dr Tom Fanshawe, University of Oxford

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SESSION 2 CHAIR: Professor Janet Peacock

14:15 - 14:30 **CASE STUDY 3: 1000 cardiac phenomes project - using computational anatomy to understand heart disease**

Dr Declan O'Regan, Imperial College London

14:30 – 14:45 **CASE STUDY 4: Diagnostic performance of [11C]choline PET/CT versus MRI in prostate cancer nodal staging: Research Challenges**

Dr Amar Challapalli, NIHR Imperial BRC &CRUK-EPSRC-MRC-NIHR Comprehensive Cancer Imaging Centre

14:45 - 15:00 **CASE STUDY 5: Imaging biomarkers in colorectal cancer**

Dr Gina Brown, NIHR Royal Marsden & ICR BRC

CSM

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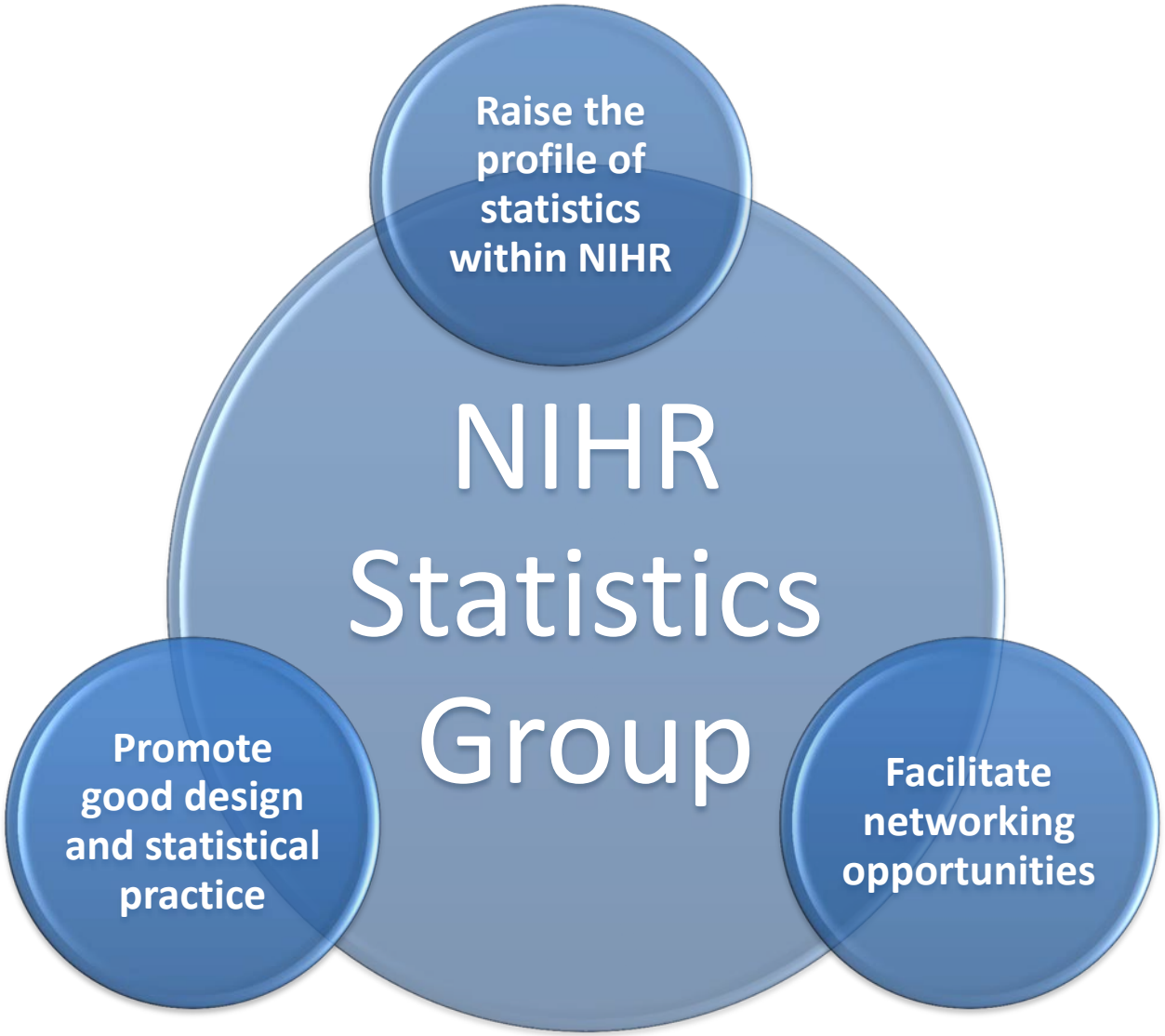

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NIHR Statistics Group

- Established 2011
- Educational meetings and workshop events
- Identifying statisticians for DMCs and TSCs

  STAT-LINK@JISCMAIL.AC.UK

  Email: listserv@jiscmail.ac.uk

  Subject: BLANK

  Message: SUBSCRIBE STAT-LINK Firstname Lastname
- Future: mentoring schemes and training

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- We are looking for statisticians to join the working committee
- We are looking for institutions who would be willing to host an event

Email: nihr-stats@kcl.ac.uk

Surgical Clinical Trials Workshop

A joint workshop for NIHR statisticians and trainee surgeons on designing, running and analysing surgical studies.

Wednesday 12th February 2014

University of Birmingham



KING'S College LONDON

University of London

Challenges for statisticians with studies in imaging

Janet Peacock

Division of Health and Social Care Research, King's College London; NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London

NIHR Statistics Group: Imaging in Translational Research
University of Oxford 1st October 2013

What do statisticians do?

- **Interdisciplinary team work**
  - Design
  - Analysis
  - Interpretation of results
  - Reporting/presenting results

  - Methodological issues

- **Both new and existing research**

- **Statistical thinking**

Eg designing an evaluation

- **What is the research question?**
- **Or what question does the data answer?**

Eg: is a new imaging device better than current one?

- How assess 'better'?
- Technological /clinical outcome?
  - eg same measurements, diagnostic accuracy, length of stay, mortality etc

What design for evaluation?

- **What design will answer the question?**
- **Or what question does design answer?**

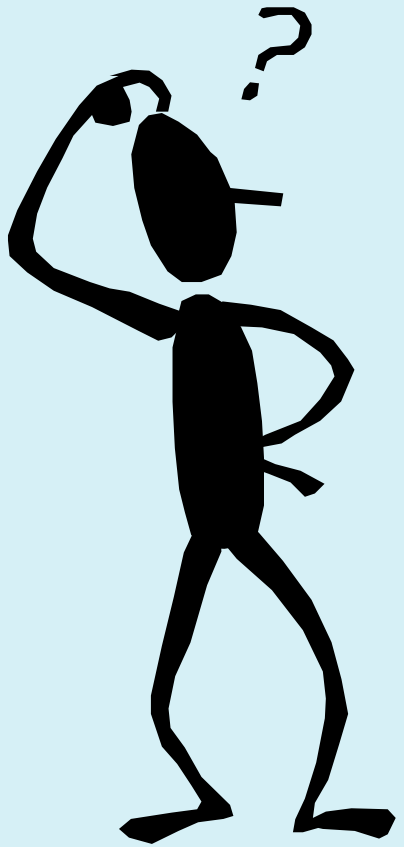
- Gold standard is randomised controlled trial
  Some issues are:
  - blinding for patient, researcher, assessor
  - Incomplete data

- Practicality may dictate observational study
  Some issues are:
  - Data quality
  - Comparability of groups & interpreting differences seen

Analysis

What approach to analysis?

- Standard method?
- Multiple approaches?
- Assumptions met?
- Straightforward to interpret?
- Easy to communicate?
- Clinically meaningful?



Reporting and interpreting results

- Transparent reporting of methods, assumptions, results

- Selection of results to present

(Clear tables, figures; all subjects accounted for, estimates & CIs)

- Conclusions mesh with data in all parts of document cf abstracts

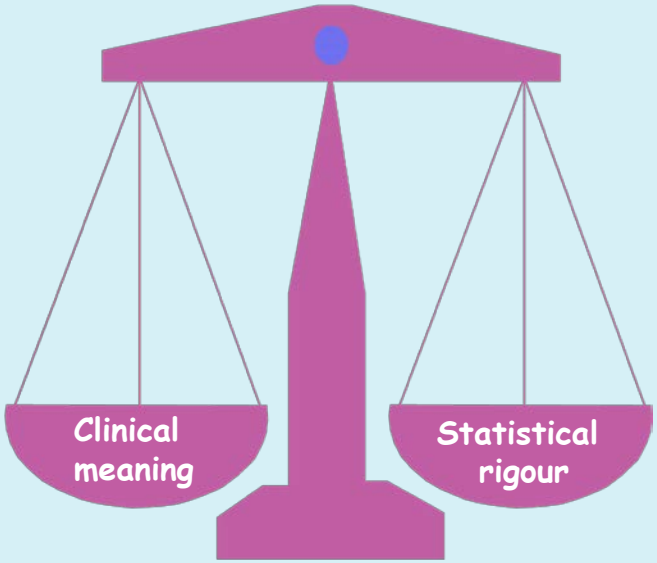
Summary

- Statisticians work collaboratively to:

  -- design and analyse studies to answer important clinical questions
  -- review research conducted by others

- Statisticians develop methodological solutions to problems

- Aim of statistics in medical research is always to balance statistical rigour with clinical meaningfulness



Tracking eye gaze during radiologist interpretation of endoluminal 3D CT colonography

Tom Fanshawe
Department of Primary Care Health Sciences
University of Oxford

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NIHR Programme Grant to investigate diagnosis of colorectal cancer using imaging technologies

Collaborators include:

Steve Halligan (UCL, lead)

Emma Helbren (UCL, radiology)

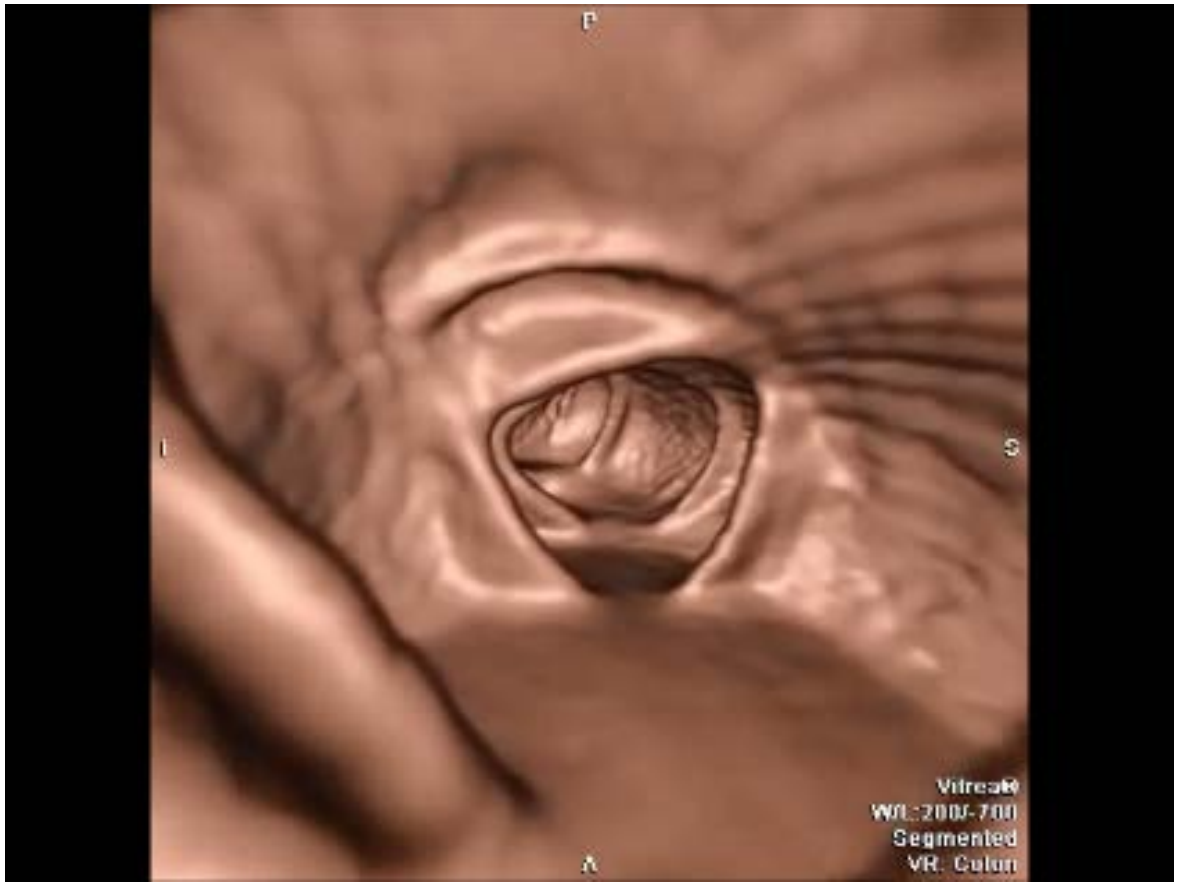
Susan Mallett (University of Oxford, statistics)

Peter Phillips (University of Cumbria, image perception)

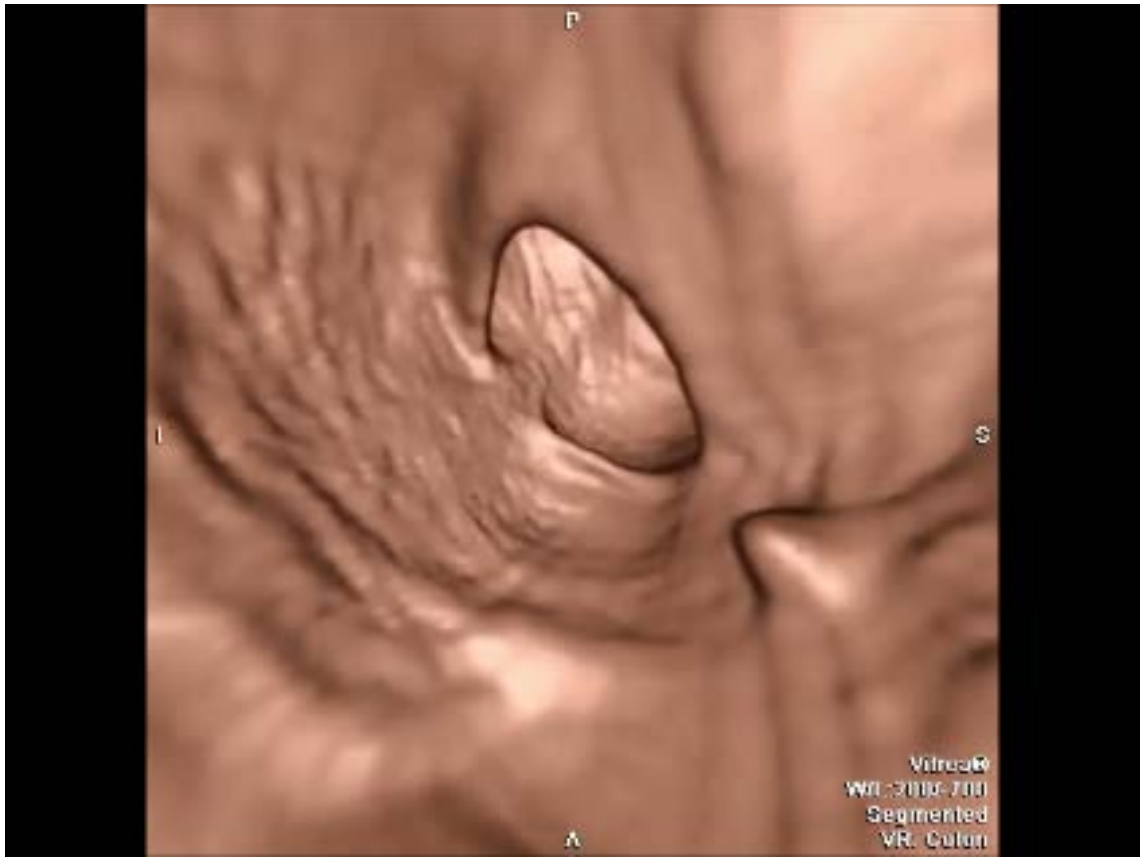
Background

- Bowel cancer has 6% lifetime prevalence in the UK
- 17,000 deaths/year in the UK, ~50% mortality rate
- Symptoms common, so diagnosis must be rapid, acceptable to patients, and cost-effective

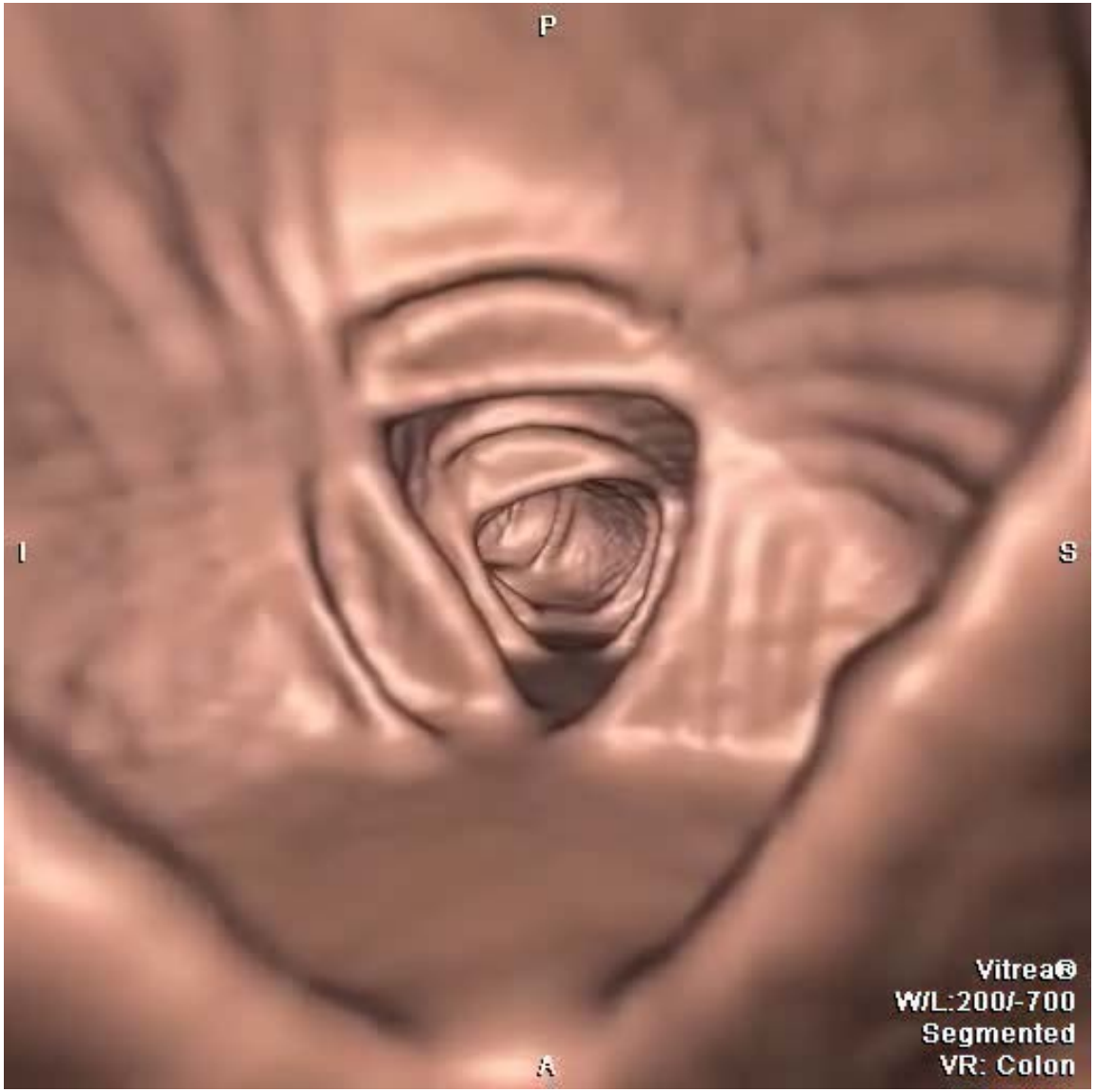
- Computed tomographic (CT) colonography: CT scanning + 3D imaging
- ‘Virtual colonoscopy’



Reader (radiologist) navigates an endoluminal reconstruction of the colon



Target for identification in this study is adenomatous polyps – precursors of colon cancer



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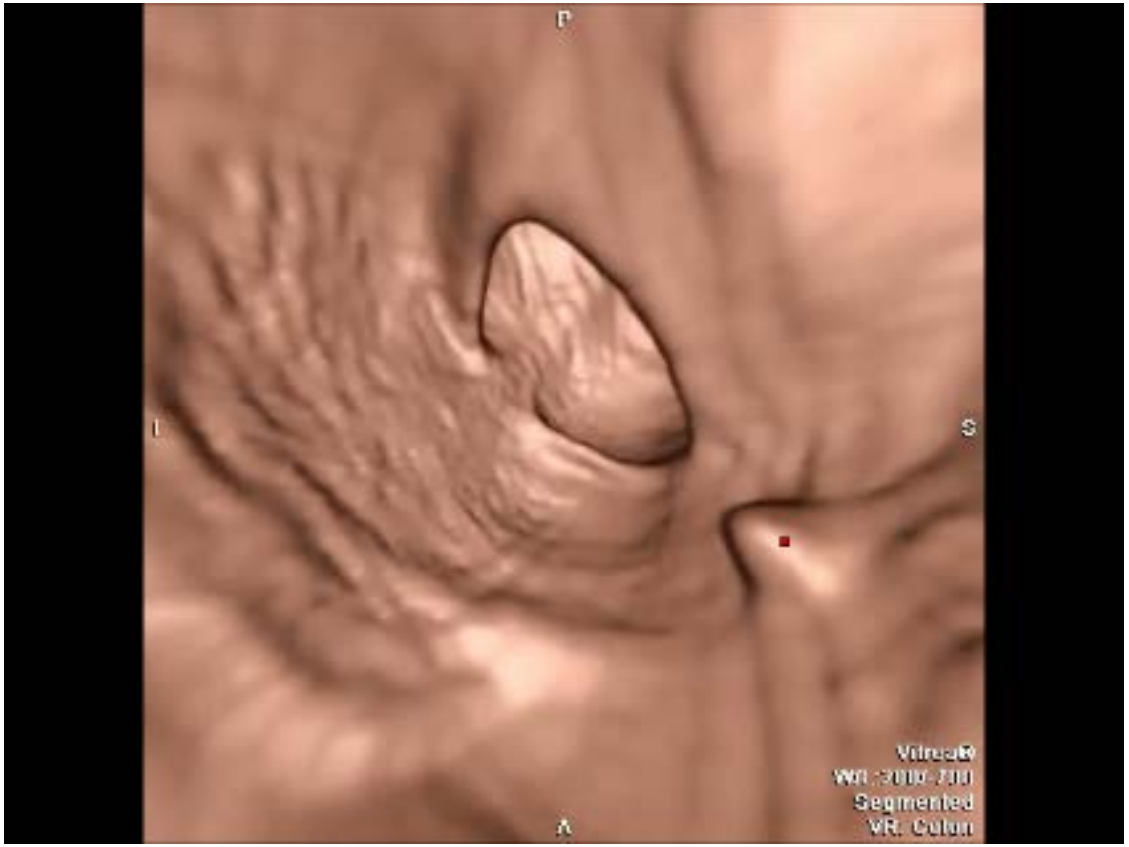
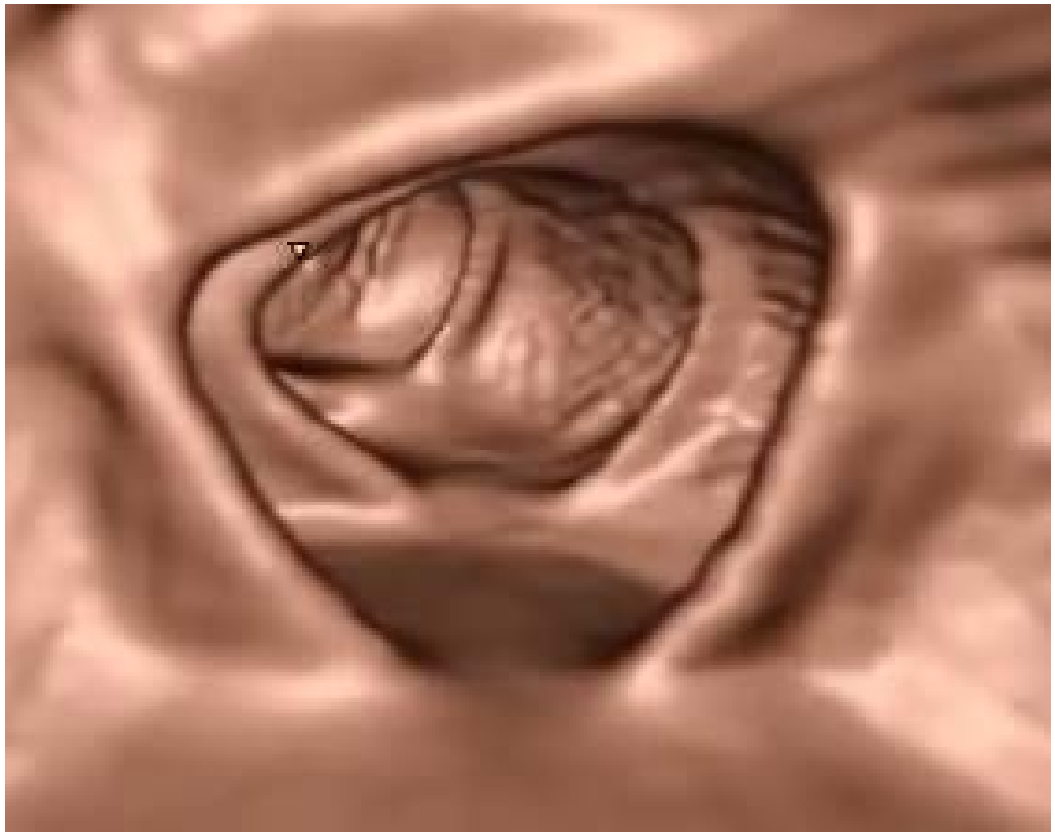


Diagnosis may be assisted by the presence of an indicative mark generated by a computer aided detection (CAD) system (Vitrea, Vital Images)

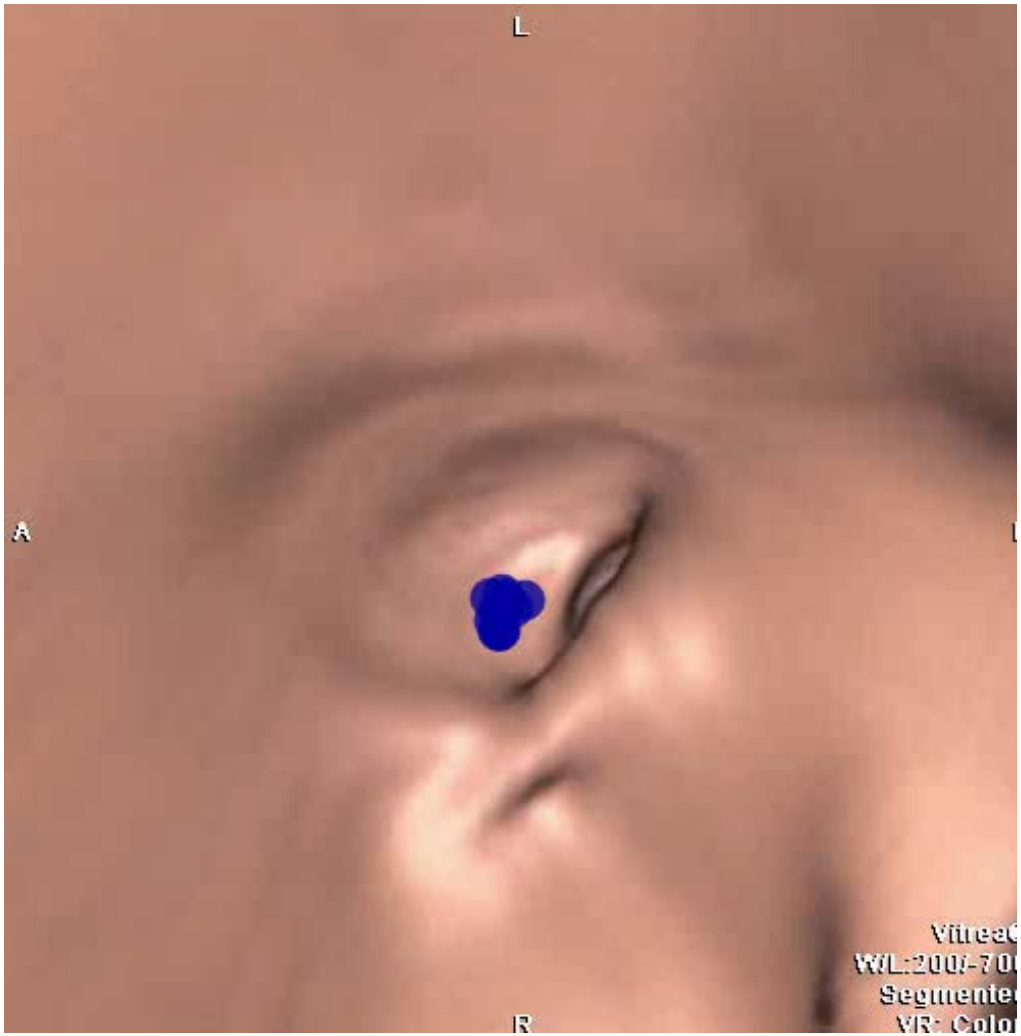


Early appearance of CAD mark

Design – computer-aided detection study

- 42 readers viewed fifteen 30-second video clips twice each
- In each video, one of the two viewings for each reader contained the CAD mark; the other did not
- Readers were asked to indicate with a mouse click when they saw a polyp
- Each video contained one polyp

Eye tracking



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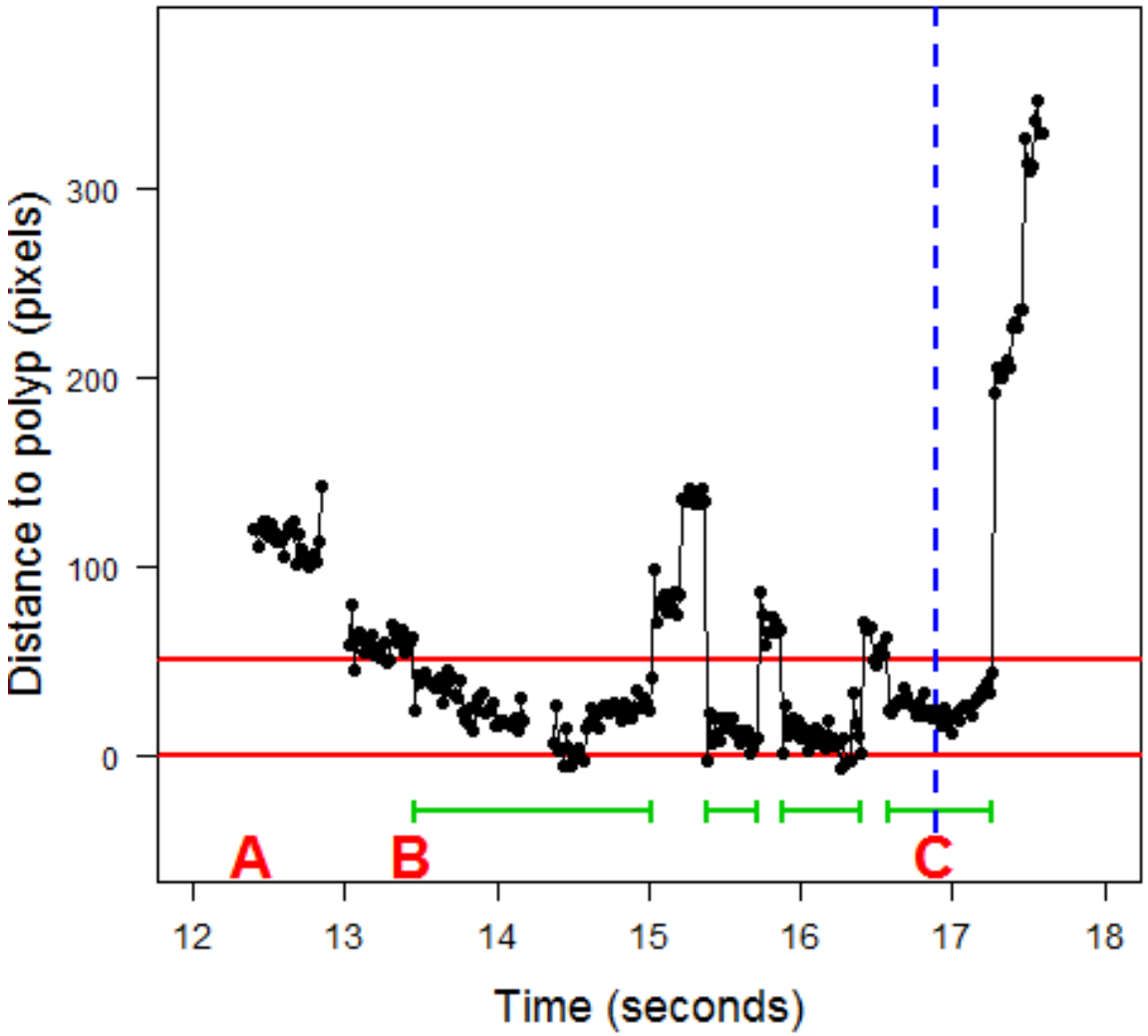
Strategy

- Main interest is in whether gaze is directed at the polyp

- Define a ‘pursuit’ of the polyp as a period when the gaze is directed:
  - Within 50 pixels of the boundary of the polyp
  - For at least 100ms of consecutive measurements

Distance to polyp

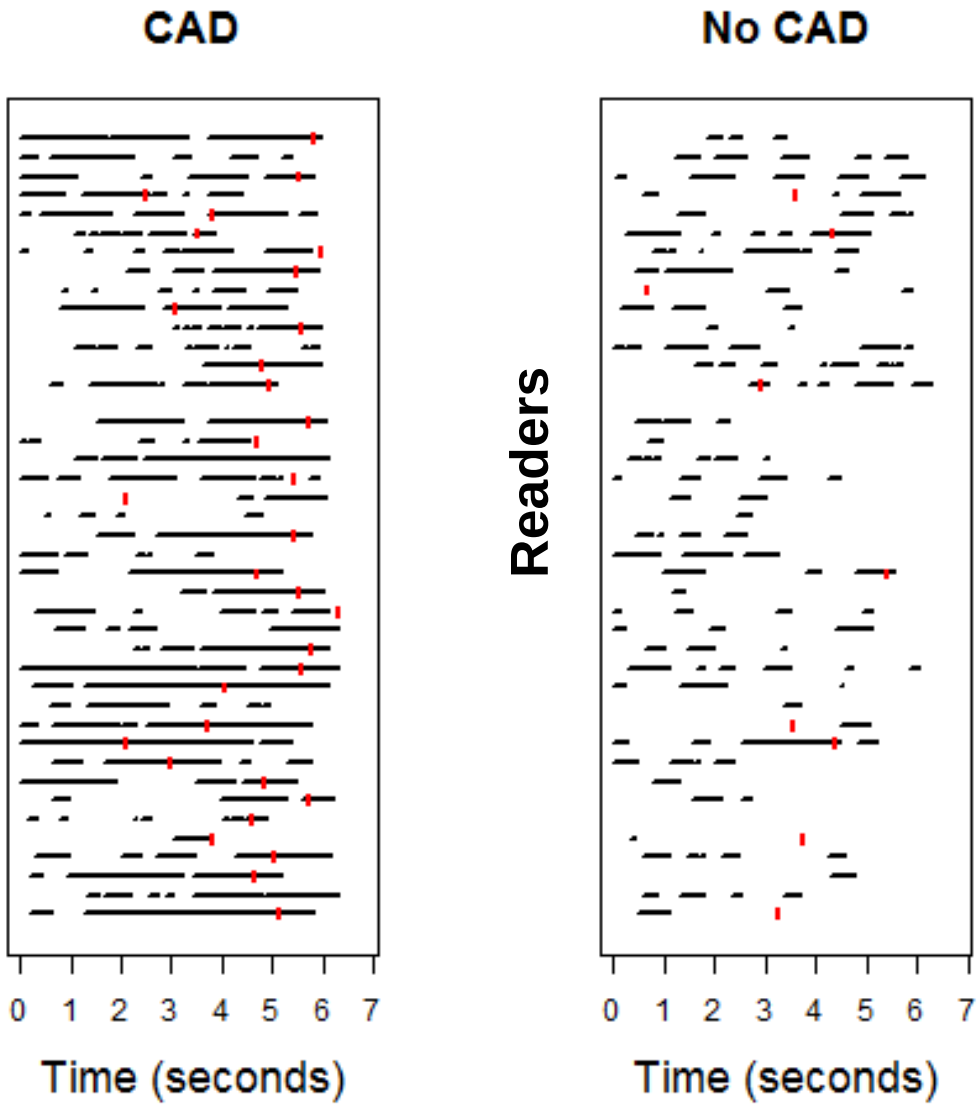


Issues in data analysis

- Reader- and case-specific measurement error
- Missing data
  - Multiple imputation
- Hierarchical data structure
  - Random effects for reader and case
- Different distributional forms for different outcomes (continuous, binary, rate, time-to-event), including zero-inflation

Results – single case

- CAD increased average time spent looking at the polyp



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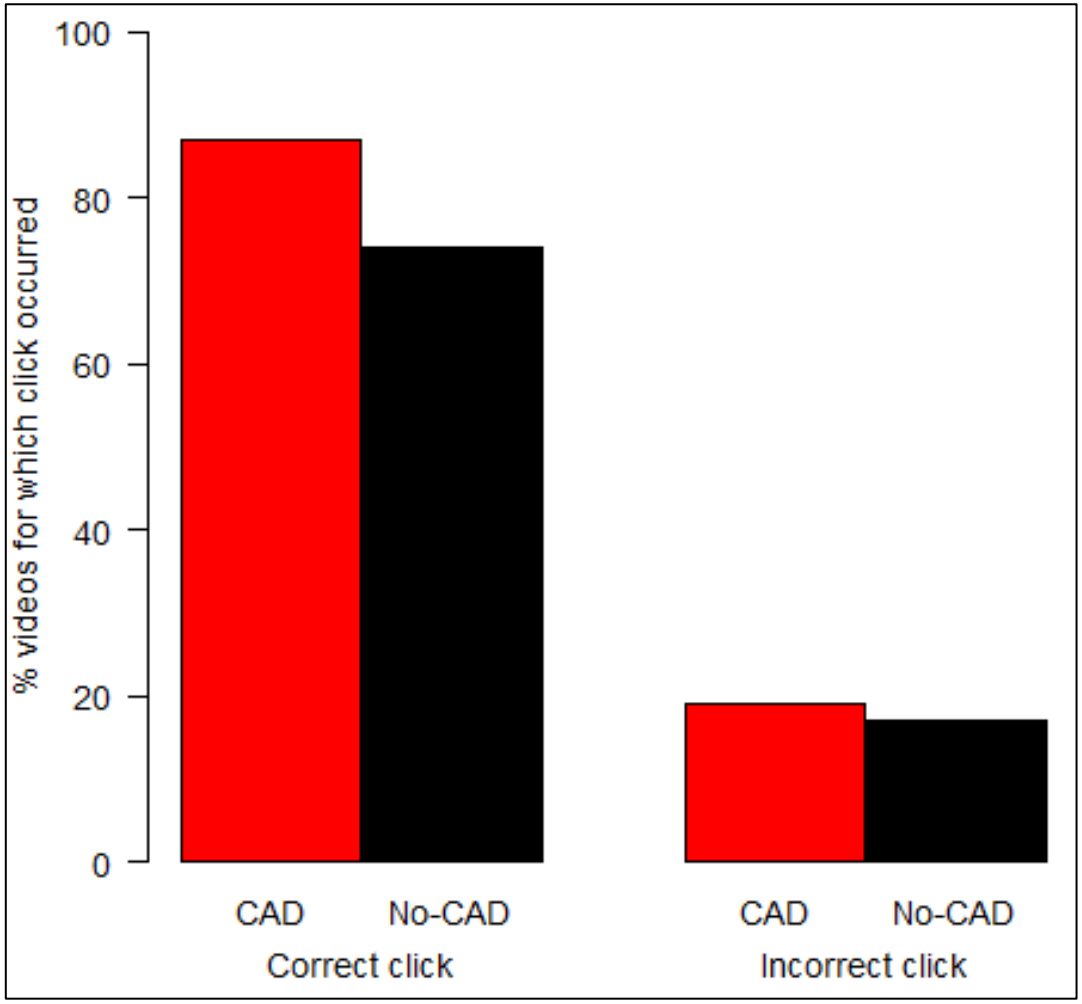
Diagnostic accuracy

- Presence of CAD resulted in an increase in number of correct polyp identifications

- No change in number of incorrect identifications



Results

Additionally, CAD is associated with:

- Shorter time to first pursuit of polyp
  0.58 to 0.48 seconds
- Quicker polyp identification
  3.24 to 3.01 seconds
- Increased rate of pursuits before polyp identification
  0.69 to 0.78 pursuits per second
- A ‘distractor’ effect
  Readers spend 24% of time looking at the CAD mark even when polyp not visible

Summary

- This is the first study to examine visual search during 3D CT colonography viewing
- Addition of a CAD mark held reader gaze and disrupted usual visual search patterns
- The CAD mark did not cause significant diagnostic confusion, and reduced identification error rate

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Phillips, P. et al (2013). Method for tracking eye gaze during intepretation of endoluminal 3D CT colonography. *Radiology* 267: 924-931.

Halligan, S. et al (2011). Incremental benefit of computer-aided detection when used as a second and concurrent reader of CT colonographic data: multiobserver study. *Radiology* 258: 469-476.

Drew, T. et al (2012). When and why might a computer-aided detection (CAD) system interfere with visual search? An eye-tracking study. *Acad Radiol* 19: 1260-1267.

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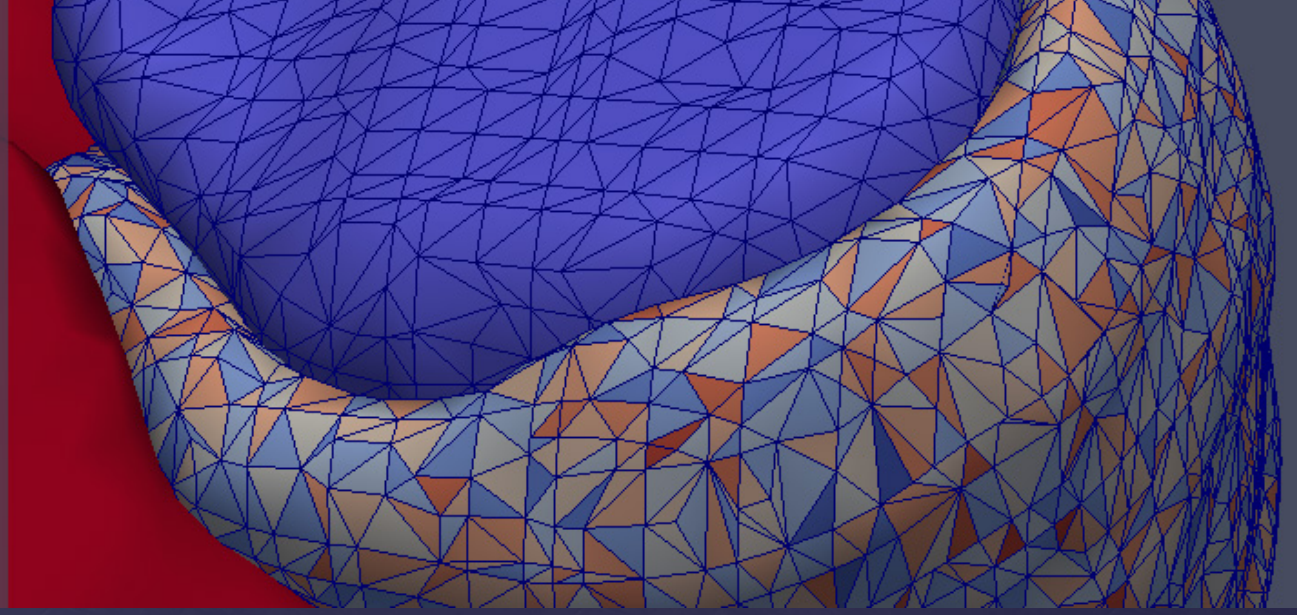
genSCAN

MRC Clinical Sciences Centre

Imperial College London

British Heart Foundation

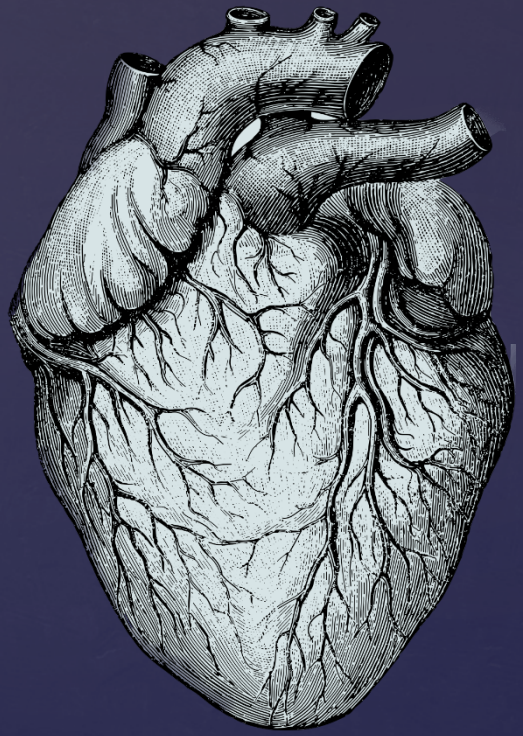


1000 Cardiac Phenomes Project

Dr Declan O'Regan
MRC Senior Clinician Scientist
CSC MR Facility

{ How do genes influence complex biological systems in humans?

Phenotyping



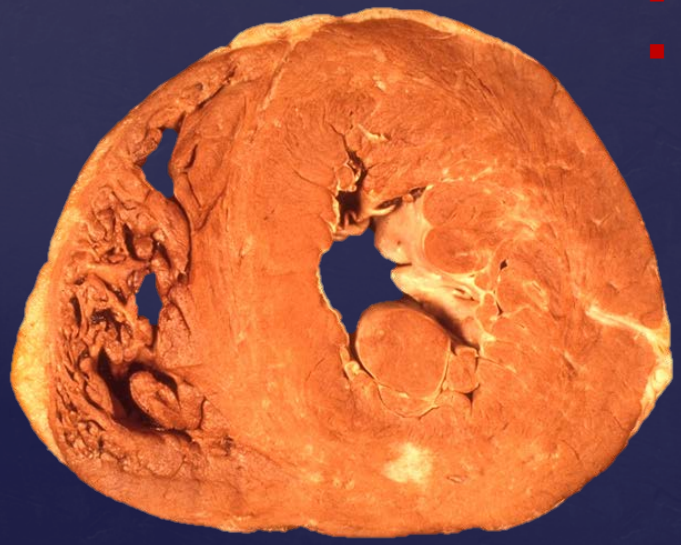
The heart is a complex electromechanical biological system.

Can we create a realistic computational model of its function and how genes control it?

Phenotyping

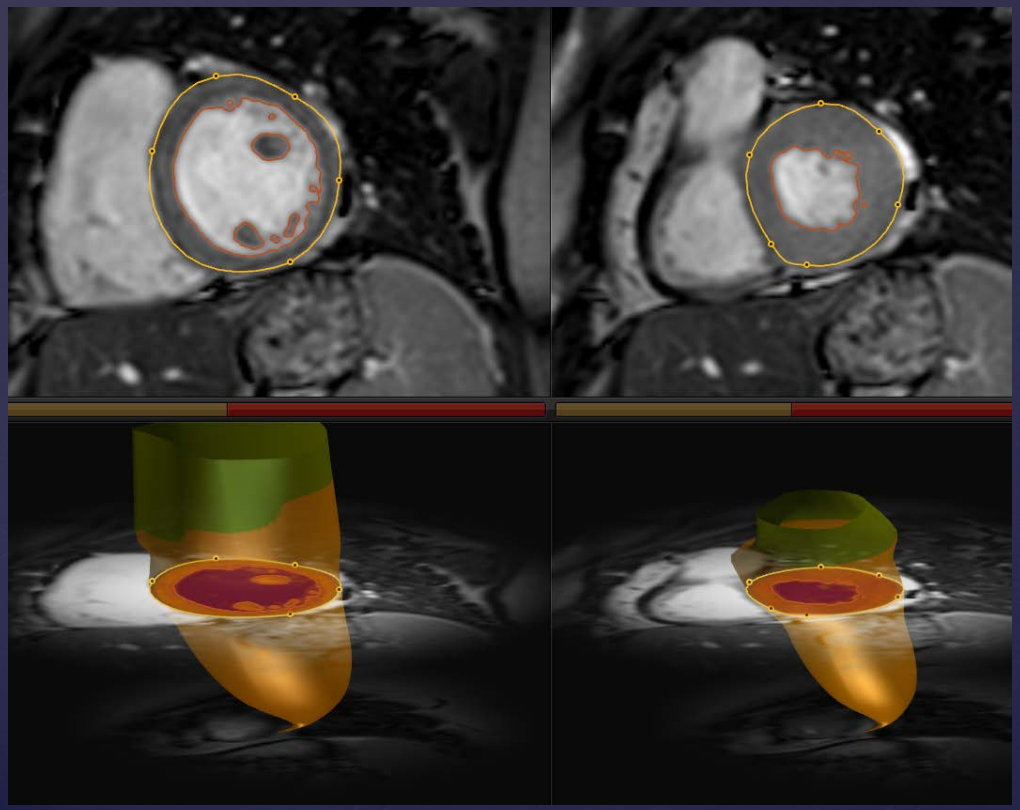
Let's take the simple but important phenotype of left ventricular hypertrophy:

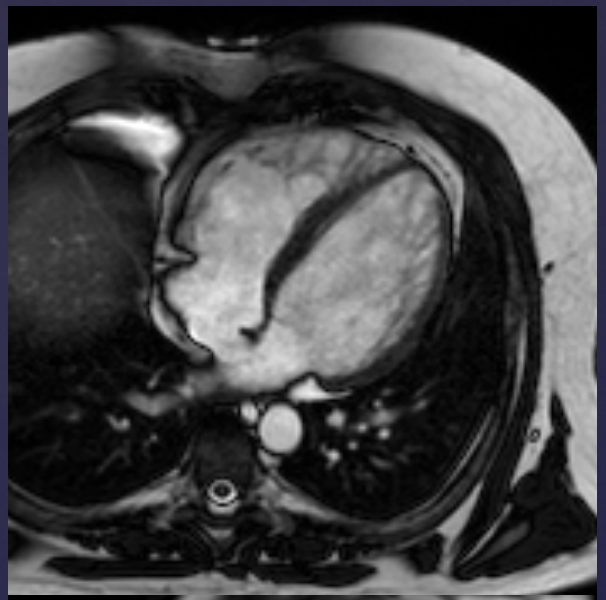
- Thickening of the heart muscle
- Predicts all cause mortality
- Amenable to treatment
- Heritability estimate 20 – 70%
- Both environmental and genetic interactions

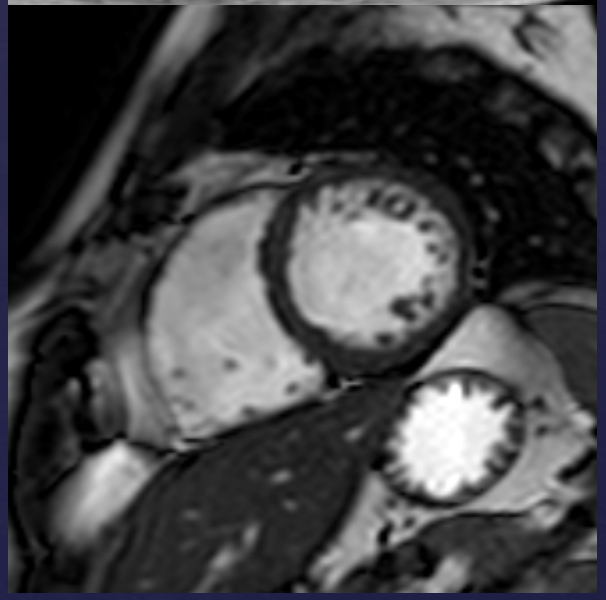


Cardiac MR Imaging

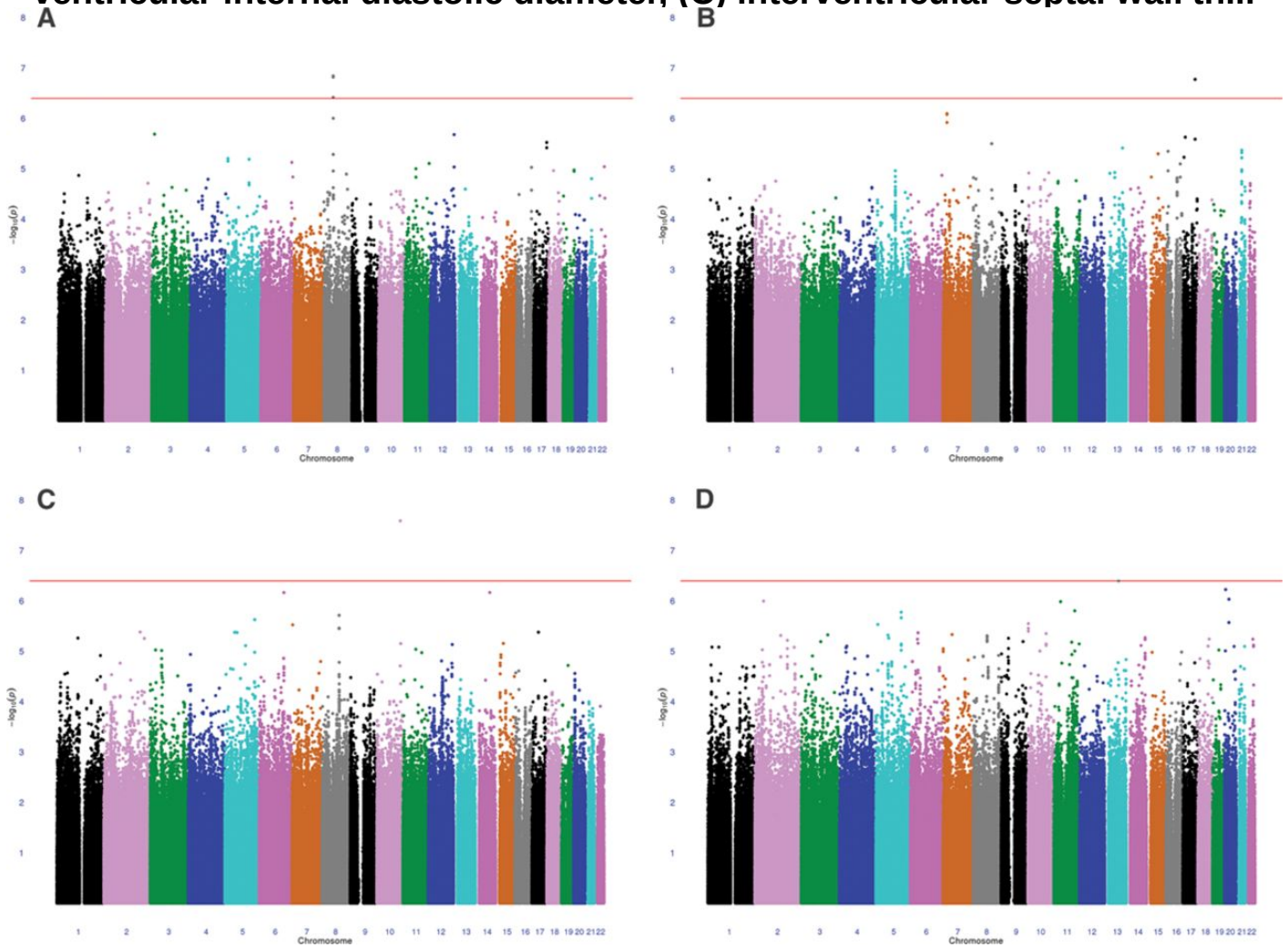
Cardiac MR Imaging





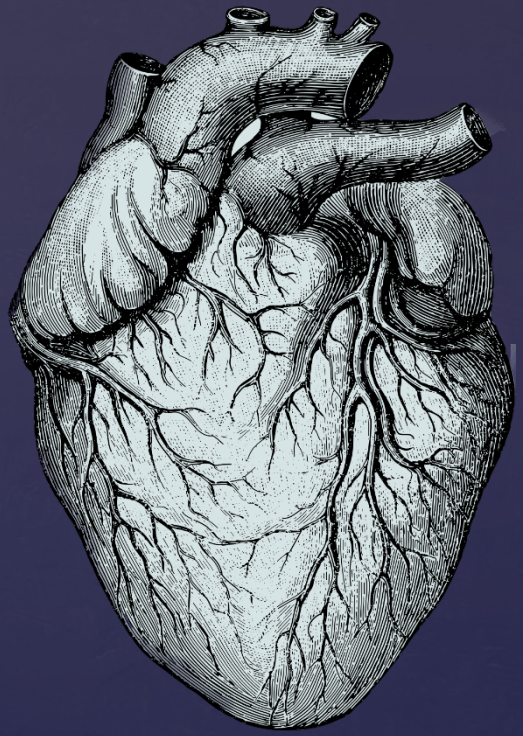


Manhattan plots showing the genome-wide –log10 P values for interrogated single-nucleotide polymorphisms across the 22 autosomal chromosomes for (A) left ventricular mass, (B) left ventricular internal diastolic diameter, (C) interventricular septal wall th...



Fox E R et al. Circ Cardiovasc Genet 2013;6:37-46

Conventional phenotyping

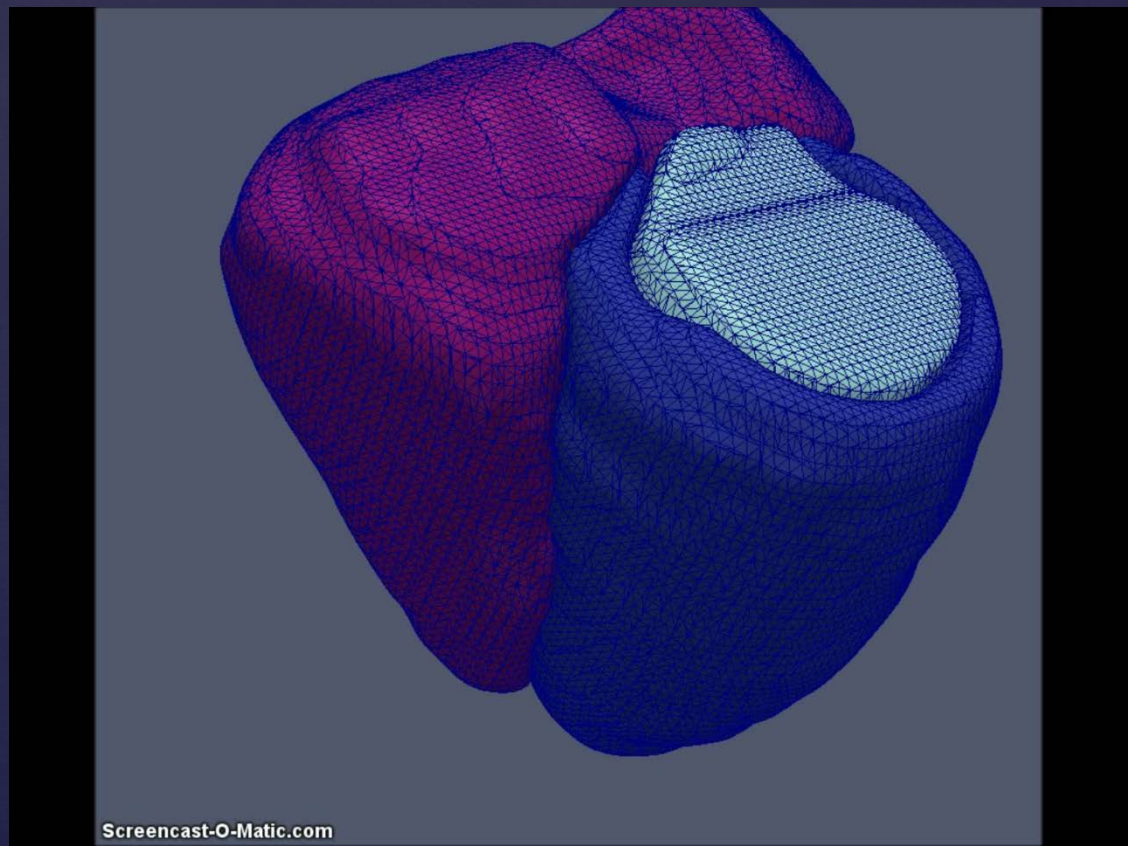


Limitations of current techniques:

- Does not model the heart as an organ system
- Measurements are subjective and global
- Inconsistent comparisons between subjects
- Complex traits of motion and strain not included

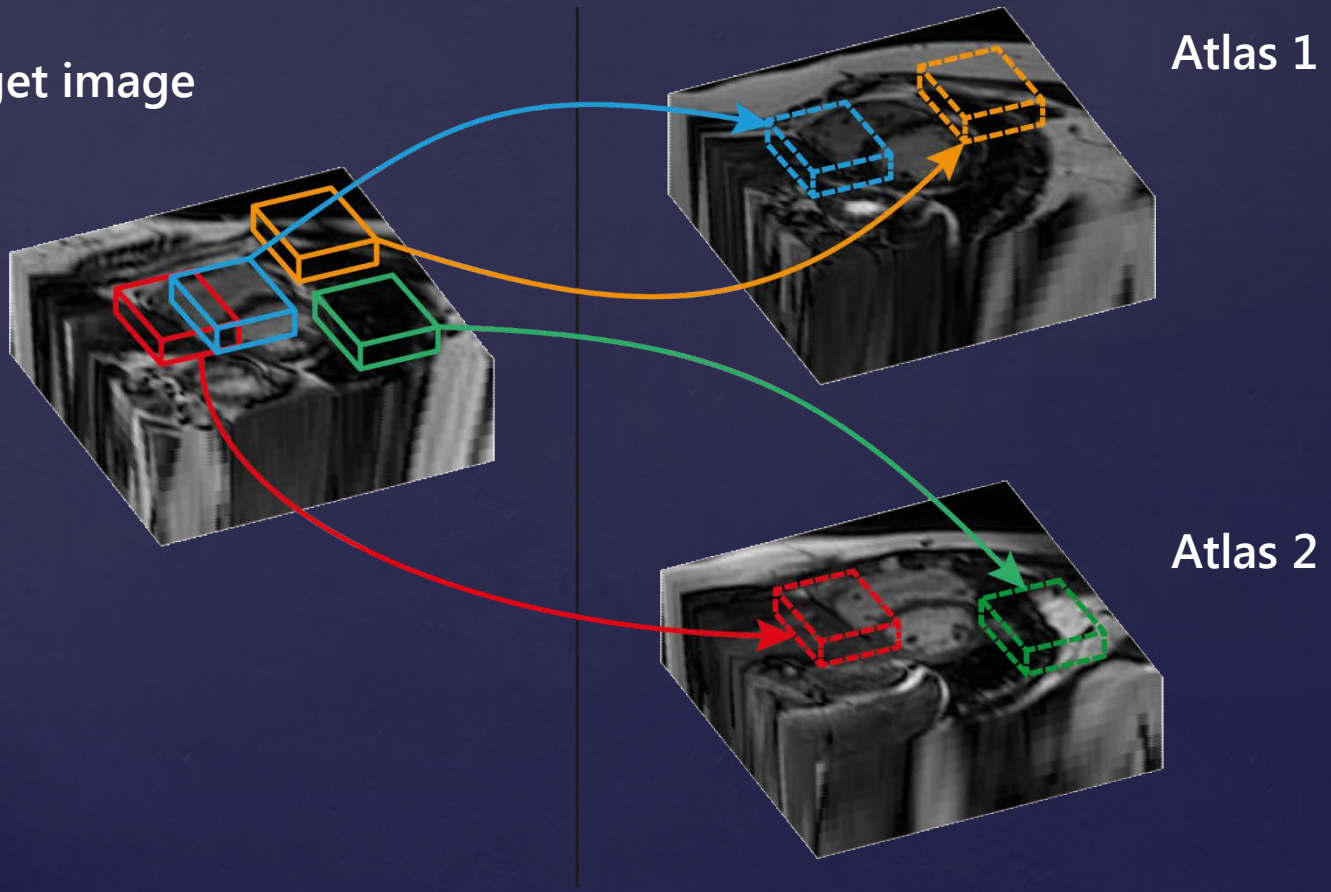
Cardiac atlas

Manually labelled images of the heart are used to guide segmentation and registration



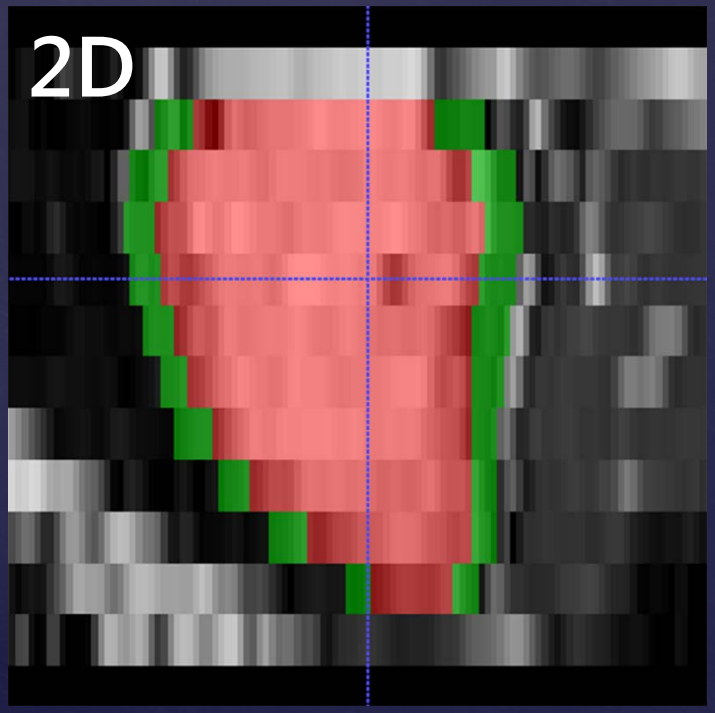
Segmentation & Co-registration

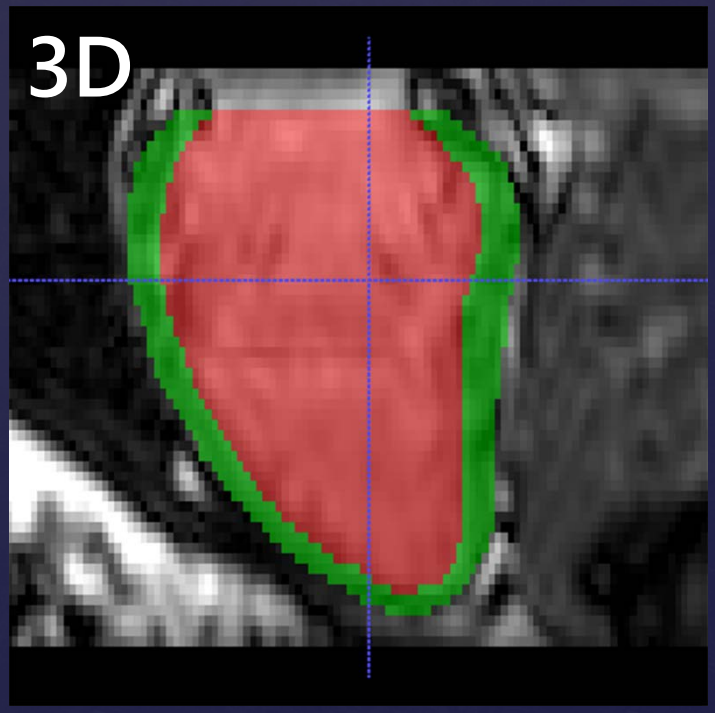
Iterative segmentation and co-registration with decision fusion.



3D whole heart MRI

High resolution MR imaging improves the precision of automated analysis





Statistical strategies

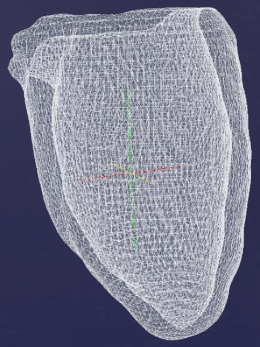
Cardiac Phenotypes

Associations

Covariates

Global

Local



Demographics

Age | Gender | BP

SNPs

AGCAAATG

Shape analysis

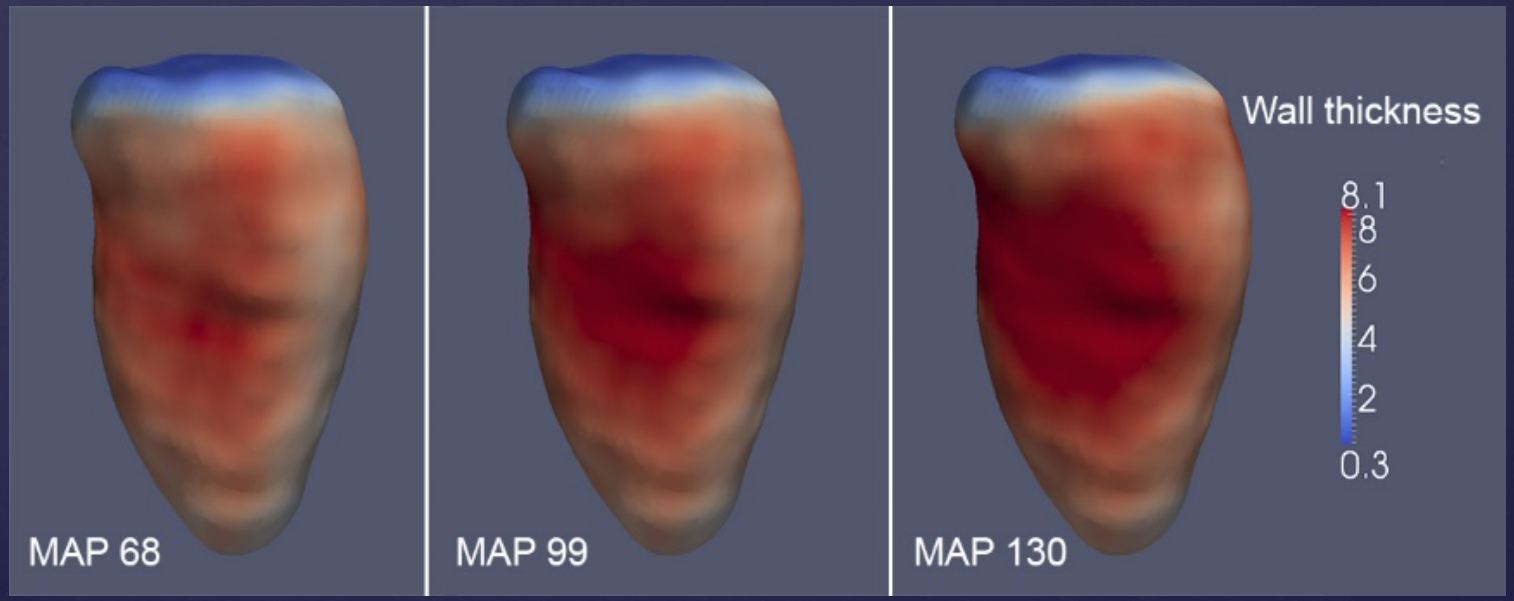
Landmark variables

Multivariate analysis

Left ventricular mass

Mass univariate linear regression with wall thickness as dependent variable with covariates held constant

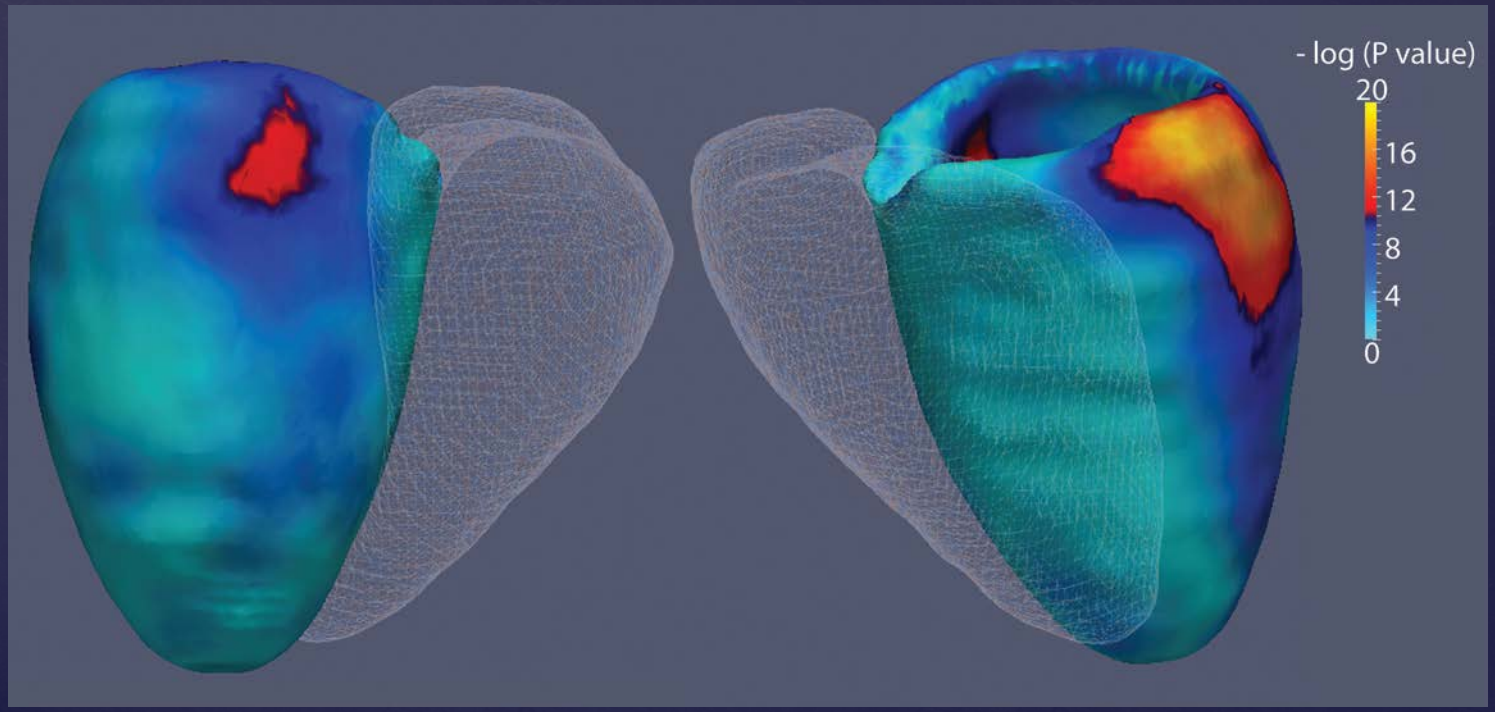
- **Sub-clinical associations are measurable**
- **Subjects can be modelled simultaneously**



Voxelwise non-parametric tests

Compare wall thickness voxel by voxel between gene variants and controls

- Bonferroni correction for multiple testing
- Analysis of covariance to correct for blood pressure and age etc.



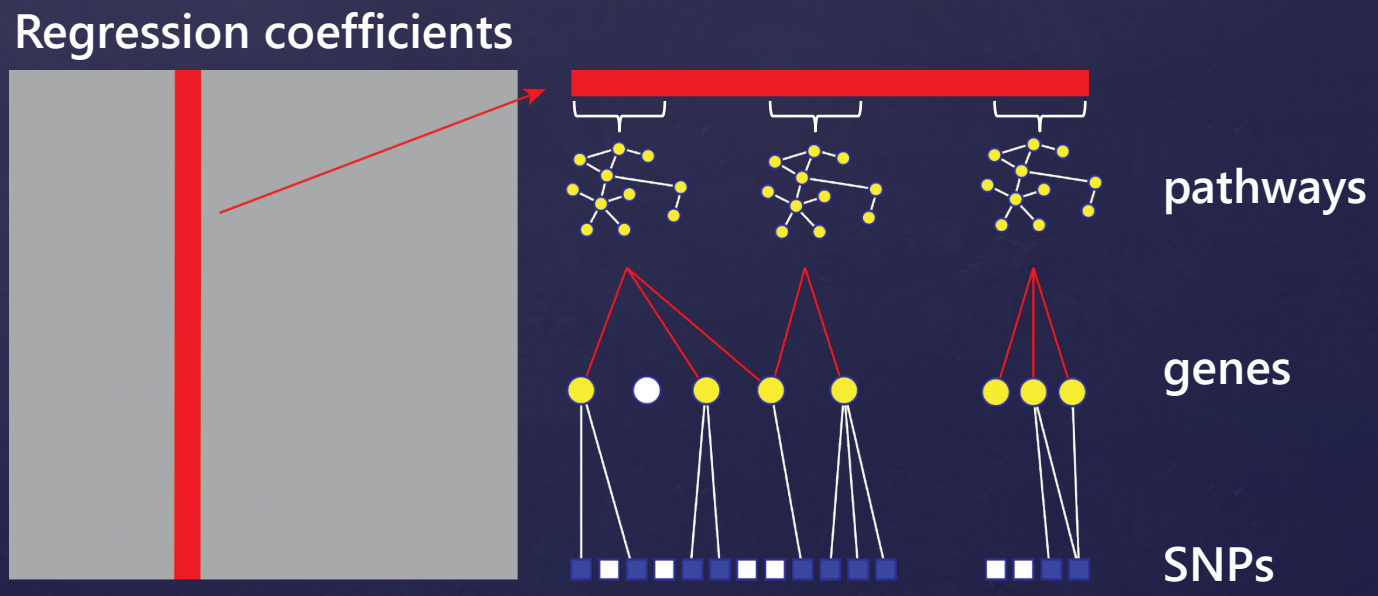
Sparse regression

To detect causal SNPs across the genome

- Large multiple testing problem
- Ignores dependencies between SNPs

Sparse regression

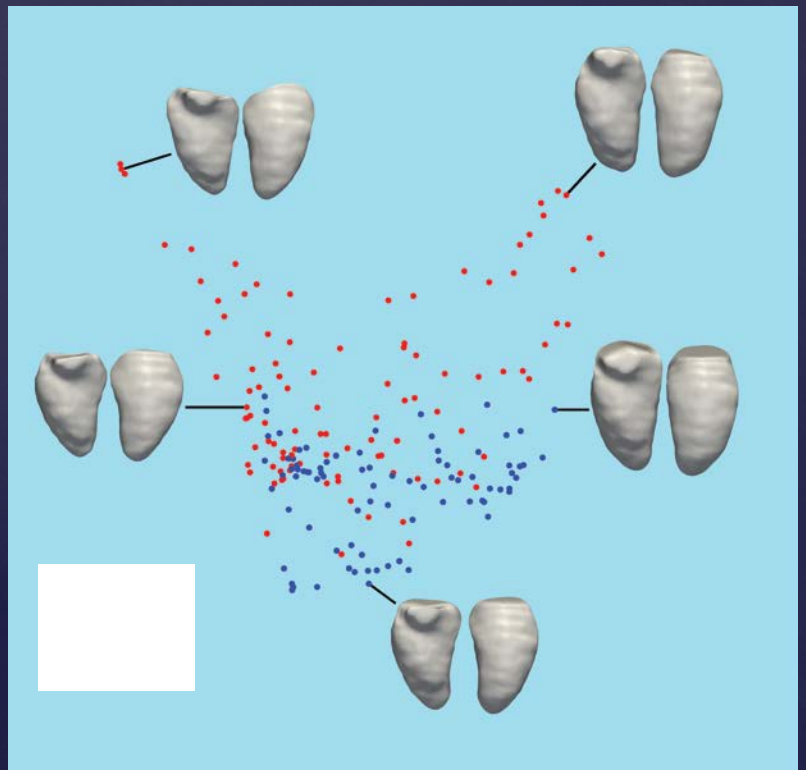
- Changes problem from “significance of each predictor” to “subset of best predictors”
- Multi-task regression incorporates sparse structure in genotypes and phenotypes

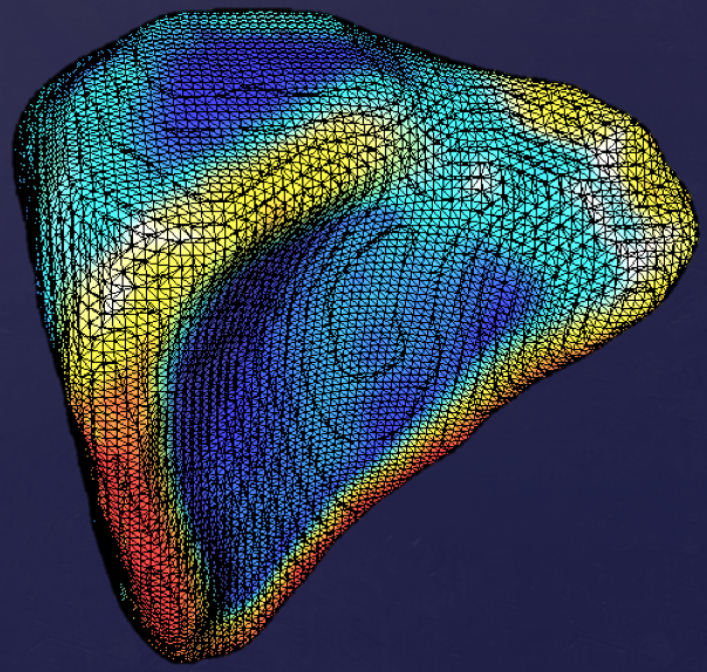


Shape analysis

Assess similarity between phenotypes without *a priori* hypotheses

- **Manifold learning finds a low-dimensional representation of a complex shape**
- **Finds clusters of similar phenotypes on a non-linear Laplacian Eigenmap**





Computational imaging-genetics

Imaging-genetics is a powerful tool for understanding the physiological effect of genetic and environmental factors on the human heart.

Future work:

- Test regression models with initial sequencing data
- Integrate strain and motion data into physiological models
- Explore phenotypic classification using manifold learning
- Support vector machine diagnosis
- Disease-specific atlases

MRC Clinical Sciences Centre
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Giuliana Durighel
Tamara Diamond
Laura Monje Garcia
Marina Quinlan

Royal Brompton Hospital
Dr Paul Barton
Dr James Ware
Dr Rachel Buchan
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Visiting workers
Dr Ben Corden
Dr Niall Keenan

Department of Computing
Prof Daniel Rueckert
Dr Wenzhe Shi

Department of Mathematics
Dr Giovanni Montana
Dr Chris Minas

Bioinformatics Support Service
Mark Woodbridge

Department of Medicine
Dr Tim Dawes
Prof Martin Wilkins

Imperial College London

Diagnostic performance of [^{11}C]choline PET-CT vs. MRI in prostate cancer nodal staging: Research challenges.

Dr. Amar Challapalli
Clinical Research Fellow, Imperial College, London

Nodal staging in Prostate cancer

- LN metastases are seen in 25-30% of pts
- LN involvement reduces disease free survival from 85% to 50%
- Pelvic LND – gold standard
  - Invasive
  - 4-5% morbidity
  - Expensive, needs hospitalization
  - May not be able to sample all potential nodal areas
- Current anatomic imaging has limited diagnostic accuracy
  - Pooled sensitivity – 39%
  - Pooled specificity – 82%

Hovels et al, Clin Radiol 2008

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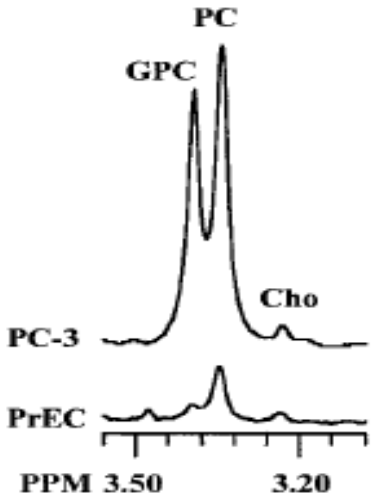
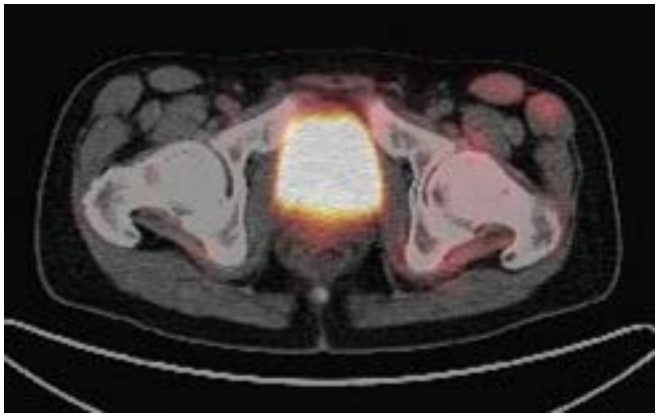
Why Choline



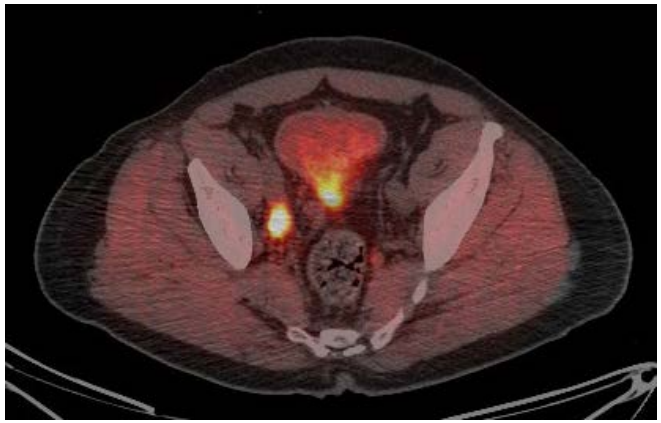
- The increased choline peak is due to altered PL metabolism.
- No GPC-> PCho switch. May be increased CK or PLA activity or Choline transport.

Ackerstaff et al, Can Res 2001: 61; 3599

[^{18}F]FDG



[^{11}C]Choline



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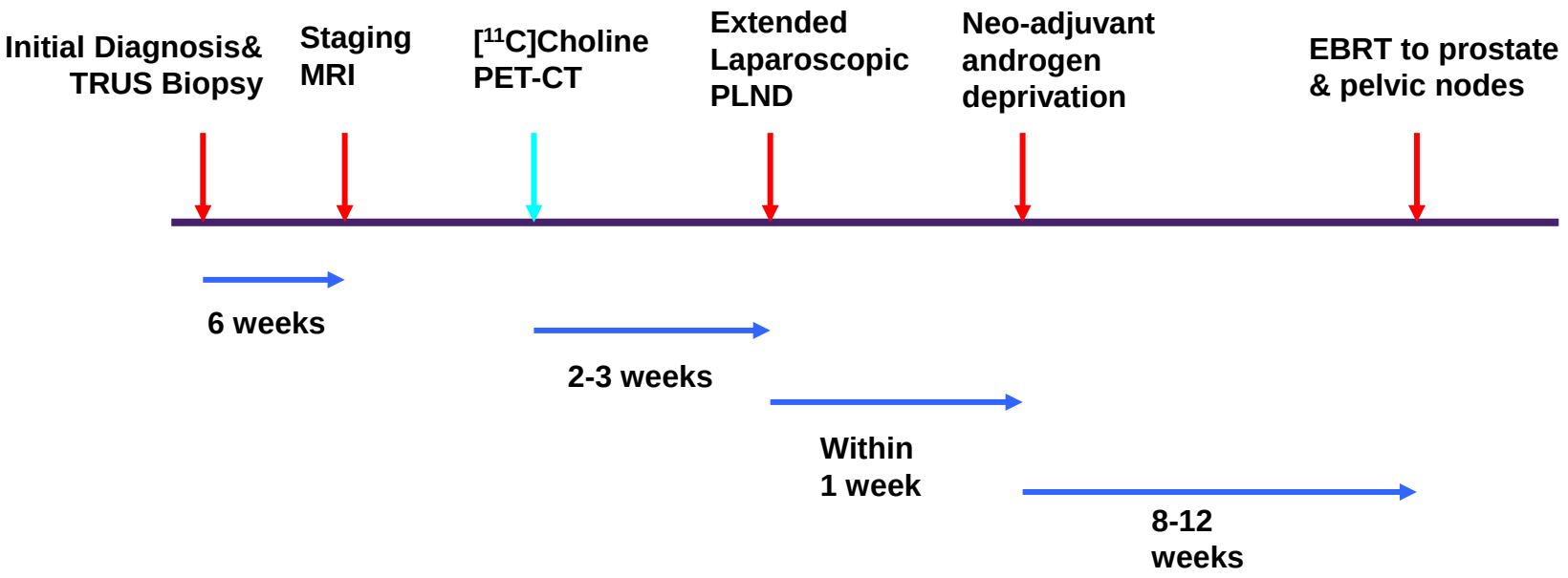
Study Schema



- 26 patients evaluable (28 recruited)
- Dynamic [^{11}C] choline-PET-CT of the pelvis and lower abdomen
- Diagnostic performance for nodal detection was calculated compared to histology
- SUV_{ave} and SUV_{max} were compared with CHKα and Ki67 IHC scores.

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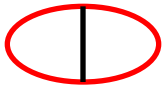
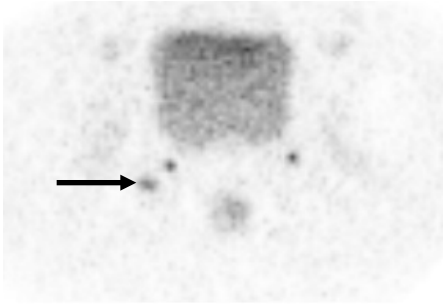
Criteria for nodal involvement

- **MRI:**  **>10 mm**  **0.8**

- **[^{11}C]Choline PET:** 

- **5 point scale for ROC analysis**

MRI	**[^{11}C]Choline PET/ PET-CT**
Nodes <4mm or not seen	Definitely normal
Nodes = 4 – 5.9 mm	Probably normal (more likely to be physiological)
Nodes = 6 – 7.9 mm	Indeterminate (equally physiological/ pathological)
Nodes ≥ 8mm but <10mm	Probably abnormal (more likely to be pathological)
Nodes ≥ 10mm	Definitely malignant

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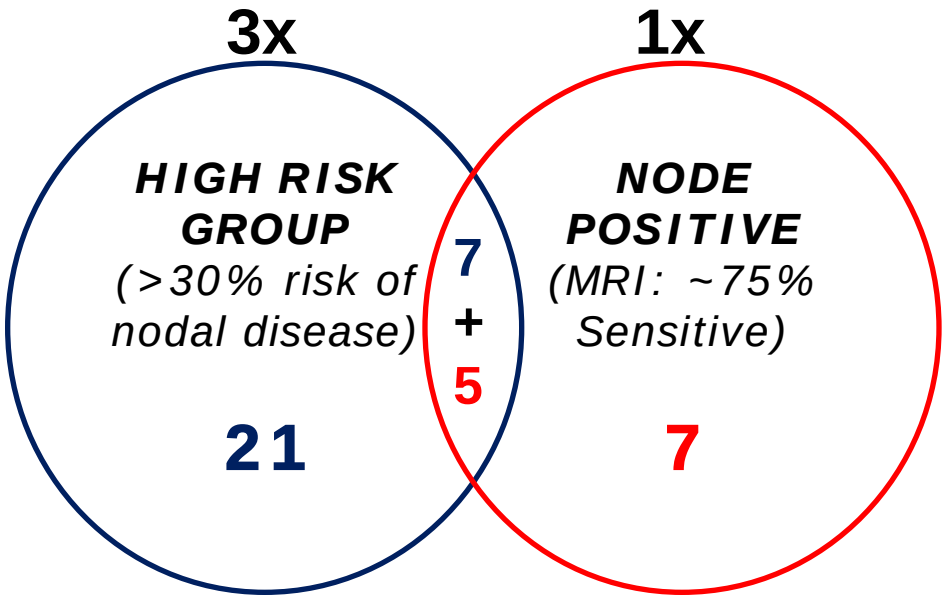
Sample size calculation

- This was a feasibility/pilot study
- We were aiming to recruit about 10-12 node positive patients



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Results

- 406 lymph nodes, in 26 patients, were assessable.
- 27 (6.7%) involved pelvic nodes at eLPL were detected in 9 patients.
- 17 out of the 27 involved nodes were sub-centimetre.

Nodal size (mm)	No of Lymph nodes (LN)	MRI + (%)	[^{11}C]choline PET + (%)	[^{11}C]choline PET-CT + (%)
0.1 – 1.9	1	0 (0)	0 (0)	0 (0)
2 – 4.9	4	0 (0)	0 (0)	1 (25)
5 – 9.9	12	0 (0)	4 (33)	4 (33)
≥ 10	10	5 (50)	7 (70)	9 (90)

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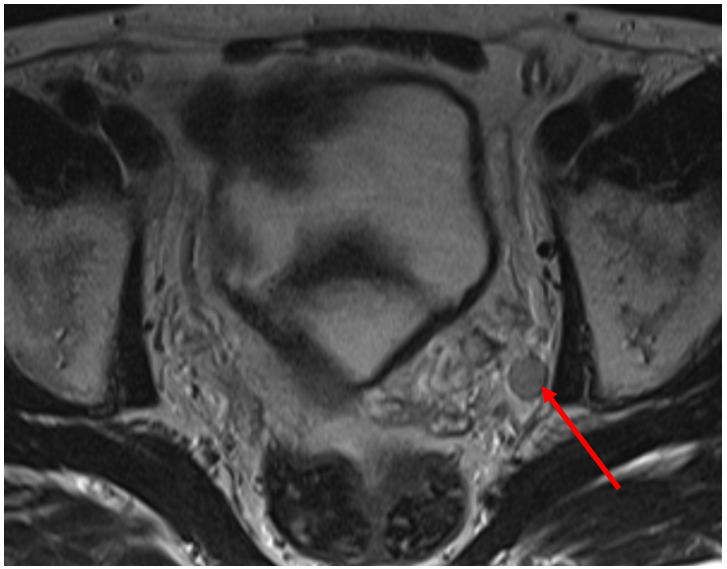
Nodal Analysis on MRI

- 5 nodes TP: median maximum diameter 11mm (9 – 21 mm)
- 22 nodes FN
  - 18 were sub centimetre
  - 4 nodes > 1 cm missed due to clustering
- 5 nodes in 4 pts FP
  - Sampling error
  - Reactive EI nodes
- Sensitivity – 50%
- Specificity – 72.2%



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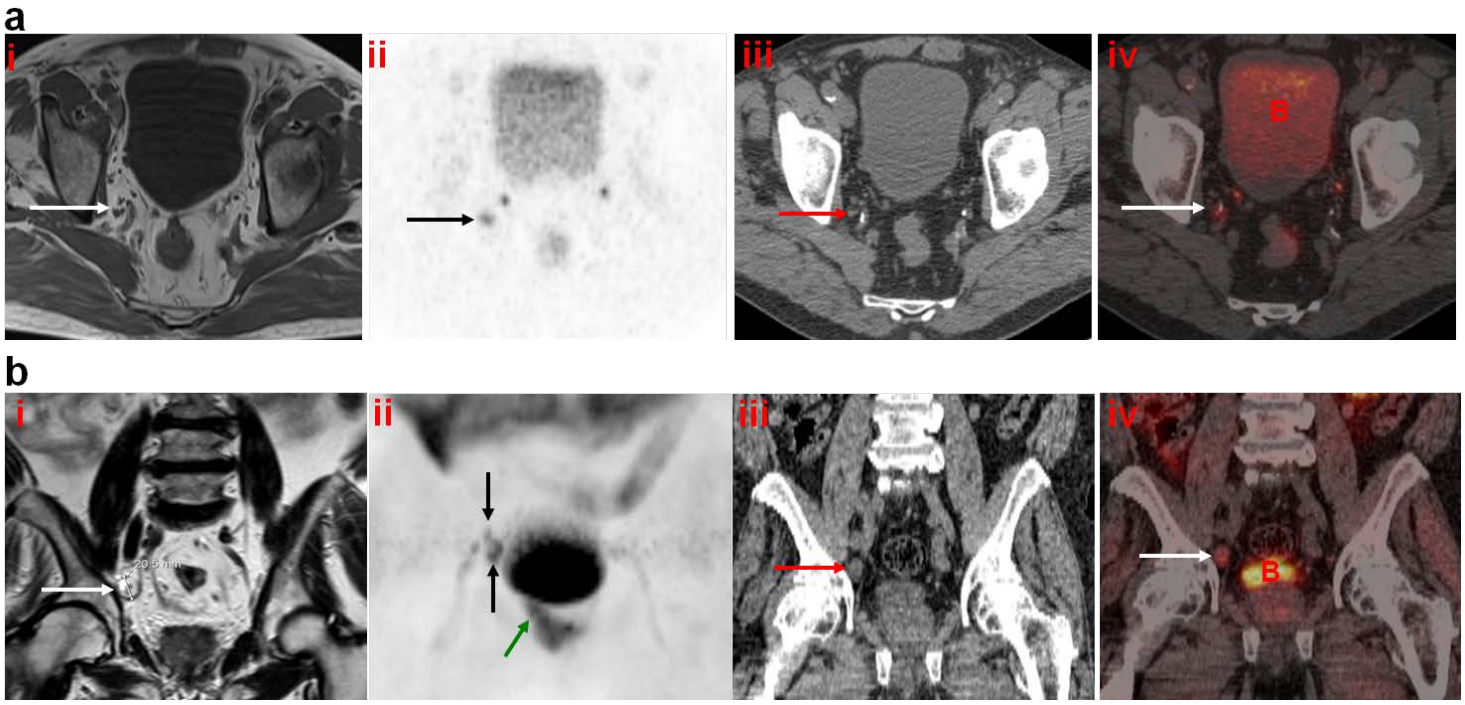
Nodal Analysis on [^{11}C]choline PET-CT: TP Nodes



- 14 nodes in 7 patients were TP
- Median maximum diameter: 9mm (4 – 20 mm)
- 13 nodes were FN – micro metastases

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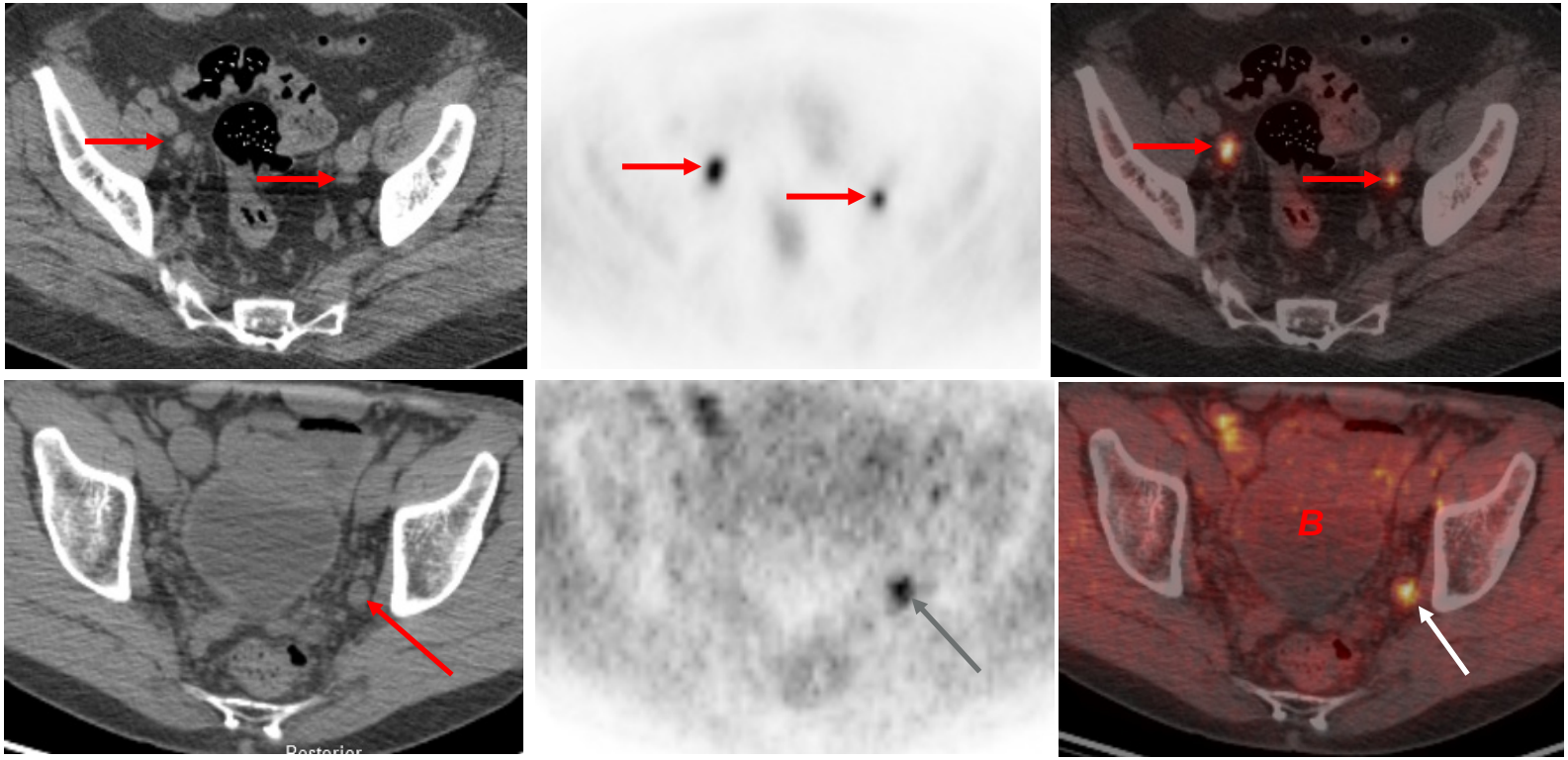
Nodal Analysis on [^{11}C]choline PET-CT: FP Nodes



- 6 nodes in 4 patients were FP
  - Reactive Ext iliac nodes
  - Sampling error

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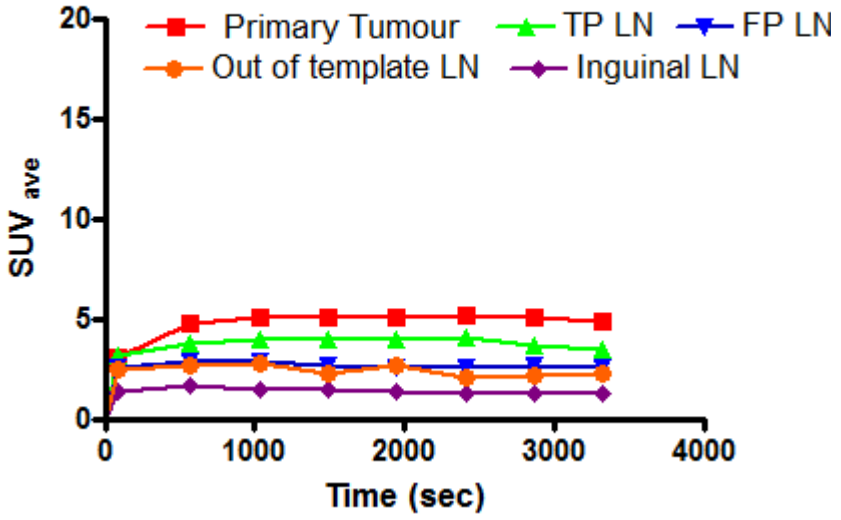
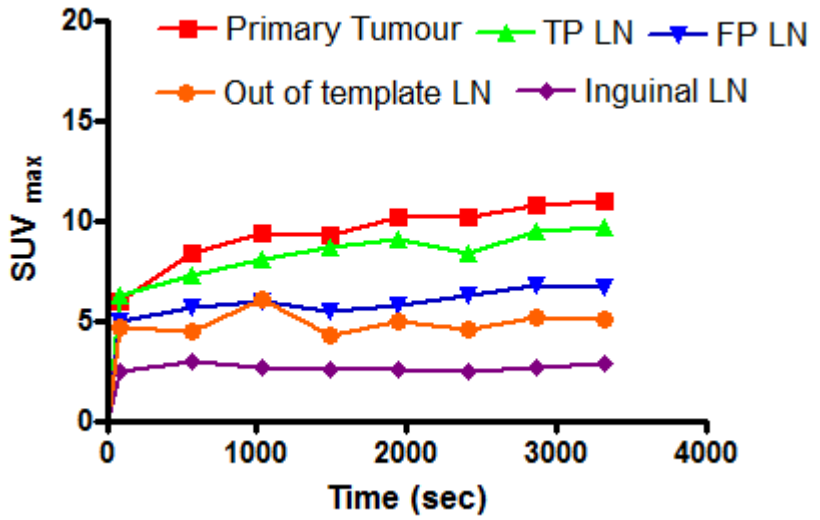
[^{11}C]Choline uptake in pelvic nodes





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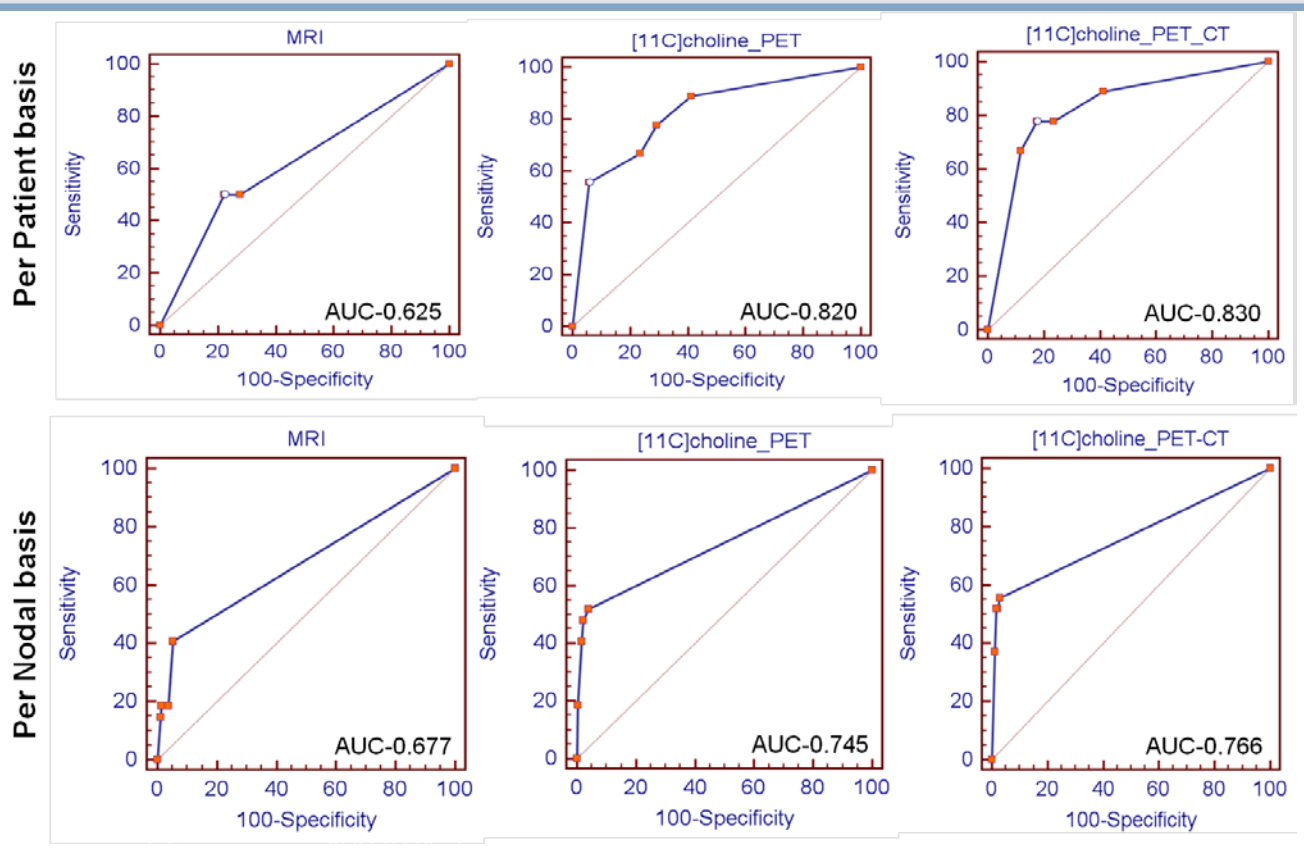
Diagnostic Performance



Imaging modality	TP	FN	FP	TN	Sensitivity	Specificity
[^{11}C]Choline PET-CT	7	2	3	14	77.7	82.4
[^{11}C]Choline PET-CT	14	13	6	373	51.9	98.4

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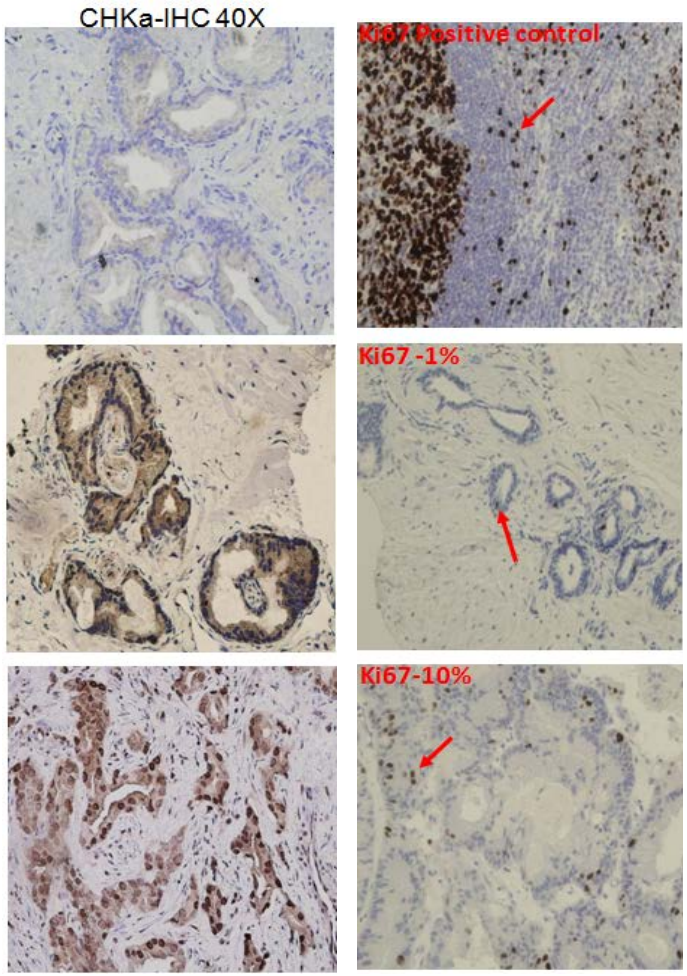
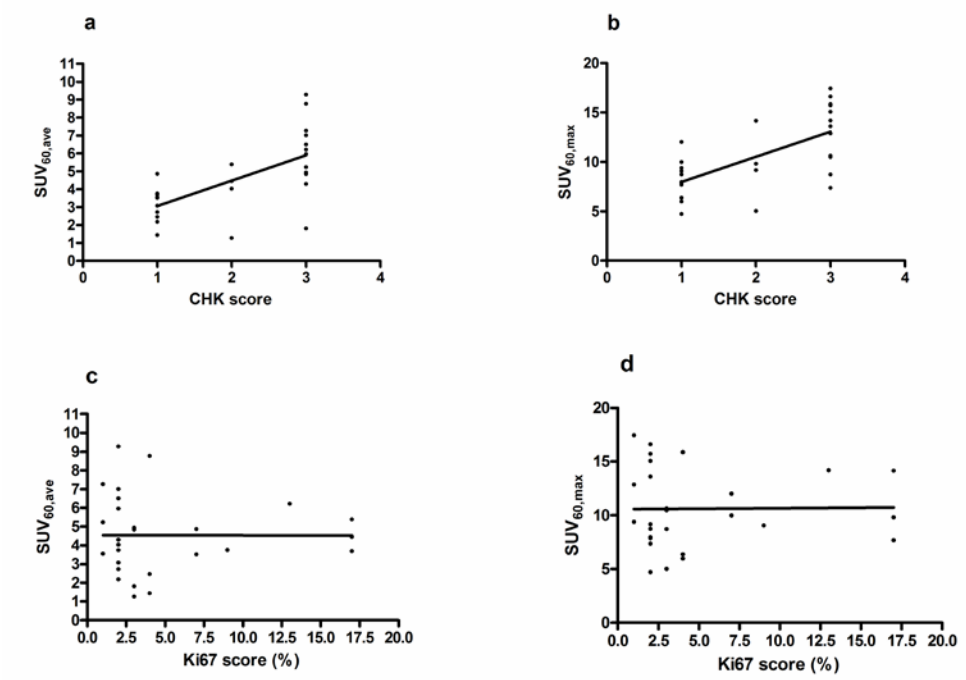
Imaging, Diagnosis, Prognosis

Clinical Cancer Research

Use of [^{11}C]Choline PET-CT as a Noninvasive Method for Detecting Pelvic Lymph Node Status from Prostate Cancer and Relationship with Choline Kinase Expression

Kaiyumars Contractor[1], Amarnath Challapalli[1], Tara Barwick[2], Mathias Winkler[1], Giles Hellawell[1], Steve Hazell[3], Giampaolo Tomasi[1], Adil Al-Nahhas[2], Paola Mapelli[1], Laura M. Kenny[1], Paul Tadrous[4], R. Charles Coombes[1], Eric O. Aboagye[1], and Stephen Mangar[1]





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Conclusions

- [^{11}C]choline PET-CT can be used as a non-invasive means of staging pelvic lymph nodes in prostate cancer - highly specific and more sensitive than PET alone or MRI
- High specificity - selecting out patients with high risk prostate cancer who may not need pelvic radiotherapy or enable dose escalation
- [^{11}C]choline PET-CT could be used as a non-invasive surrogate for CHK expression

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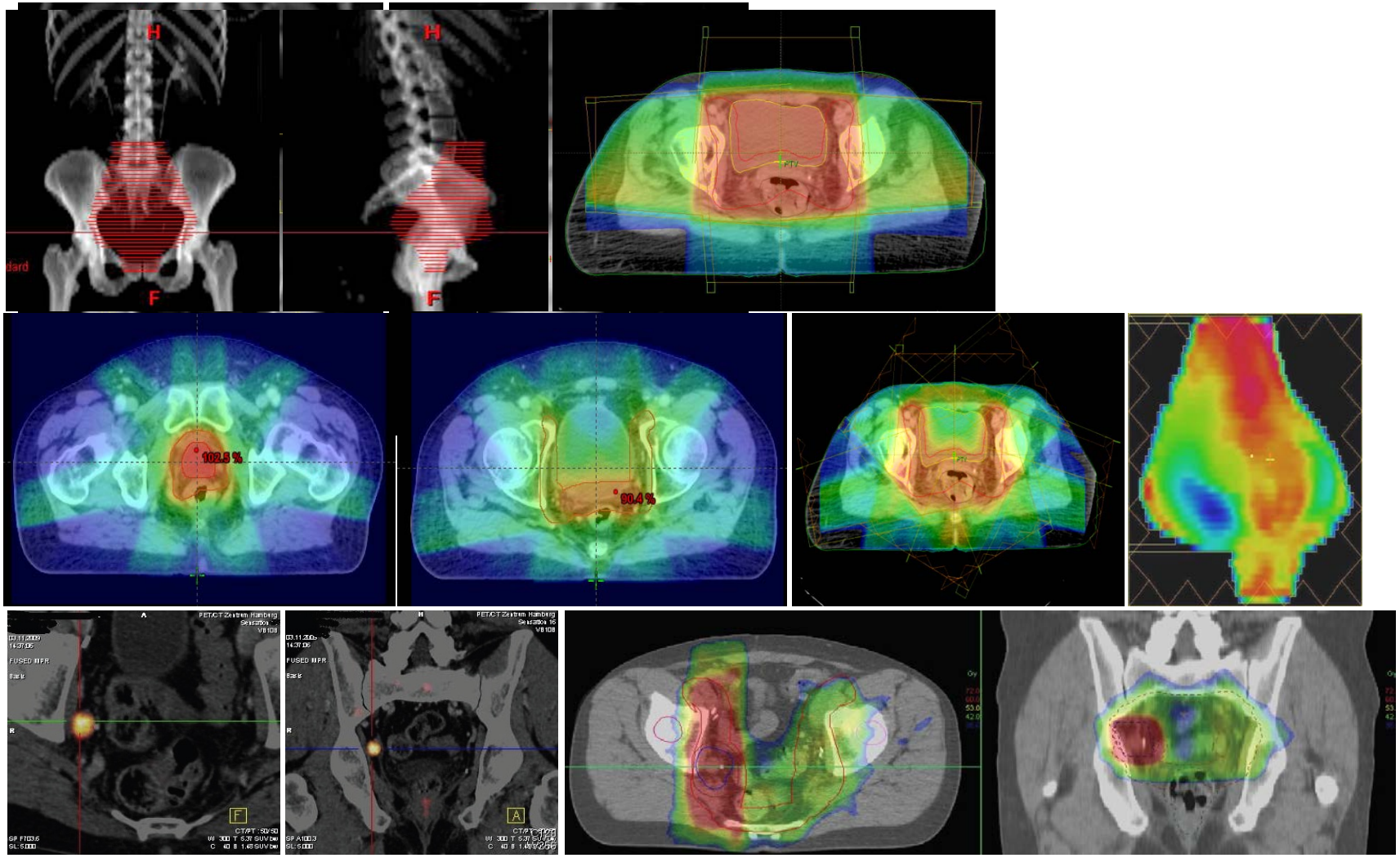
Prostate RT Planning: A Paradigm shift



Würschmidt et al, Radiation Oncology 2011

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Research Challenges

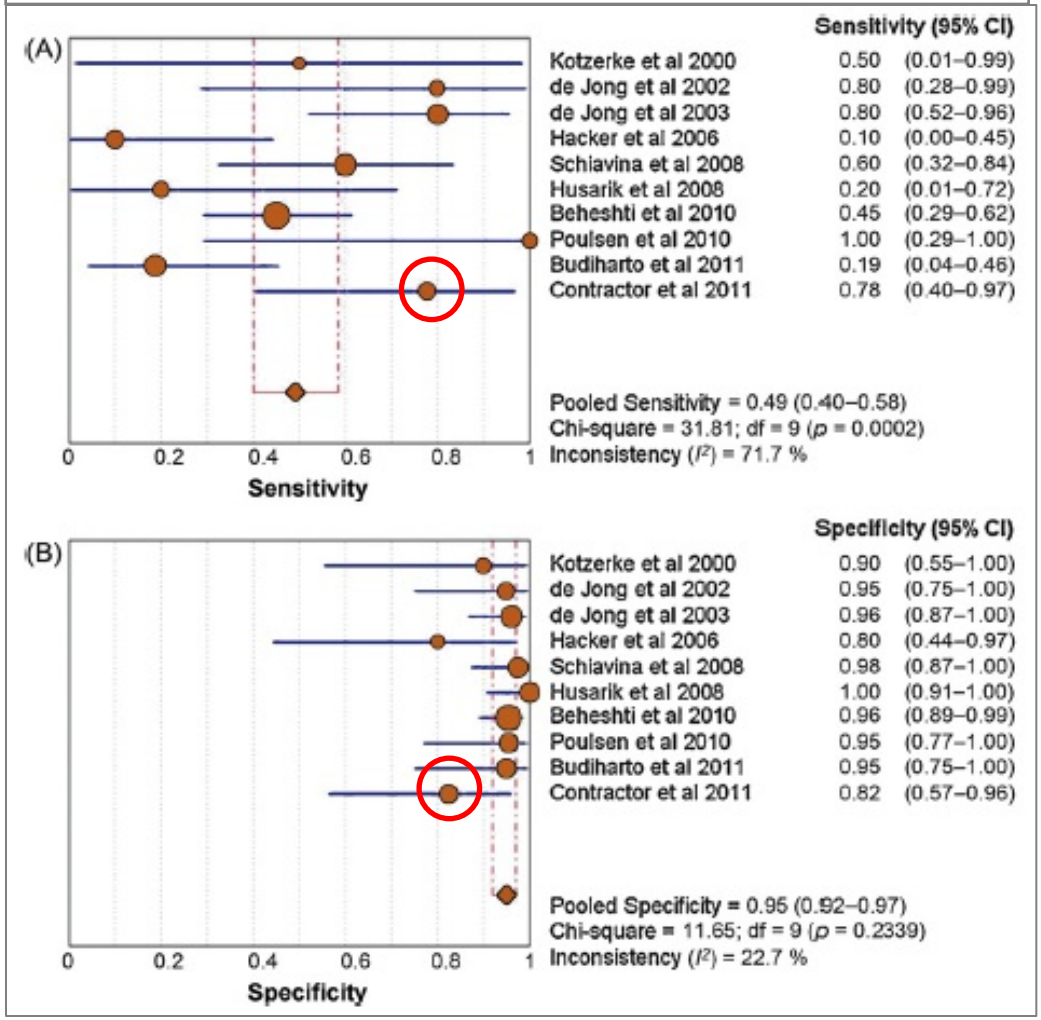
- Duration of recruitment
- Single centre vs. Multi centre
- Co-ordination with Nuclear Medicine Radiologists/ Urologists/ Oncologists/ Pathologists
- Sample size
- Funding for the scans

Review – Prostate Cancer

Utility of Choline Positron Emission Tomography/Computed Tomography for Lymph Node Involvement Identification in Intermediate- to High-risk Prostate Cancer: A Systematic Literature Review and Meta-analysis

Laura Evangelista [a,*], *Andrea Guttilla* [b], *Fabio Zattoni* [b], *Pier Carlo Muzzio* [c], *Filiberto Zattoni* [b]

[a] Radiotherapy and Nuclear Medicine Unit, Istituto Oncologico Veneto IOV – IRCCS, Padua, Italy; [b] Department of Oncological and Surgical Sciences, Urology Clinic, University of Padua, Italy; [c] Radiology Oncology Unit, Istituto Oncologico Veneto IOV – IRCCS, Padua, Italy



No. of patients	Radiopharmaceutical and imaging scan	Scan
12	11C-Choline	PET
25	11C-Choline	PET
67	11C-Choline	PET
20	18F-Choline	PET/CT
57	11C-Choline	PET/CT
43	18F-Choline	PET/CT
130	18F-Choline	PET/CT
25	18F-Choline	PET/CT
36	11C-Choline	PET/CT
26	11C-Choline	PET and PET/CT

Heterogenous sensitivity

- *Patient selection*
- *Surgical technique*

Evangelista et al, Eur Urol, Jun, 2013

Imperial College
London

CANCER RESEARCH UK
EPSRC Engineering and Physical Sciences Research Council
MRC Medical Research Council
NHS National Institute for Health Research

**CR-UK & EPSRC Cancer Imaging Centre at Imperial College, London,
in association with the MRC and Department of Health (England)**

NIHR Statistical Group: Imaging in Translation Research Meeting

15:30 – 16:00

Delegate feedback and panel questions

SESSION 3 CHAIR: Professor Doug Altman

Dr Tom Fanshawe
Mr Mark Samuels
Dr Declan O'Regan
Prof Steven Keevil
Dr Gina Brown
Prof Janet Peacock
Dr James Moon
Dr Amar Challapalli