Translating MRS into clinical benefit for children with brain tumours

Andrew Peet

NIHR Research Professor

Childhood Cancer – The Facts

- Cancer is the most common cause of death from disease in childhood

- Brain tumours are
  - the most common solid tumours in children
  - the most common cause of cancer death in children

- 50 years ago 10% of children with cancer survived now more than 80% survive

- Improvements have not been so good in brain tumours

MRI and its limitations

Key component of the care for children with solid cancers
Exquisite structural detail

BUT:

- Is it a tumour?

- If so what type?

- Is it aggressive?

- Will it respond to treatment?

Harry's Story

Presented 8 years old, visual problems

Biopsy 1/1,000 of the tumour

Chemotherapy – failed
Radiotherapy - stable

I've been treating Harry for three years now. Being able to get a clearer picture of how his tumour reacts to treatment is invaluable, as it helps us to tailor that treatment to Harry's needs.

This MRI scan shows Harry's tumour around the time when he was diagnosed

We're still a long way from individual treatments for individual patients, but new technologies such as cancer imaging are helping to pave the way – and people like Harry are already benefiting.

This MRS scan provides more detailed information to help guide treatment – including the typical chemical makeup of the tumour.

4 years later tumour reactivated, intratumoural bleed

"The complete doctor"
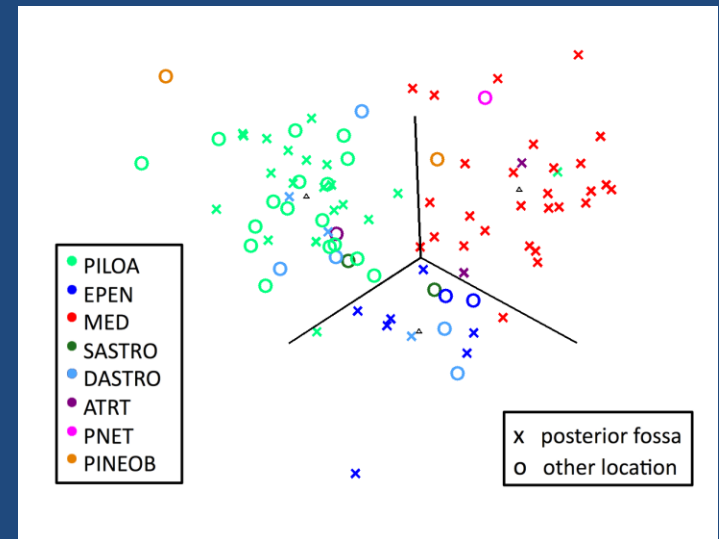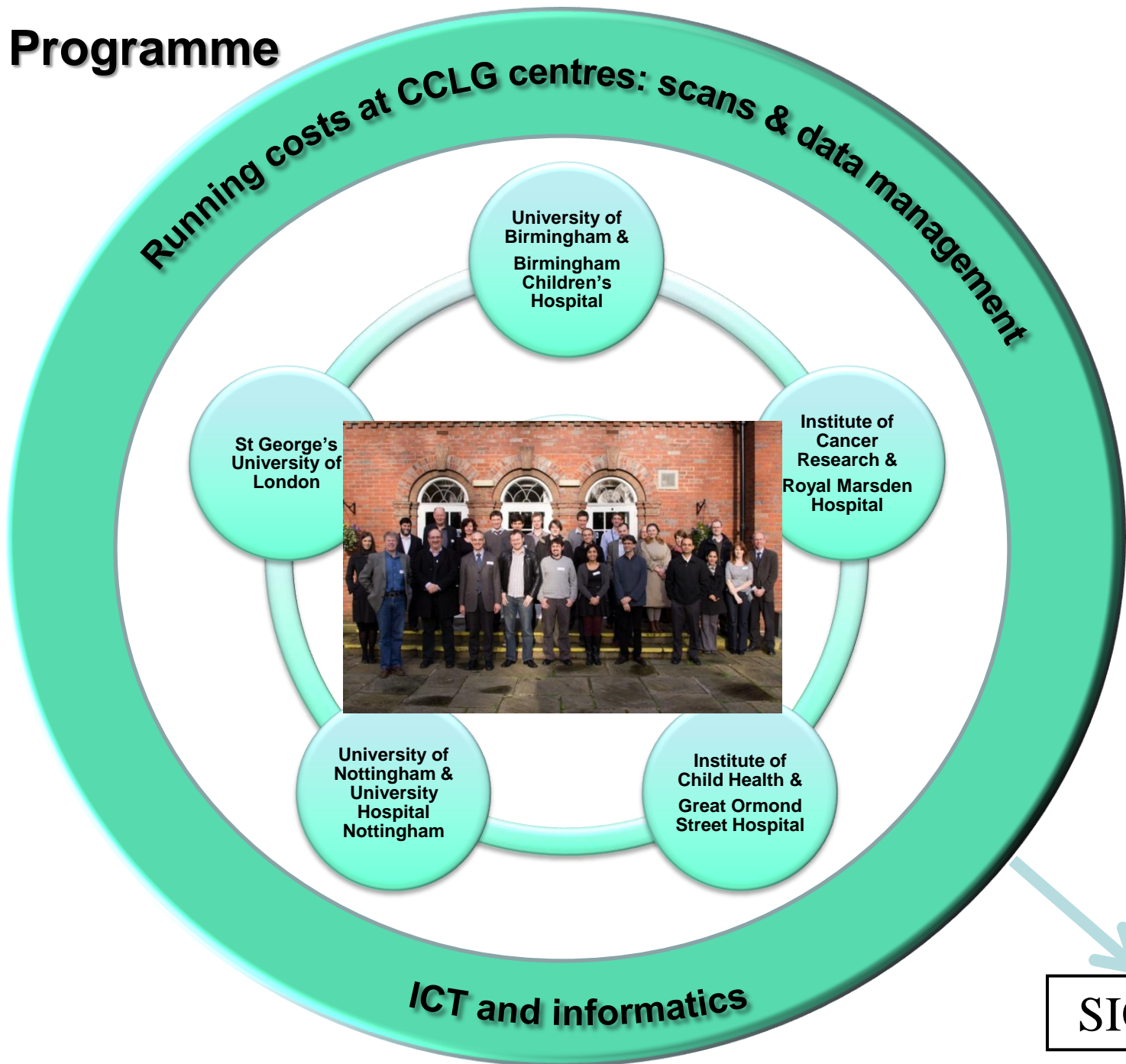
Help Harry Help Others

Non-invasive diagnosis
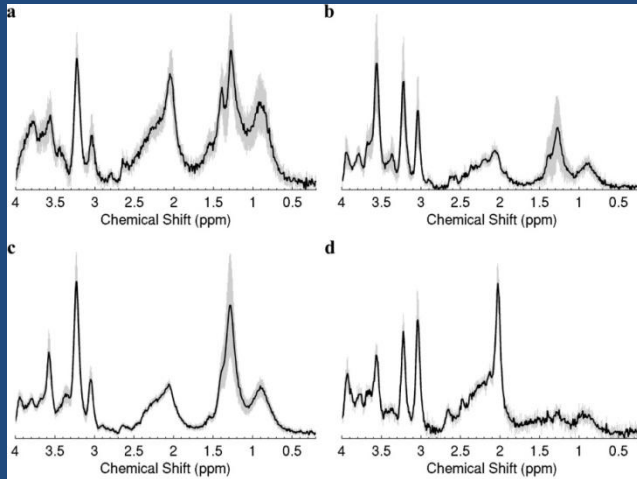
Metabolite profiles differ
between the tumours
Davies et al NMR Biomed 2008

10 hospitals from 7 countries
98% accuracy in determining
the diagnosis,
100% accuracy for broad
tumour categories

"This study is the proof that MRS is useful and comparable even in a
multicenter and multimodal setting in children."

Vincente et al. EJC, 2013

CCLG Programme

Running costs at CCLG centres: scans & data management

ICT and informatics

University of Birmingham & Birmingham Children's Hospital

Institute of Cancer Research & Royal Marsden Hospital

St George's University of London

Institute of Child Health & Great Ormond Street Hospital

University of Nottingham & University Hospital Nottingham

SIOPE

Prospective Evaluation

- Accuracy ~ 91% (vs 93% predicted)

- 3/33 incorrect :

  2 anaplastic ependymomas

  1 medulloblastoma with very unusual features

- Some cases classified correctly but with low confidence estimate
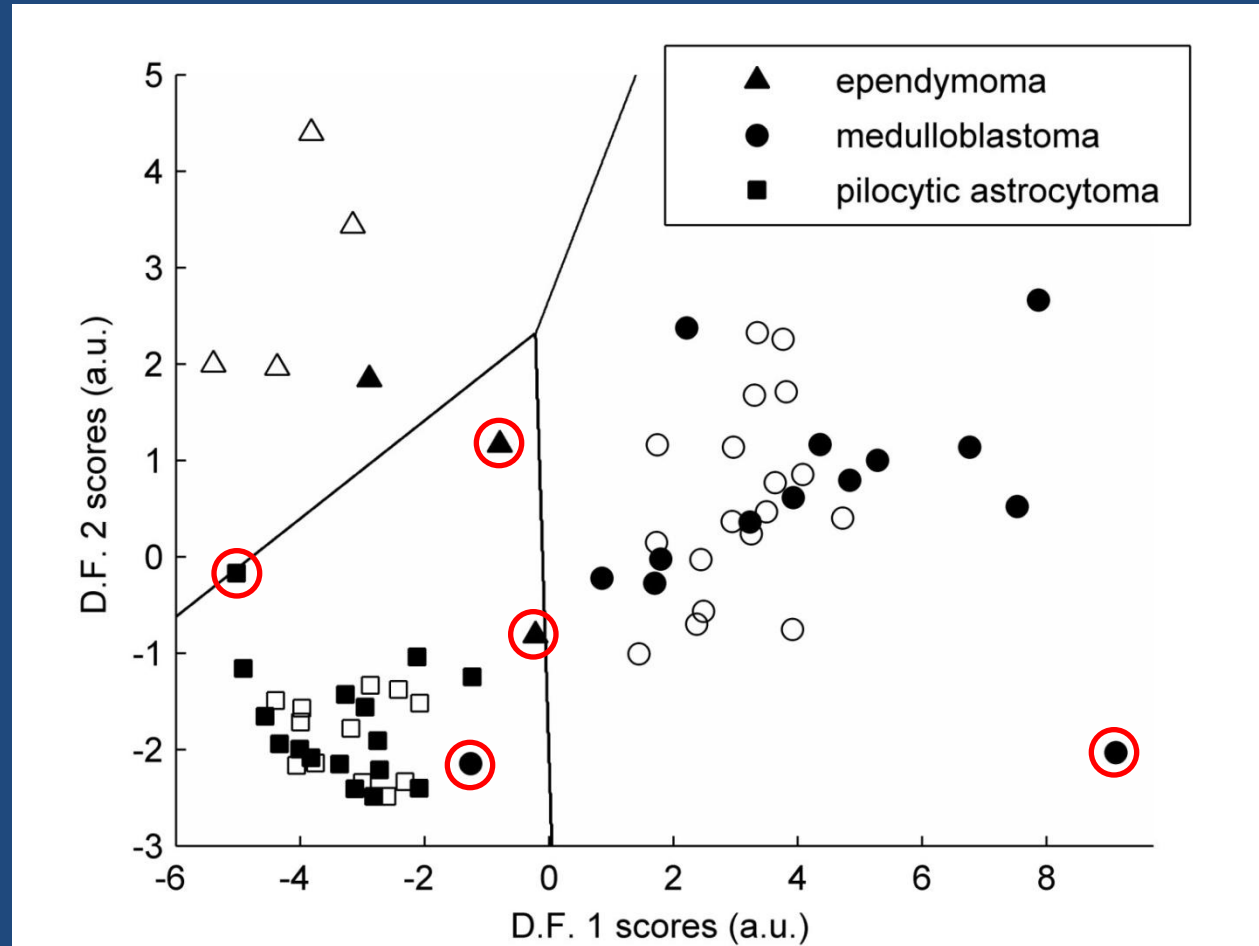
But can't we diagnose them with MRI?

	T2-w	FLAIR	T1-w	T1-w +Gd	ADC
Medulloblastoma					
Pilocytic Astrocytoma					
Ependymoma					
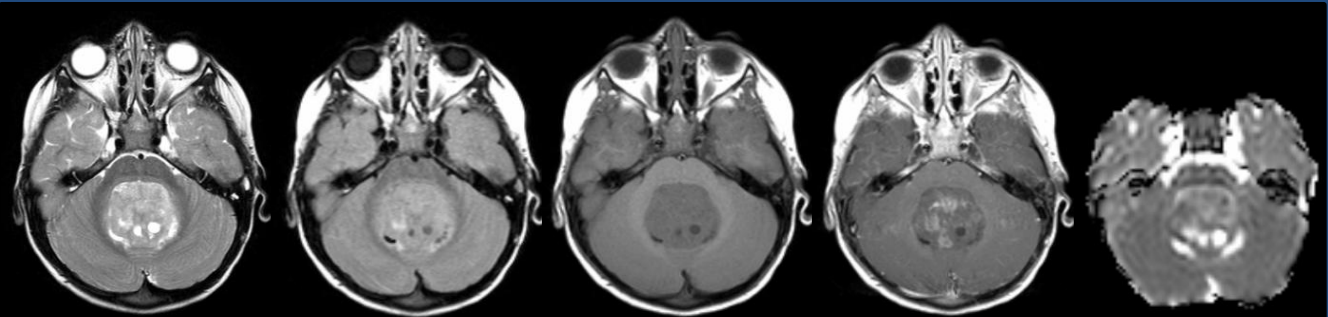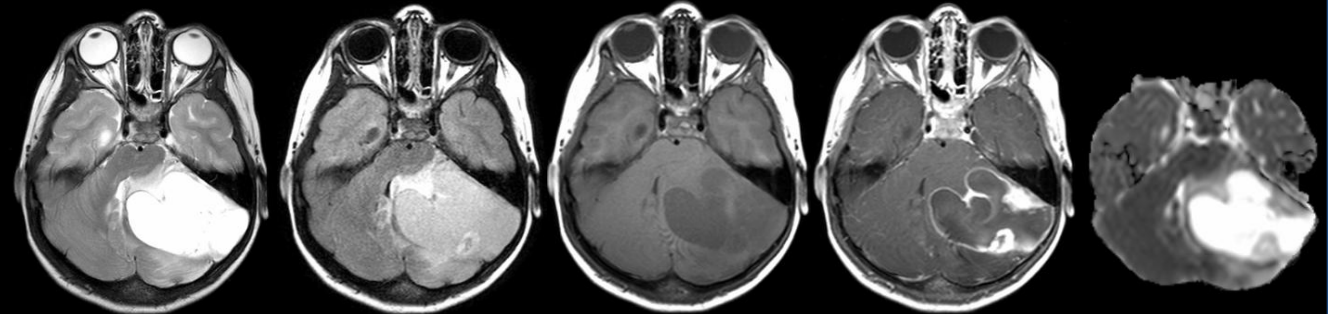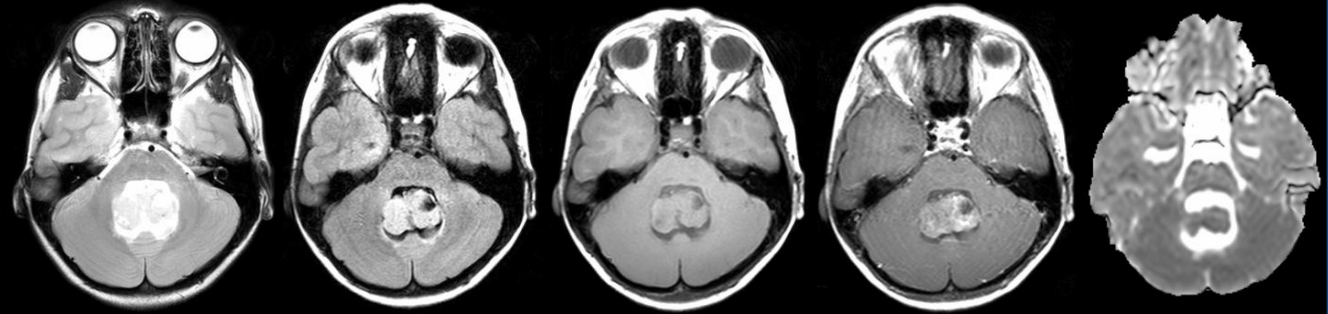
Different morphological appearances but significant overlap

Establishing improved diagnostic accuracy
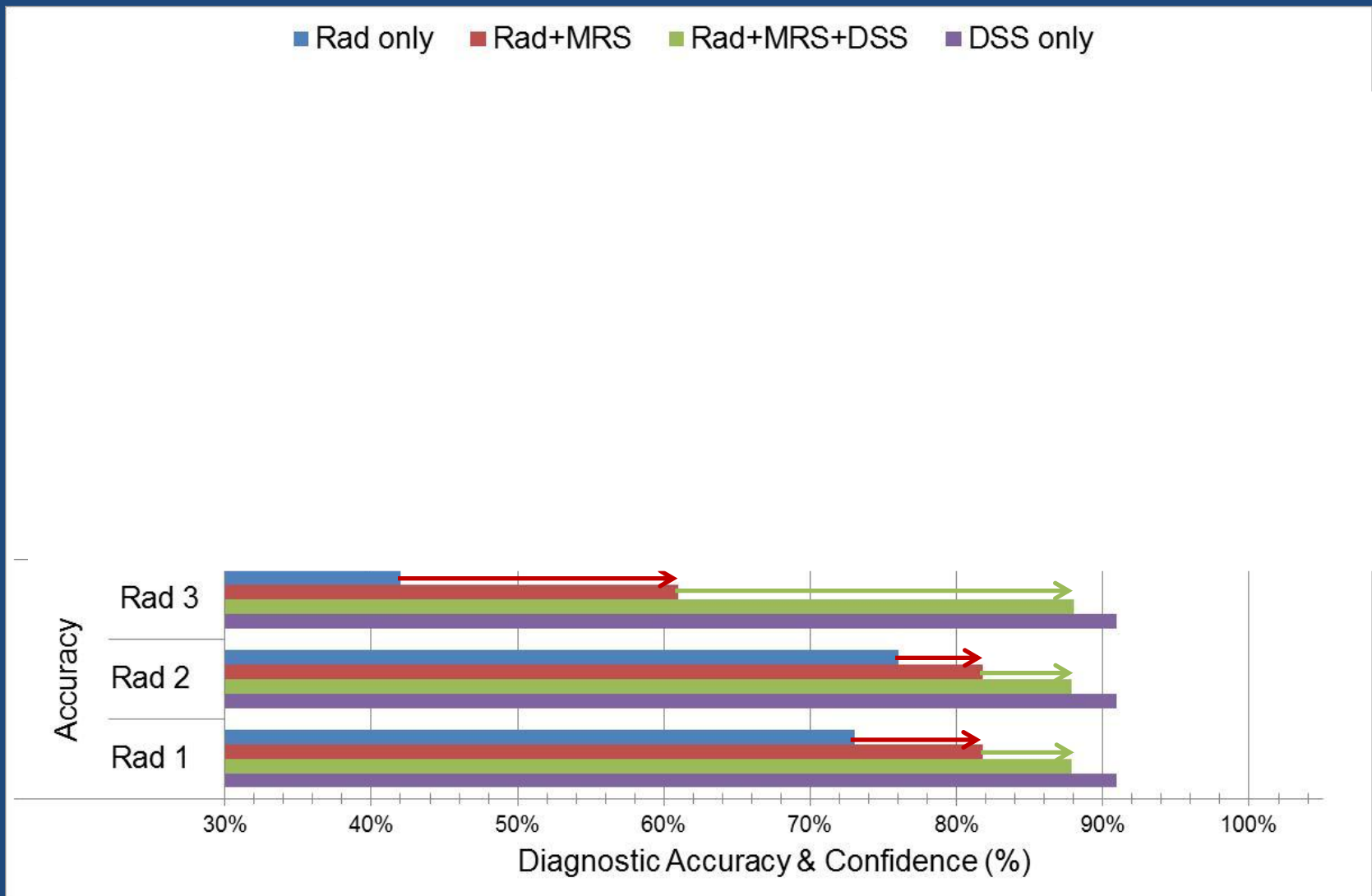
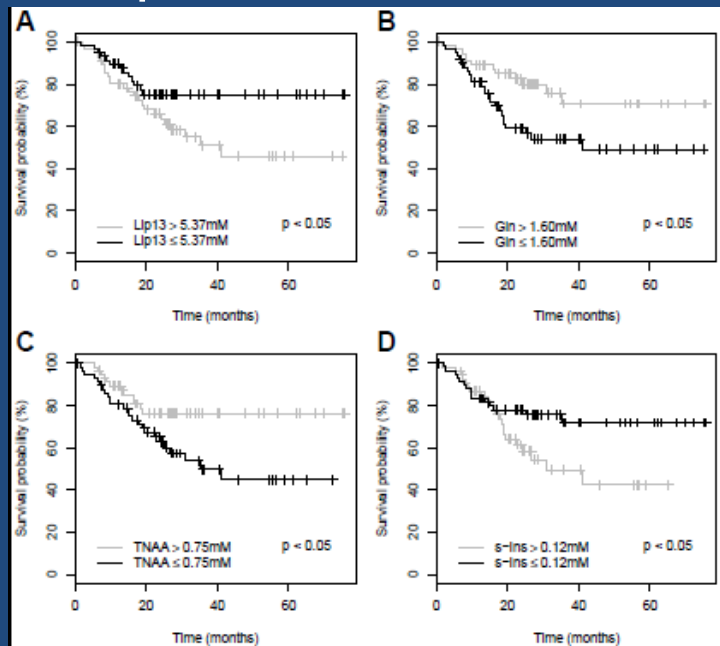# How do we use it? Added value and application in a clinical environment

TARQUIN

R

Predicted diagnosis : Pilocytic astrocytoma

CE ?

Radiologist evaluation
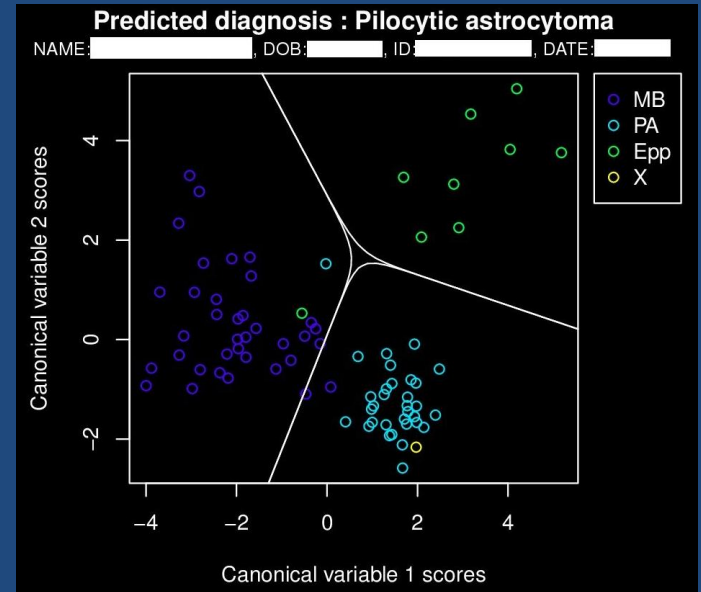
Wilson and Reynolds

Prognostic Biomarkers

MRS at diagnosis in 155 children with brain tumours

Kaplan-Meier curves

A. Lipids
(prior hypothesis)
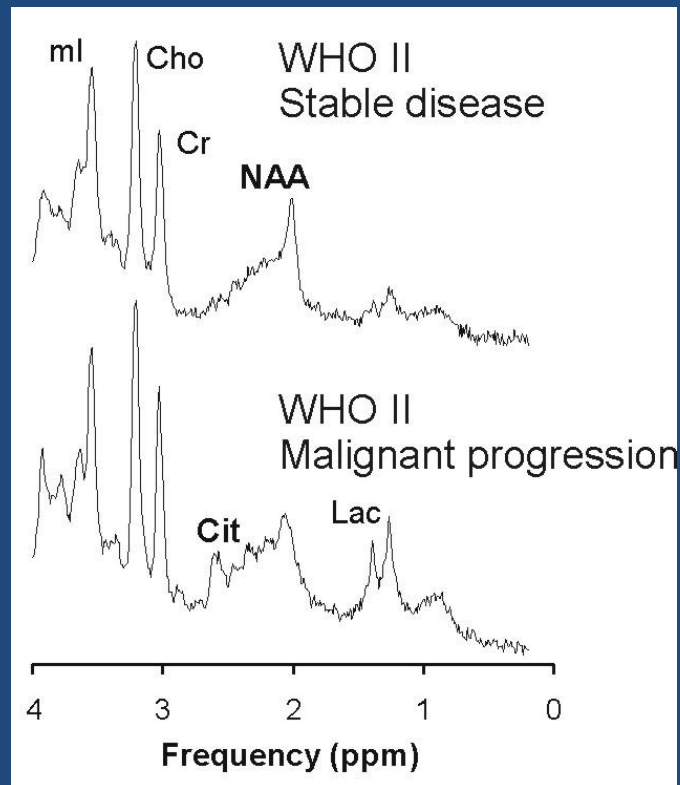B Glutamine
C N Acetyl
   Aspartate
D Scylloinositol
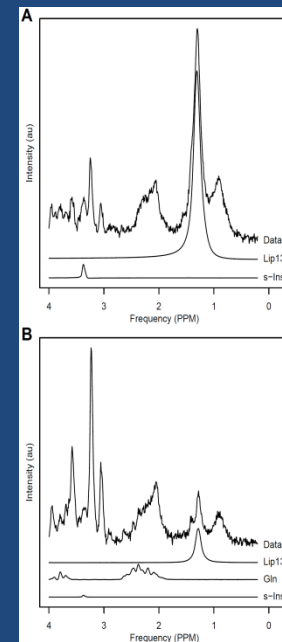
Poor
Prognosis

Good
Prognosis

Significant in Cox regression and likelihood ratio tests.
Objective: incorporation into international clinical trials

Wilson et al. EJC, 2013

High Citrate indicates poor prognosis in diffuse astrocytomas

Bluml Neuro-oncology, 2011

Glutamate as a biomarker of poor prognosis in medulloblastoma

Subtle changes in vivo – need high quality signal processing

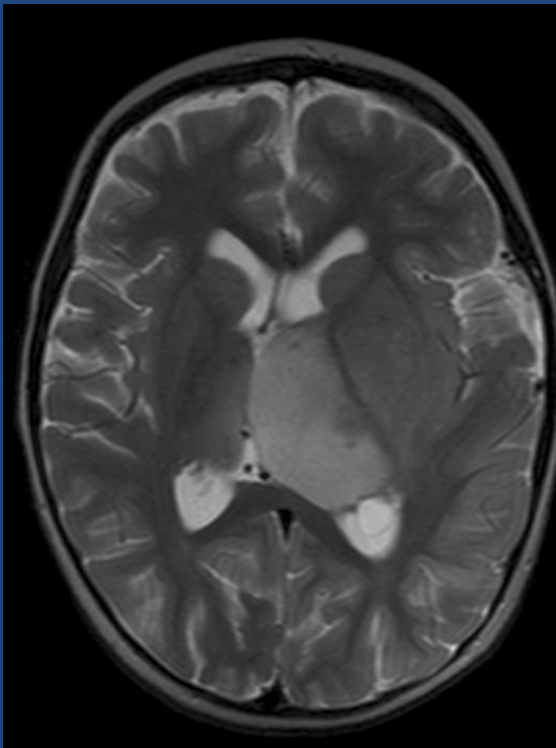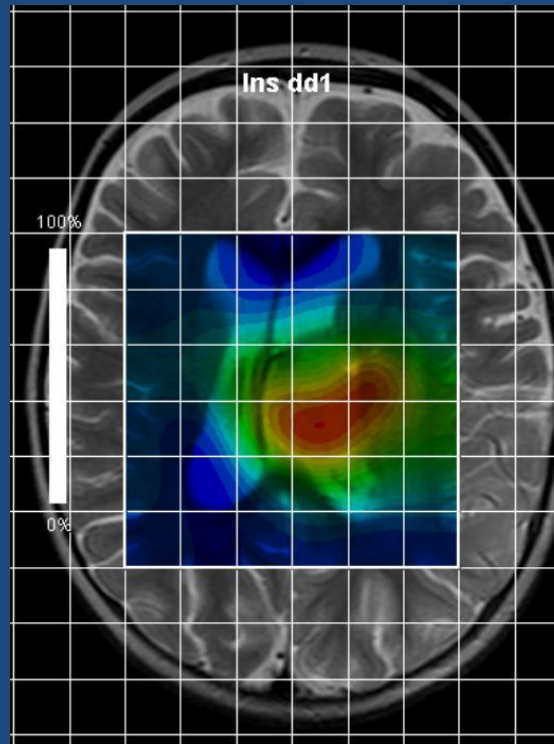Wilson et al Clin Cancer Res 2014
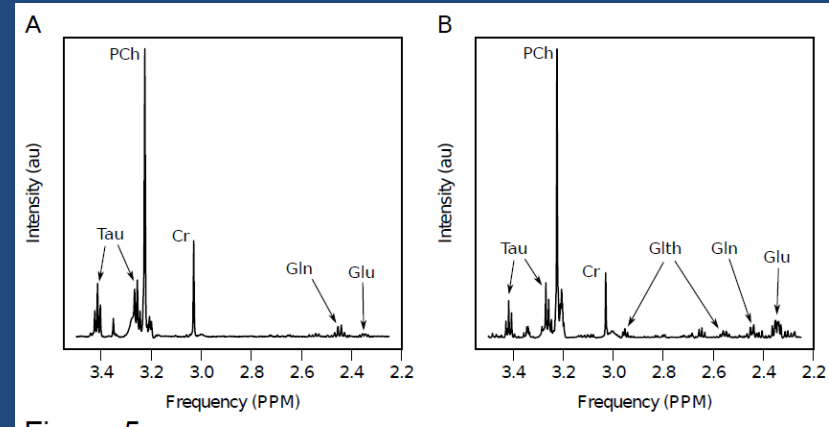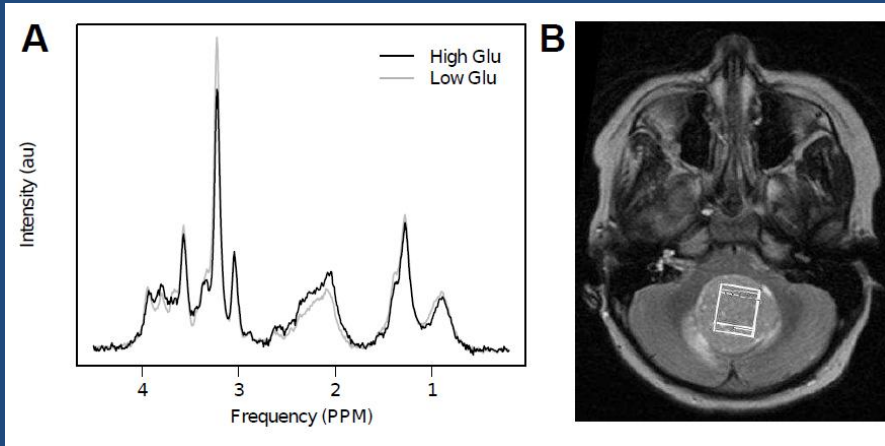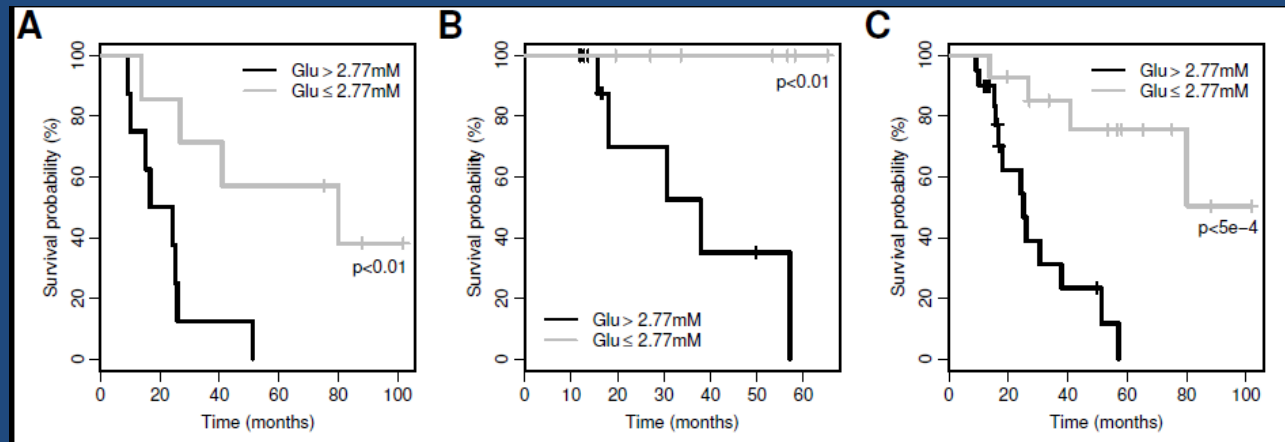
Tissue validation

Prospective validation

University of Birmingham

Birmingham Children's Hospital NHS Trust

Tumour Heterogeneity and spectroscopic imaging
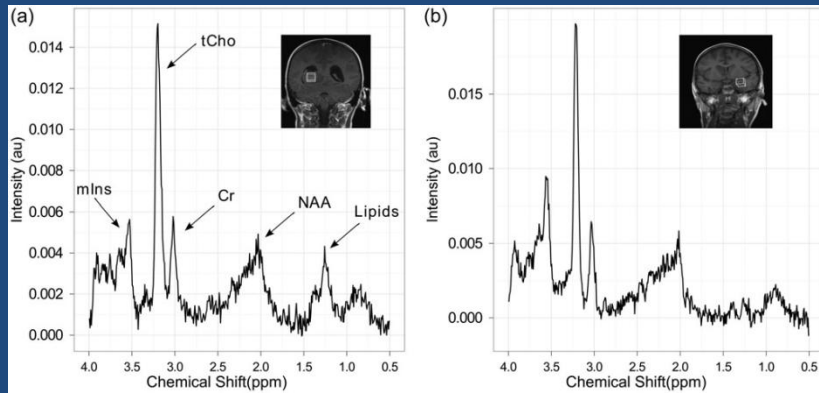
Thalamic diffuse astrocytoma
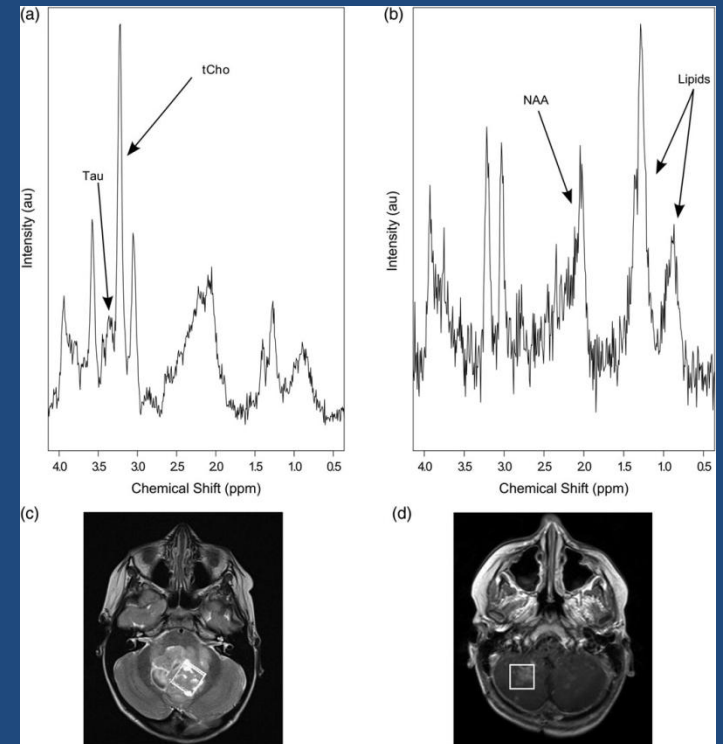
mIns – low grade

Cho – high grade
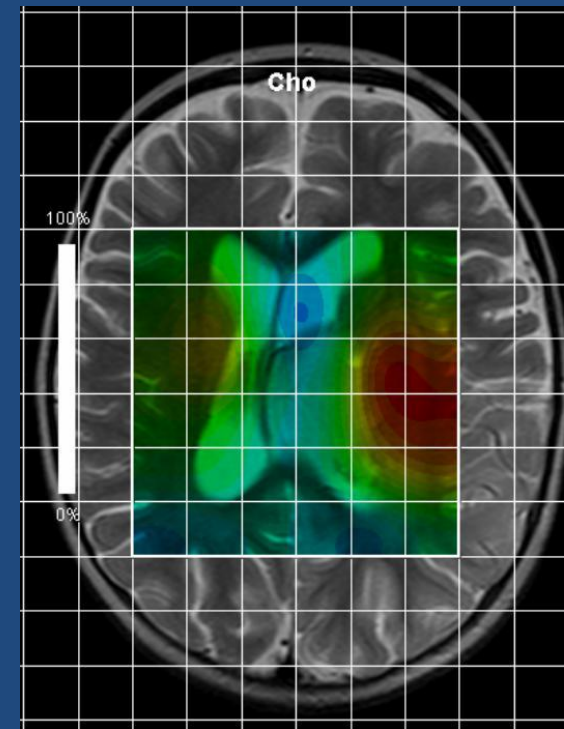
Distinguishing relapse from pseudo-progression

MRS at diagnosis very similar to that at relapse even when relapse is at a distant site

Enhancing lesion post treatment uncertain on MRI if relapse but MRS very different to diagnosis
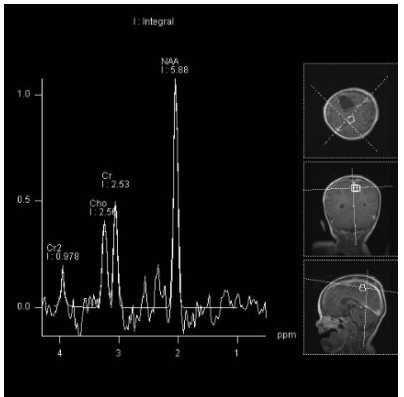
Gill et al Neuro-oncology 2013

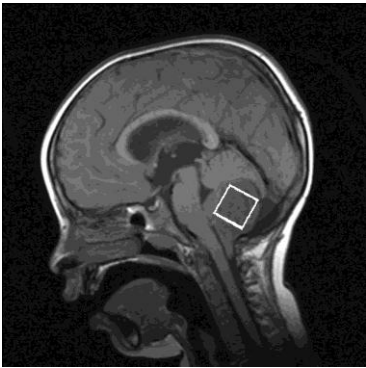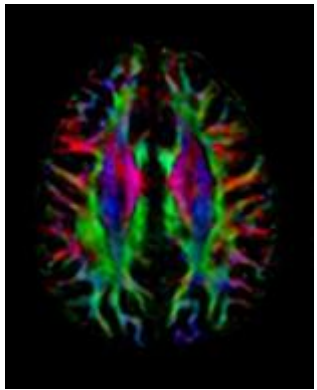# State of the art facilities for paediatric research embedded in the NHS

An Eye to the future
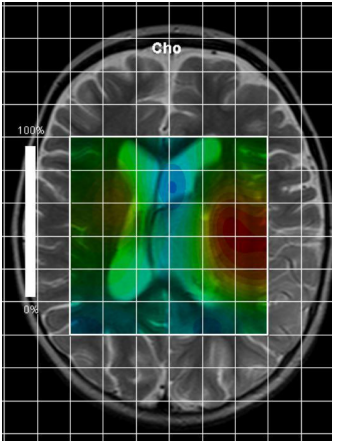# Functional Imaging combine rather than compete:

Metabolite profiles

Quantitative imaging

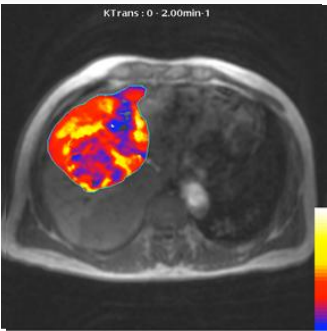Investigating children's cancer using functional imaging

Diffusion imaging

Metabolite maps
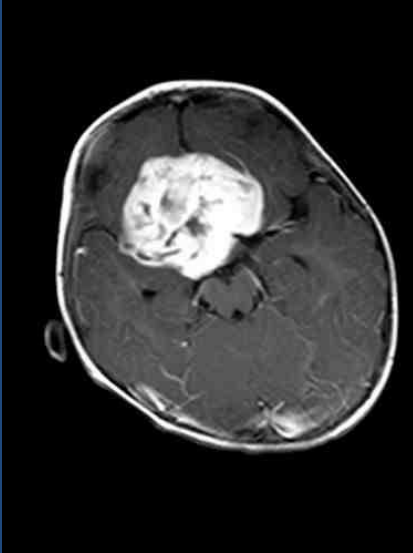

Perfusion

Tractography
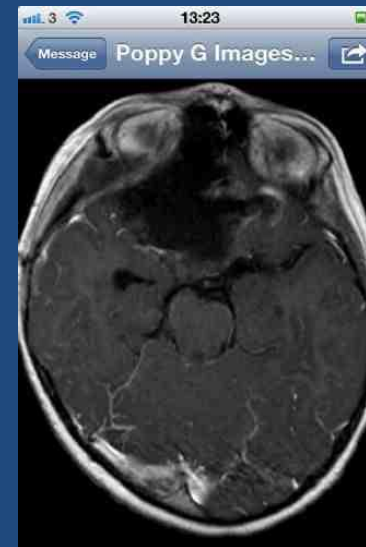
Peet et al. Nature Rev Clin Onc
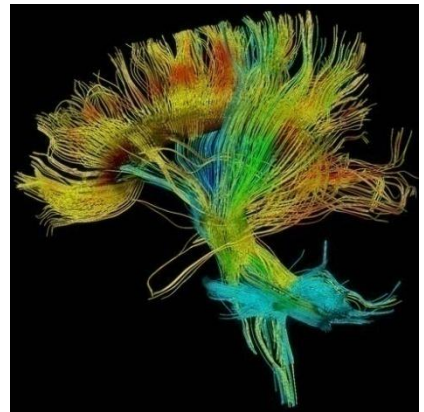
Poppy's Story

Diagnosed as an infant

Surgery 4 times
Chemotherapy multiple courses
Radiotherapy

50 MRI scans - each decision is made on a complex set of information

10 years later

Conclusions

- New imaging methods can greatly enhance the management of patients

- Physics and engineering advances are required in many areas to enable their translation to clinical practice

- Collaboration between fundamental scientists, clinical scientists and clinicians is required in the translation.

Thanks to

- All those who have contributed to the research and provided slides
- Those who have funded the research
- The children and families who have supported and contributed to the research
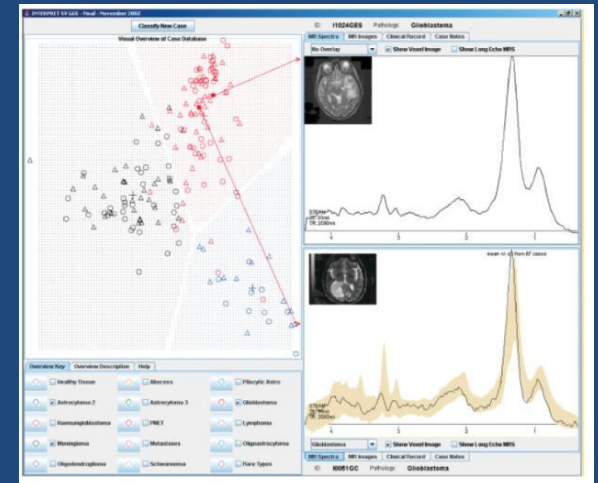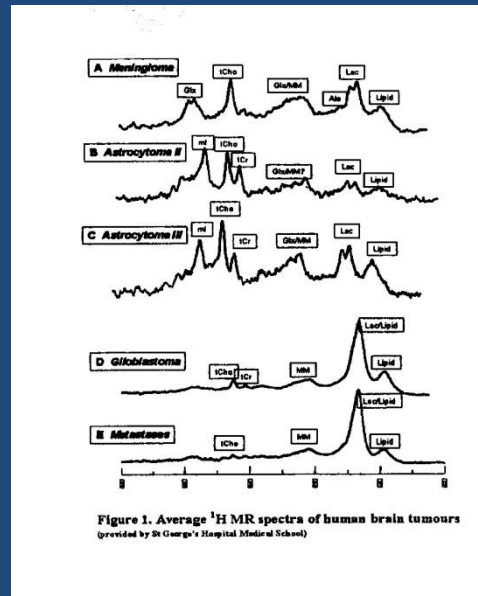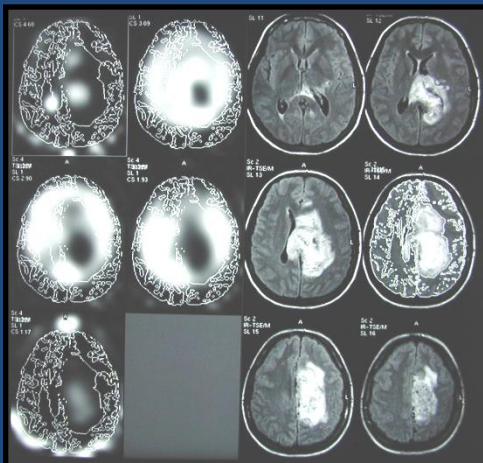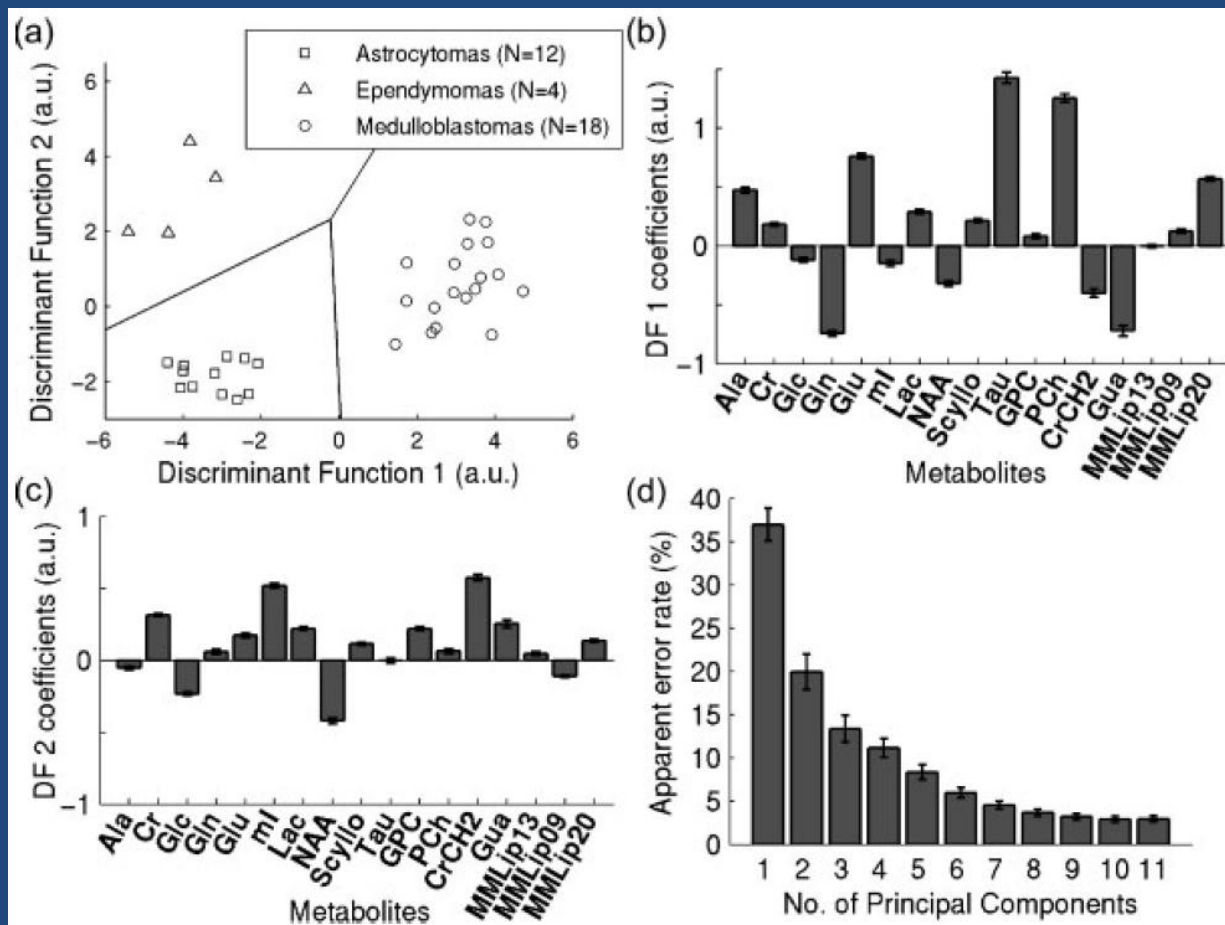
- Harry and Poppy's families.

In vivo clinical studies in adults with brain tumours

Single Centre – Pruel, Nature Medicine 1996
Multi centre – INTERPRET, Tate MRM 2003

Figure 1. Average ¹H MR spectra of human brain tumours
(provided by St George's Hospital Medical School)

Diagnosing Childhood Brain Tumours MRS Classifier Development

- Cerebellar tumours with pre-treatment MRS at 1.5T

- N=34 (after QC)

- 12 PA, 18 MB, 4 EP on histopathology

- Spectral fitting: LCModel

- PCA $\Rightarrow$ LDA

- Cross-validation

- Accuracy ~ 93%

Davies et al, NMR in Biomed 2008