Imperial College London

Prevention of Liver Fibrosis and Cancer - Northern Territory

Can hepatocellular carcinoma be detected earlier than current screening methods using a urine test?

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Project Supervisor: Dr Jane Davies

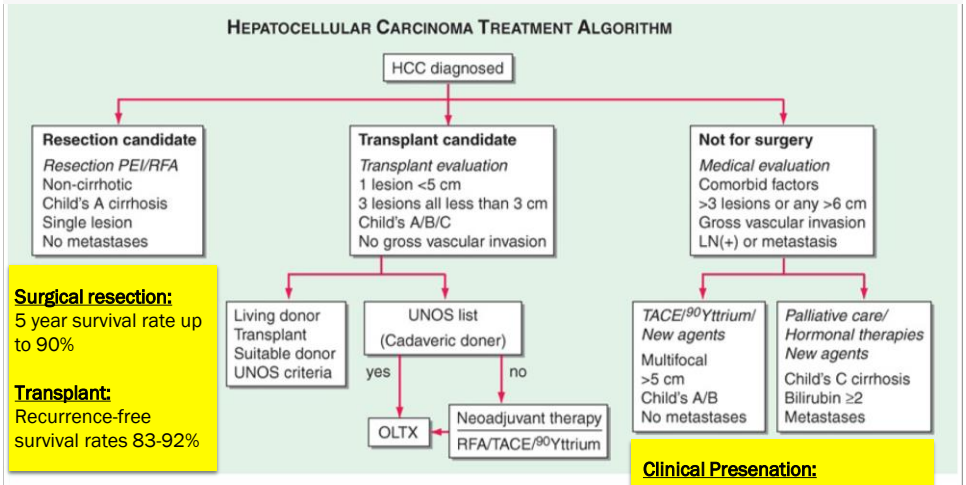
Hepatocellular Carcinoma (HCC)

- Liver cancer was the second most common cause of cancer death worldwide in 2015
- HCC is the most common primary liver malignancy with ≈ 800,000 deaths per year globally
- High mortality rate of HCC is largely attributable to insufficient diagnostic resources
- Hepatitis B Virus (HBV) is the most prevalent risk factor for HCC

HBV in the Northern Territory

- In 2014 estimated that 22,000 Aboriginal and Torres Strait Islander people living with HBV, ≈ 3,500 in the NT
- 90% of children with acute infection will progress to chronic hepatitis B, increasing their risk of HCC
- Median Survival from HCC Diagnosis to death for Aboriginals within the NT is 64 days

Treatment Options



Surgical resection:
5 year survival rate up to 90%

Transplant:
Recurrence-free survival rates 83-92%

Clinical Presenation:
65% - 3 or more tumours
75% - portal vein invasion

Project Aims

- Adapt a urinary metabolite test to screen for HCC that is:
  - suitable for use within the Australian and Northern Territory context
  - sufficiently sensitive to detect HCC at stages amenable to curative therapies

Why conduct Australian Study?

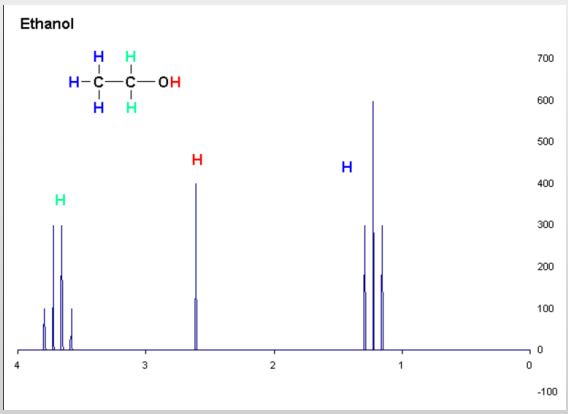
- Heterogenous metabolic profiles vary amongst ethnic groups, due to dietary, genetic and environmental factors
- HBV/C4 genome different characteristics
- Require specific metabolic studies or validation studies as a minimum

Finding biomarkers - Metabonomics

- Methods of metabolite characterisation - proton nuclear magnetic resonance (H NMR) spectroscopy and mass spectrometry (MS)

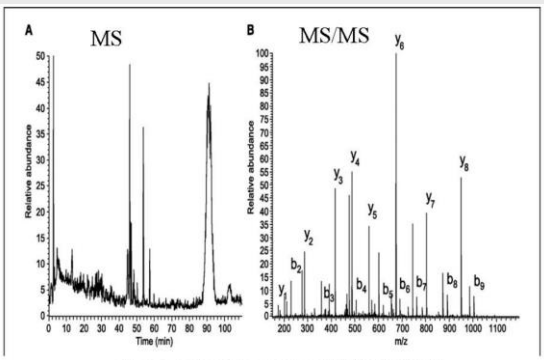
Metabolic profiling

- H NMR - based on behaviour of nuclei subjected to a magnetic field
- signal returns from molecules containing hydrogen provide a high-resolution metabolic NMR spectra



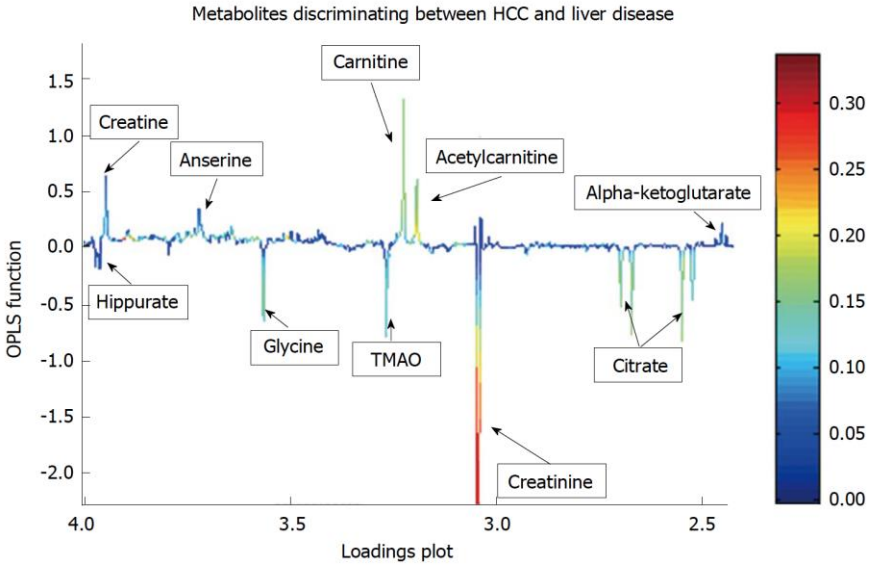
Metabolic profiling

- MS - constituent fragments are detected and distinguished by their molecular weight & ionic charge

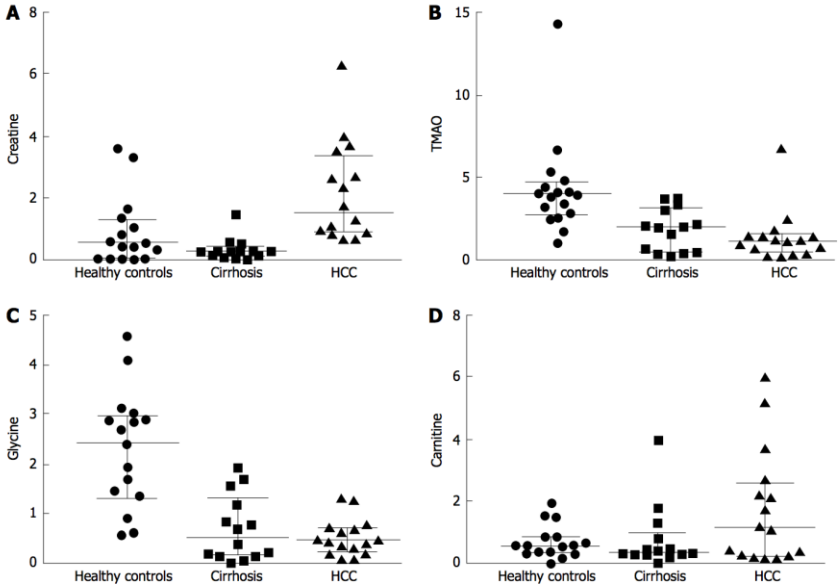


Zhang, J. et al. Cancer Res 2008;68:1046-1054

Metabolic profiling

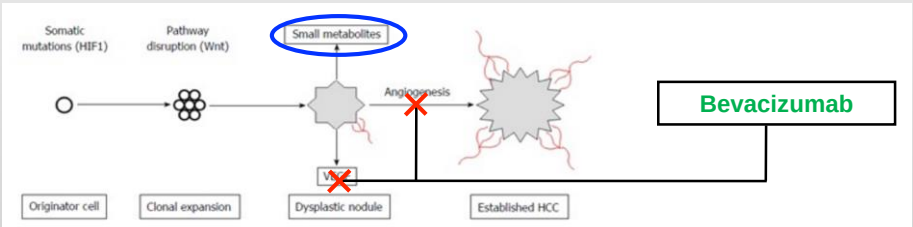


Metabolic profiling



Clinical Application of Biomarkers

- Complex molecular and metabolic interactions occur as HCC develops and progresses
- Identification of a single biomarker to assess presence and severity of HCC is unlikely



"Angiogenic switch" in hepatocellular carcinoma. VEGF: Vascular endothelial growth factor; HCC: Hepatocellular carcinoma; HIF 1: Hypoxia inducible factor 1.

Collaboration with Imperial College

Biological question

Experimental Design

Sample collection & Questionnaire

Sample preparation

1. Healthy control population (N=20)
2. Hepatitis B infected individuals without cirrhosis (li
3. Hepatitis B infected individuals with cirrhosis (N=1(
4. Patients with hepatocellular carcinoma (N=10)

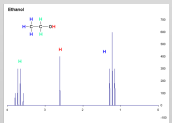
1. Blood
2. Ultrasound
3. Fibroscan
4. Urine

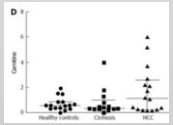
Sample analysis

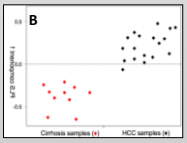
Data pre-processing

Data analysis

Biological interpretation







The Project, so far…

Literature Review — Dec 2015 – Jan 2016

Design Study Protocol — Jan – March 2016

Design & Trail of Epidemiological Questionnaire

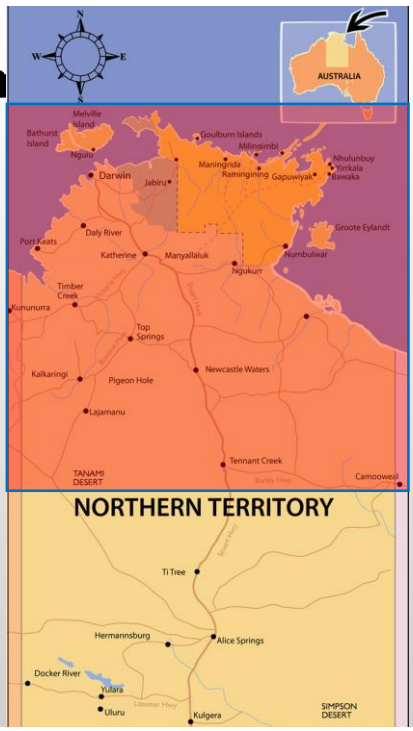
Ethics Approval — May 2016

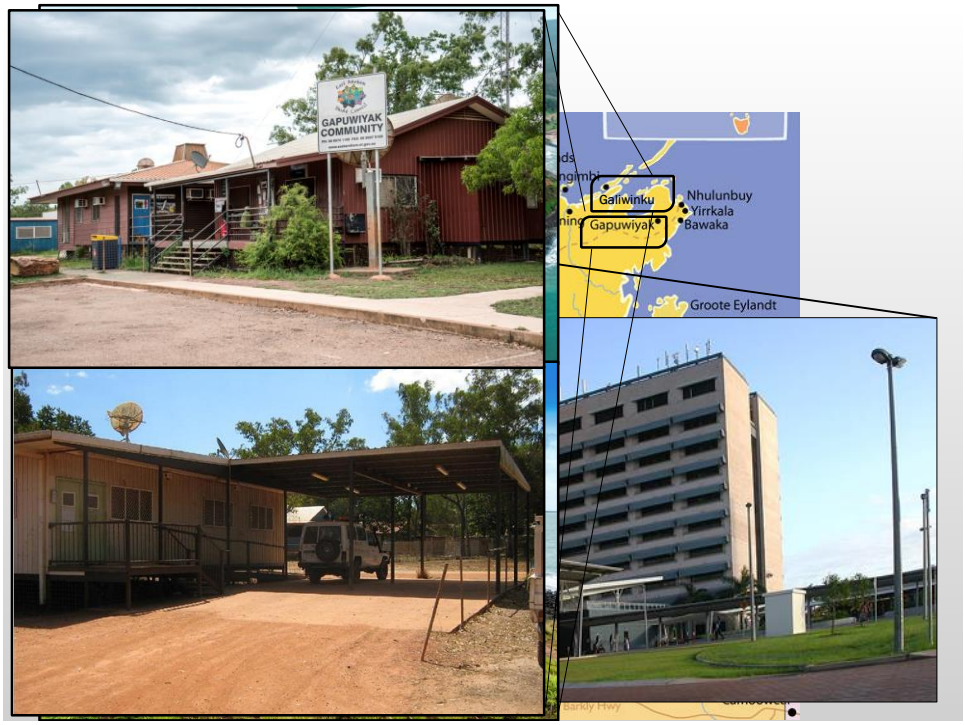
Oct 2016 – Current — Ongoing Recruitment & Sample Collection

Feb 2018 — Preliminary Results

Dec 2018 — Final Results

Recruitn

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Galiwinku
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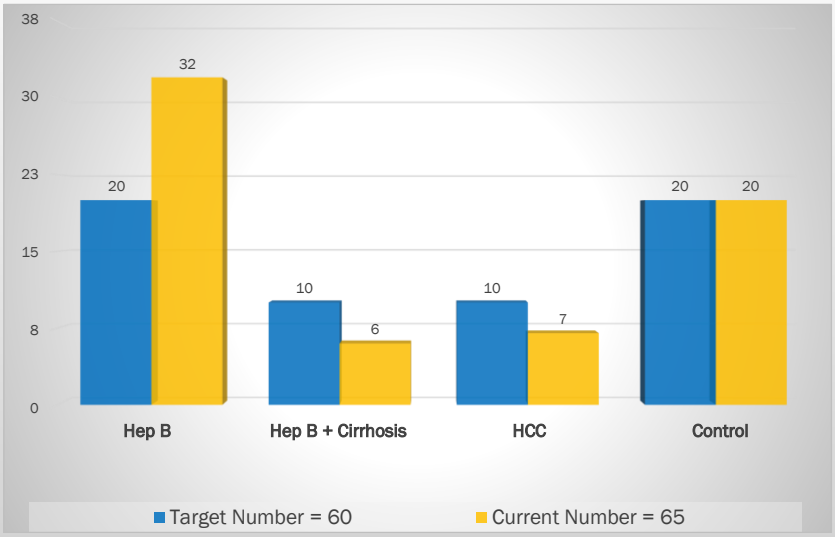
Bawaka
Groote Eylandt
Barkly Hwy


Kalkaringi
Pigeon Hole
Newcastle Waters
Lajamanu
Tennant Creek
TANAMI DESERT
Barkly Hwy
Camooweal

Recruitment



Preliminary Results

- Samples from 54 participants underwent initial principal component analysis in Dec 2017

1. Healthy control: 10 (20)
2. HBV no cirrhosis: 32 (30)
3. HBV with cirrhosis: 5 (10)
4. HCC: 7 (10)

- Promising initial data, need further sample and data analysis, and investigations into feasibility and diagnostic accuracy

Preliminary Results

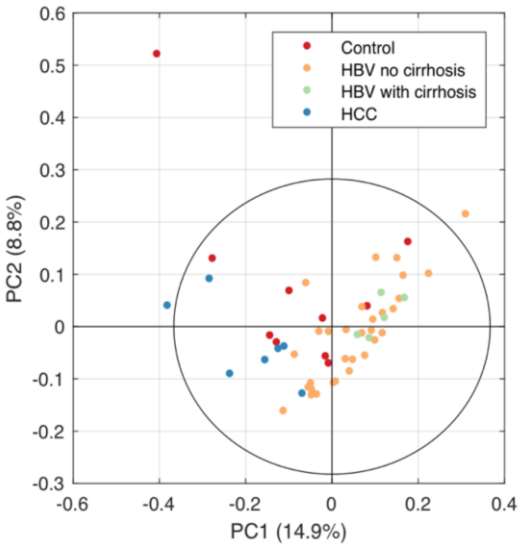


Figure 1: Principal component analysis

- HCC samples (**blue**) are separated from other groups, suggesting compositional difference between the groups

Preliminary Results

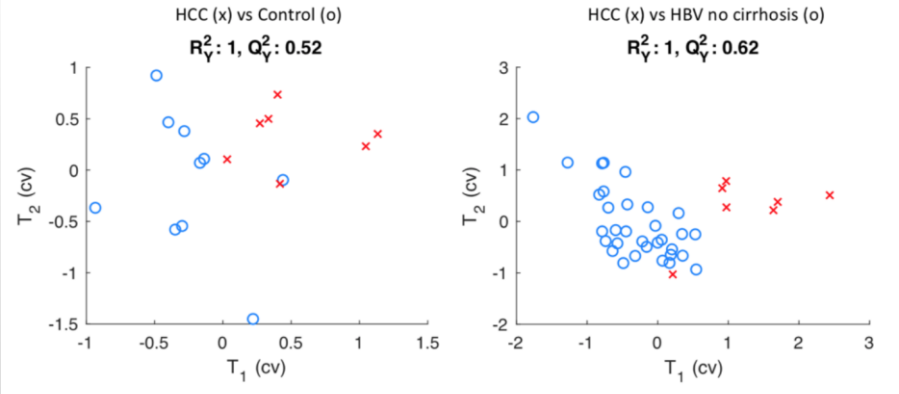


Figure 2: Partial least squares-discriminant analysis

- Plots demonstrate the predictive ability of the models.
- High Q^2Y value of 0.52 (HCC vs control) and 0.62 (HCC vs HBV w/o cirrhosis), suggesting that the models are predictive

Expected Key Outcomes

- Identify discriminatory metabolites to generate a urinary biomarker panel
- Study will serve as a proof of concept to inform and enable a subsequent validation study (NHMRC grant application submitted)

Acknowledgments

- Supervisor - Dr Jane Davies
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Questions?