SUPER: SOLVING UNKNOWN PRIMARY CANCER

AN UPDATE ON THIS NATIONAL AUSTRALIAN STUDY

PROFESSOR PENELOPE SCHOFIELD

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SWINBURNE UNIVERSITY OF TECHNOLOGY

Australian Government
Cancer Australia

Project support: Cancer Australia and Victorian Cancer Agency

JANE BARRETT

VIRTUALLY NO EVIDENCE TO GUIDE MANAGEMENT

Comprehensive clinical diagnostic work up

- Full physical exam (breast, rectal and pelvic examination)
- Basic blood profile (FBE, CUE, LFT, LDH)
- Gastroscopy and colonoscopy/FOBT (gastrointestinal primary)
- Chest x-ray and CT (thorax, abdomen and pelvis)
- Mammography (women), PSA (men) +/- PET (SCC H&N), Immunohistochemistry and circulating biomarkers
- Other tests for specific symptoms/laboratory abnormalities

Diagnostic workup of CUP patients can be lengthy, delays initiation of treatment and patients may deteriorate

Only 8 phase II trials (including 2 RCTS), and 4 prospective observational series have investigated chemotherapy regimens

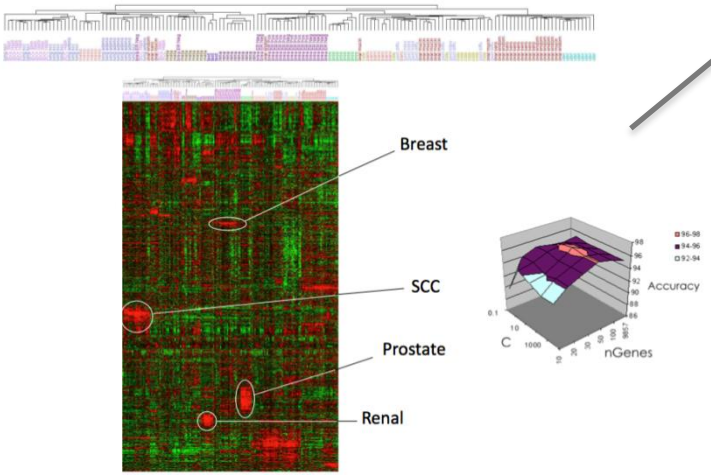
SUPER (Solving Unknown Primary cancER)

Principle Investigator: Penelope Schofield

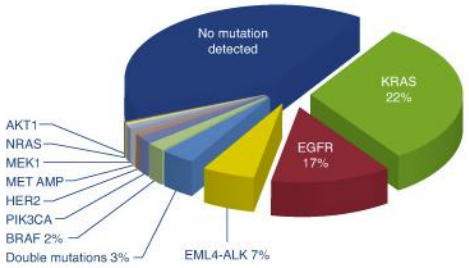
Cohort recruitment

Psychosocial studies

Clinical protocol development



CUP diagnostic test



Actionable mutations

Tothill et al (Can Res 2005)

SUPER: AIMS

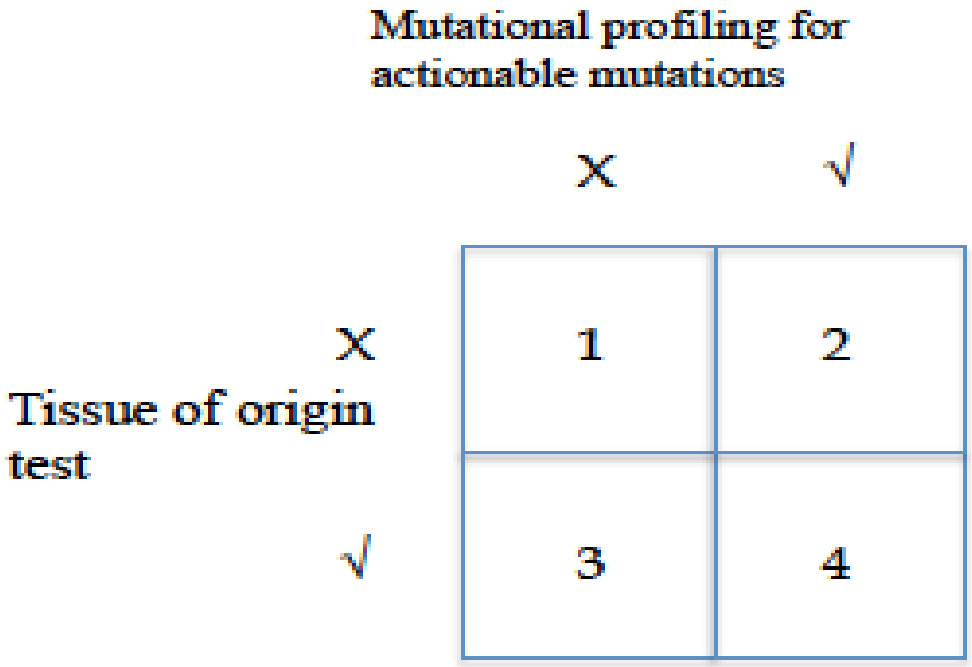
1. To establish a cohort of CUP patients with associated biospecimens, clinical, quality of life and psychosocial data.

2. To determine the frequency of clinically actionable mutations in CUP tumour samples and explore the molecular biology of CUP

3. To establish the quality of life and psychosocial needs of patients with CUP compared to a matched sample of patients with metastatic cancer of a known primary

RECUPERATE: CAN REALTIME MOLECULAR PROFILING IN CARCINOMA OF UNKNOWN PRIMARY IMPROVE TREATMENT OUTCOMES?

Principle Investigator: Linda Mileshkin



ADDITIONAL FUNDING REQUESTED

- To enroll an additional 180 patients from metropolitan and rural/regional
- To feedback molecular information to clinicians in real time for the entire cohort
- To assess the impact of this approach on clinical care and patient outcome by collecting detailed follow-up information.

RECUPERATE: AIMS

1. To provide molecular diagnostic and therapeutically actionable data to clinicians in real-time and assess the impact of this information
2. To understand the costs of care of CUP patients.
3. To compare the supportive care needs, quality of life and communication experiences of CUP patients and advanced cancer patients with known primary sites.
4. To compare the supportive care needs, quality of life and communication experiences of CUP patients treated in rural/regional and metropolitan areas.

DESIGN

A prospective, longitudinal matched cohort study of 300 patients with a matched sample of 200 patients.

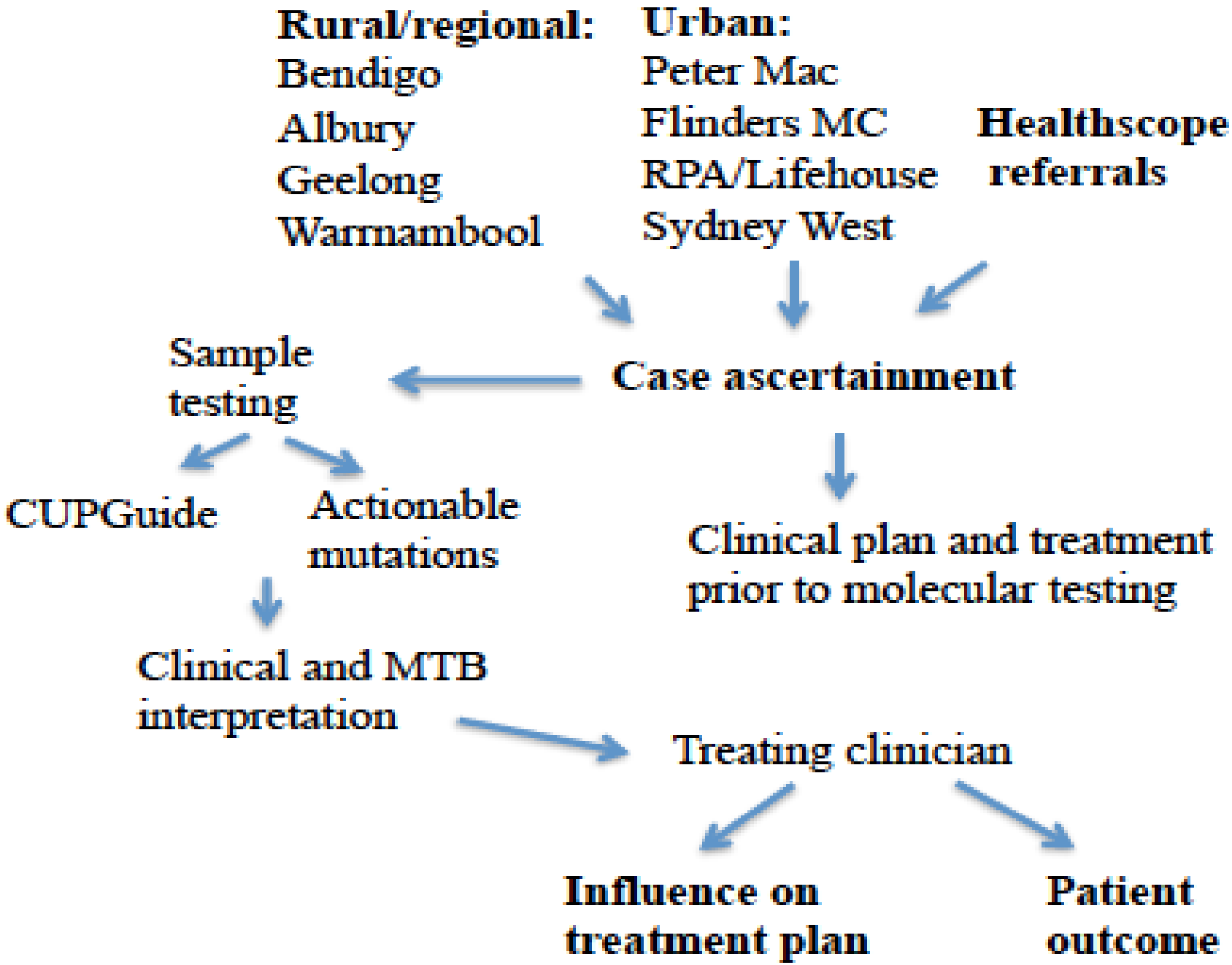
Biospecimens (FFPE mainly and 3-5mL of blood) will be collected at baseline and retained indefinitely

Mutation and site of origin profiling data will be provided to clinicians

Clinical treatment plans assessed prior to and post receiving the molecular results

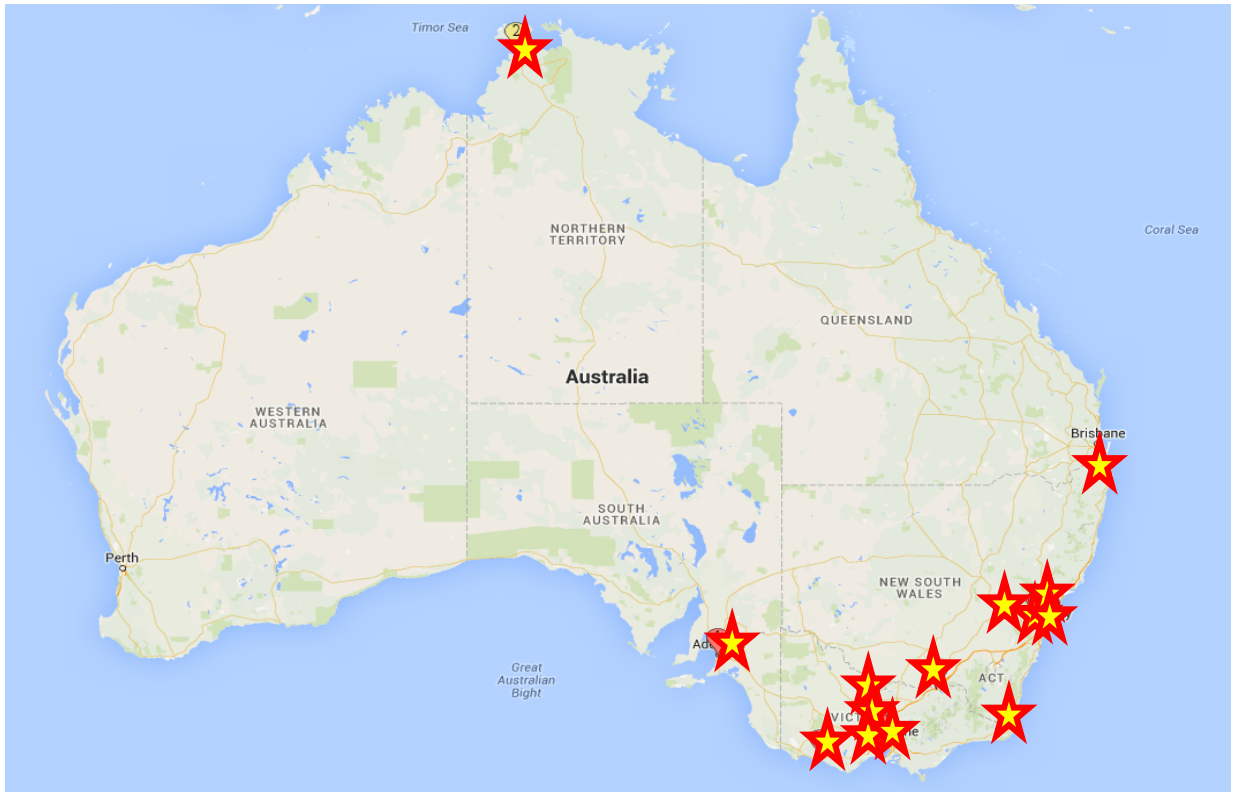
Clinical data collection will occur at baseline, 6 months and 12 months post-baseline

Patient reported outcome and health economic data will be collected from the CUP and non-CUP sample at baseline and at 3, 6, 9 and 12 months post-baseline (or to death).


Rural/regional:
Bendigo
Albury
Geelong
Warrnambool
Urban:
Peter Mac
Flinders MC
RPA/Lifehouse
Sydney West
Healthscope referrals
Case ascertainment
Sample testing
CUPGuide
Actionable mutations
Clinical plan and treatment prior to molecular testing
Clinical and MTB interpretation
Treating clinician
Influence on treatment plan
Patient outcome

SUPER Sites

- 11 current sites with Darwin, Canberra and Brisbane sites being explored
- Rural and regional sites



CUP SAMPLE

Inclusion criteria:

1.Presenting with carcinoma of no confirmed primary site and had a preliminary diagnostic work-up,

a detailed clinical assessment; a CT scan of the chest, abdomen, and pelvis; pathological review of tumour tissue; other gender appropriate diagnostic tests (eg PSA; mammogram).

2. Yet to commence treatment, or have commenced treatment no more than 6 months ago

3. Able to read and write in English

Exclusion criteria:

1.Are under 18 years;

2.Have a poor ECOG performance status (≥ 3)

3.Have uncontrolled medical or psychological conditions

MATCHED CONTROL SAMPLE

Inclusion criteria

1.Presenting with cancer of a known primary tumour with metastatic disease; when possible matched by dominant metastatic sites, decade of life, gender & ECOG

2.Yet to commence treatment or have commenced treatment no more than 6 months prior to the time of recruitment

3.Able to read and write in English

Exclusion criteria

1.Under 18 years;

2.Poor ECOG performance status ($\geq$ 3); or

3.Uncontrolled medical or psychological conditions

SUPER – STUDY UPDATE 14/09/2015

Sites	Site Status	No. Recruited
Peter Mac (Melbourne, VIC)	Active since 4/11/13	68
Westmead H (Sydney, NSW)	Active since 06/14	12
Nepean H (Sydney, NSW)	Active since 06/14	11
Blacktown Mount Druitt H (Sydney, NSW)	Active since 19/05/14	7
Flinders Medical Centre (Adelaide, SA)	Activated 06/14	14
Geelong Hospital (Geelong, VIC)	Activated 08/14	10
South West Healthcare (Warrnambool, VIC)	Activated 10/14	3
Cabrini H (Melbourne, VIC)	Activated 09/14	5
Border Medical Oncology (Wodonga , VIC)	Activated 13/3/15	3
Healthscope Pathology	Activated 12/14	5
Bendigo Health	Activated 07/15	1

MOLECULAR BIOLOGY

Lead: David Bowtell

To determine the frequency of clinically actionable mutations in CUP tumour samples and explore the molecular biology of CUP

Specifically, we seek

(i) to identify clinically actionable mutations – targeted therapy

(ii) to explore diagnostic utility of mutation profiling - interplay between actionable mutations and site of origin.

(iii) to explore the biology of CUP tumours.

Why determine site of origin in CUP?

Clinical utility

- Focus clinical investigation and reduce time to treatment
- Allow patient access to anatomically-based therapy – either conventional or clinical trials

Improve patient wellbeing

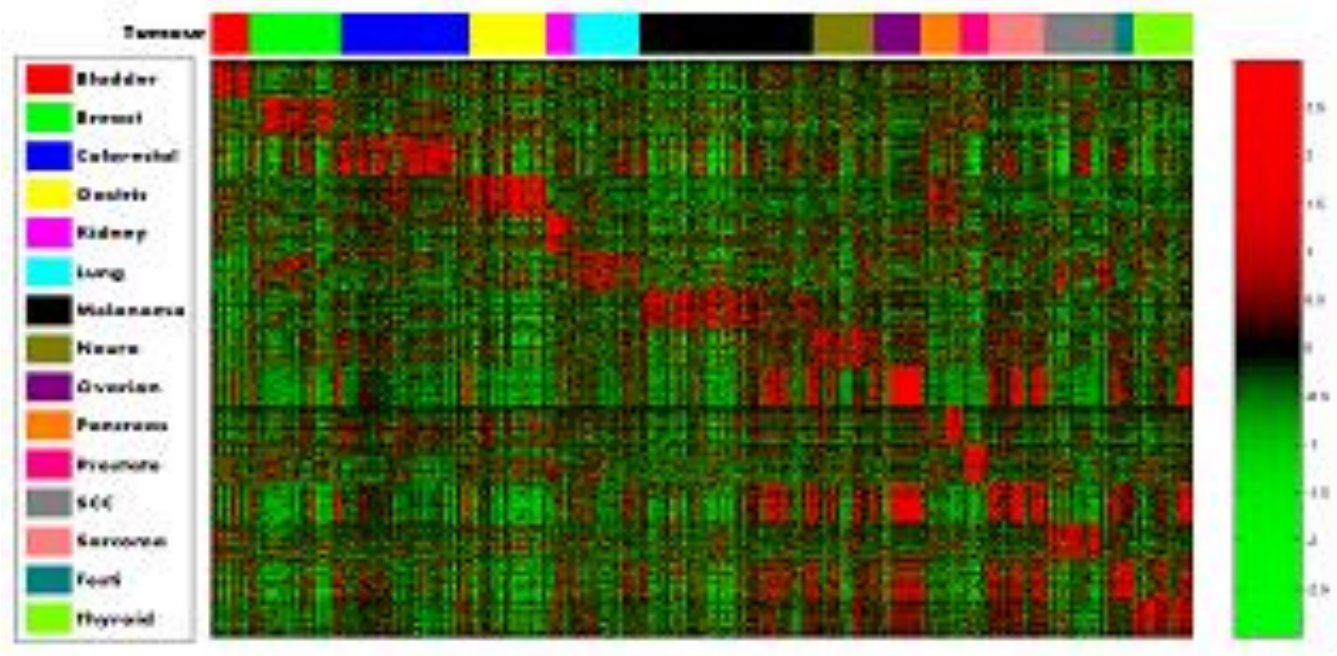
- Reduce patient anxiety and morbidity associated with investigations
- Potentially improve patient outcome

Limit health costs associated with investigations

- Estimated average workup for CUP case in US $US4,500~$US18,000 ($US1.5Billion Annually)*

*Dowell JE: Am J Med Sci 2003;326:35–46.

CUPGuide



Training set of known tumours: *n*= 553

18 cancer types (Metastases: 84%, Primaries: 16%)

Validation set of known tumours *n*=90

Accuracy : Top ranked: **91%** Within top two ranked**: 97%**

Healthscope PATHOLOGY

Massively-parallel sequencing assists the diagnosis and guided treatment of cancers of unknown primary

Tothill *et al* 2013 Journal of Pathology

Conventional cancer treatment is dictated primarily by the origin of primary tumour.

What to do when a primary cannot be identified?

Cohort

16 CUP cases selected from tissue bank

Workup

Patient Hx

Histopathology (incl. IHC)

Gene Expression Profiling: Site of Origin

Sequencing

701 gene panel

- Kinases (NKI, Rene Bernards)
- Additional cancer genes

Agilent SureSelect capture enrichment (Illumina HiSeq 2000)

Tissue Samples and matching blood

12 fresh frozen

4 FFPE (>300ng)

14 with blood samples

Application of classifier to CUP cases

Cancer Research

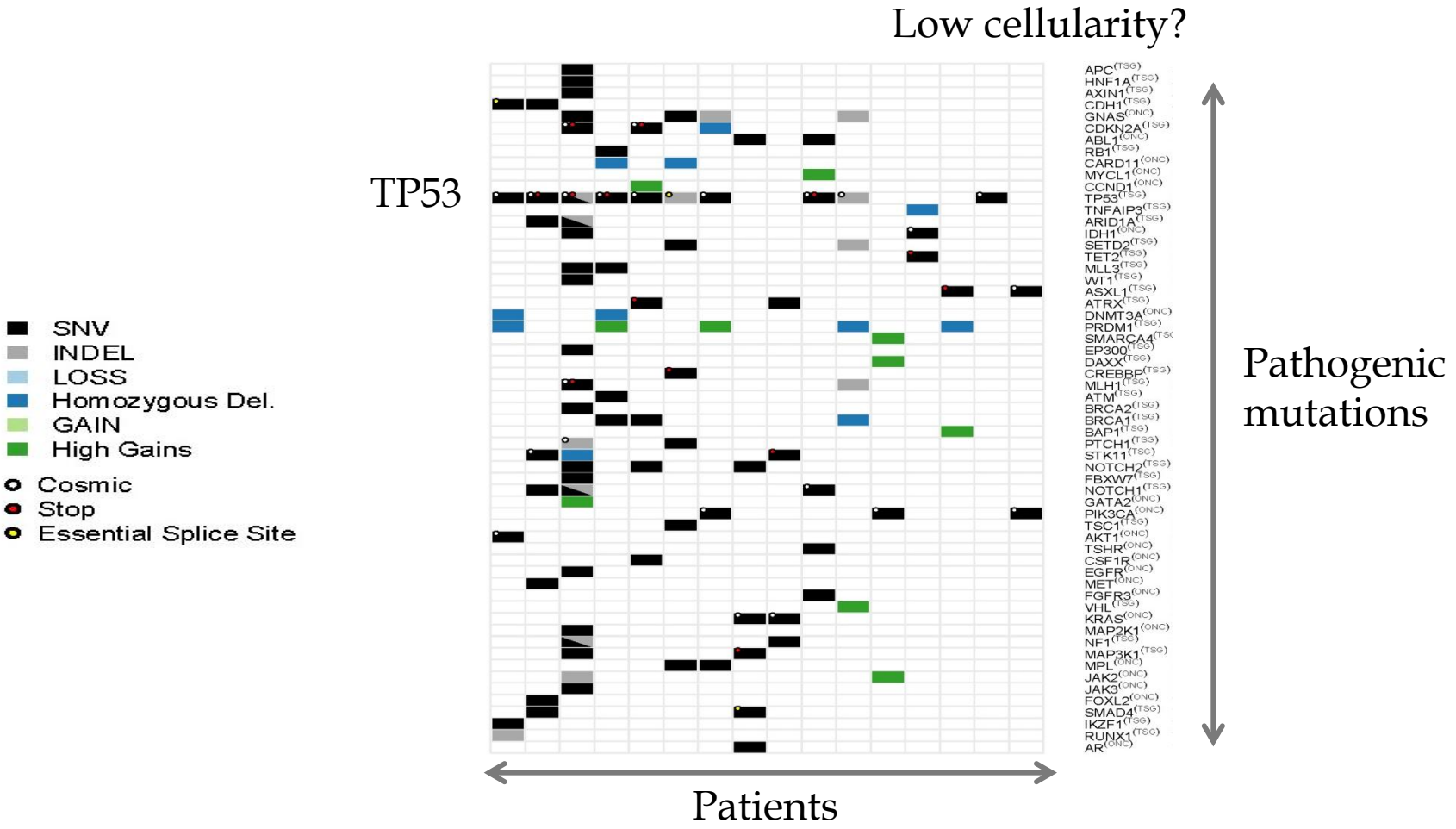
Table 3. Summaries of clinical history and array predictions for unknown primary samples

Disease presentation and histology	Differential at initial presentation	Array prediction and outcome
P00459: 40-y-old male nonsmoker, no previous history. Supraclavicular and mediastinal lympadenopathy, lymphangitis of lung, right upper lobe mass, and liver metastases. Poorly differentiated adenocarcinoma.	Clinical picture most consistent with lung but uncertain in a young nonsmoker.	Lung (70). Minor response to platinum/ gemcitabine, stable disease for 3 mo on gefitinib and progressive disease with docetaxel.
P01328: 52-y-old female, no previous history. Extensive abdominal tumor. Adenocarcinoma.	Ovary, gastric, and breast	Breast (100). Left supraclavicular fossa and axillary nodes developed within 2 mo of chemotherapy.
P01405: 66-y-old male nonsmoker, no previous history. Paraaortic lymphadenopathy and bone metastases. Clear cell epithelioid tumor.	Pathology review favored sarcomatoid renal cell cancer; but renal CT and MRI normal.	Renal (88).
P01698: 37-y-old female, no previous history. Pelvic mass, ascites, and left pleural effusion. Moderately differentiated adenocarcinoma with occasional signet ring features.	Pathologist thought that morphology strongly suggested nonovarian origin (e.g., gastric, colorectal, pancreas, or lung). Clinical picture consistent with ovarian cancer.	Ovarian (92). Treated with taxol/carboplatin for presumed ovarian primary. Good clinical response with normalization of CA125
P01946: 49-y-old female smoker, no previous history. Liver, bone, adrenal, and mediastinal disease. Atypical infiltrating epithelial cells forming glandlike structures.	Lung, colorectal.	Lung (60)

High confidence 11/13 cases

Tothill et al (2005) Cancer Research

Mutation profiling by targeted pull down

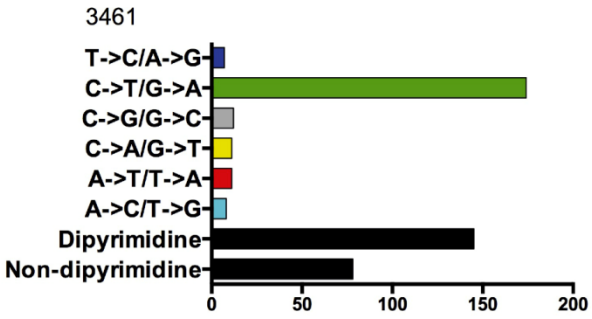


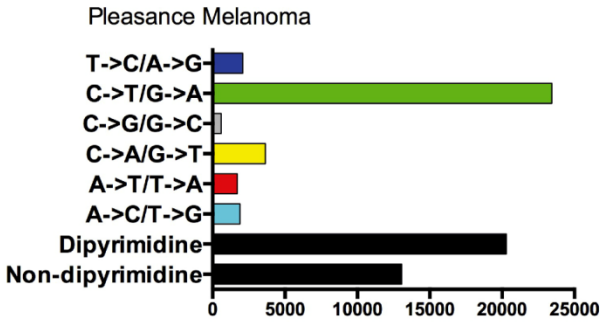
Mutation profiling revealed therapeutic gene targets and pathways in 12/16 cases, providing potential targetted treatment options.

	Actionable lesions	Drugs
Category 1		
1005	*PIK3CA p.*E545K	PIK3CA/AKT/mTORi (eg PX866 or temsirolimus)
1698	*BRCA1 Homozygous deletion*	PARPi (e.g. olaparib)
1382	*KRAS p.*G12C	MEKi (e.g. selumetinib)
8593	*KRAS p.*G12C	MEKi
2864	*PTCH1* FS	SMOi (e.g. vismodegib)
Category 2		
168	*IDH1 p.*R132L	IDH1i (e.g. AGI-5198)
563	*AKT1 p.*E17K	AKTi (e.g. SC66)
Category 3		
1478	*CCND1* HLG	CDK4/CDK6i (e.g. palbociclib)
1184	*PIK3CA p.*E81K (VUS)	PIK3CA/AKT/mTORi
1005	JAK2 *High level CN-gain*	JAKi (e.g. ruxolitinib)
91	*PIK3CA p.*E81K (VUS)	PIK3CA/AKT/mTORi
3461	*FGFR3 p.*T742I(VUS)	FGFRi (e.g. ponatinib)
3282	*MET p.*R400S (VUS)	METi (e.g. crizotinib)

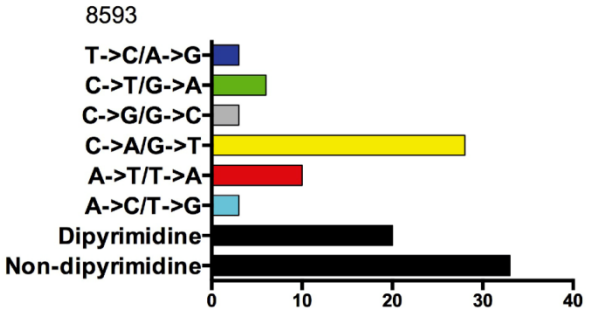
Clinical Pre-clinical Suggestive data

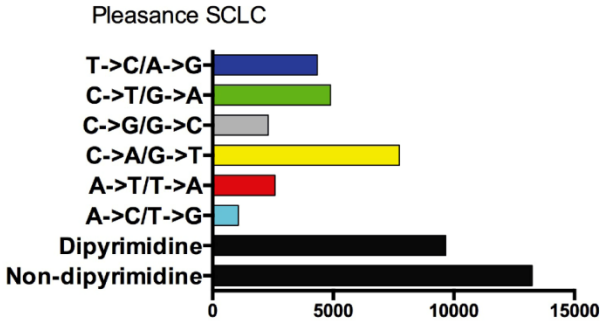
Mutation signatures provides clues to disease aetiology





UV





Smoking

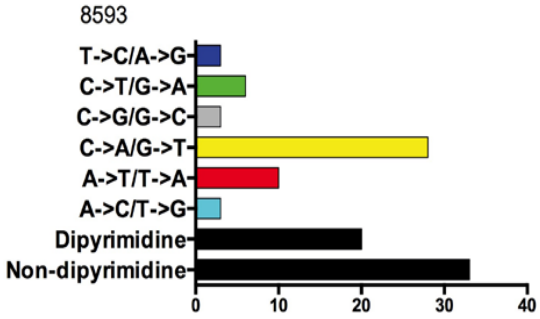
CUP

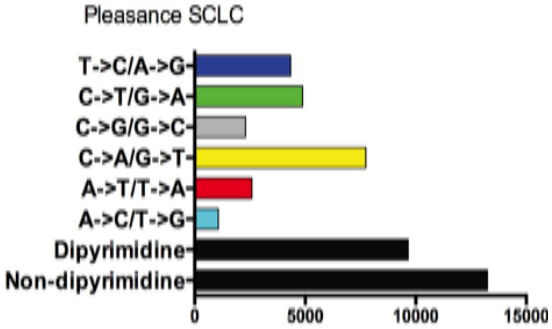
Published WGS Data

RENAL OR LUNG ?

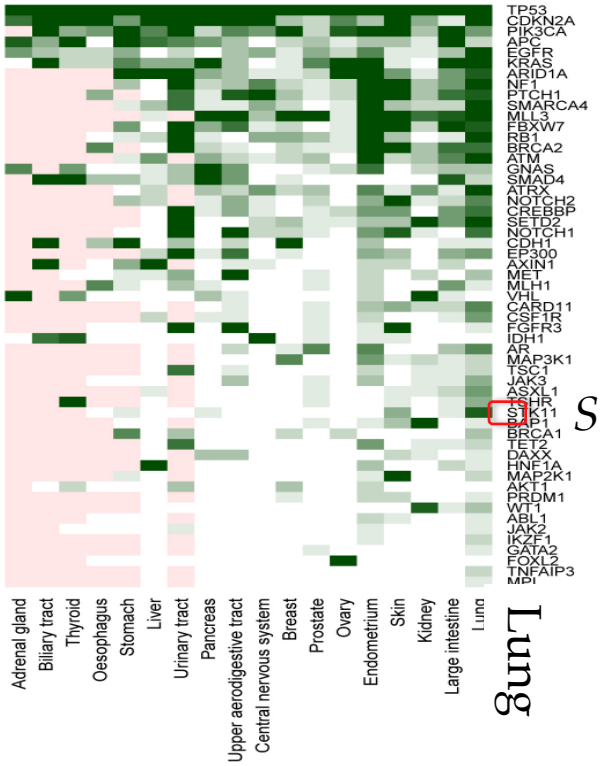
- 74 year old female smoker with previous history of renal cell tumour treated by nephrectomy, presented with bone metastases right ileac
- crest.
- On CT there was a small but spiculated lesion in the left lung of uncertain significance not suitable for biopsy.

- **Gene expression profiling assay consistent with lung adenocarcinoma**





Mutation frequency by tumor type

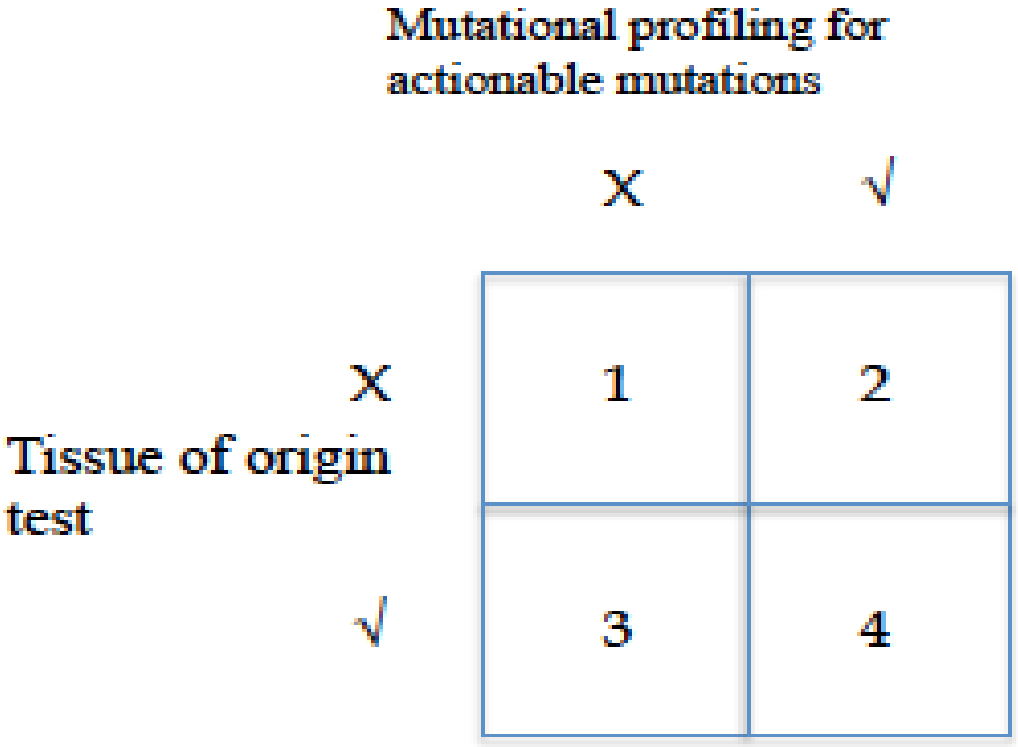


STK11

RECUPERATE: CAN REALTIME MOLECULAR PROFILING IN CARCINOMA OF UNKNOWN PRIMARY IMPROVE TREATMENT OUTCOMES?

Principle Investigator: Linda Mileshkin

Aim: To provide molecular diagnostic and therapeutically actionable data to clinicians in real-time and assess the impact of this information to inform clinical management



Treatment will depend on the strength of the findings with each assay, the availability of appropriate drugs, and whether the assays suggest a concordant or discordant approach

DIAGNOSIS & TREATMENT

Lead: Linda Mileshkin

To establish a cohort of CUP patients and to provide molecular diagnostic and therapeutically actionable data to clinicians in real-time and assess the impact of this information

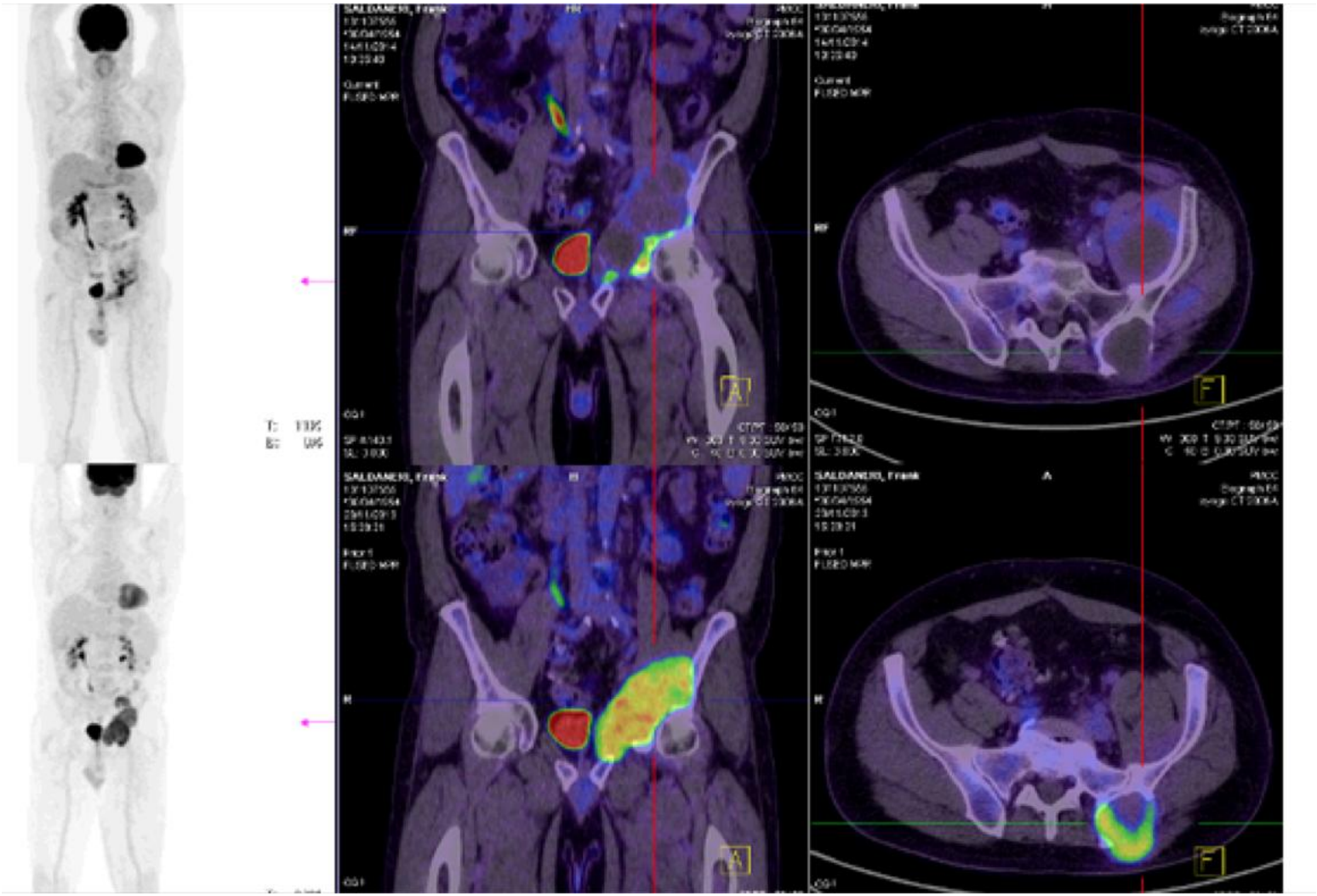
Specifically, we seek:

(i) to better understand clinical heterogeneity of patients assigned the broad label of CUP

(ii) to understand the costs of care of CUP patients.

(iii) to feed back molecular diagnostic and therapeutically actionable data to clinicians in real-time and assess the impact of this information

12 MONTHS RESPONSE TO PAZOPANIB



Nov 2014 - Near complete metabolic response on PET/CT

Dec 2013

Left iliopsoas mass eroding acetabulum

Left Posterior iliac lesion

PSYCHOSOCIAL IMPACT

Lead: Penelope Schofield

To establish the quality of life and psychosocial needs of patients with CUP compared to a matched sample of patients with metastatic cancer of a known primary

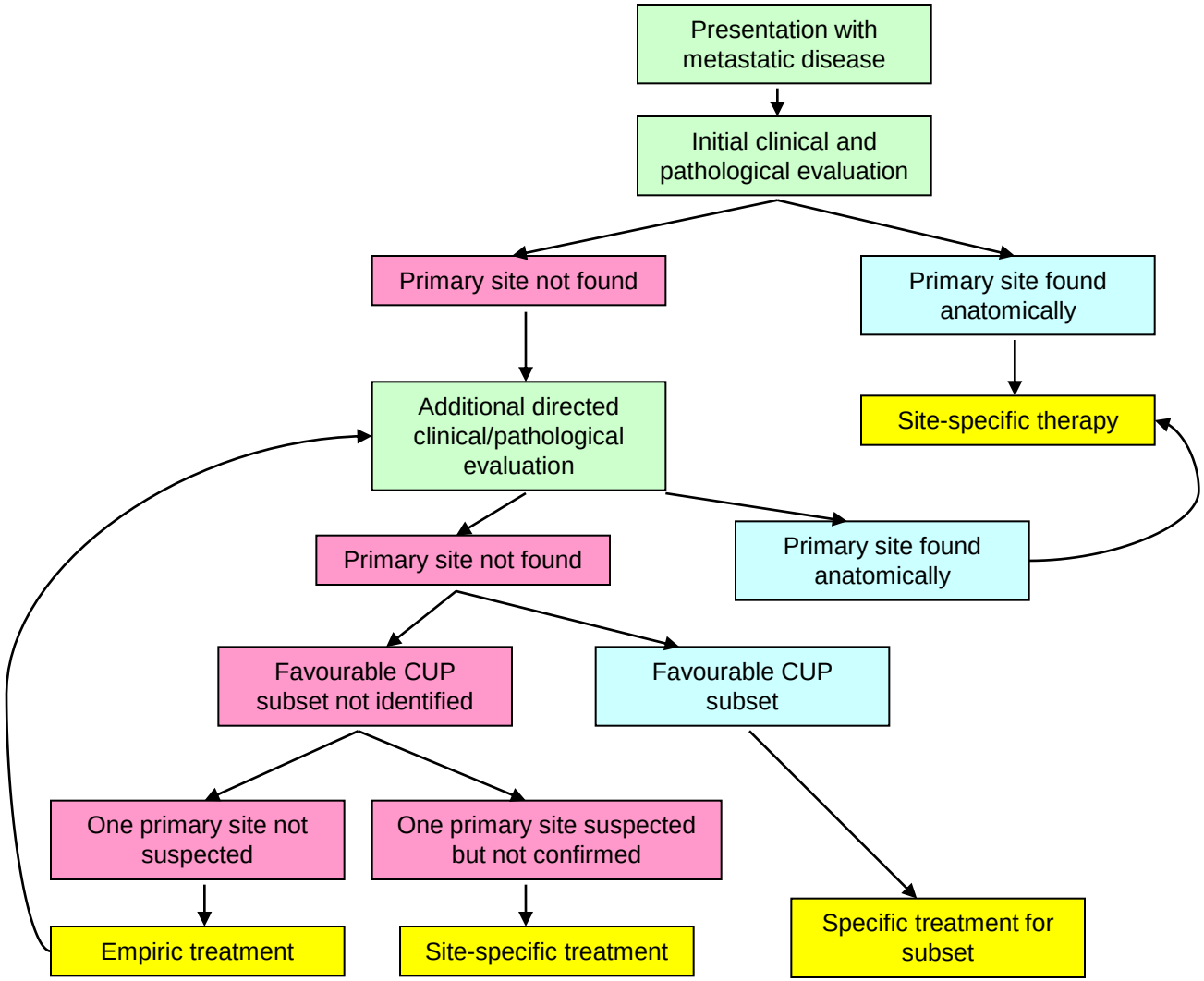
Specifically, we seek:

(i) to establish reliable estimates for quality of life and psychosocial needs across the CUP illness trajectory

(ii) to identify similarities and differences between CUP and non-CUP patients from baseline to 12-month follow-up.

(iii) to compare the psychosocial needs, quality of life and communication experiences of CUP patients treated in rural/regional and metropolitan areas

Complex and arduous illness trajectory



WHAT DO WE KNOW ABOUT THE EXPERIENCE OF CUP?

- **Extensive literature search revealed only three published studies on the experiences of people with CUP**

- **Richardson et al (2014) have published qualitative paper N=17 describing the patients (n=17), carers(n=14) and health professionals(n=13) experiences of CUP**

Psycho-Oncology
Psycho-Oncology **22:** 2009–2015 (2013)
Published online 29 January 2013 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3244

Psychiatric manifestations, personality traits and health-related quality of life in cancer of unknown primary site

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Abstract

***Objective*: Psychiatric manifestations and personality traits are known to influence cancer patients. We aimed to assess psychological distress symptoms, psychosocial factors and health-related quality of life (HRQoL) in cancer of unknown primary site (CUP) and to test whether these parameters differ between CUP and Metastatic (MKPC) or Non-Metastatic Known Primary Cancers (N-MKPC) after controlling for demographics and clinical variables.**

***Methods*: In this cross-sectional study, we recruited 50 CUP, 264 N-MKPC and 52 MKPC participants. We assessed depressive symptoms (Center for Epidemiologic Studies-Depression [CES-D]), psychological**

METHODS

Design

A prospective, longitudinal study with matched control group over one year with 120 cases per group

Patient reported outcome data will be collected at baseline and at 3, 6, 9 and 12 months post-baseline (or to death).

MATCHED CONTROL GROUP

Inclusion criteria

1. Presenting with advanced cancer of a known primary tumour (carcinoma of lung, upper or lower gastro-intestinal system, breast or head and neck) with metastatic disease;
2. Yet to commence treatment or have commenced treatment no more than 3 months prior to the time of recruitment
3. Able to read and write in English

Exclusion criteria

1. Under 18 years;
2. Poor ECOG performance status ($\leq$ 3); or
3. Uncontrolled medical or psychological conditions

MEASURES

1.Physical, social and mental health **Patient Reported Outcomes Measurement Interactive System (PROMIS®) : Anxiety; Depression; Fatigue; Pain Interference; Pain Intensity; Sleep Disturbance; Physical Function; Satisfaction with Social Roles and Activities**

2.Cancer-specific health-related quality of life **EORTC Quality of Life Questionnaire – C30 (EORTC QLQ-C30)**

3.Medical communication/information and psychological needs**: Needs Assessment for Advanced Lung Cancer Patients (NA-ALCP)**

4.Hopelessness : **Hopelessness Assessment in Illness (HAI)**

5.Communication about and understanding of illness and treatment**: a purpose-built questionnaire.**

DESIGN CHANGES

How to achieve a sample which is comparable and the key difference is whether site of primary is known or unknown?

- **Shift from design using case-control with one to one matching to case-control cohort with frequency matching and a unifying event.**

  - The unifying event is 0-2 months within first doctors appointment to recruitment site

  - Frequency matching for 1) rural vs urban, 2) palliative vs curative 3) dominant metastatic site.

RESEARCH CHALLENGES

- Difficulties in defining and identifying these patients within the system
- Many doctors provide a 'likely' diagnosis to gain access drugs and so patients don't identify with CUP label
- Poor prognosis means research is challenging
- Extremely time consuming to gather medical records data
- Mutation analysis expensive, fail quality assurance and time consuming can take a week to curate.
- Challenging to define and locate the most appropriate matched sample

CONCLUSIONS

- CUP patients are a sizable group of patients with unique and complex needs
- CUP patients appear to have higher levels of distress than other cancer patients but this needs to be confirmed with a large sample.
- Very little is known at this point about their patient experiences of the health system; communication and informational needs and feelings of hopelessness.
- The CUPGuide gene expression-based diagnostic may facilitate a more rapid diagnosis of site of origin in some patients
- Mutational data can narrow likely site of origin and identify actionable mutations, however drugs may not be available
- Optimum clinical management is likely to require an integrated genomic analysis involving both site of origin classification and mutation detection

OUR TEAM

Chief Investigators

Schofield Behavioural science

Bowtell Molecular Biology/Genomics

Mileshkin Medical Oncology

Waring Pathology

deFazio Cancer Cell Biology

Tattersall Medical Oncology

Karapetis Medical Oncology

Richardson Medical Oncology

Associate Investigators

Barrett Consumer Advocate (deceased)

Bryant Consumer Advocate & Nurse

Gooden Nurse

Thomas Medical Oncology

Mitchell Medical genetics

Wasan Medical Oncology

Lipton Medical oncology

Ashley Medical Oncology

Tothill Molecular Biology

Zalcberg Medical Oncologist

Lorgelly Health Economics & quality of life

Fox Pathology