SUPER: SOLVING UNKNOWN PRIMARY CANCER
AN UPDATE ON THIS NATIONAL AUSTRALIAN STUDY

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SWINBURNE UNIVERSITY OF TECHNOLOGY

Project support: Cancer Australia and Victorian Cancer Agency
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)

Cohort recruitment

Clinical protocol development

Psychosocial studies

CUP diagnostic test

Tothill et al (Can Res 2005)

Principle Investigator: Penelope Schofield

Actionable mutations
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).
SUPER Sites

• 11 current sites with Darwin, Canberra and Brisbane sites being explored
• Rural and regional sites
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 (≥ 3); or

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

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: \( 97\% \)
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
### Table 3. Summaries of clinical history and array predictions for unknown primary samples

<table>
<thead>
<tr>
<th>Disease presentation and histology</th>
<th>Differential at initial presentation</th>
<th>Array prediction and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>P01328: 52-y-old female, no previous history. Extensive abdominal tumor. Adenocarcinoma.</td>
<td>Ovary, gastric, and breast</td>
<td>Breast (100). Left supraclavicular fossa and axillary nodes developed within 2 mo of chemotherapy.</td>
</tr>
<tr>
<td>P01405: 66-y-old male nonsmoker, no previous history. Paraaortic lymphadenopathy and bone metastases. Clear cell epithelioid tumor.</td>
<td>Pathology review favored sarcomatoid renal cell cancer; but renal CT and MRI normal. Pathologist thought that morphology strongly suggested nonovarian origin (e.g., gastric, colorectal, pancreas, or lung). Clinical picture consistent with ovarian cancer.</td>
<td>Renal (88).</td>
</tr>
</tbody>
</table>

**High confidence 11/13 cases**
Mutation profiling by targeted pull down

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

Patients

Pathogenic mutations

Low cellularity?

TP53

SNV
INDEL
LOSS
Homzygous Del.
GAIN
High Gains

○ Cosmic
∆ Stop
★ Essential Splice Site

APC
HPF1
AXIN1
CDH1
GNAS
CCND1
ABL1
RB1
CARD11
MYCL1
CCNE1
TP53
TNFAIP3
ARID1A
IDH1
SETD2
TET2
MLL3
WT1
ASXL1
ATRX
DNMT3A
PDGDM
SMARCA4
EP300
BAX
CREBBP
RET
BRCA2
BRCA1
BAP1
PTCH1
STK11
NOTCH1
FBXW7
NOTCH1
GATA2
PLK1
TSC2
AKT1
TSHR
CSF1R
EGFR
MET
FGFR3
VHL
KRAS
MAD2L1
NF1
MAP2K1
MPL
JAK2
JAK1
FOXL2
SMAD4
IKZF1
RUNX1
AR
<table>
<thead>
<tr>
<th>Category 1</th>
<th>Actionable lesions</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1005</td>
<td>PIK3CA p.E545K</td>
<td>PIK3CA/AKT/mTORi (eg PX866 or temsirolimus)</td>
</tr>
<tr>
<td>1698</td>
<td>BRCA1 Homozygous deletion</td>
<td>PARPi (e.g. olaparib)</td>
</tr>
<tr>
<td>1382</td>
<td>KRAS p.G12C</td>
<td>MEKi (e.g. selumetinib)</td>
</tr>
<tr>
<td>8593</td>
<td>KRAS p.G12C</td>
<td>MEKi</td>
</tr>
<tr>
<td>2864</td>
<td>PTCH1 FS</td>
<td>SMOi (e.g. vismodegib)</td>
</tr>
<tr>
<td>Category 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>168</td>
<td>IDH1 p.R132L</td>
<td>IDH1i (e.g. AGI-5198)</td>
</tr>
<tr>
<td>563</td>
<td>AKT1 p.E17K</td>
<td>AKTi (e.g. SC66)</td>
</tr>
<tr>
<td>Category 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1478</td>
<td>CCND1 HLG</td>
<td>CDK4/CDK6i (e.g. palbociclib)</td>
</tr>
<tr>
<td>1184</td>
<td>PIK3CA p.E81K (VUS)</td>
<td>PIK3CA/AKT/mTORi</td>
</tr>
<tr>
<td>1005</td>
<td>JAK2 High level CN-gain</td>
<td>JAKi (e.g. ruxolitinib)</td>
</tr>
<tr>
<td>91</td>
<td>PIK3CA p.E81K (VUS)</td>
<td>PIK3CA/AKT/mTORi</td>
</tr>
<tr>
<td>3461</td>
<td>FGFR3 p.T742I(VUS)</td>
<td>FGFRi (e.g. ponatinib)</td>
</tr>
<tr>
<td>3282</td>
<td>MET p.R400S (VUS)</td>
<td>METi (e.g. crizotinib)</td>
</tr>
</tbody>
</table>

- Clinical
- Pre-clinical
- Suggestive data
Mutation signatures provides clues to disease aetiology
• 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
RECUPERATE: can REALTIME molecular profiling in CARCINOMA of UNKNOWN PRIMARY IMPROVE TREATMENT OUTCOMES?

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

<table>
<thead>
<tr>
<th>Tissue of origin test</th>
<th>Mutational profiling for actionable mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
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
Presentation with metastatic disease

Initial clinical and pathological evaluation

Primary site not found

Additional directed clinical/pathological evaluation

Primary site not found

Favourable CUP subset not identified

One primary site not suspected

Empiric treatment

One primary site suspected but not confirmed

Site-specific treatment

Primary site found anatomicallly

Site-specific therapy

Primary site found anatomicallly

Favourable CUP subset

Specific treatment for subset

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.
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 (<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