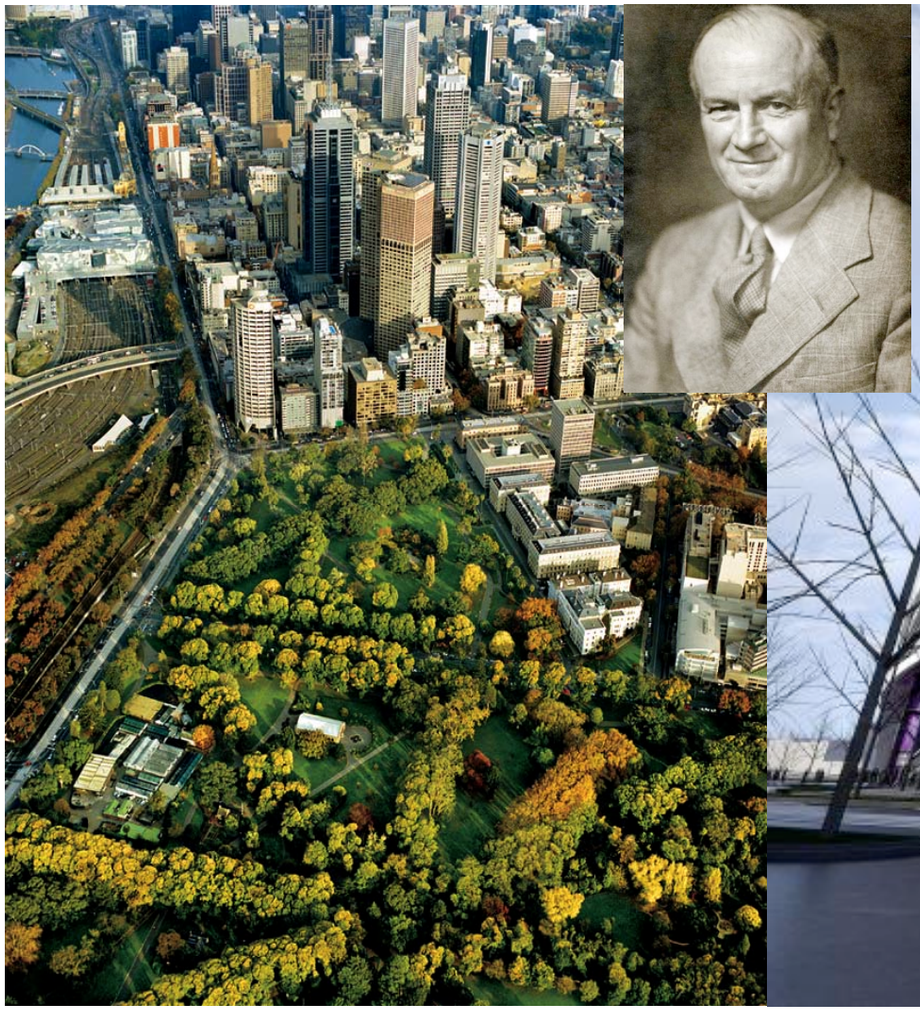
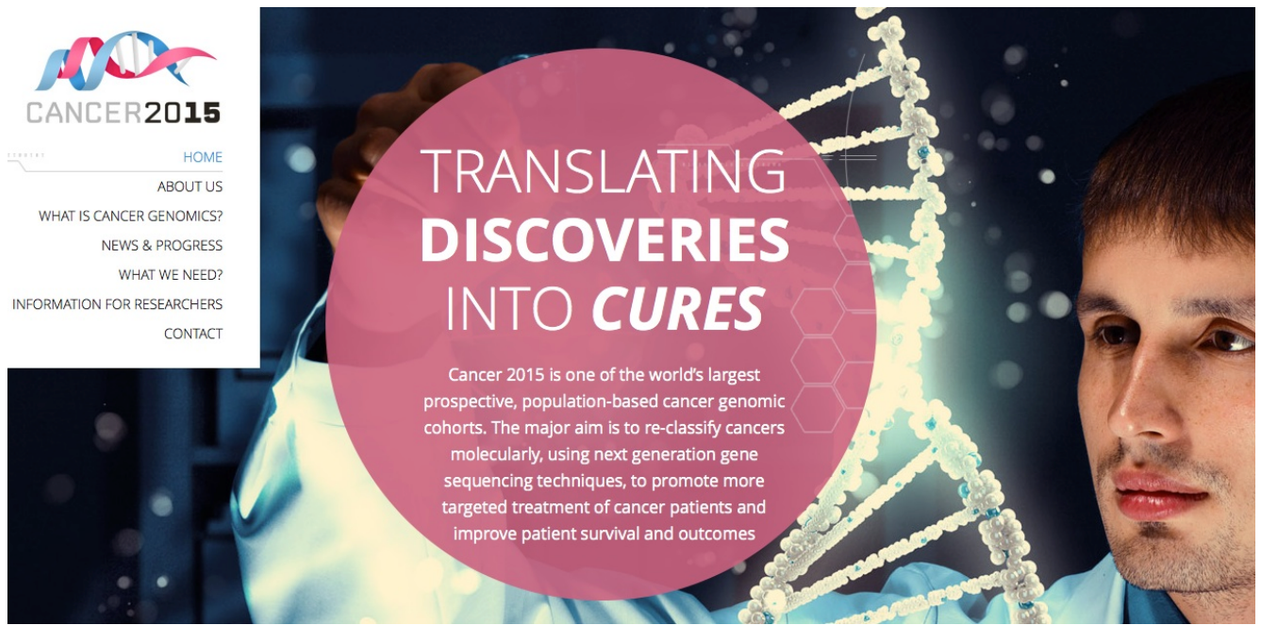
Global Genomic Medicine Collaborative (G2MC): Australia country update: **Cancer2015**



Stephen B Fox
Department of Pathology
Peter MacCallum Cancer Centre
Melbourne, Australia

Cancer 2015

- whole of health system "Framingham" type cancer cohort on a scale to impact Victorian health outcomes
- prospective collection of newly diagnosed cancer patients
- Total cancer journey from diagnosis, **agnostic** to cancer type, age, gender, stage, locus of care
  - epidemiological and QoL
  - clinical information, treatment and follow up
  - conventional and molecular pathology
  - clinical trials
- Cost of cancer to state, federal, insurers, patients of personalised medicine and targeted therapies
  - linkages to Cancer Registry, State and Federal databases
- **policy**



www.cancer2015.org

Cancer 2015

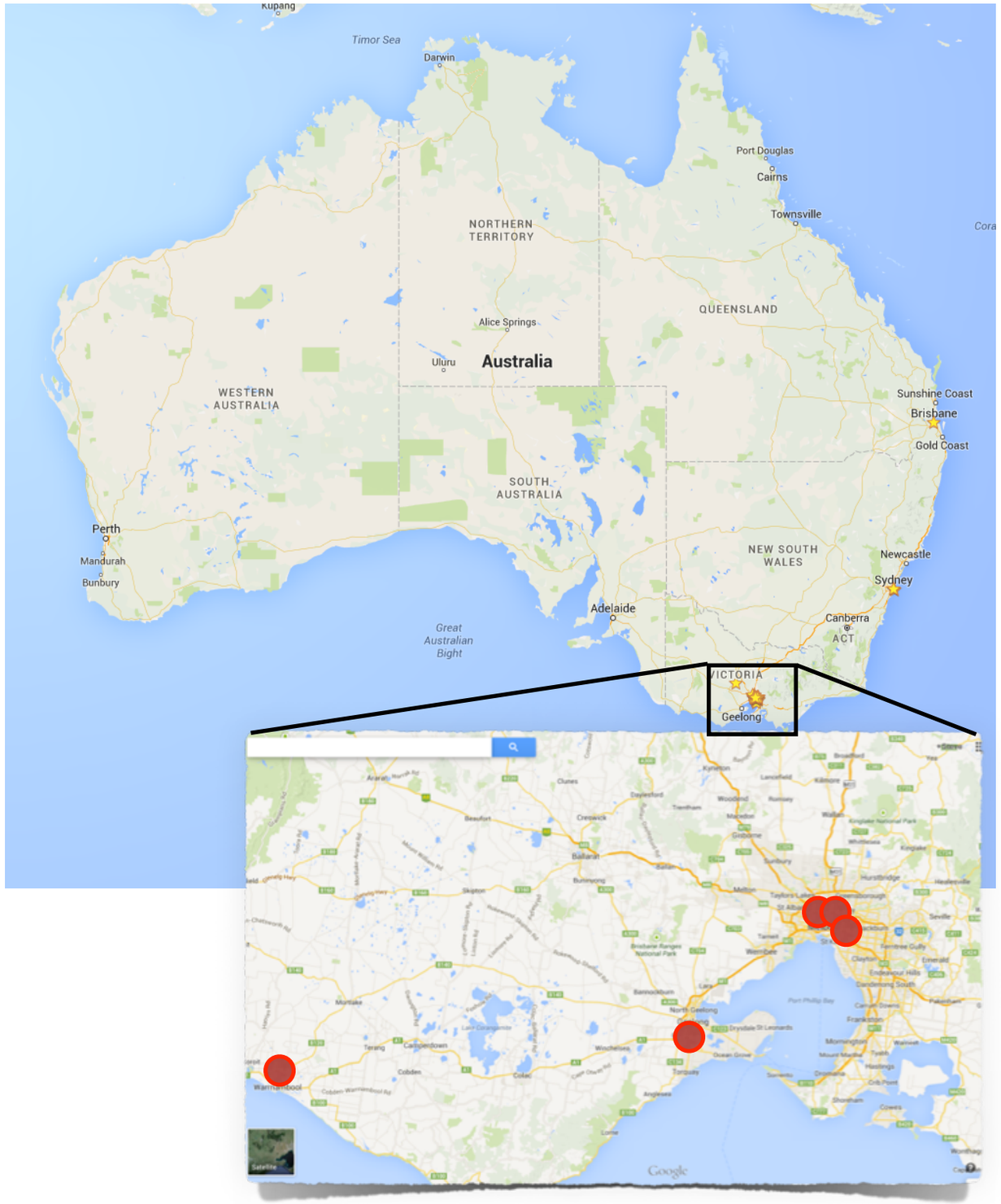
- **Primary Aims**
  - map variation in cancer care and outcomes
  - assess quality of life
  - measure health costs and societal value of cancer treatment
  - map the true prevalence of actionable mutations agnostic to cancer type
- **Secondary Aims**
  - *Facilitate the integration of molecular pathology into routine cancer care*
  - Provide a large-scale longitudinal cancer cohort for research

Overview

Phase 0 6 months 2011	Phase 1 24 months 2012/13	Phase 2 36 months 2014/16
System design	Feasibility	Implementation
•Governance •Architecture •Ethics •Databases •Select sites	•Recruit 1000 •test federal/ state linkages •molecular pathology	•Recruit 3000 •articulate research vision •Real time reporting

Recruiting sites: Cancer 2015

- Peter Mac
- Barwon Health
  - Geelong
  - Warrnambool
- RMH
- Cabrini



www.cancer2015.org

Molecular diagnostics

Research test ⟶‖⟶ **Diagnostics**

Laboratory Challenges

- capital
- accreditation
  - laboratory
  - scientific and clinical staff
  - quality assurance
- bioinformatics
- clinical informatics
- input material (FFPE)
- TATs

Scope of Accreditation NATA

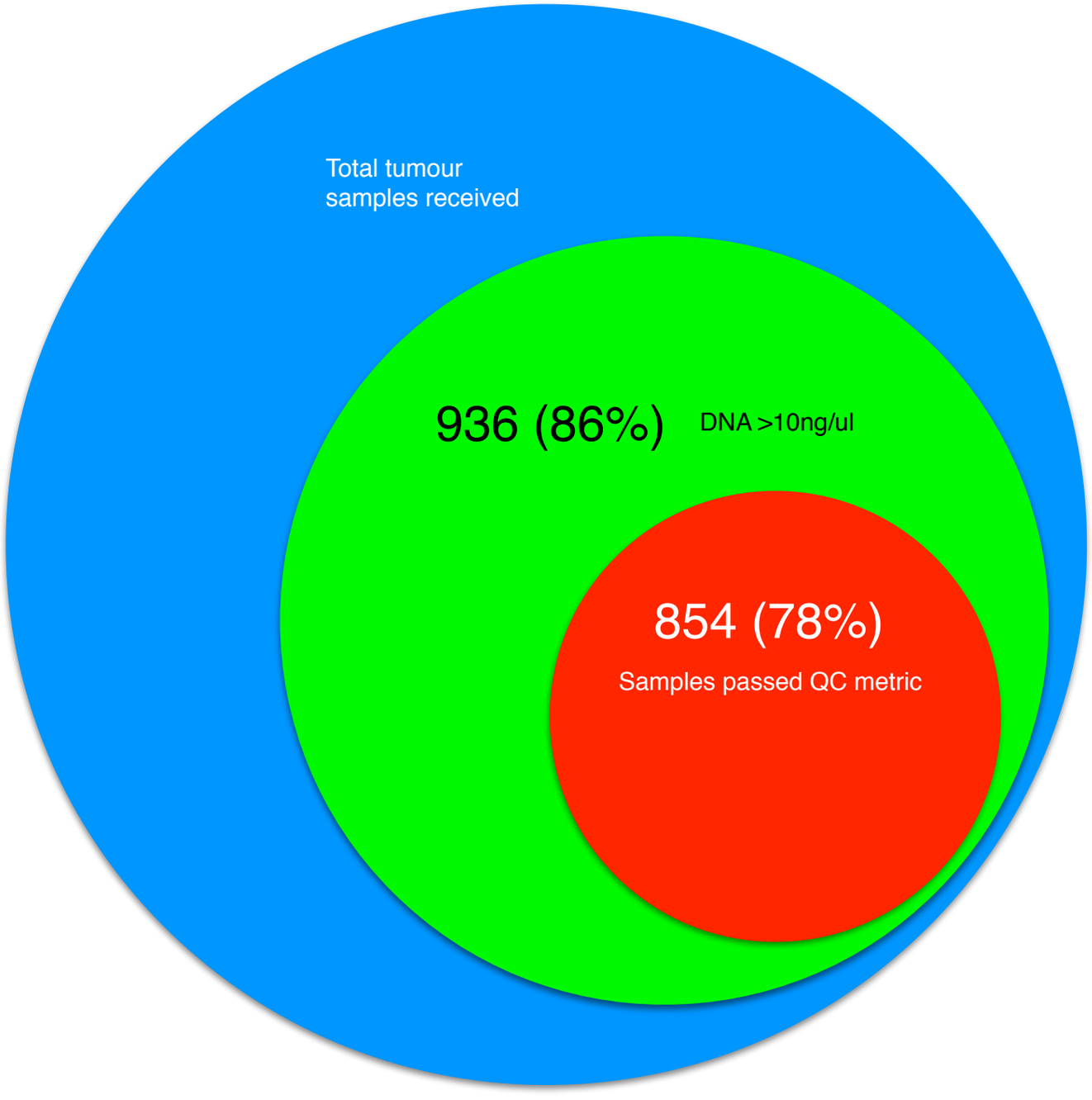
ACCREDITATION NO: 2465

Peter MacCallum Cancer Centre

Department of Pathology
Smorgon Family Building
St Andrew's Place
EAST MELBOURNE VIC 3002

10.75 Molecular genetics
.16 Predictive genetic testing
.17 Pharmacogenetic testing
.18 Genetic testing for mosaic gene variants (cancer and somatic mosaicism)
.20 Assay for a defined mutation or polymorphism
.23 Next generation sequencing
Targeted gene panel excluding exome and genome sequencing studies

Molecular pathology



Br J Cancer 2015

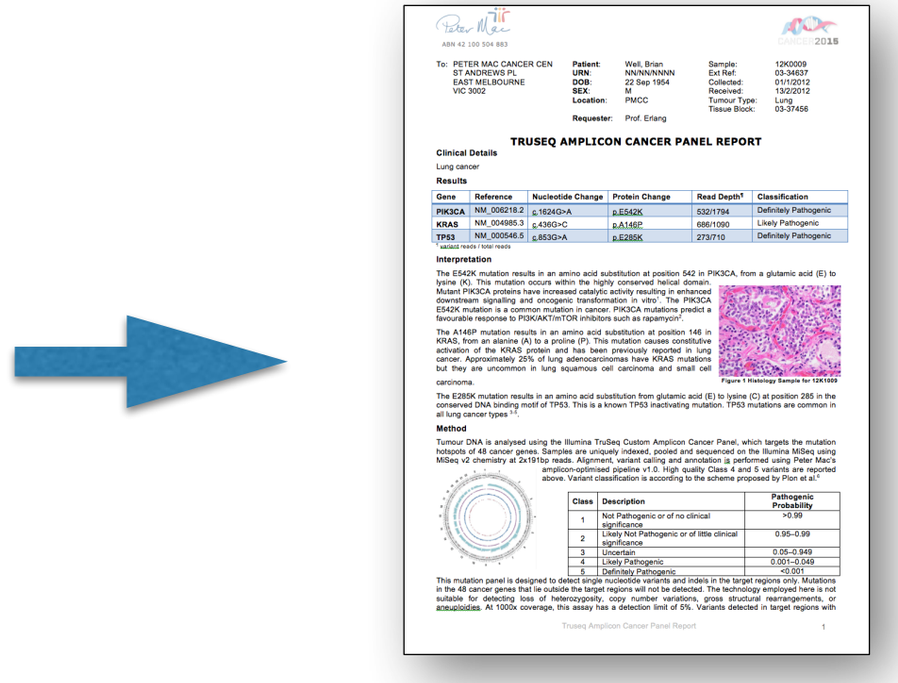
- ABL1
- AKT1
- ALK
- APC
- ATM
- BRAF
- CDH1
- CDKN2A
- CSF1R
- CTNNB1
- EGFR
- ERBB2
- ERBB4
- FBXW7
- FGFR1
- FGFR2
- FGFR3
- FLT3
- GNA11
- GNAQ
- GNAS
- HNF1A
- HRAS
- IDH1
- JAK2
- JAK3
- KDR
- KIT
- KRAS
- MET
- MLH1
- MPL1
- NOTCH1
- NPM1
- NRAS
- PDGFRA
- PIK3CA
- PTEN
- PTPN11
- RB1
- RET
- SMAD4
- SMARCB1
- SMO
- SRC
- STK11
- TP53
- VHL

Scope of Accreditation NATA

ACCREDITATION NO: 2465

Peter MacCallum Cancer Centre

Department of Pathology
Smorgon Family Building
St Andrew's Place
EAST MELBOURNE VIC 3002



ABN 42 100 504 883

To: PETER MAC CANCER CEN
ST ANDREWS PL
EAST MELBOURNE
VIC 3002

Patient: Well, Brian
URN: NN/NN/NNNN
DOB: 22 Sep 1954
SEX: M
Location: PMCC
Requester: Prof. Erlang

Sample: 12K0009
Ext Ref: 03-34637
Collected: 01/1/2012
Received: 13/2/2012
Tumour Type: Lung
Tissue Block: 03-37456

TRUSEQ AMPLICON CANCER PANEL REPORT

Clinical Details

Lung cancer

Results

Gene	Reference	Nucleotide Change	Protein Change	Read Depth†	Classification
PIK3CA	NM_006218.2	c.1624G>A	p.E542K	532/1794	Definitely Pathogenic
KRAS	NM_004985.3	c.436G>C	p.A146P	686/1090	Likely Pathogenic
TP53	NM_000546.5	c.853G>A	p.E285K	273/710	Definitely Pathogenic

† variant reads / total reads

Interpretation

The E542K mutation results in an amino acid substitution at position 542 in PIK3CA, from a glutamic acid (E) to lysine (K). This mutation occurs within the highly conserved helical domain. Mutant PIK3CA proteins have increased catalytic activity resulting in enhanced downstream signalling and oncogenic transformation in vitro[1]. The PIK3CA E542K mutation is a common mutation in cancer. PIK3CA mutations predict a favourable response to PI3K/AKT/mTOR inhibitors such as rapamycin[2].

The A146P mutation results in an amino acid substitution at position 146 in KRAS, from an alanine (A) to a proline (P). This mutation causes constitutive activation of the KRAS protein and has been previously reported in lung cancer. Approximately 25% of lung adenocarcinomas have KRAS mutations but they are uncommon in lung squamous cell carcinoma and small cell carcinoma.

Figure 1 Histology Sample for 12K1009

The E285K mutation results in an amino acid substitution from glutamic acid (E) to lysine (C) at position 285 in the conserved DNA binding motif of TP53. This is a known TP53 inactivating mutation. TP53 mutations are common in all lung cancer types[3,4].

Method

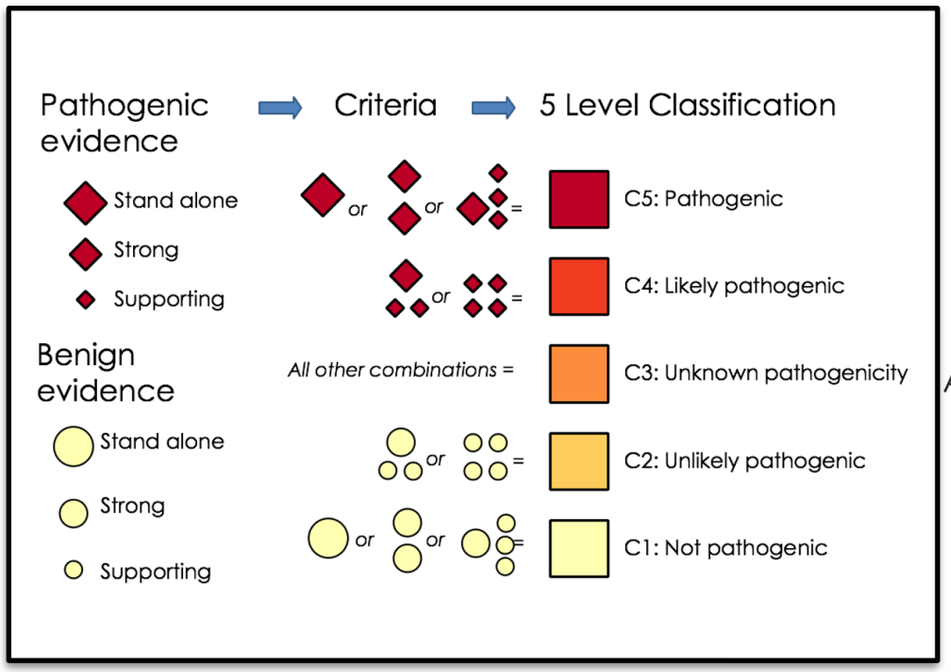
Tumour DNA is analysed using the Illumina TruSeq Custom Amplicon Cancer Panel, which targets the mutation hotspots of 48 cancer genes. Samples are uniquely indexed, pooled and sequenced on the Illumina MiSeq using MiSeq v2 chemistry at 2x191bp reads. Alignment, variant calling and annotation is performed using Peter Mac's amplicon-optimised pipeline v1.0. High quality Class 4 and 5 variants are reported above. Variant classification is according to the scheme proposed by Plon et al.[5]

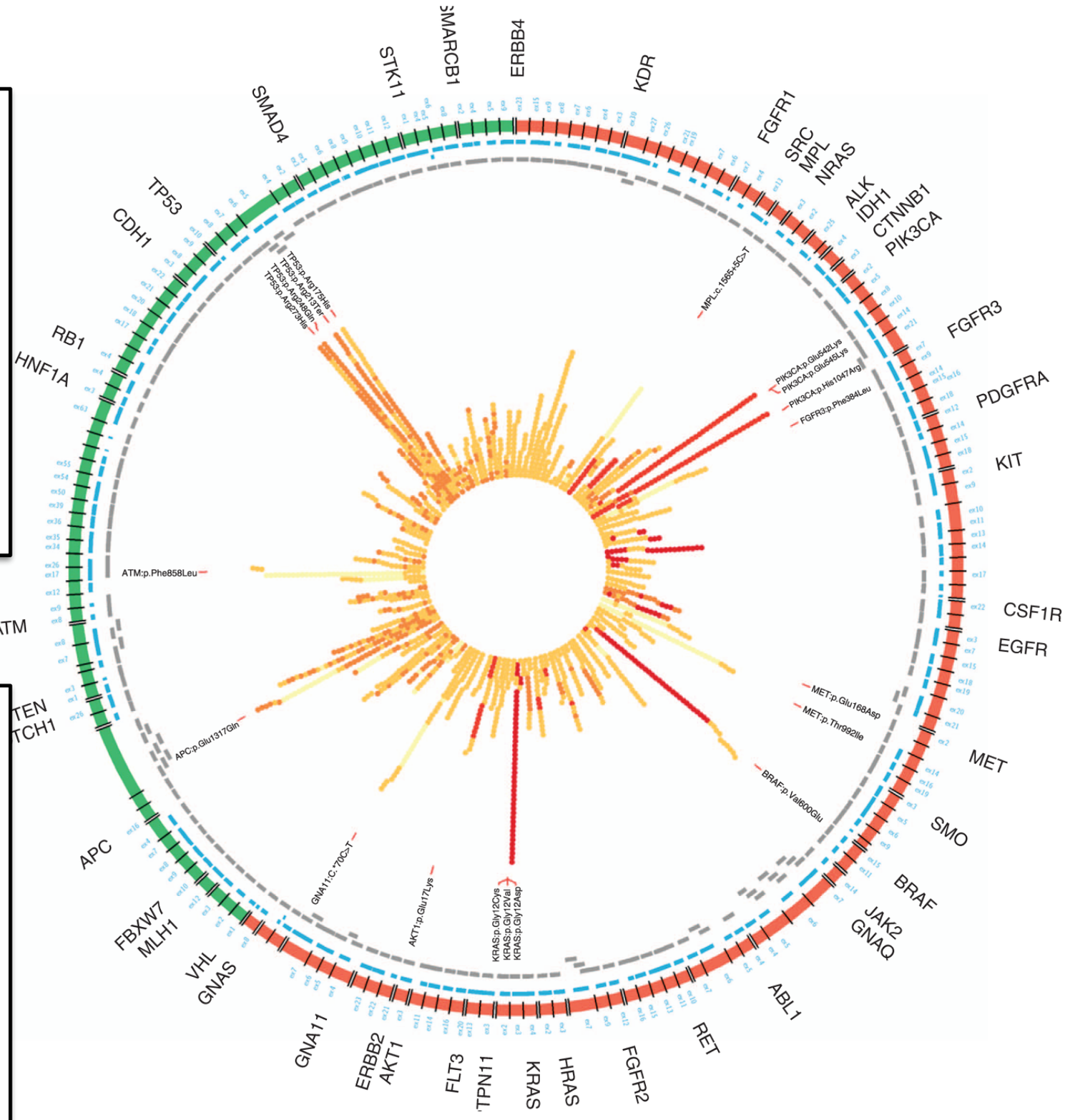
Class	Description	Pathogenic Probability
1	Not Pathogenic or of no clinical significance	>0.99
2	Likely Not Pathogenic or of little clinical significance	0.95–0.99
3	Uncertain	0.05–0.949
4	Likely Pathogenic	0.001–0.049
5	Definitely Pathogenic	<0.001

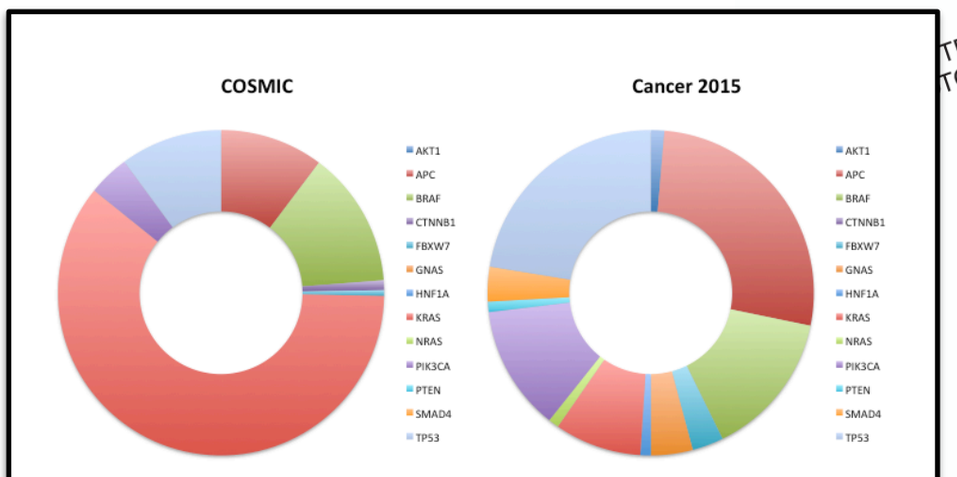
This mutation panel is designed to detect single nucleotide variants and indels in the target regions only. Mutations in the 48 cancer genes that lie outside the target regions will not be detected. The technology employed here is not suitable for detecting loss of heterozygosity, copy number variations, gross structural rearrangements, or aneuploidies. At 1000x coverage, this assay has a detection limit of 5%. Variants detected in target regions with

Truseq Amplicon Cancer Panel Report 1

Landscape of actionable mutations



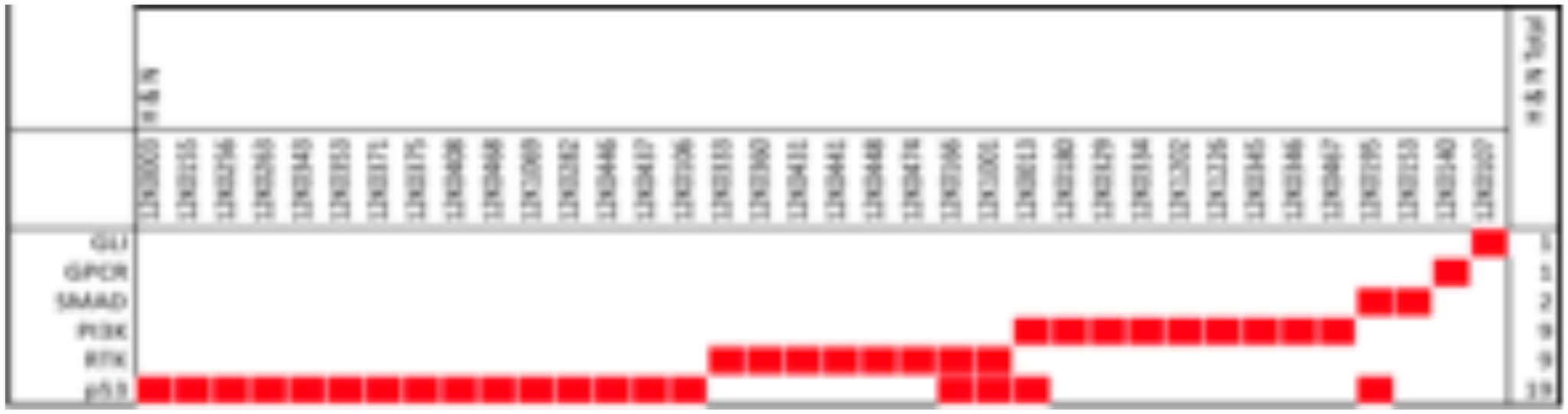


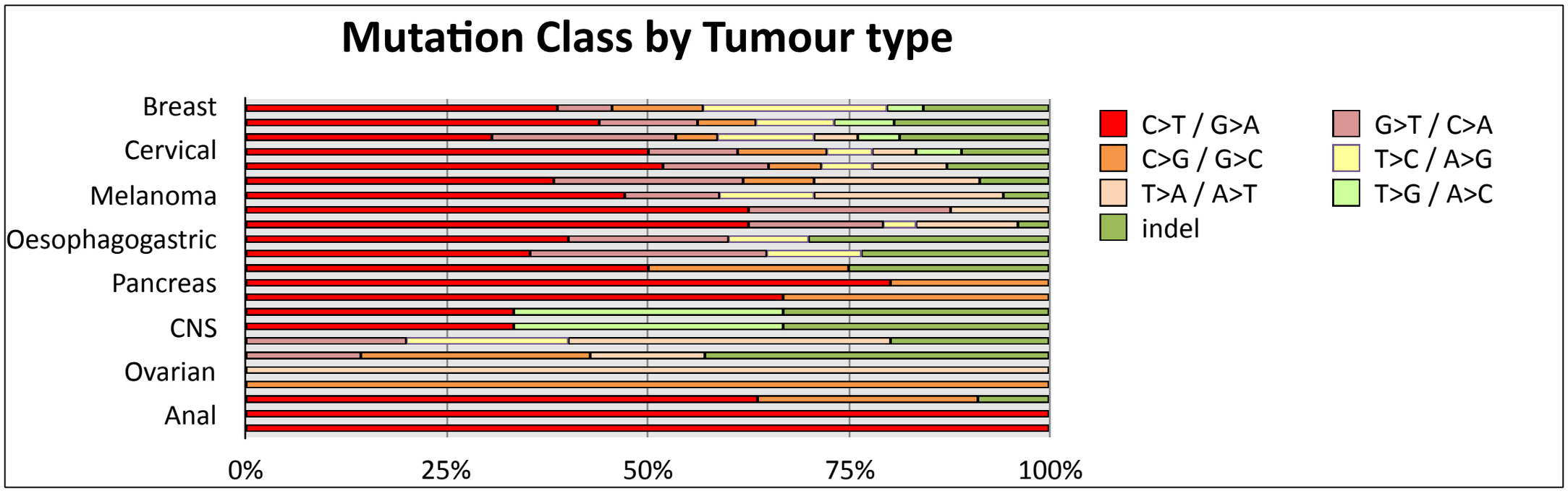


Melanoma 38%

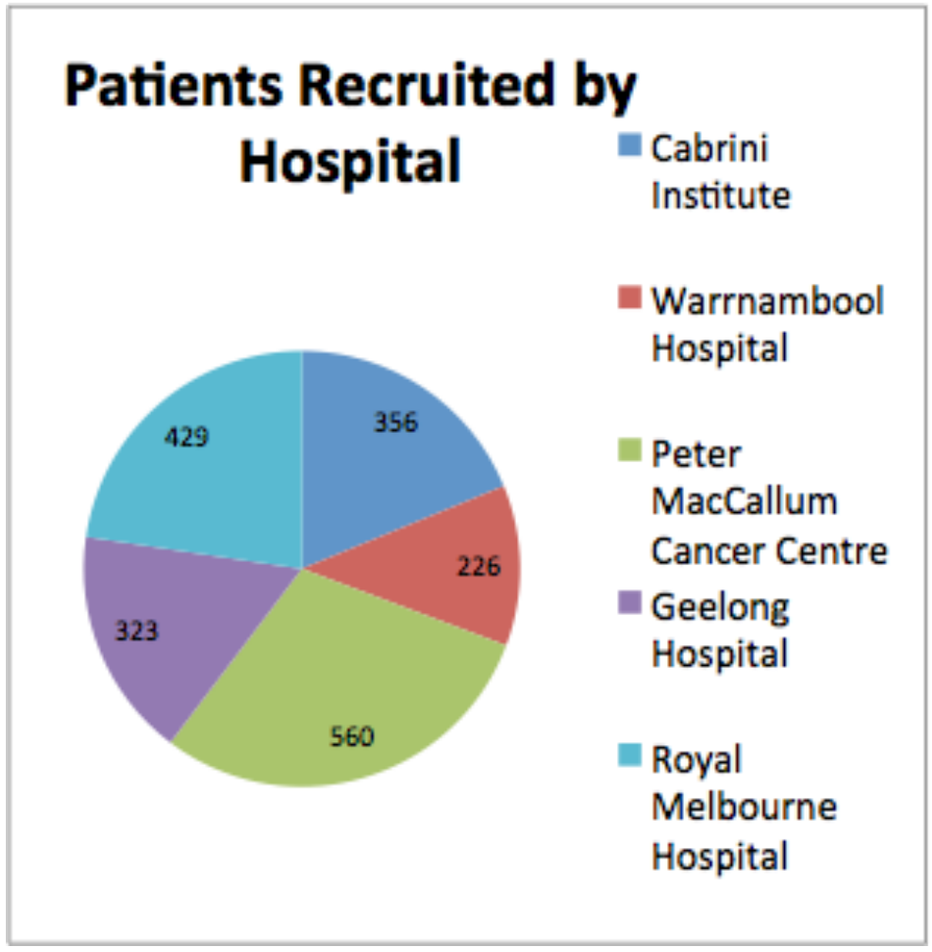
BJC 2015

New pathways for investigation

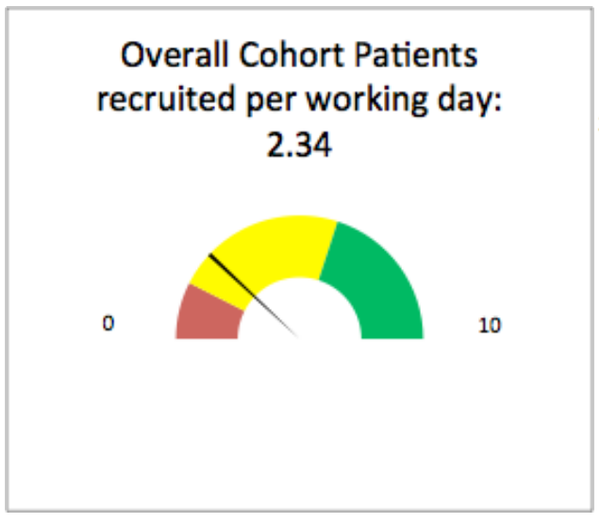


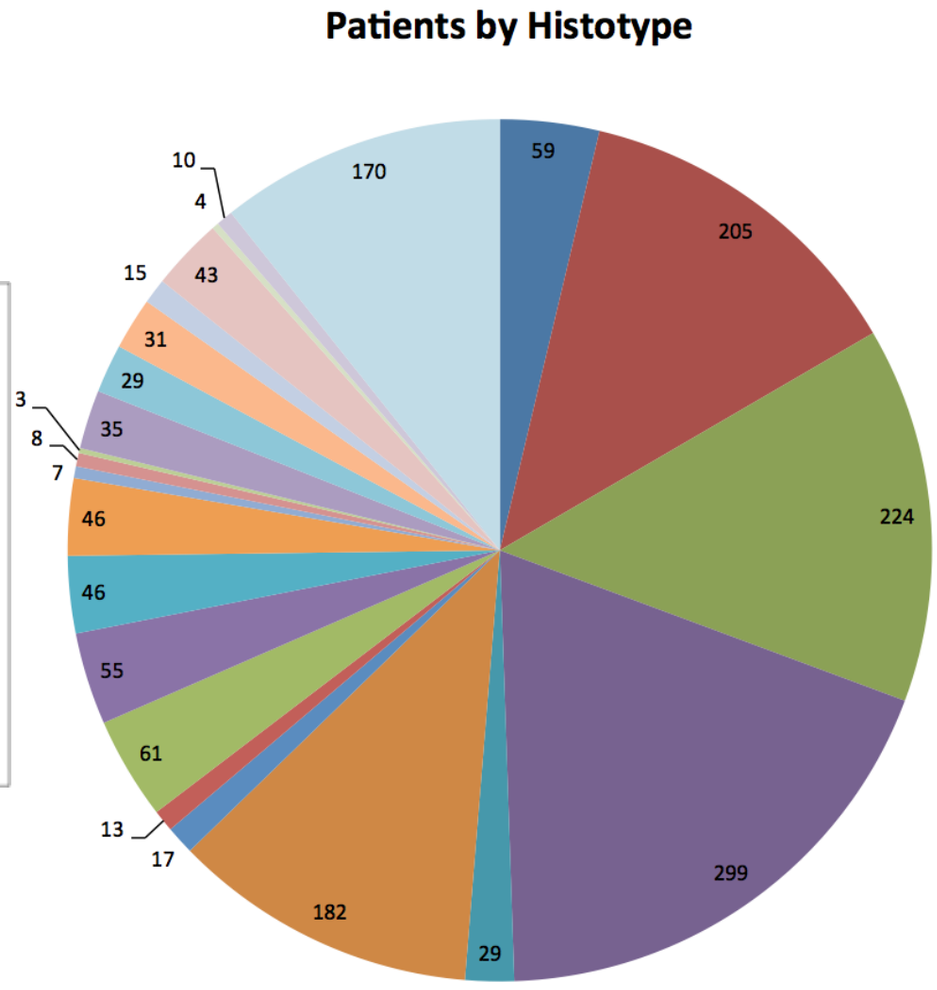


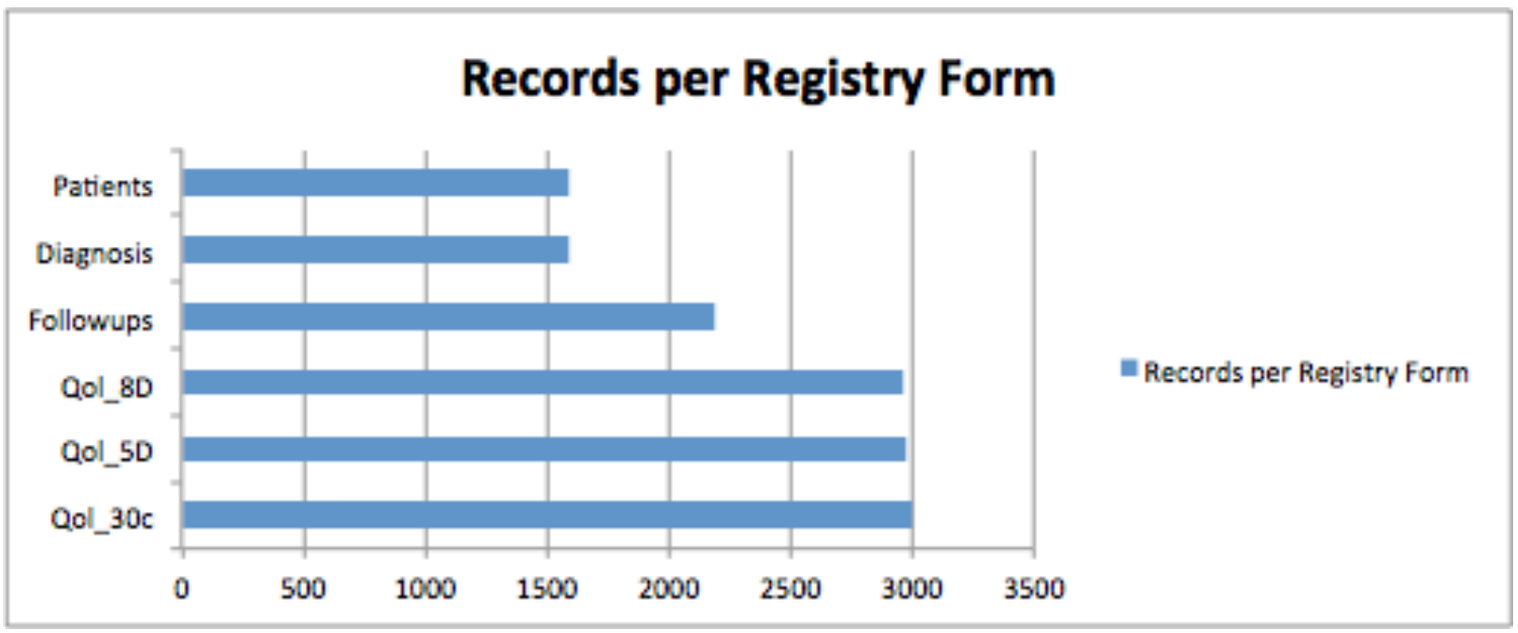
Cancer 2015 snapshot



n=2290

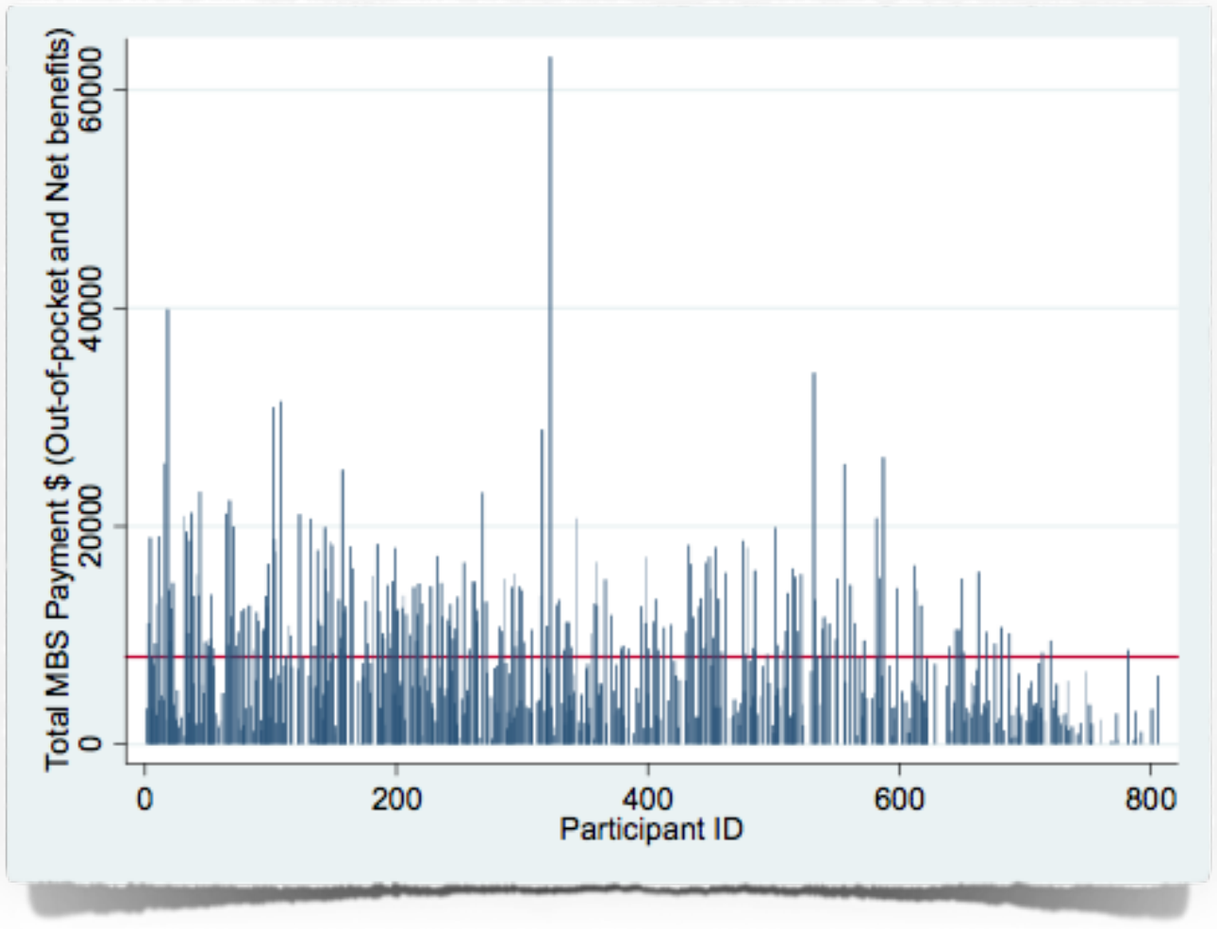






www.cancer2015.org

Health economics
MBS data (N=523, first linkage)



Total Per Participant MBS Cost
(Out-of-pocket and Net benefit)
Mean $7997
Min: $31.20
Max: $62,992

Total Per Participant MBS Cost
(Out-of-pocket cost only)
Mean: $1,675
Min: $0.00
Max: $24,303

Total Per Participant MBS Cost
(Net benefit cost only)
Mean: $6,322
Min: $31.20
Max: $38,688

Cancer 2015 investigators

Chief Investigators

Joe Sambrook

Michael Wright

David Thomas

Investigators

University of Melbourne: Paul Waring, Graham Taylor, Mark Jenkins, Melissa Southey

WEHI: Melanie Bahlo, Tony Papenfus

RCH: Paul Ekert, Francois Mechinaud, Richard Sullivan

RMH: Lara Lipton

RWH: Orla McNally, Michael Quinn

Cabrini: Gary Richardson

St Vincent's Hospital: Ray Snyder

Barwon Health: David Ashley

Peter Mac: David Thomas, Paul James

Alfred Hospital: Andrew Wei

Austin: Jonathan Cebon, Tom John, Alex Dobrovic

Monash: Neil Watkins, John McNeil, Paula Lorgelly, Gail Risbridger

Bendigo: Rob Blum

Cancer 2015 Staff

PeterMac

Kate Crough
Kristy Barnes-Cullen
Jess McDonald
Heather Thorne (KConFab)
KConFab staff

Mandy Ballinger /Kim Riddell/Jasmine Marr (ISKS)
Ann Officer/Renee Webb (Lung Cohort)
Anne Fennessy/Sonia Mailer (MMP)
Andrew Fellowes/Anthony Bell (MolP))

Cabrini Health

Laura Zamurs
Kate Hurford
Kate Richards
Barbara Scher

Barwon Health

Judi Broad
Lea-Anne Harrison
Carolyn Wielens
Anne Woollett
Sandra Robinson
Marcelle Hennig

Melbourne Health

Stefanie Hartley
Lidia Vecia (Uro-Onc)
Pat Bugeja (Uro-Onc)
Christopher Bates

DBase Development Team

Suvarna Joshi
Mark Lucas
David Morrison/Ravi Ravindran
Chris Reid (Monash CIDMU)
Julie Johns (BioGrid)

CANCER2015

An Australian Government Initiative

National Collaborative Research Infrastructure Strategy

Victorian Cancer Agency

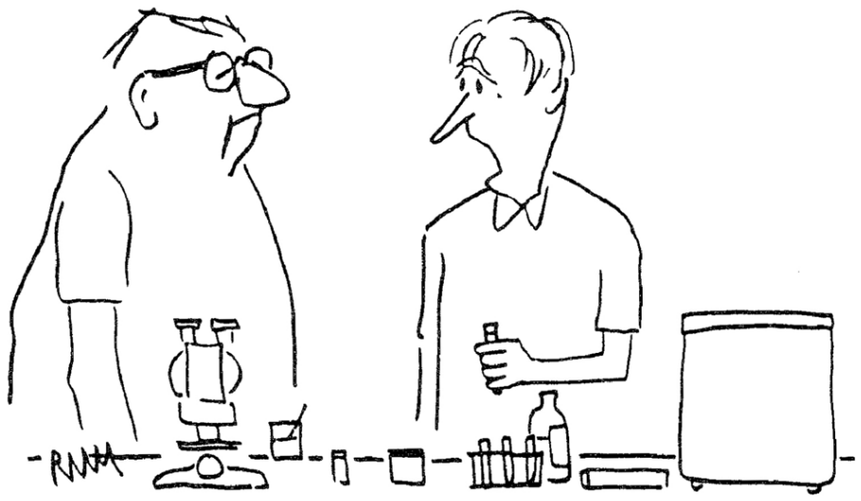
Linking research and patient care

Funded by The VCA

Session questions: lab perspective

- **Primary activities undertaken/accomplishments**
  - reconfiguration of diagnostic cancer lab to NGS-based somatic and germline testing from hardware refresh to workforce including education and training
  - implementation of automated clinical cancer diagnostic and IT systems to process samples from sequencer through to reporting
  - implementation of decision support tools to aid the curation of clinical diagnostic samples
  - competency in diagnostic NGS with NATA (ISO) accreditation
  - integration with research genomics and bioinformatics, close clinical collaborations
  - establishment of a Molecular Tumour Board
- **Key challenges**
  - funding! capital, personnel etc
  - bioinformatic support for diagnostic assay/pipeline development, software engineers
  - clinical grade databases, immaturity of bioinformatics software, unskilled diagnostic workforce
  - staccato supply chain from vendors that does not support diagnostic labs
  - resource burden of cycle of development whilst still supporting clinical service
- **Opportunities**
  - annotated databases, cancer pathology issues

Questions



"I've narrowed the diagnosis down to 16 possibilities."

Data and informatics issues

	Mitigation	Suggested guidelines
Most variant databases were created for research, not clinical use, and have unknown error rates and varying formats and semantics Laboratories are using databases without understanding their limitations Accessing the data in a useable way requires data manipulation skills beyond those of most people working in laboratories	A review of variant databases that are being used for clinical oncology is urgently needed, together with a certification process for individual variants Global initiatives such as GA4GH and ClinGen[2] are standardising variant databases Data federation application programming interfaces are needed to standardise access to clinical variation data	Clinical variants should use Human Genome Variation Society[1] nomenclature including genome build and transcript Databases maintain a uniform application programming interfaces to retrieve clinical variants Clinical variants are annotated with phenotype and pathogenicity conforming to standard ontologies Clinical variants are annotated with a standardised certification of confidence or trust
Data used for clinical diagnostics must be timely Many laboratories are unaware of the timeliness of database variants and might be relying on old or superseded data	Online clinical data federation or periodic refresh ensures the latest knowledge is used in diagnostic reports Diagnostic reporting systems should notify clinicians of variant pathogenicity changes in either local or external variants	Underlying data sources should be indicated in clinical reports together with version or access date, or both
Sharing of variant data characterising the function of rare variants is lacking	The GA4GH Matchmaker Exchange initiative targets this need along with initiatives to aggregate well curated datasets—eg, ClinGen[2]	Reported variants should be uploaded to a database accessible by the public along with the phenotypes
Phenotype corresponding to a genotype is poorly captured at sample registration Phenotype information is not often associated with variants in databases	Standards for phenotype ontology need to be captured at sample registration by web page embeddable software The GA4GH and ClinGen working groups are addressing this issue	A uniform phenotype ontology (eg, Human Phenotype Ontology, International Statistical Classification of Diseases and Related Health Problems 10th Revision, and Systematized Nomenclature of Medicine) should be used to record a patient's phenotype before diagnostic analysis
The high turnover of technology is driving laboratories to create ad-hoc bioinformatic solutions without robust assay validation Generic pipelines are being used rather than those matched to the assay characteristics	The use of software engineering test methods needs to be applied to pipeline validation An accredited pipeline validation framework, independent of assay or bioinformatics, is needed urgently	Clinical pipelines should be independently validated by software engineering testing for the combined pipeline and assay
The biochemical focus of existing diagnostic assays is too restricted for the development of data-centric HTS assays	Laboratories need to outsource HTS diagnostics to suitably resourced institutions or build up an in-house team of bioinformatics and data manipulation specialists	Accreditation agencies need to expand to cover the information technology aspects of laboratory accreditation
Insufficient curation decision support has resulted in labour-intensive curation restricting sample processing capacity	The development of robust web applications is needed for a molecular diagnostic environment that must integrate global clinical quality knowledge-bases	Clinical variant curation needs to be accredited by national professional pathology organisations
Concordance is lacking between pipeline results from different laboratories[3,4]	Assays combined with their analytical software and data sources need to be standardised urgently Variants including copy number and structural variants should be represented uniformly	Pipeline analysis should be standardised and accredited by professional pathology organisations for common assays

Doig et al Lancet Oncol 2015