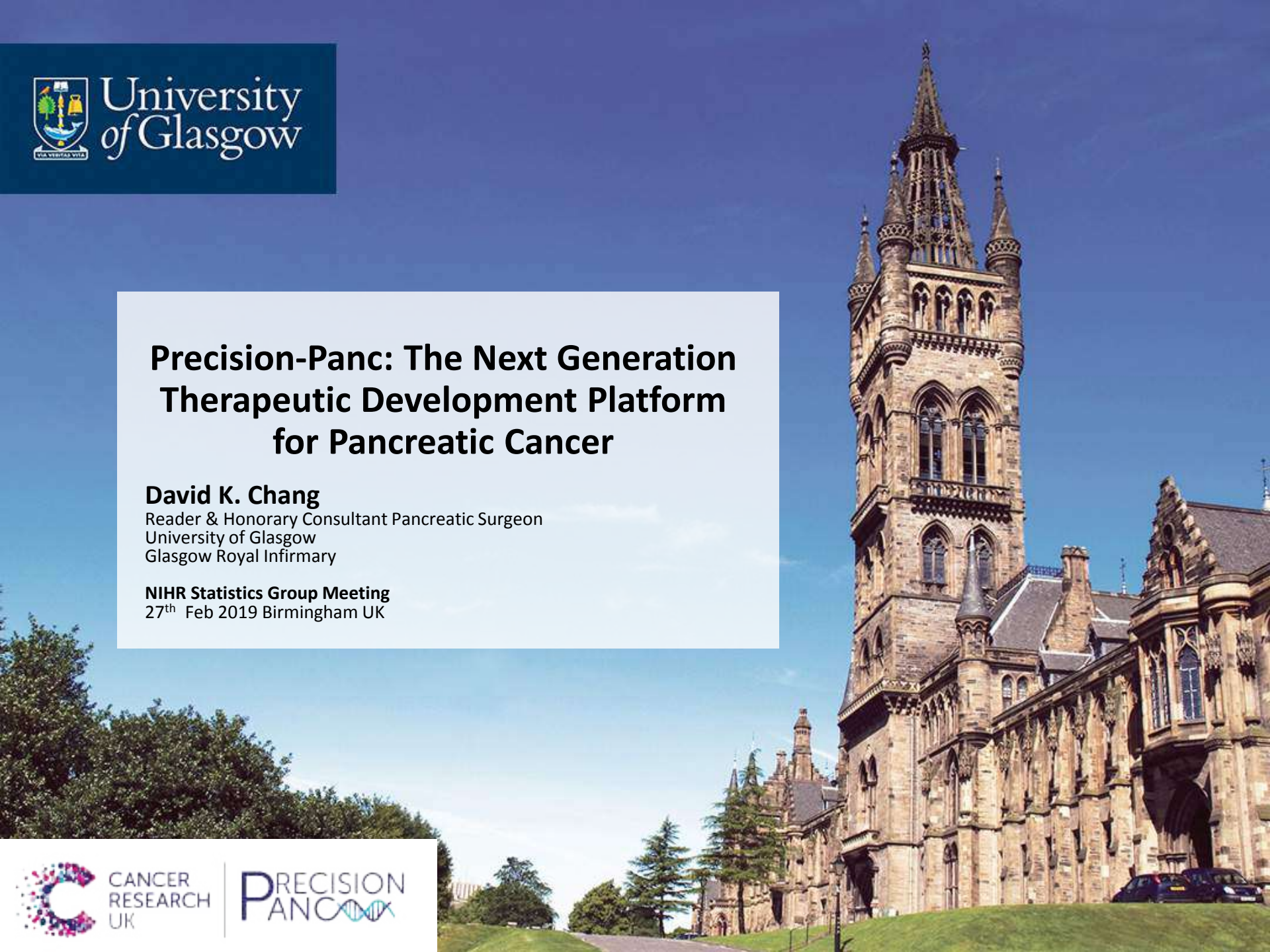


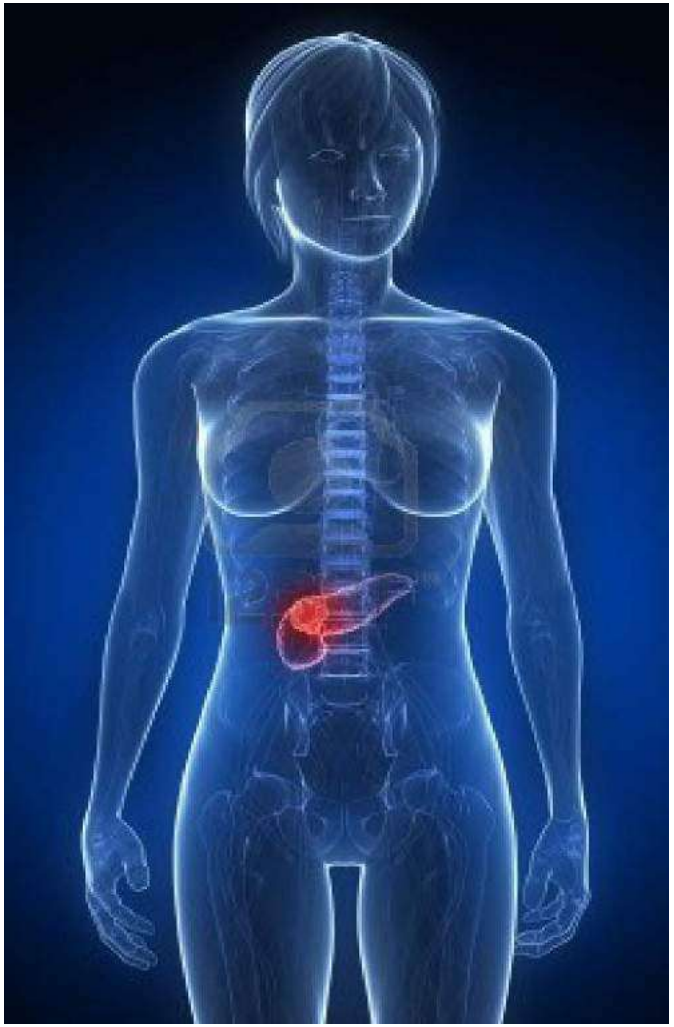
Precision-Panc: The Next Generation Therapeutic Development Platform for Pancreatic Cancer

David K. Chang
Reader & Honorary Consultant Pancreatic Surgeon
University of Glasgow
Glasgow Royal Infirmary

NIHR Statistics Group Meeting
27th Feb 2019 Birmingham UK

Pancreatic Cancer

- 3rd cause of cancer death (2nd within a decade)
- 5% alive at 5 years
- Average survival ~6 months
- 90% die within a year
- Surgery only cure (~20%)
- **Mortality not significantly changed for 50 years**
- Chemotherapy modestly effective – but some **significant responses in undefined subgroups**
- Majority metastatic – chemotherapy and targeted therapy. **However therapeutic development has been challenging**



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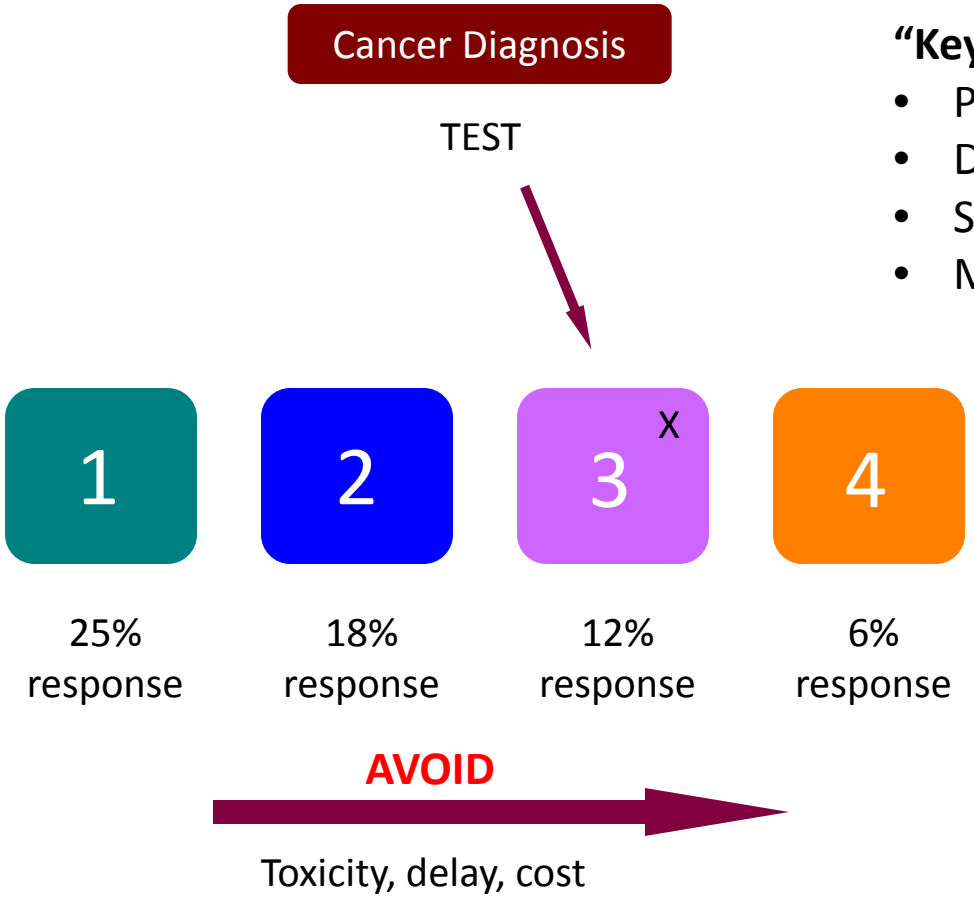
"Precision Medicine"

– Matching the Right Treatment to the Right Patient

- Cancer subtype responds to treatment 'X'



"Key Ingredients"

- Patients
- Drugs
- Selection biomarker
- Molecular assay

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Challenges of Therapeutic Developments in PDAC

- **Not enough patients**
  - relatively rare cancer, but high mortality
  - Rapid deterioration of PS
  - Need collaboration/consortium approach

- **No drugs made specifically for PDAC**
  - (Apart from PEGPH20)
  - Need to “repurpose” or “rescue”
  - Need to make PDAC “attractive” investment for pharma

- **No strong well validated biomarkers**
  - Needs better understanding of molecular pathology
  - Needs stronger pre-clinical evidence (clear line of sight)
  - Needs novel clinical trial design to seek signals

- **No molecular assay** made specifically for PDAC
  - (Apart from HA)
  - Need custom build

Transforming research and treatment approaches for Pancreatic Cancer

PRECISION-Panc

Improving outcomes through a dynamic research & development platform for Precision Medicine

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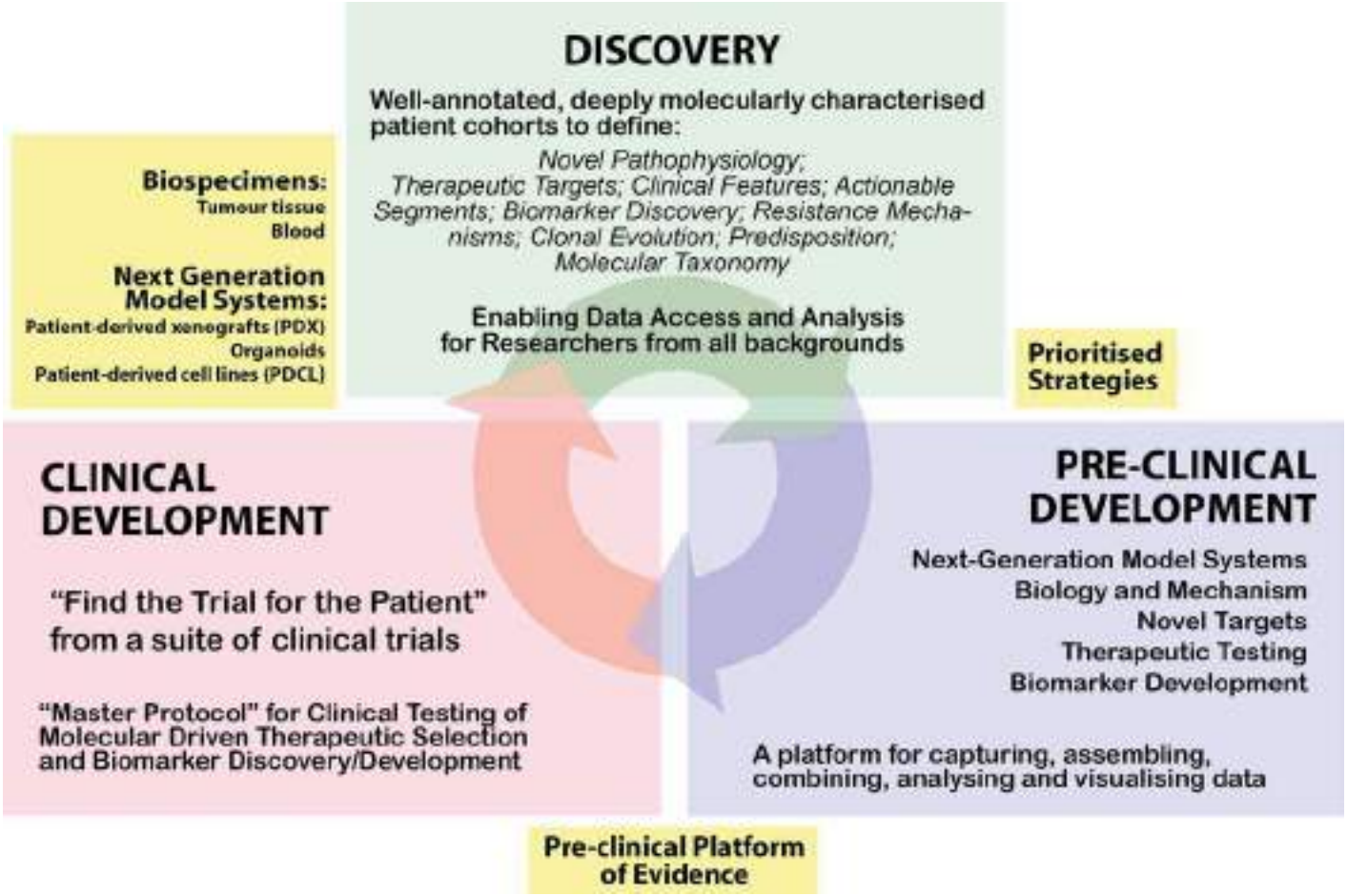
Precision-Panc UK (Global)

Dynamic therapeutic development platform taking advantage of a continuous loop of discovery, learning, refinement, and implementation



International Cancer Genome Consortium

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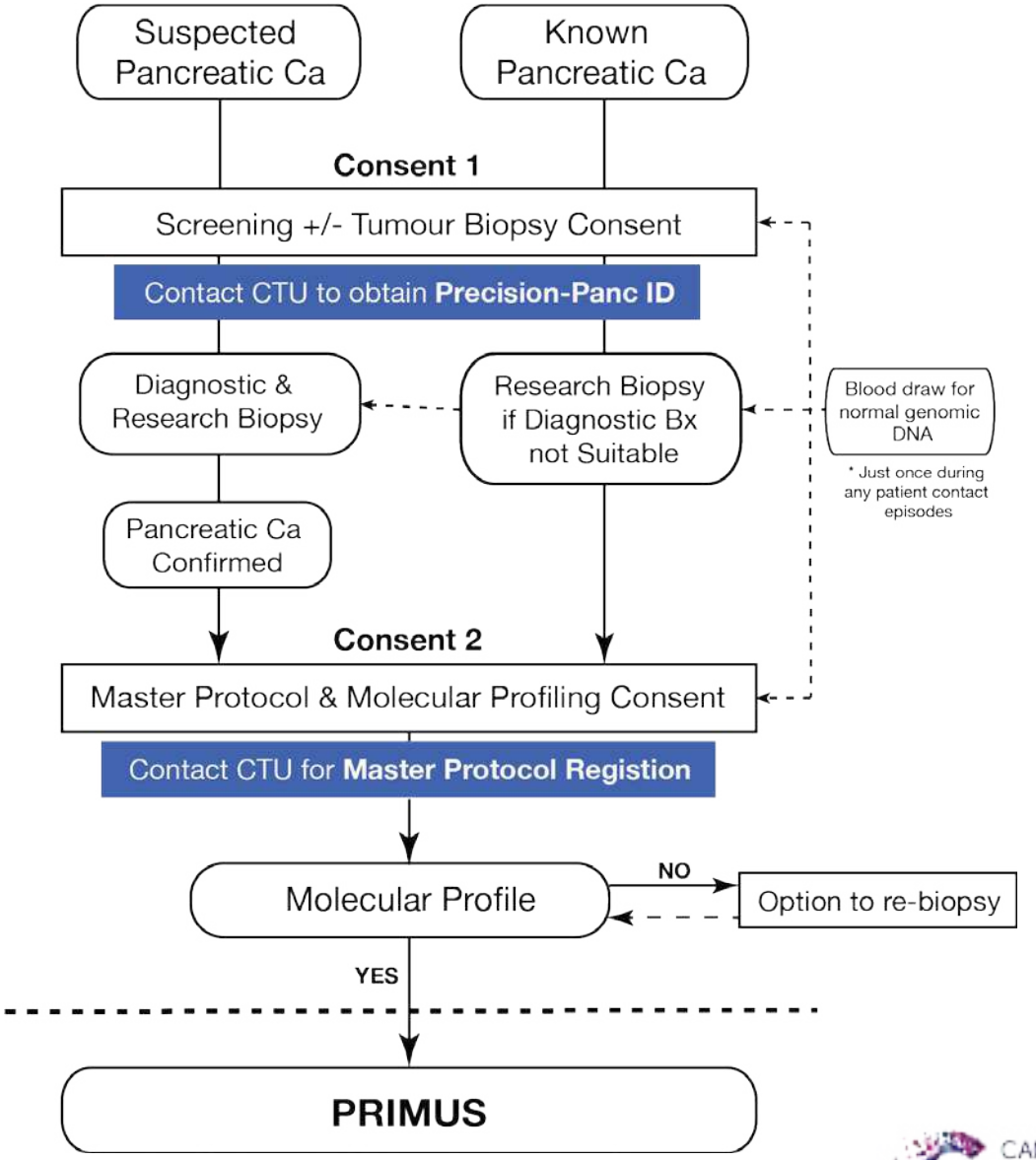
Accelerating Research in Genomic Oncology

Precision-Panc Master Protocol



Clinical CI: Juan Valle
Translational CI: David Chang

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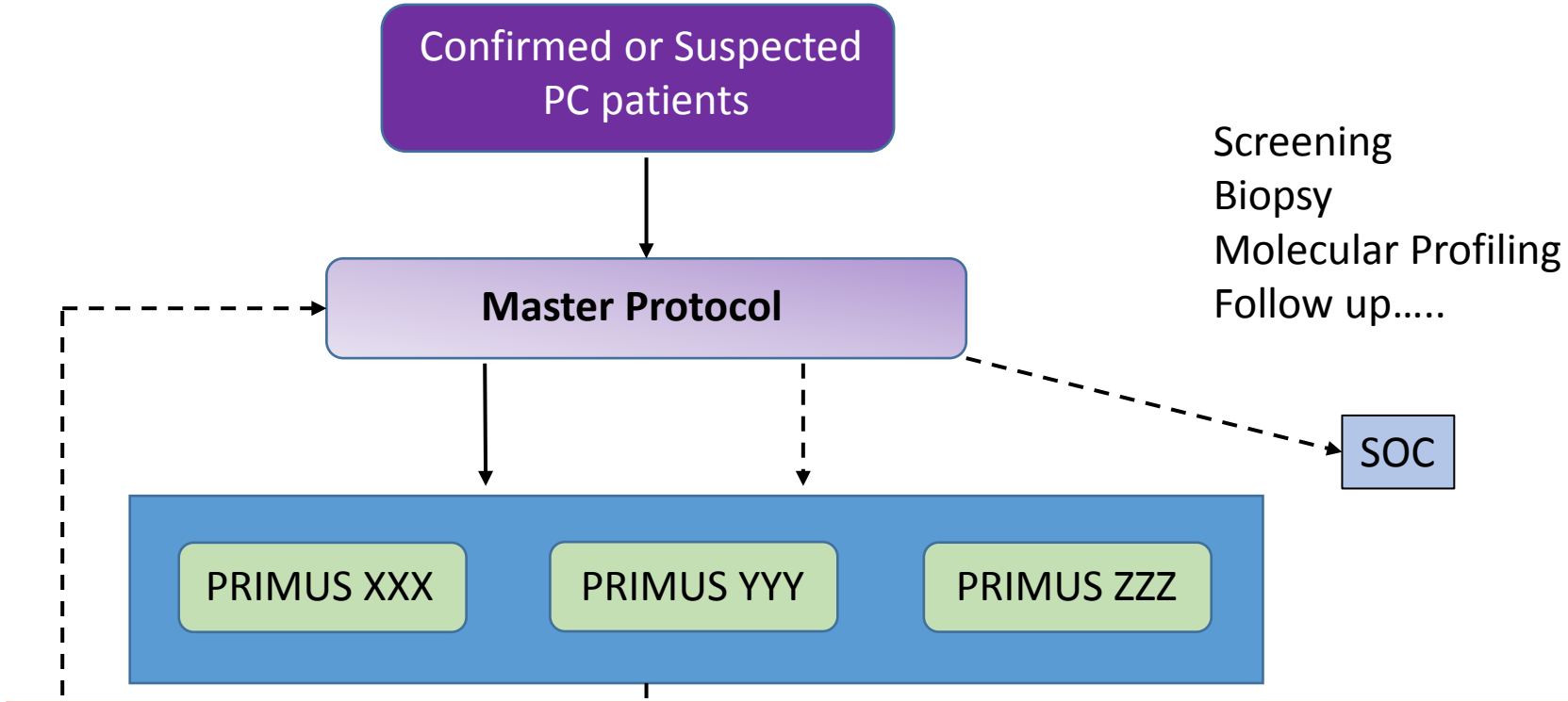
The Master Protocol: what does it do



Screening
Biopsy
Molecular Profiling
Follow up…..

Lots of opportunities for complimentary, non-competing trials
Therapeutic and biomarker development
A platform for all to use
Pharma & industry buy ins

- Adjuvant

Biomarker validation/development….

Molecular Profiling

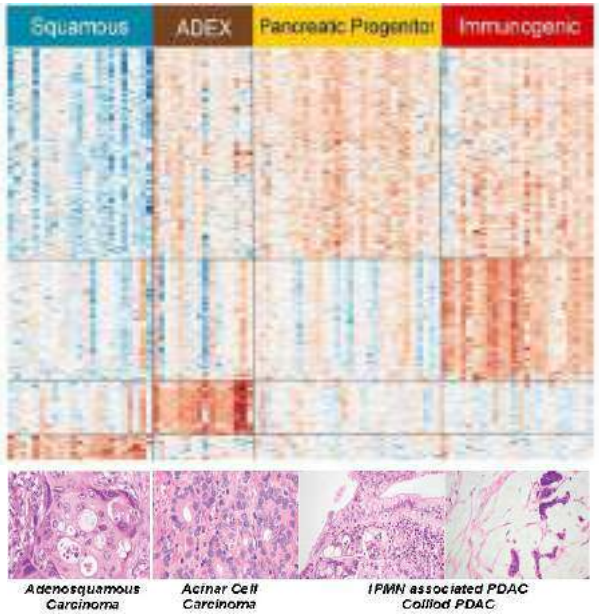
Harmonised molecular profiling platform **designed specifically for pancreatic cancer**

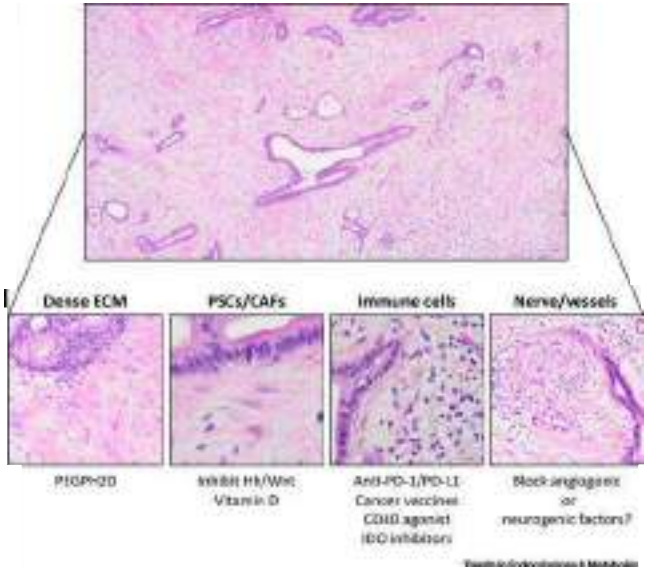
Clinical Sequencing (real time)

1) GPOL Clinical Cancer Genome
2) Integration with histopathology

Research Sequencing (batched)

1) WGS (when possible)
2) Transcriptome Sequencing
3) Liquid biopsy (Manchester)





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Assay design: platform selection

Targeted capture sequencing is the platform of choice for a **clinically-focussed assay**

Variant type	Amp	TCS	WGS	WES
Sequence level, coding	Yes	Yes	Yes	Yes
Sequence level, non-coding	Yes	Yes	Yes	No
Copy number changes, gene level	±	Yes	Yes	Yes
Copy number changes, chromosome level	No	Yes	Yes	Yes
Tumour suppressor inactivation	No	Yes	Yes	No
Regulatory region disruption	±	Yes	Yes	No
Gene fusions from DNA	No	±	Yes	No
Mutational signatures	No	Yes	Yes	±

Amp: amplicon-based sequencing
TCS: targeted capture sequencing
WGS: whole genome sequencing
WES: whole exome sequencing

Genomic assay requirement	TCS	WGS	WES
Detect clinically significant events	Yes	Yes	No
Real-world compatible (FFPE, low input DNA/tumour cellularity)	Yes	No	±
Cost efficient (data production, analysis and archiving)	Yes	No	±
Clinically meaningful turnaround time (sample to report)	Yes	No	No

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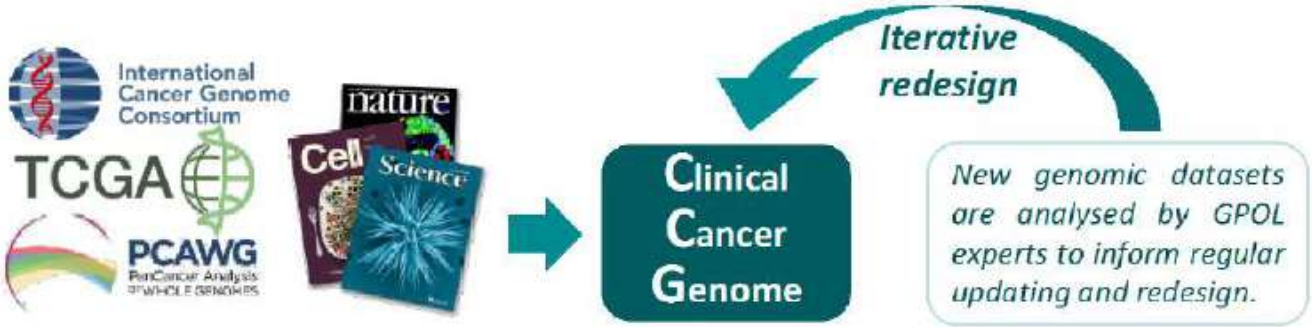
Clinical Cancer Genome

GPOL Glasgow Precision Oncology Laboratory

- Bespoke design for PDAC
- Agilent baits
- Illumina sequencing
- ~ 300 - 500X coverage

2. TCS delivers high quality data on all classes of clinically-relevant alteration

3. Assay content informed by expert data analysis & curation



Susie Cooke, Philip Beer

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GPOL Glasgow Precision Oncology Laboratory

Patient ID:
Tumour type: Pancreatic adenocarcinoma
Sample source:
Sequencing date: 04 FEB 2018
Sample type: Pancreatic resection (macrodissected)
Test requester:

Tumour cellularity was estimated at 40% by pathology and 36% by sequencing.

This sample harbours pathogenic mutations in *KRAS* and *TP53*, has loss of *CDKN2A/2B* and *SMAD4*, amplifications of *CCND1* and *AKT2* and a pattern of structural variants consistent with homologous recombination deficiency (HRD). This spectrum of mutations is consistent with Pancreatic Ductal Adenocarcinoma (NOS). HRD is associated with response to platinum-based chemotherapy or PARP inhibition.

Somatic driver alteration	Potential therapies, trials or biomarkers
KRAS G12V, VAF 18%, 463x coverage	**Potential clinical trial (MEK inhibitor, ERK inhibitor)**
TP53 Frameshift, VAF 19%, 560x coverage	*No current therapeutic options*
SMAD4 Homozygous deletion	*No current therapeutic options*
CDKN2A/2B Homozygous deletion	**Potential clinical trial (CDK4/6 inhibitor)**
CCND1 Amplification 7+ copies	**Potential clinical trial (CDK4/6 inhibitor)**
AKT2 Amplification 9+ copies	**Potential clinical trial (AKT inhibitor/MTOR inhibitor)**

Homologous Recombination Deficiency Present	**Microsatellite Instability** Not detected	**Tumour Mutation Burden** <12 mutations per Mb
HLA Typing In development	**Tumour-Normal pair genotype match** 100%	**Sample Contamination** None

Passenger mutations and Variants of Unknown Significance: NIL

For internal use only

Metric	Score	Metric	Score	Metric	Score	Metric	Score
DI	200	UF	0.34%	IS	181	Gene	718
LC	Pass	DP	1.78%	ID	84.2	SNP	508
OT	N	DR	0.29%	RT	0.70%	Other	387
SV/D	19.3/43%	GS	100%	Ave	507	INS/M	1/1

GPOL Glasgow Precision Oncology Laboratory

Patient ID:
Tumour type: Pancreatic adenocarcinoma
Sample source:
Sequencing date: 04 FEB 2018
Sample type: Pancreatic resection (macrodissected)
Test requester:

[illegible]

Genes included in sequencing assay and types of alterations reported

[illegible]

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Tissue: Why EUS-guided biopsy?

- There is always a primary to biopsy (any clinical stage)
- May select patients with low volume metastatic disease (better PS)
- Same setting as ERCP
- Can biopsy some of the liver and nodal lesions at the same time
- Additional research samples can be obtained at the same time
- If we can sequence this, should have no issues with perc biopsy
- Enables precision medicine approach

Stephan Dreyer

Colin McKay

Fraser Duthie

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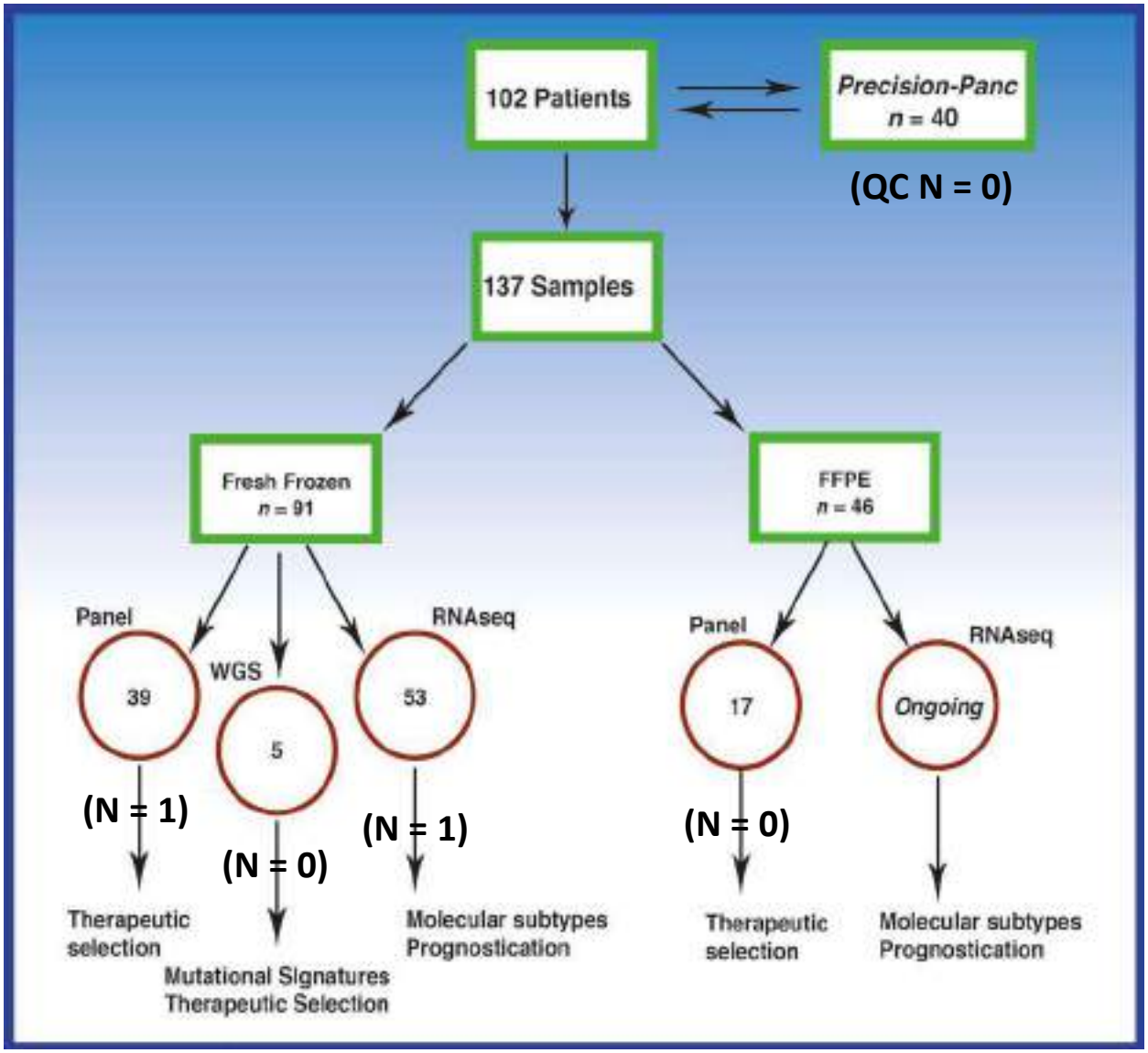
Study progress: low failure rate



(failure)

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Precision-Panc Clinical Trials

- **PRIMUS-001:** 1st line metastatic (FOLFOX-A Vs AG)
  - Adaptive randomised Phase II/III, up to 460 patients, ongoing
  - DDR biomarker

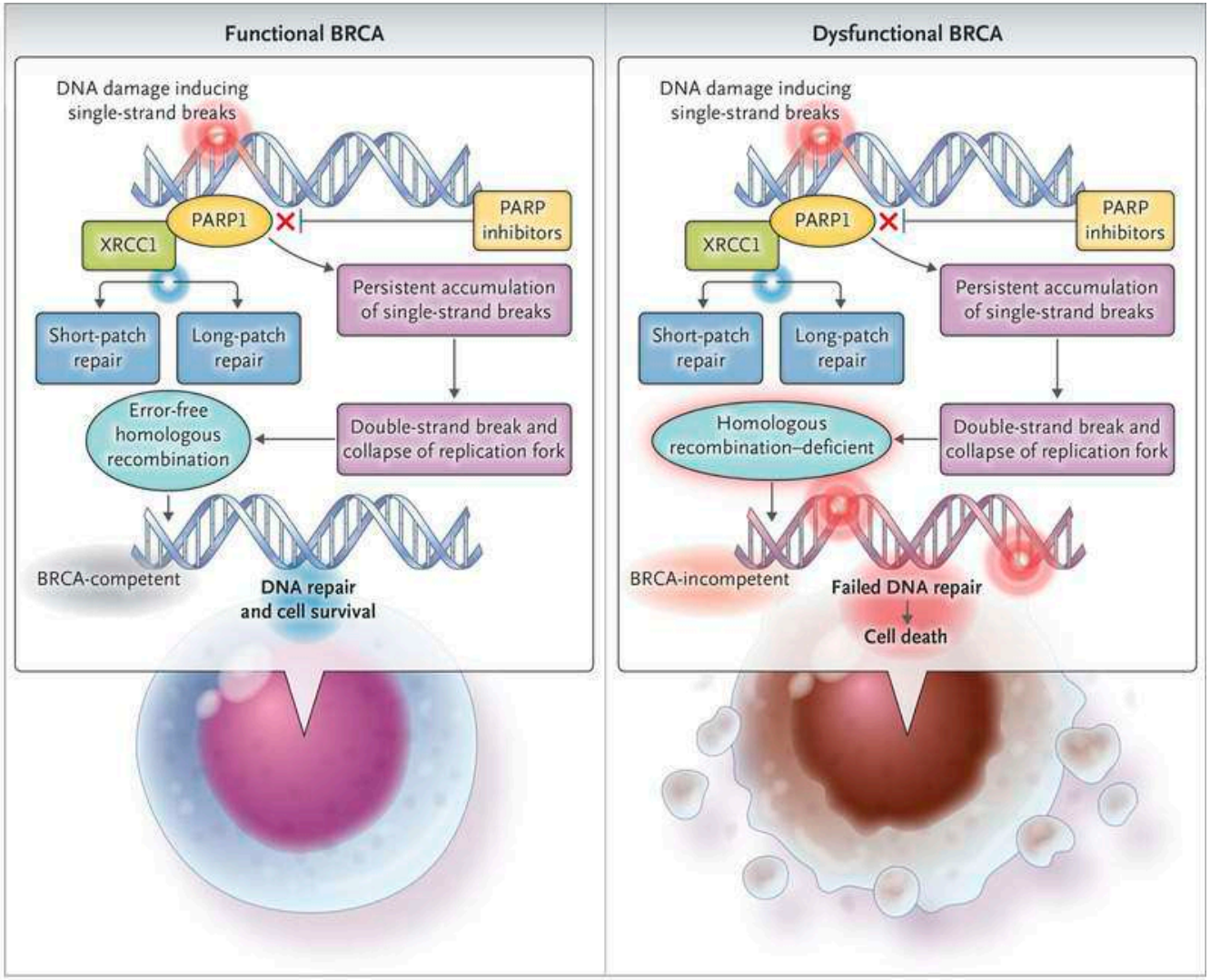
- **PRIMUS-002:** neoadjuvant (FOLFOX-A & AG)
  - Phase II, up to 250 patients, starts March 2019
  - DDR biomarker

- **PRIMUS-003:** 2nd line metastatic (CXCR2 + PDL-1)
  - Phase Ib, 20 patients, complete
  - Immune & Tumor microenvironment

- **PRIMUS-004:** 2nd line metastatic umbrella
  - Currently 1 appendix (2 cohorts) , 90 patients, start Q2 2019
  - PARPi + ATRi combination over come acquired platinum resistance

- More under plan (neoadjuvant & adj/maintenance umbrella)
  - Preclinical Therapeutic Testing Board
  - NCRI CSG Subgroup / Master Protocol Strategy Board

Synthetic Lethality as Therapeutic Strategy in Cancer



McLornan et al NEJM 2014

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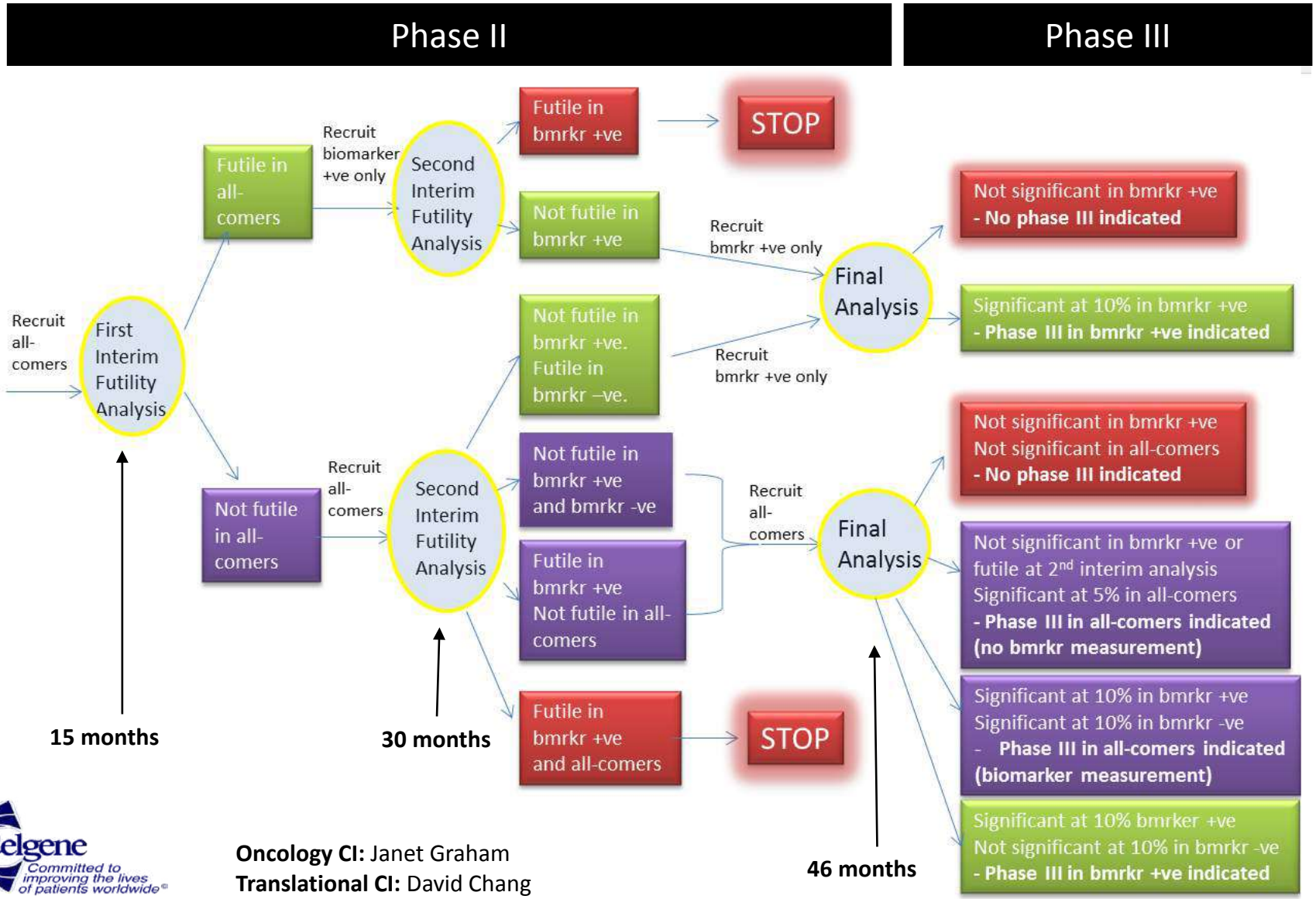
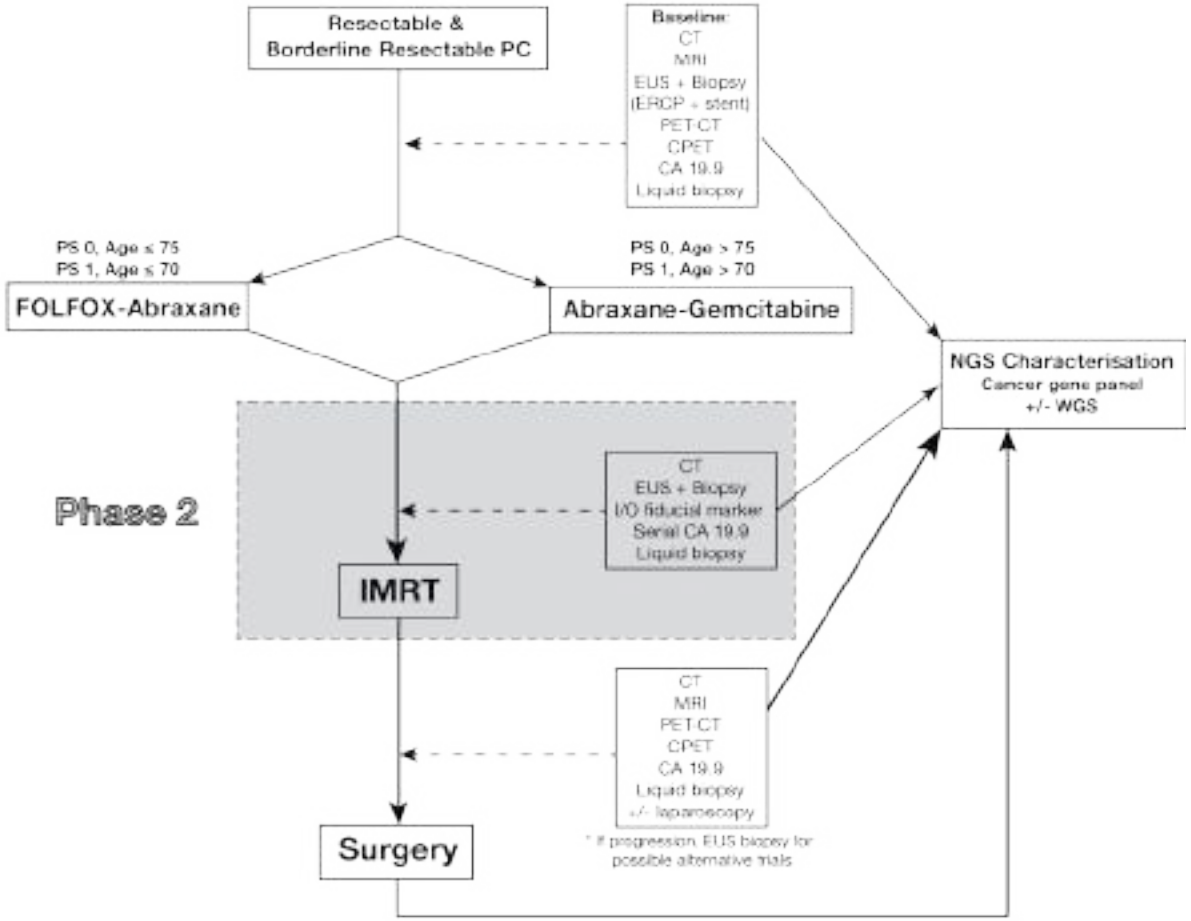
PRIMUS-001: A randomised adaptive Phase II/III study of **FOLFOX-A** versus **AG** in metastatic PC, with integrated **DDR biomarker** evaluation.



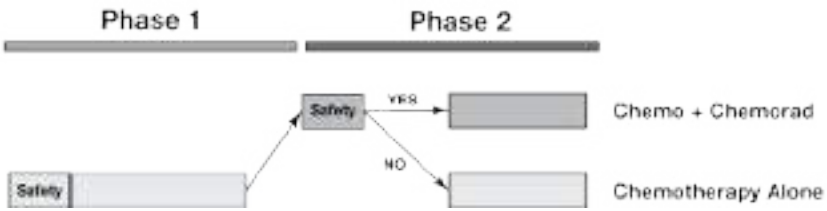
Oncology CI: Janet Graham
Translational CI: David Chang

PRIMUS-002

An umbrella phase II study examining two neo-adjuvant regimens (FOLFOX-A and AG) in resectable and borderline resectable Pancreatic Ductal AdenoCarcinoma (PDAC), focusing on biomarker and liquid biopsy development

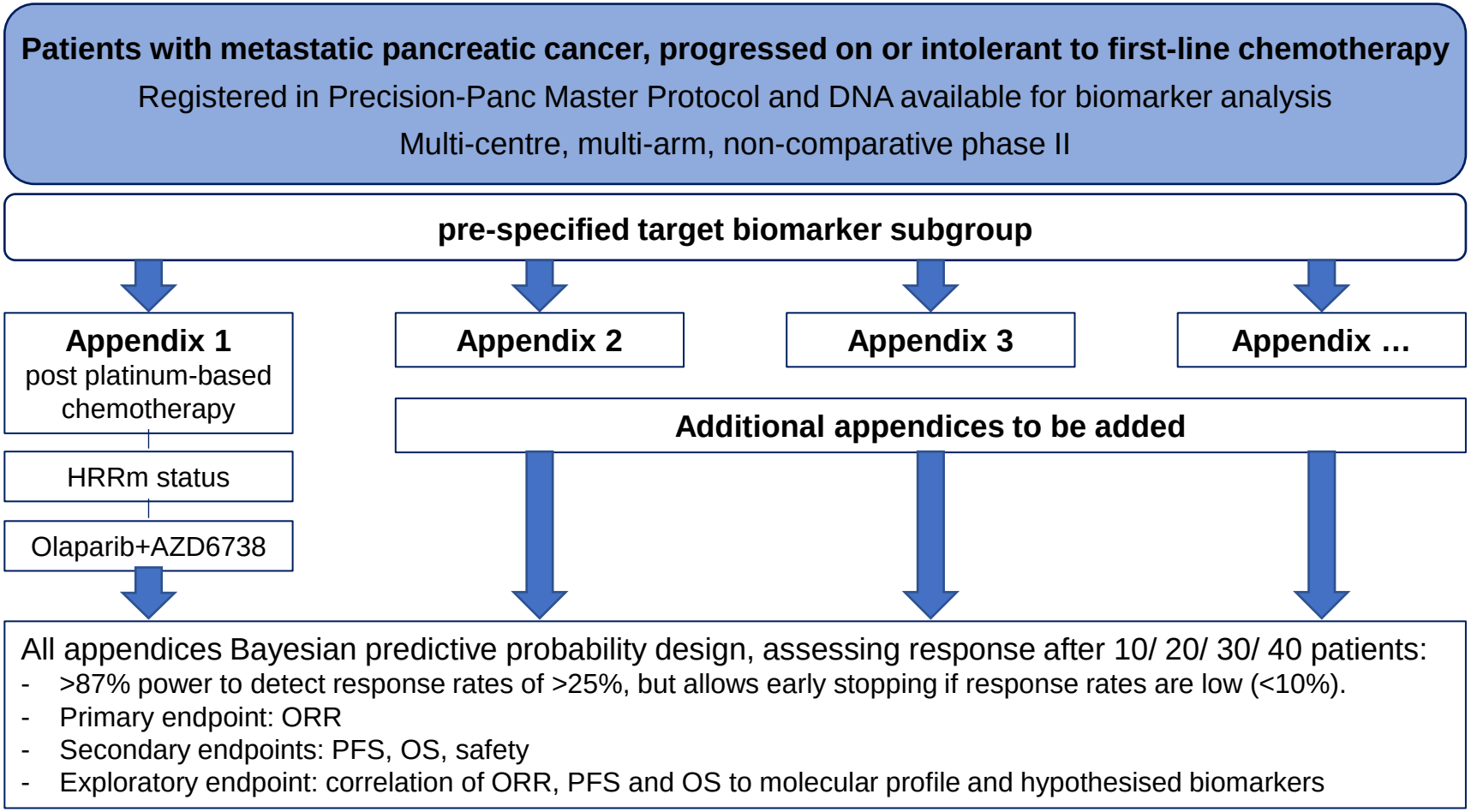


- DDR BM evaluation
- Clonal evolution
- Intra-tumoral heterogeneity
- Resistance mechanism
- Feasibility of liquid biopsy



Oncology CI: Derek Grose
Surgical/Endoscopy CI: Colin McKay
Translational CI: David Chang

PRIMUS-004: 2nd line Metastatic Umbrella



Translational CI: David Chang
Clinical CI: Fieke Froeling

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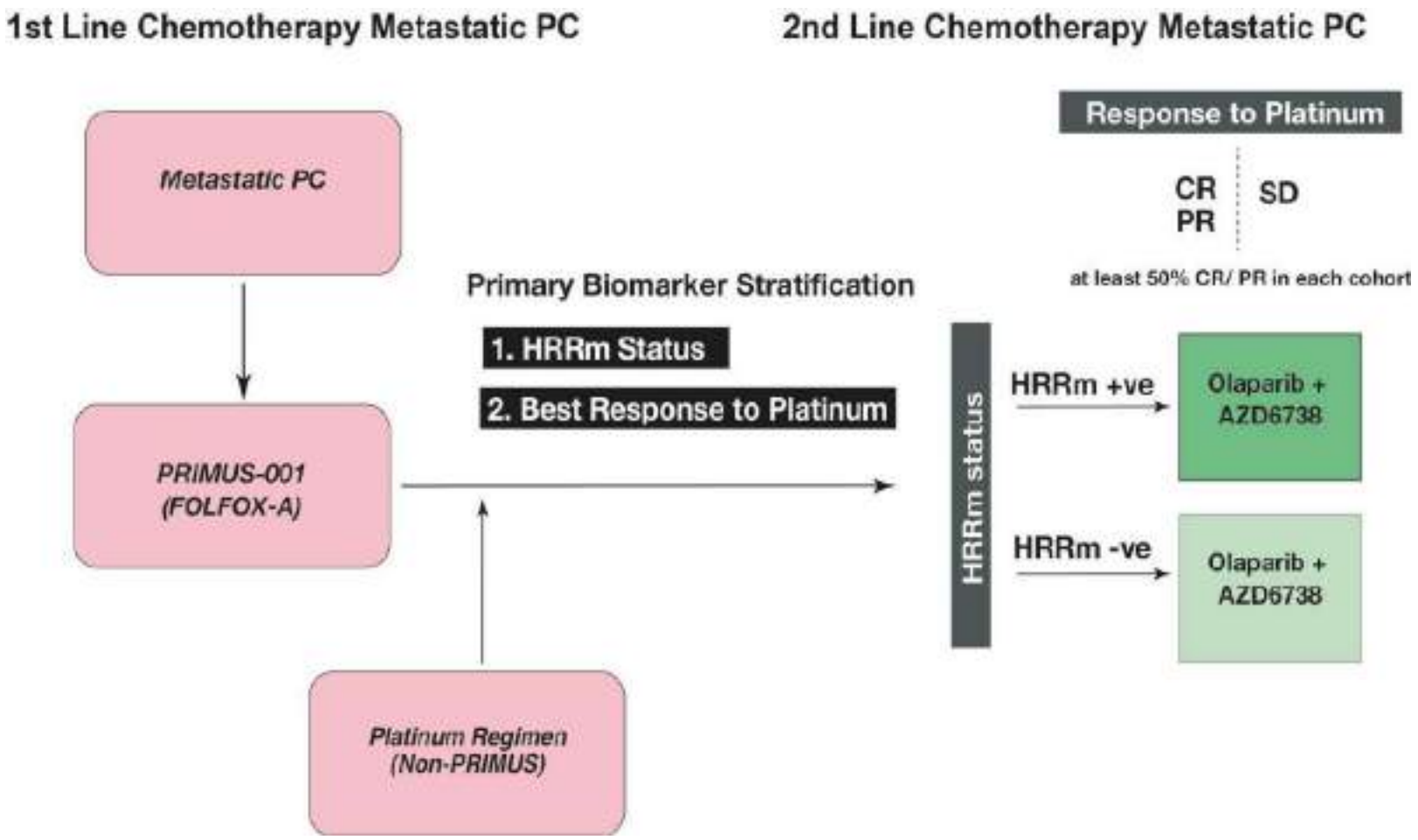
PRIMUS-004 (Appendix 1)



Oncology Lead: Mairead McNamara
Translational Lead: Stephan Dreyer

AstraZeneca

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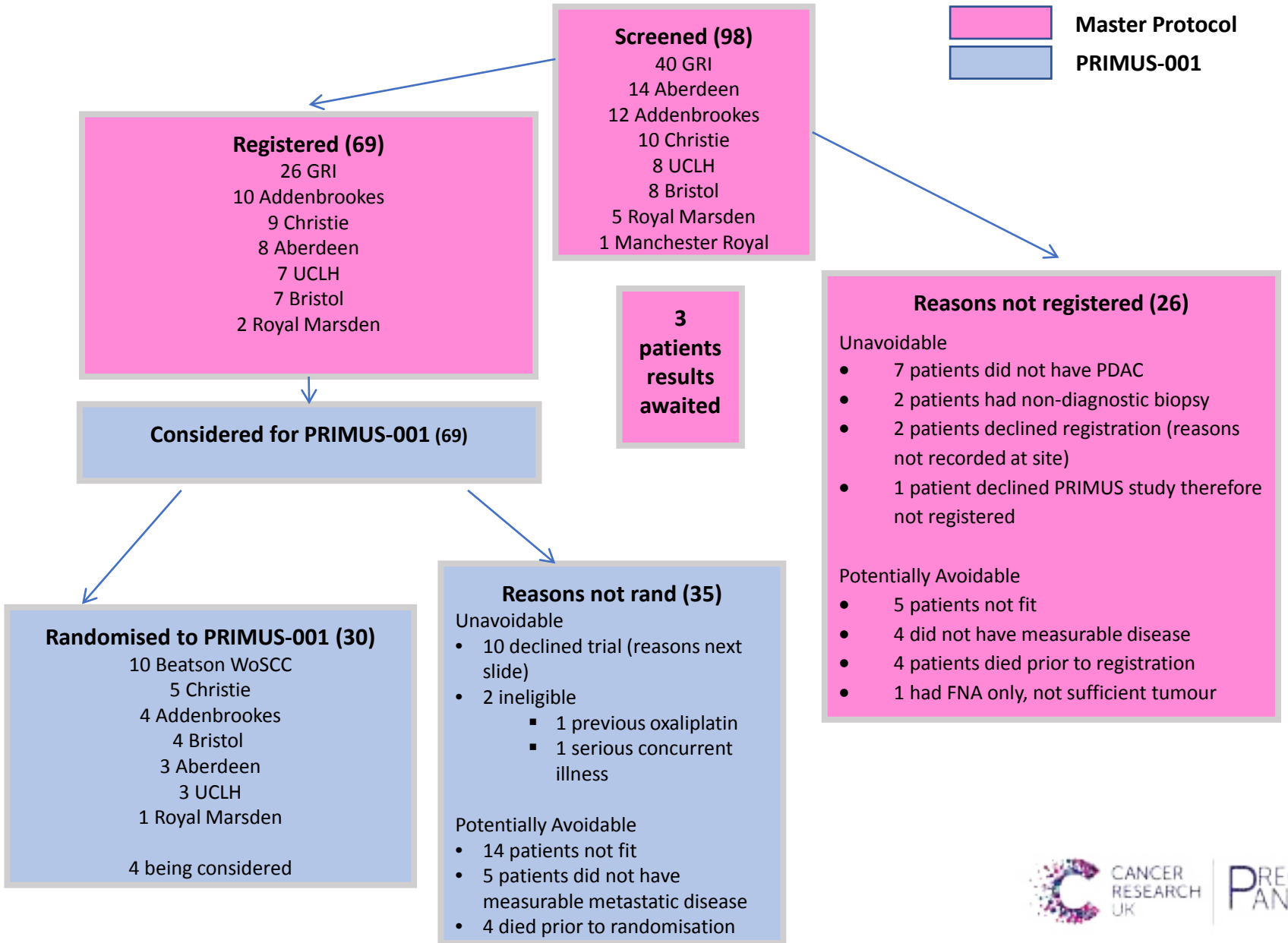
Precision-Panc / PRIMUS Recruitment (22 Jan 2019)



Reasons for Declining PRIMUS-001 (N = 10)

- 2 x wanted to start chemotherapy immediately
- 2 x wanted Standard of Care treatment
- 2 x due to travel
- 2 x declined all treatment
- 1 x chose FOLFIRINOX due to gBRCA carrier
- 1 x chose single agent chemotherapy

Lessons Learnt…

- Be as patients and clinicians friendly as possible
  - Patient pathway
    - Embed research activities into SoC
    - Shorten & simplify
    - Attractive and available trial options (stages & PS)
    - Novel trial designs (adaptive with integrate biological Qs)
  - Tissue pathway
    - Use “surplus”
    - Use exist structure/pathway if possible
    - Bring cyto/pathology & biorepository together
    - Clinically meaningful TAT
- Be pragmatic & realistic (clinical Vs research)
- Help each site set up (strength vs challenges)
- Identify “champions” from each specialty @ each site
- Start small, then grow…
- Ensure “**key ingredients**” of precision medicine are secured

Glasgow Precision Oncology Laboratory

University of Glasgow

Andrew Biankin

David Chang
Susie Cooke

Judith Dixon-Hughes
Anna Morris

Sarah Allison
Maja Bailey
Dario Beraldi
Holly Brunton
Giusy Caligiuri
Euan Cameron
Ricky Cunningham
Stephan Dreyer
Lisa Evers
Amanda Ewing
James Stuart

Eirini-Maria Lampraki
John Marshall
Brian McDade
Daniel McElroy
Liz Musgrove
Viola Paulis- Hock
Donna Ramsay
Rosie Upstill-Goddard
Derek Wright
Donna Ramsay
Paul Grimwood

WORLD CHANGERS WELCOME

/precisionpanc

@precisionpanc

Search: University of Glasgow

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NHS Greater Glasgow and Clyde

Glasgow Royal Infirmary

Colin McKay
Ross Carter
Euan Dickson
Nigel Jamieson
Fraser Duthie
Lyn Smith
Janet Graham
Derek Grose
David McIntosh
Abdulla Al-Adhami
Elspeth Cowen
Kimberley Booth
Endoscopy staff

Queen Elizabeth University Hospital

Nicola Williams
Paul Westwood
Clinical Genetics lab
Christine Whilshire
GGC Biorepository

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Patients and families

University of Glasgow
CRUK Glasgow Centre
Andrew Biankin
David Chang
Jeff Evans
Susie Cooke
Fraser Duthie
Judith Dixon
Anna Morris
Janet Graham
Derek Grose
Nigel Jamieson
Robert Jones
Colin McKay

Beatson Institute of Cancer Research
Owen Sansom
Jen Morton
Catherine Winchester

Cambridge University
CRUK Cambridge Institute
Duncan Jodrell
Bristi Basu
Pippa Corrie
Tessa Kasia

Glasgow CTU
James Paul
Jamie Stobo
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Ged Brady
Mairead McNamara
Derek O'Reilly

University of Oxford
Cancer Research UK Oxford Centre
Eric O'Neill
Somnath Makerjee

The Institute of Cancer Research, London
Chris Lord

Precision-Panc centres around the UK


Celgene
Committed to improving the lives of patients worldwide


CANCER RESEARCH UK
PRECISION PANCOAM


VIA VERITAS VITA
University of Glasgow


THE HOWAT FOUNDATION


CHIEF SCIENTIST OFFICE


Pancreatic Cancer UK


SGP
Scottish Genomes Partnership


Stratified Medicine Scotland


AstraZeneca


wellcome


PCS
PANCREATIC
CANCER SCOTLAND

Thank you for your attention

University of Glasgow | Institute of Cancer Sciences

David.Chang@glasgow.ac.uk & **Judith.Dixon@glasgow.ac.uk**

DNA / RNA Yield sufficient for NGS

		Fresh Frozen	
	Size	DNA Yield (mean, range (ng))	RNA Yield (mean, range (ng))
Boston Acquire®	22G	1819 (133 – 7350)	191 (30 – 1187)
Sharkcore®	19G	2170 (11.4 – 6000)	N/A
Sharkcore®	22G	2939 (1134 – 7595)	481 (40 – 1790)
Cook Procore®	20G	1745 (290 – 4750)	18 (3.6 – 44)
		FFPE	
	Needle Size	DNA Yield (mean, range (ng))	RNA Yield (mean, range (ng))
Training set (n = 14)	22G	1819 (133 – 7350)	191 (30 – 1187)
PRECISION-Panc EUS set (n = 27)	22G	1740 (102 – 2860)	n/a
PRECISION-Panc Core set (n = 19)	Various	550 (0 – 1730)	

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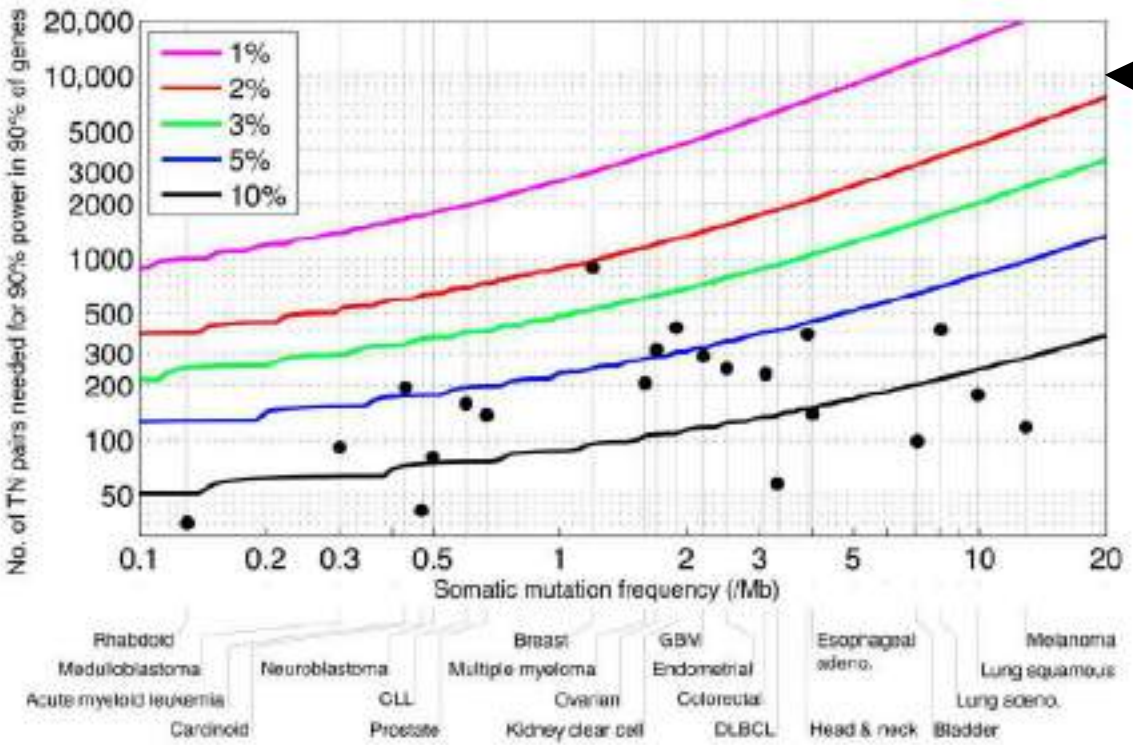
The discoverable space: novel cancer genes

Current knowledge of cancer genes is **close to saturation**



TCGA exomes

Undiscovered cancer genes:

- Biologically weak drives
- Too rare for prognostic models
- Unattractive therapeutic targets

Lawrence et al. Nature. 2014 January 23; 505(7484): 495–501
Bailey et al. Cell. 2018 Aug 9;174(4):1034-1035

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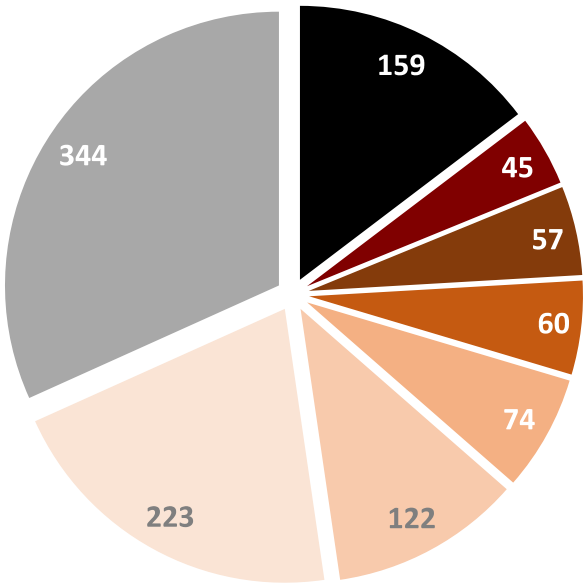
Assay design: defining content

Commercial and LDT cancer panels show **poor concordance** in gene selection, likely due to lack of objective methodologies



Panel genes overlap

- All 8 panels
- 7 of 8
- 6 of 8
- 5 of 8
- 4 of 8
- 3 of 8
- 2 of 8
- 1 of 8

n=1,084 genes

Panel	No. of genes
Ion AmpliSeq comprehensive	409
FoundationOne CDx	309
Caris Molecular Intellegence	593
Illumina TSO500	523
Tempus xT	594
Dana Farber OncoPanel V3	447
MSK-IMPACT 468	468
MD Anderson v1	409

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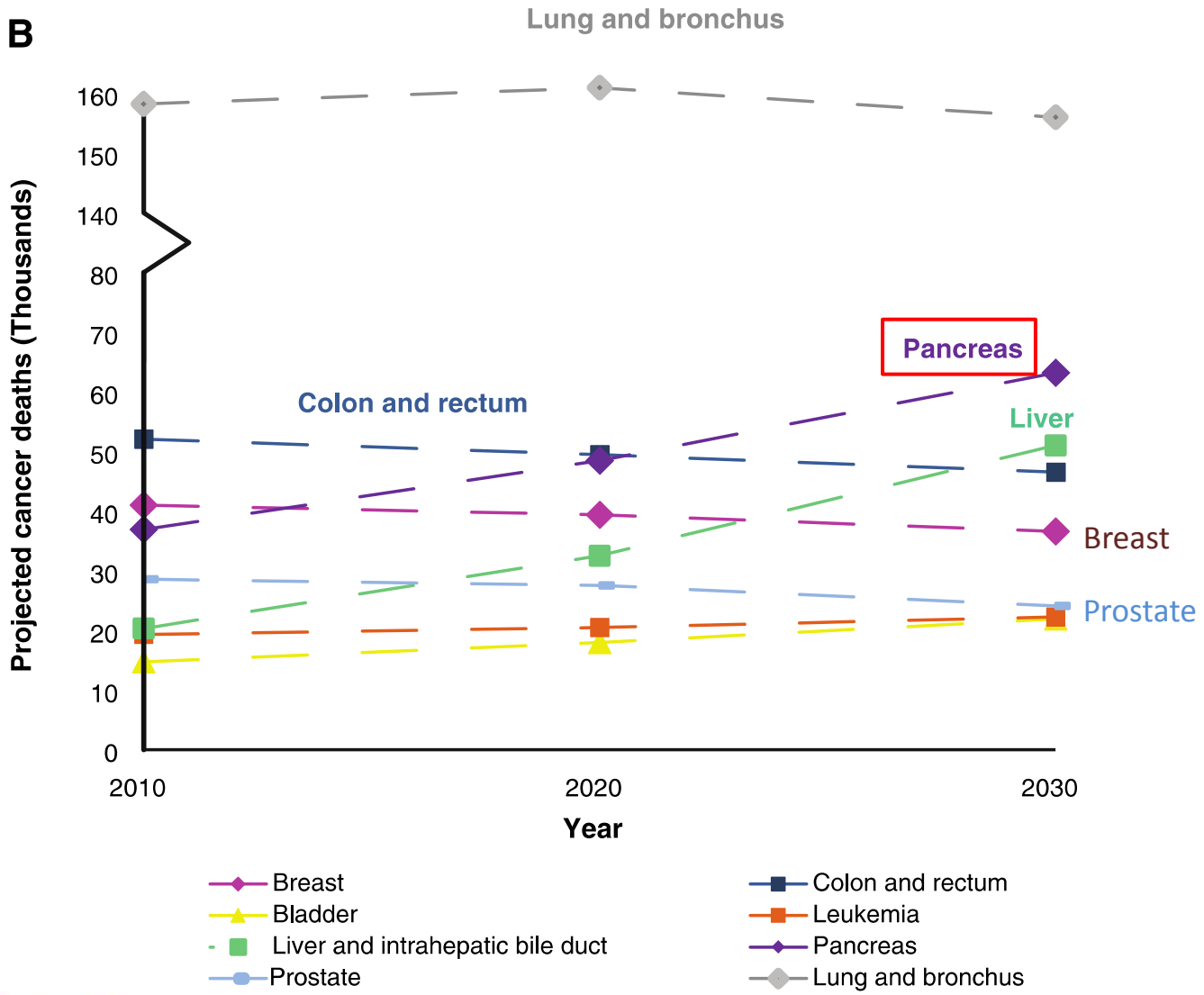
2nd Highest Cause of Cancer Mortality Soon



Rahib et al *Cancer Res* 2014