University College London Hospitals NHS
NHS Foundation Trust

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A UK Perspective on the CUPISCO Trial The Agony and the Efficacy

RCP CUP Conference

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Disclosures

Remuneration reasons: attendance at advisory boards; chairing educational meetings; giving invited lectures; travel, accommodation and registration at national/international meetings, consultancy

Companies:

Amgen, BMS, BTG, Guardant Health, Merck Group, MSD, Roche, Sirtex, Servier

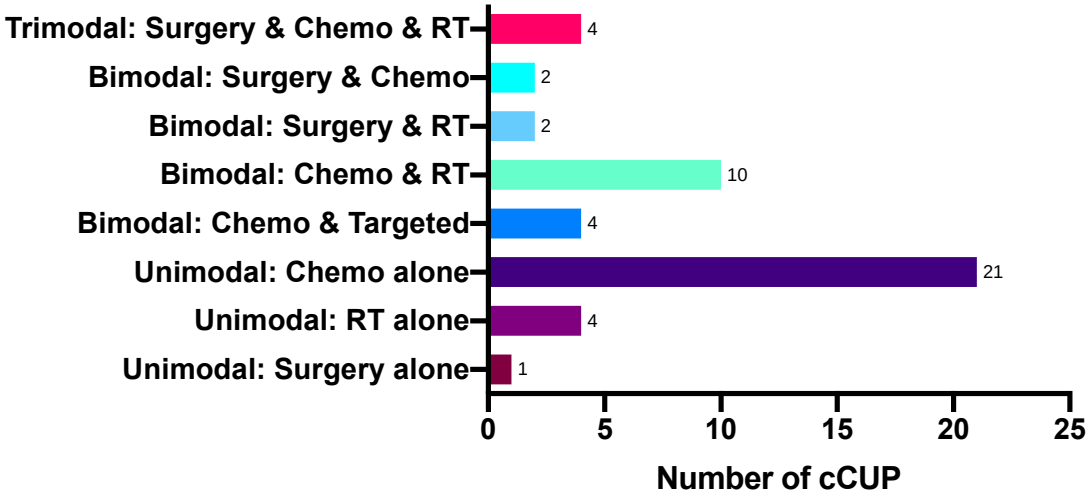
Funding for UCLH trials and research:

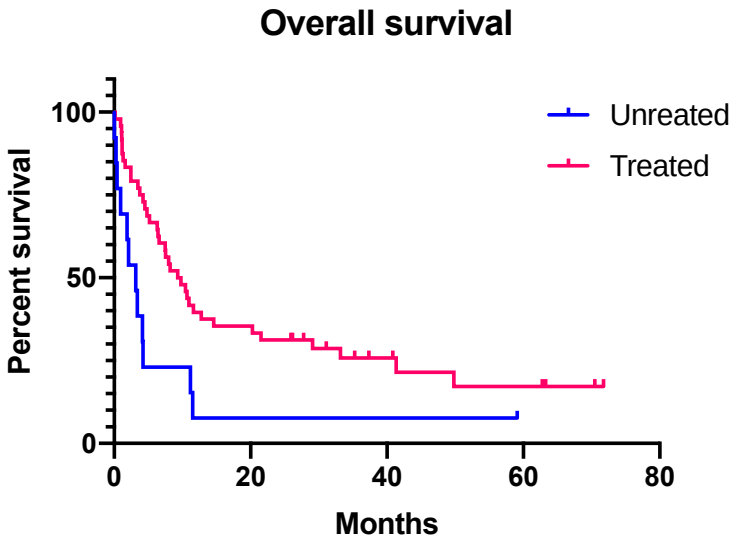
Amgen, BMS, Guardant Health, Merck Group, MSD, Roche

Focus on 3 main strategies for CUP patients

STRATEGY		HYPOTHESIS
1) Find the molecular primary	CONVERSION →	Primary-specific therapies will be more effective
	IHC MIRNA METHYLATION	
2) Find the therapeutic target	ACTIONABLE →	Targeted therapy is feasible, safe and efficacious
	IHC MRNA ACTIONABLE MUTATIONS/ALTERATIONS (WHOLE GENOME MUTATION) (EXOME SEQUENCE)	
3) Access a clinical trial		

UCLH CUP MDT 2013-2017: cCUP patients who embark on therapy (n= 48/61)





Mean Performance Status 1.5 (0-4)
Median OS 9.5 months, 1 year survival 40%
On a trial? 1 in first 4 years, now 4 in last 6 months

(Hessey, Mcvinnie, Shiu – Poster)

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The CITA IMDC* Platform

DNA

Next Gen sequencing

Genetic alterations, ITH

RNA

RNAseq/ TCR Seq

Transcriptional profiles

NanoString

Protein

Mass spectrometry

Sciomics protein profiling

Proteomic signatures

Tumour and immune cells

Flow and mass cytometry

Phenotypic characterisation

Functional assays

Key regulatory components

Tissue sections

Immunohisto-chemistry

Topology of TME

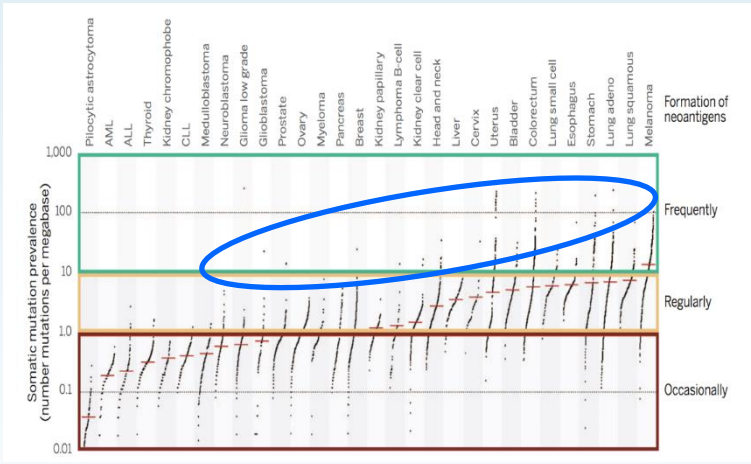
Bioinformatic multi-level data integration with clinical response data

Identification of mechanisms and biomarkers of response, resistance, and toxicity

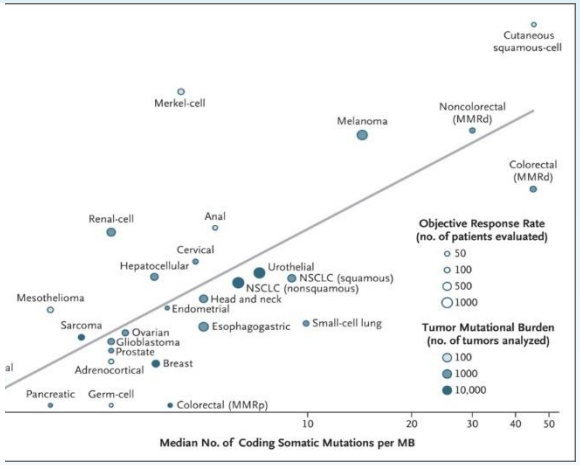
CANCER IMMUNOTHERAPY NETWORK ACCELERATOR

*Immune Monitoring and Discovery Core

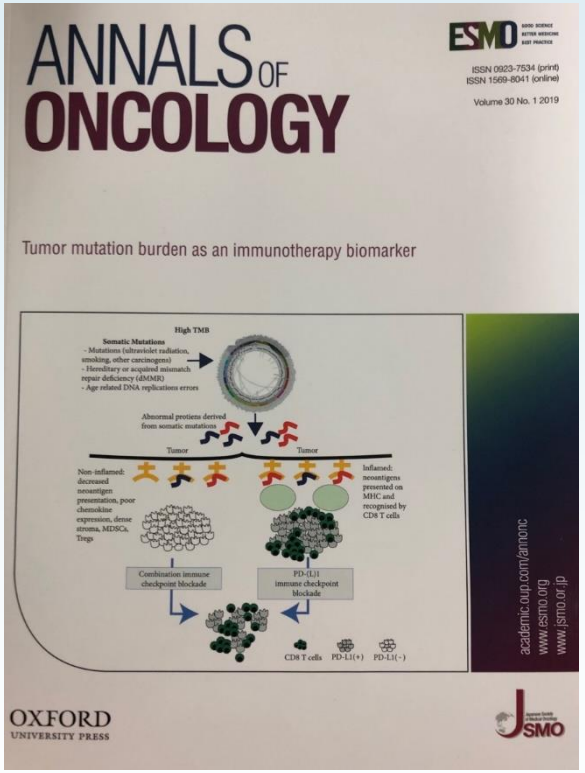
Is TMB a good immunotherapy biomarker?



Schumacher Science 2015



Yarchoan M et al, N Engl J Med 2017



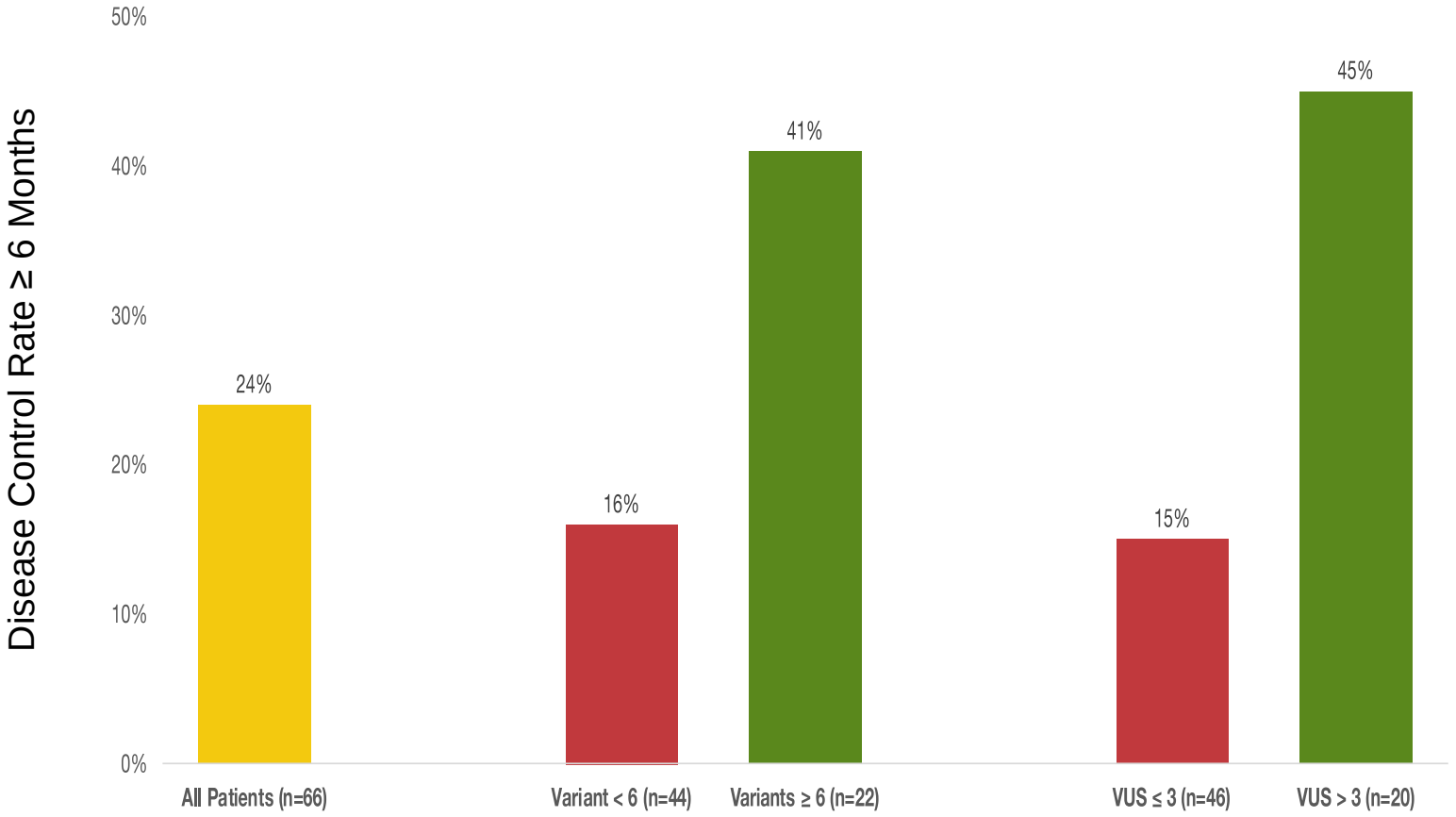
…it can't be as simple as that...

And blood TMB is coming…..

Mutation Burden (Guardant360) Predicts IO Outcomes

Six or more Variants
Higher SD ≥ 6 mos/PR/CR
(P=0.025)

More than three VUS's*
Higher SD ≥ 6 mos/PR/CR
(P=0.014)



* VUS = Variant of Unknown Significance

Circulating Tumour DNA (ctDNA) Experience in Patients with Cancer of Unknown Primary (CUP)

Kai Keen Shiu[1,2], Helen Winter[1], Mariana Kushnir[1], Gabriel Mak[1], Carmen Murias[1], Charles Swanton[2], Richard Lanman[3], Iris Faull[3], Hendrik-Tobias Arkenau[1,2]

[1]Drug Development Unit, Sarah Cannon Research Institute UK, London, United Kingdom; [2]University College London Cancer Institute, London, United Kingdom, [3]Guardant Health, California, United States of America

SARAH CANNON
Research Institute UK

The median turnaround time (TAT) from sample collection to report was 10 days (range 6-15).
Seventeen patients had potentially actionable mutations (17/25 = 68%)

4 patients had no mutations detected which might be explained by: 1 patient had post resection; 2 patients were responding to chemotherapy; 1 patient was sampled prior to commencing chemotherapy.

Significant actionable targets included: 2 $BRAF^{V600E}$; 5 KRAS mutations; FGFR; MYC amplifications; KIT; PIK3CA; *ERRB2.*

Three or more somatic mutations (including variants of uncertain significance (VUS)) were found in 12 patients; six or more mutations were found in 6 patients.

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Future Value of IO therapy?

63 year old man: poorly differentiated carcinoma, CK7 focally +ve, all other markers –ve

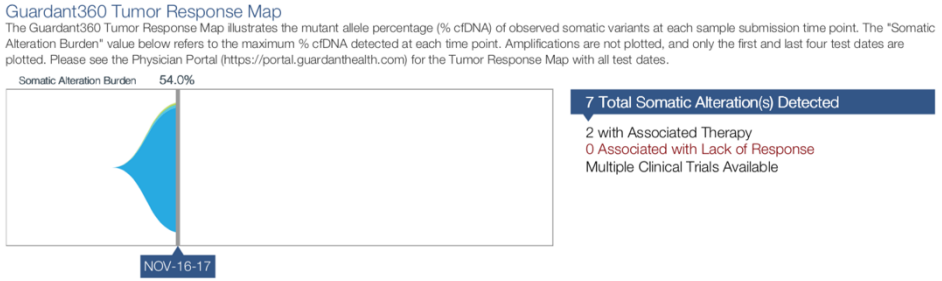
Good response to 6 cycles of Cisplatin-Capecitabine

Now progression

Taxane?

Irinotecan?

Immunotherapy?



Summary of Somatic Alterations & Associated Treatment Options

The percentage of altered cell-free DNA (% cfDNA) circulating in blood is related to the unique tumor biology of each patient. Factors that may affect the % cfDNA of detected somatic alterations include tumor growth, turn-over, size, heterogeneity, vascularization, disease progression, and treatment.

Alteration		% cfDNA or Amplification	FDA Approved in Indication	Available for Use in Other Indications	Clinical Drug Trials
			see page 5	see page 5	see page 15
Relevant for Therapy Selection					
TP53	*W23**	54.0	None	None	Trials Available
MYC	*AMP*	+++	None	None	Trials Available
PDGFRA	*AMP*	+	None	Dasatinib, Imatinib, Lenvatinib, Nilotinib, Nintedanib, More drugs available	Trials Available
KIT	*AMP*	+	None	Axitinib, Cabozantinib, Dasatinib, Imatinib, Lenvatinib, More drugs available	Trials Available
Additional Alterations Detected					
FGFR1	*Q594L*	0.4	The functional consequences and clinical significance of this gene variant are not established. Similar to other alterations in circulating cfDNA, the amount (% cfDNA) of this variant may reflect disease progression or response to treatment; clinical correlation is advised.		
NF1	*R262C*	0.2	The functional consequences and clinical significance of this gene variant are not established. Similar to other alterations in circulating cfDNA, the amount (% cfDNA) of this variant may reflect disease progression or response to treatment; clinical correlation is advised.		
MYC	*R439G*	0.1	The functional consequences and clinical significance of this gene variant are not established. Similar to other alterations in circulating cfDNA, the amount (% cfDNA) of this variant may reflect disease progression or response to treatment; clinical correlation is advised.		

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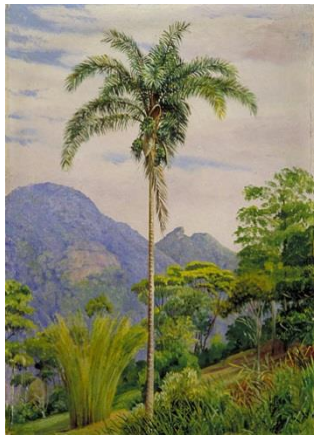
Trunk and branch clonal diversity (& clinical outcome)

Palm | **Chestnut** | **Baobab Tree** | **Dying Muhly Bush**




Successful Predictive Biomarkers and Drug Targets
HER2/*EGFR*/*KRAS*/*ALK*/*BRAF*

Swanton NEJM 2012
Roylance et al 2011
Birkbak et al 2011

Aim – gently push or big kick?

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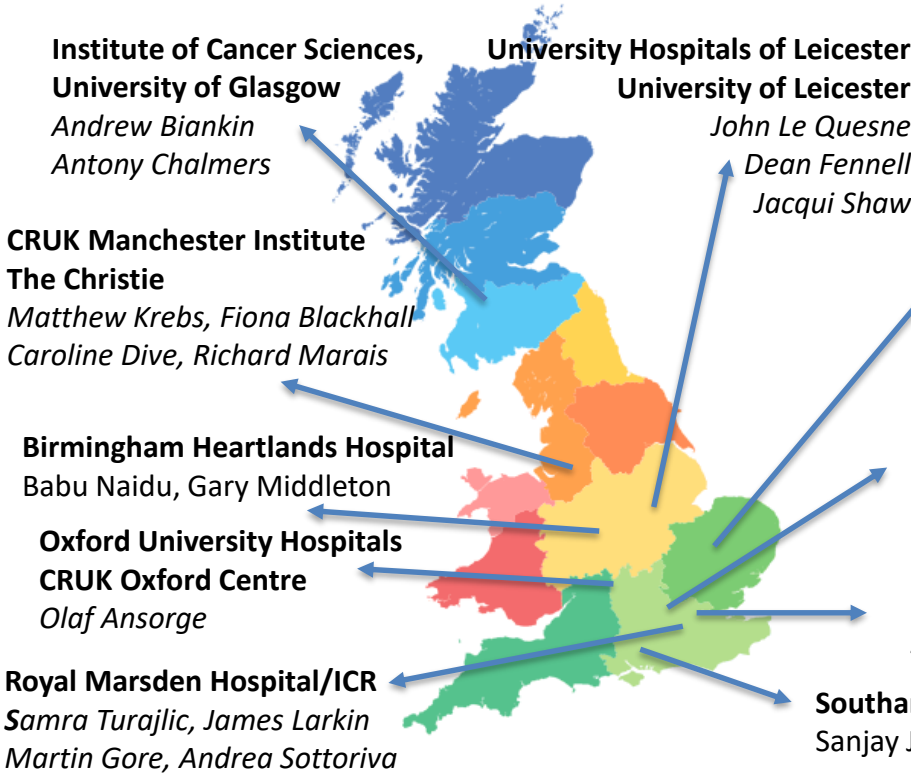
The PEACE (Posthumous Evaluation of Advanced Cancer Environment) consortium

A national post-mortem programme and consortium



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PEACE

National prospective observational study intended to facilitate tissue donation, in metastatic cancer, from multiple tumour sites in the post-mortem setting

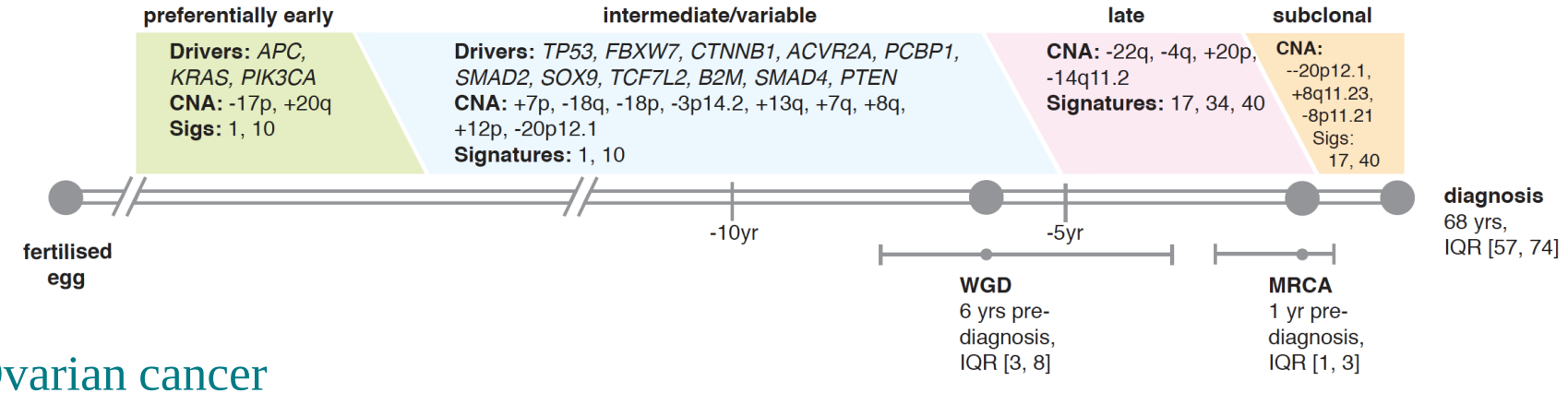
Funded by a Cancer Research UK Centre Network Accelerator Award

Aim: establish a national PM protocol and a resource of tissue & blood in highly clinically annotated patient cohorts (500 PMs over 5 years) leveraging investment in CRUK-funded clinical studies

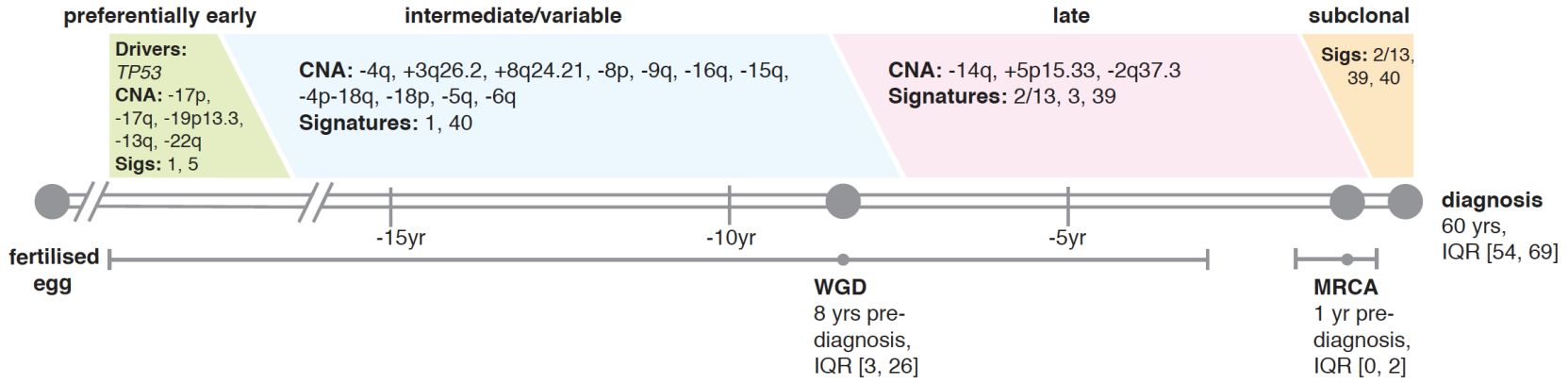
Mariam Jamal-Hanjani

Timelines of cancer development

Colorectal cancer



Ovarian cancer



Jolly and Van Loo Genome Biology (2018) 19:95

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Perspectives for CUP

- **Molecular archaeology of cancer**: massively parallel sequencing and bioinformatics algorithms can **disentangle the subclonal architecture and life history of tumours**
- **Post-mortem sampling** allows **tracking evolution** of clones and subclones over time and space
- Could answer key questions in CUP:
  - Evolutionary history of CUP: track the **pattern of spread** and the **site of origin**
  - Are **common aetiologies/drivers/pathways** underlying early metastatic dissemination?
  - Can we **identify early events** and develop **early diagnosis approaches**?

Biobank all pCUP/cCUP

STRATEGY

STUDY/TRIAL/ARENA

CONVERSION

1) Find the primary using molecular profiling →

MUO/pCUP
TIMELY
APPROPRIATE
MANAGEMENT
QOL/PROM/PREMS

Primary-specific therapies will be more effective

ACTIONABLE

2) Find the therapeutic target →

SMDTs
Genomic Boards
Trials for Good Prognosis cCUP
Poor PS subgroups
QOL/PROM/PREMS

Targeted therapy is feasible, safe and efficacious

3) Access a clinical trial →

The optimal way to test a treatment strategy

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Thank you

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