Why do we inflict research biopsies on our patients?

ECMC Annual Meeting – 18 May 2016

Dr. Richard Baird - University of Cambridge

CANCER RESEARCH UK | CAMBRIDGE CENTRE

ECMC

Cambridge Cancer Centre

UNIVERSITY OF CAMBRIDGE | Cambridge University Hospitals NHS NHS Foundation Trust

Why do we inflict research biopsies on our patients?
Talk Outline

- Why do we inflict research biopsies on our patients?
- Contemporary drug development
- Risks of research biopsies to patients

- Research biopsies - how can we improve?
- For the future …

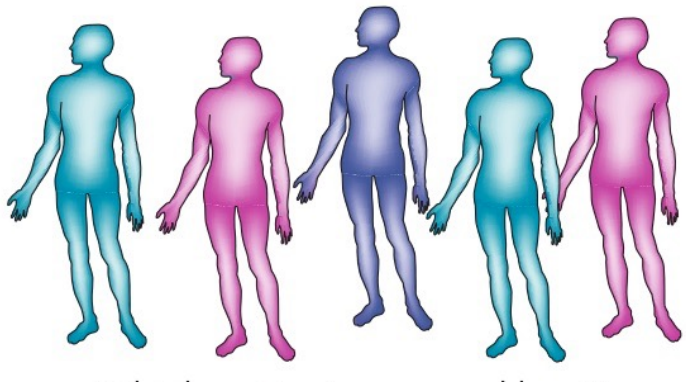
Why do we inflict research biopsies on our patients? 2 main reasons:

1. Individual patients respond differently to the same treatment
2. A cancer within an individual patient can change over time, and may therefore require a change in treatment

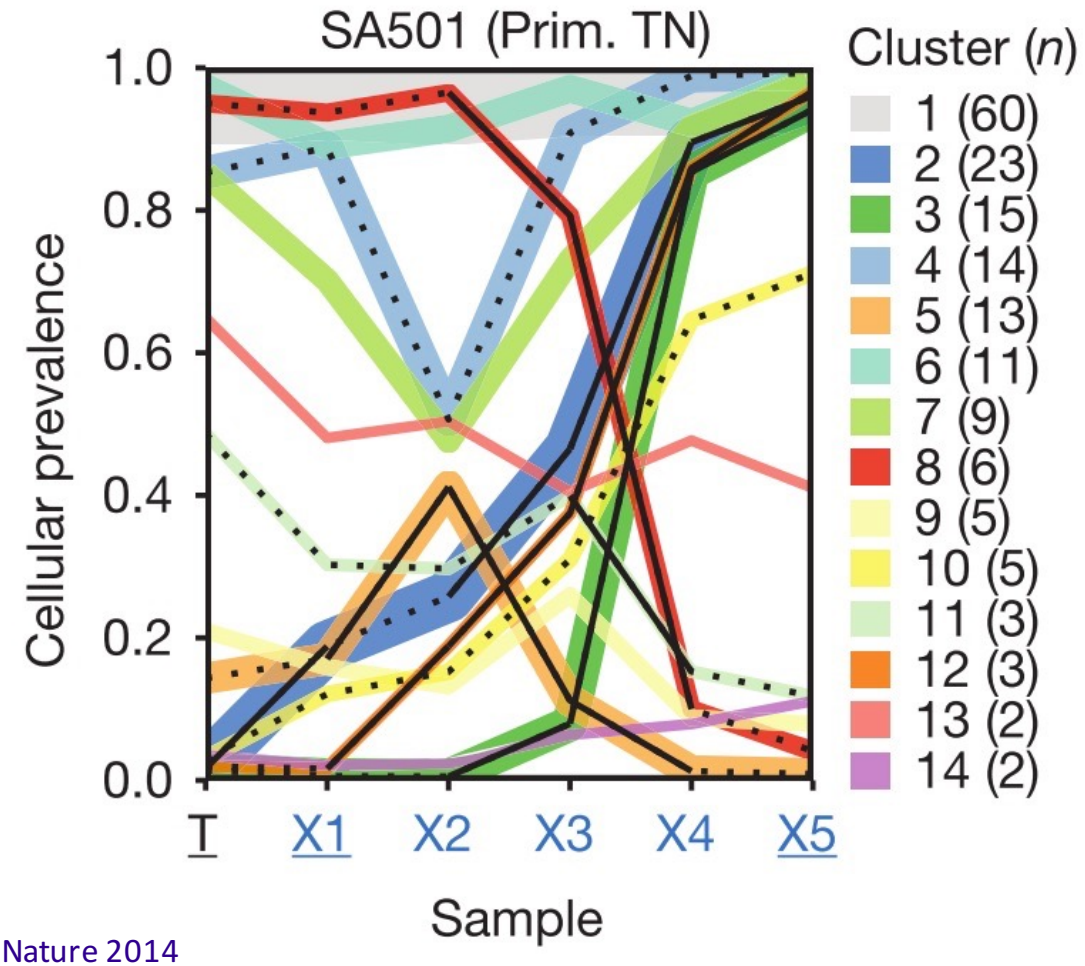
Precision / personalised medicine approaches aim to match the (current) molecular profile of an individual patient's cancer to the best possible targeted therapy

Personalised / precision medicine: Patients respond differently to the same treatment

- No two cancer patients are identical
- Two cancer patients with the same tumour type and stage may have completely different responses to the same (drug) treatment
- These differences in clinical outcomes can in some situations be explained by differences in the molecular profiles of their tumours
- Examples in standard practice:
  - Breast cancer: ER / HER2
  - Lung cancer: EGFR mutation / ALK translocation
- One of the key aims of research biopsies today is to develop the predictive biomarkers of tomorrow



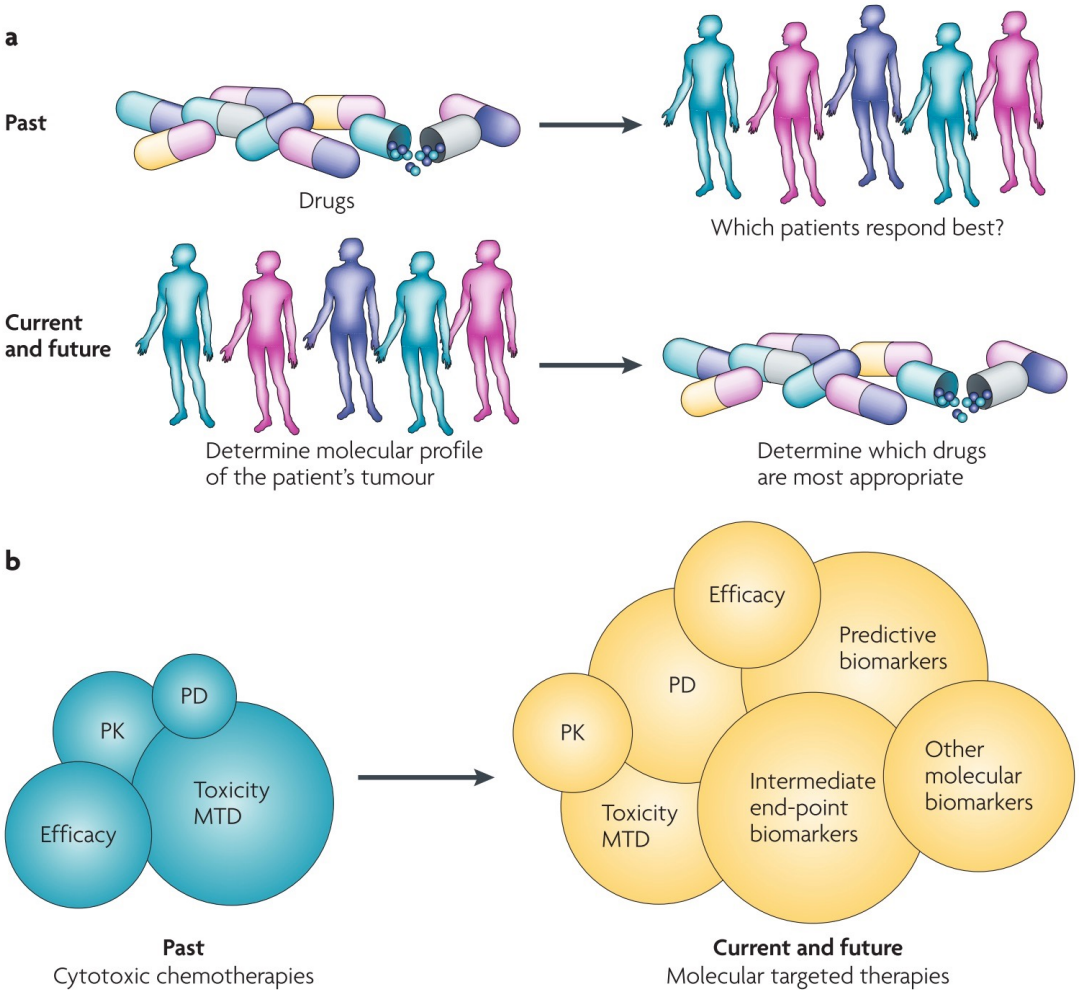
Personalised / precision medicine: Cancers change over time



Eirew Nature 2014

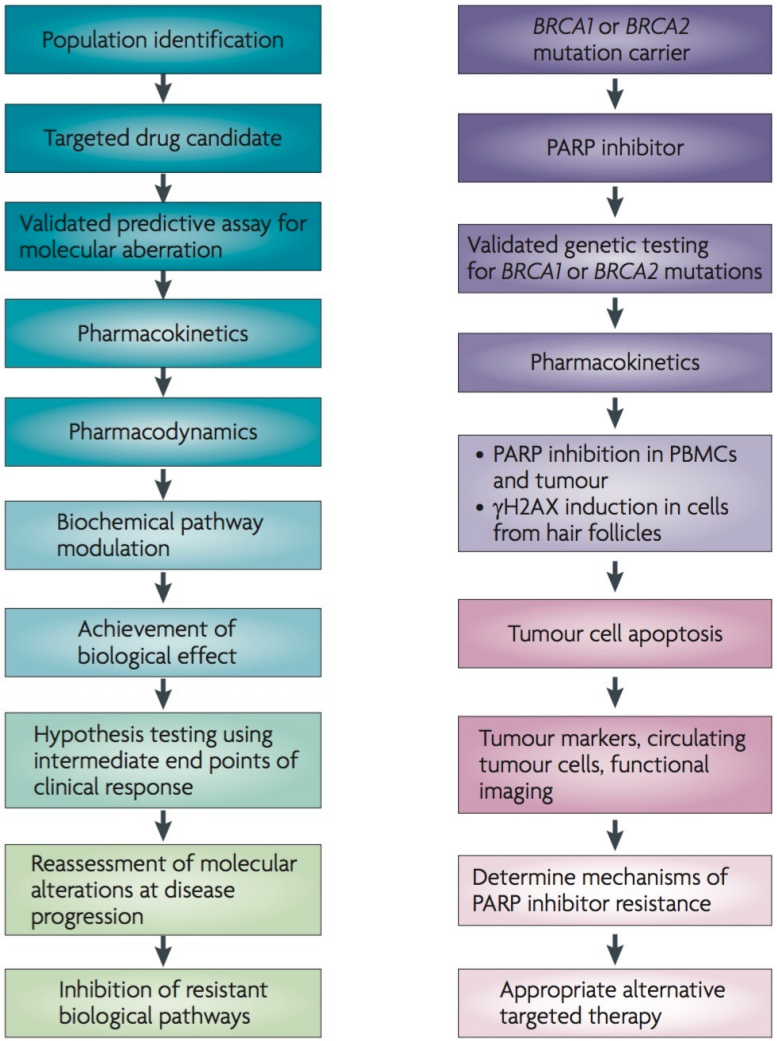
- Triple negative breast cancer
- Different colours represent different sub-clones of cancer cells within the tumour
- Looks like tumours can be complex mixes of cell populations which compete with each other
  > natural selection
  > clonal evolution

Personalised / precision medicine: Trends in contemporary drug development



Yap Nature Reviews Cancer 2010

Personalised / precision medicine: Contemporary drug development – "pharmacologic audit trail"



- To really understand why a drug works in one patient and not another
- We need to understand a sequence of scientific questions
- So-called "Pharmacologic audit trail"

Yap Nature Reviews Cancer 2010

Personalised / precision medicine: Contemporary drug development – what can be achieved

Phase	Drug	Target	Disease	ORR	References
2	Trastuzumab	HER2	Breast cancer	12%	Baselga JCO 1996
1	Imatinib	BCR-ABL C-KIT	CML GIST	54% 54%	Druker NEJM 2001 Demetri NEJM 2002
1	Olaparib	PARP	BRCA mutant cancers (breast, ovary, prostate)	47%	Fong NEJM 2009
1	Vismodegib	SMO, PTCH1 Hedgehog mutations	Advanced basal cell carcinoma	55%	Von Hoff NEJM 2009
1-2	Ruxolitinib	JAK2	Myelofibrosis	52%	Verstovsek NEJM 2010
1	Vemurafenib	BRAF V600E mutant	Melanoma	81%	Flaherty NEJM 2010
1	Crizotinib	ALK translocations	NSCLC	57%	Kwak NEJM 2010
1	CAL-101 / GS1101	PI3K δ-isoform	NHL/MCL CLL	62% 56%	Kahl ASH 2011 Brown ASCO 2013
Post-approval	Gefitinib / Erlotinib	EGFR mutant	NSCLC	66% 82%	Inoue JCO 2009 Zhou Lancet Oncol. 2011

Risks of research biopsies - to patients: What level of risk is acceptable (to patients & their doctors)

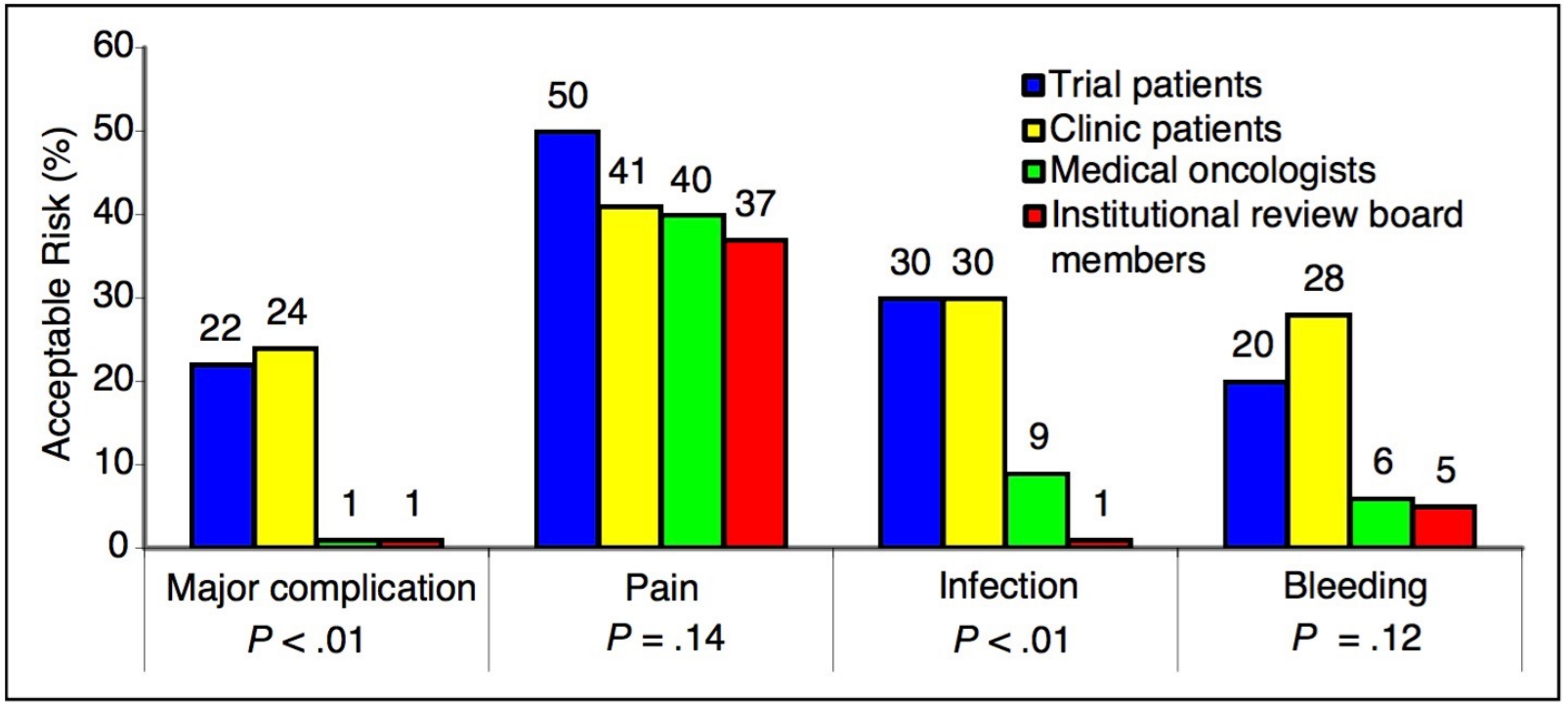


Fig 1. The percentage of trial patients, clinic patients, medical oncologists, and institutional review board members who would accept a 5% to 10% risk of a major complication, pain, infection, or bleeding associated with the research-related biopsy.

Agulnick .. Siu JCO 2006

Risks of research biopsies - to patients: What level of risk actually occurs?

Location	No. of Biopsies (N = 745)	% Total Biopsies Performed	Major Complications [CTCAE grade 3]		Minor Complications [CTCAE grade 1 or 2]	
			No.	%	No.	%
Chest-intrathoracic	211	28.3	5	2.4	31	14.7
Pulmonary	177					
Mediastinal/hilar	13					
Pleural	20					
Pericardial	1					
Abdomen/pelvis-solid organ	189	25.4	1	0.53	2	1.1
Liver	151					
Adrenal	34					
Kidney	2					
Spleen	1					
Uterus	1					
Nonsolid organ	345	46.3	0		0	
Head and neck*	88	11.8				
Chest-extrathoracic†	110	14.8				
Extremities‡	11	1.6				
Abdomen/pelvis-intraperitoneal§	34	4.6				
Abdomen/pelvis-retroperitoneal‖	27	3.6				
Abdomen/pelvis-extraperitoneal‖	75	10.1				

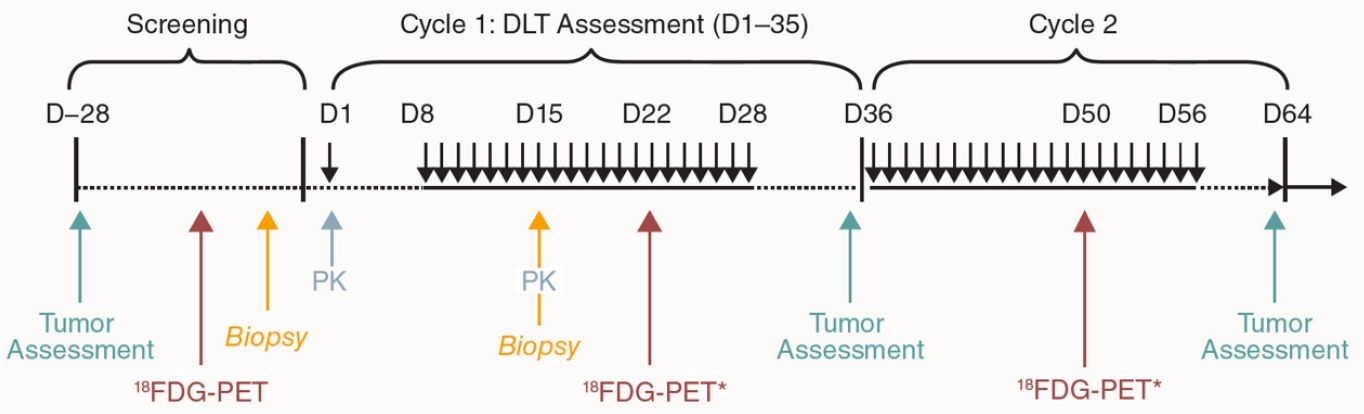
Overman JCO 2010

- MD Anderson series (745 biopsies)
- Overall complication rate 5.2%
- Major complication rate 0.8%
- Overall complication rate by site:
  - Intrathoracic 17.1%
  - Abdominal / pelvis solid organ 1.6%
- Similar results from other institutions

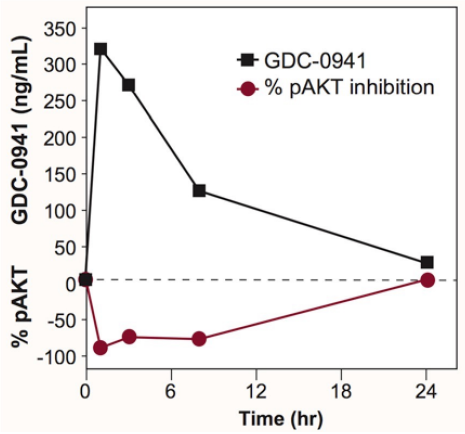
Dana-Farber Boston [Vas-Luis Br.Can.Res.Treat 2013]
Royal Marsden London [Sarker NCRI 2009]

Personalised / precision medicine: Contemporary drug development –trials can be intense

- Example of contemporary, biomarker intensive phase 1 study
- GDC-0941 – pan-PI3kinase inhibitor (Genentech) – (Baird, de Bono et al. ASCO 2010 #2613)
- Timeline for assessments during the first 2 cycles:



- Pharmacodynamic studies provided proof of target inhibition and elaboration of PK-PD relationships



Personalised / precision medicine: Biomarker studies in phase 1 trials - criticisms

- Most attempts to identify predictive biomarkers in phase 1 "nothing more than expensive fishing expeditions"
  - drug response is multifactorial (may not just depend on target inhibition)
- Our assumptions about the true drug mechanism of action may be wrong
  - eg. multi-kinase inhibitor sorafenib (originally developed as a RAF inhibitor, later shown to exert antitumour activity through VEGF inhibition)
- Performing extra research tumour biopsies poses an significant increased risk and may be unethical
- Incorrectly applied biomarker studies run the risks of:
  - exposing patients to ineffective drugs
  - discarding useful drugs

Ratain CCR 2007 13(22):6545-6548

Personalised / precision medicine: The value of biomarker studies in phase 1 trials

- Understanding the true mechanisms for drug sensitivity and resistance in the clinic is needed as soon as possible for any drug – this requires biomarker studies
- There is little evidence that extra research tumour biopsies in phase 1 studies pose an excessive risk[1,2]; tumour biopsies for PD studies are often restricted to:
  - patients with easily accessible tumours, likely to be safe
  - dose levels likely to be biologically active (eg. at predefined PK levels, after PD effects seen in surrogate tissues)
- Increasing number of examples where well-designed phase 1 biomarker studies have made a significant contribution to successful drug development
  - HER2 - trastuzumab / other HER2-directed therapies
  - BRCA mutations - olaparib / other PARP inhibitors
  - ALK translocations - crizotinib / other ALK inhibitors

[1]Dowlati CCR 2001 (7) 2971-6
[2]Sarker NCRI 2009 Abstract C143

Risks of research biopsies - to patients
The importance of fully informed consent

"You might feel a little prick."

Risks of research biopsies - to patients
The importance of fully informed consent

Does the patient information sheet include:

- Statement regarding the research nature of biopsy?
- Statement regarding the lack of personal benefit from biopsy?
- A description of the scientific rational for research biopsies?
- Mention that image-guidance will be used?
- A description of the level of risk for different biopsy sites
- (Overman JCO 2013: 57 research studies)

Overman JCO 2010

Table 3. Inclusion of Research Biopsies in Study Informed Consents

Characteristic	Total		Optional Research Biopsy Studies		Mandatory Research Biopsy Studies: Integral Biomarker		Mandatory Research Biopsy Studies: Correlative Science	
	No.	%	No.	%	No.	%	No.	%
Statement regarding research nature of								
Study	57	100	19	100	18	100	20	100
Biopsy	12	21	1	5	3	17	8	40
Optional procedures*	52	91	18	95	16	89	18	90
Statement regarding lack of benefit from								
Study	57	100	19	100	18	100	20	100
Biopsy	0		0		0		0	
Optional procedures*	32	56	14	74	10	56	8	40
Statement regarding alternatives to undergoing								
Study	57	100	19	100	18	100	20	100
Biopsy	0		0		0		0	
Optional procedures*	50	88	19	100	16	89	15	75
Scientific rationale for biopsy provided	48	84	17	89	17	94	14	70
Statement describing the use of a needle to obtain biopsy†	38	67	14	74	9	50	15	75
Use of image guidance mentioned	14	25	1	5	6	33	7	35
Statement regarding safety or accessibility of biopsy site	20	35	8	42	6	33	6	30

Why do we inflict research biopsies on our patients? 2 main reasons:

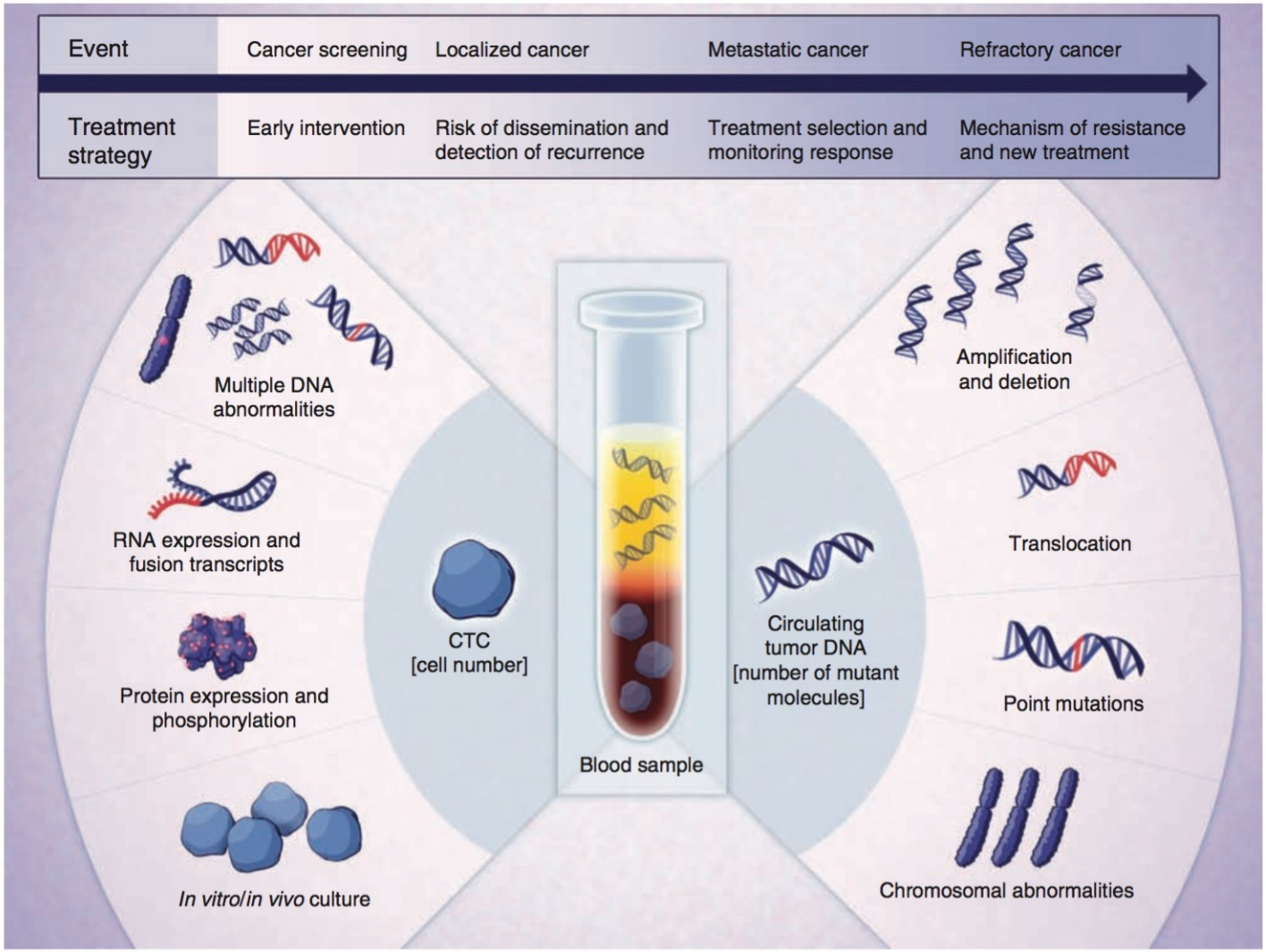
1. Individual patients respond differently to the same treatment
2. A cancer within an individual patient can change over time, and may therefore require a change in treatment

Robust studies correlating cancer molecular profiles with response to different treatments are crucial to improve clinical outcomes for patients with cancer – research biopsies will continue to be important for this … but we can improve ...

Research biopsies – how can we improve?

1. Ensure strong scientific rationale (including statistical plan)
2. Ensure fully informed patient consent
3. Minimise risk on the day of biopsy
   - image-guidance, skill of operator, pressure / observation afterwards
4. Clinical governance around biopsies - monitor adverse events
5. Ensure quality of tissue acquisition, processing and storage
6. Ensure that we complete and report biomarker data on research biopsies
7. And finally … develop less-invasive methods for biomarker research
   - liquid biopsies (circulating tumour DNA), imaging etc..

Research biopsies – is the future liquid?



Thank you – any questions?