Strategies For Meaningful Biomarkers in Neoadjuvant Trials

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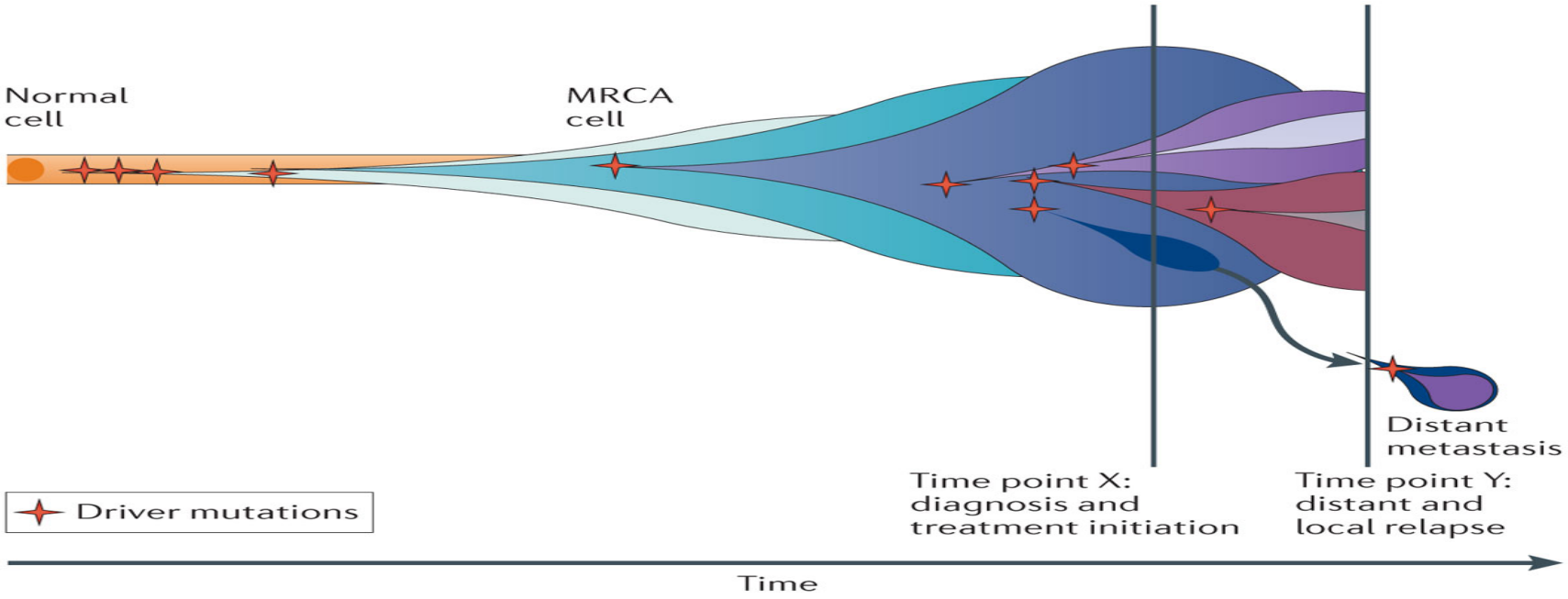
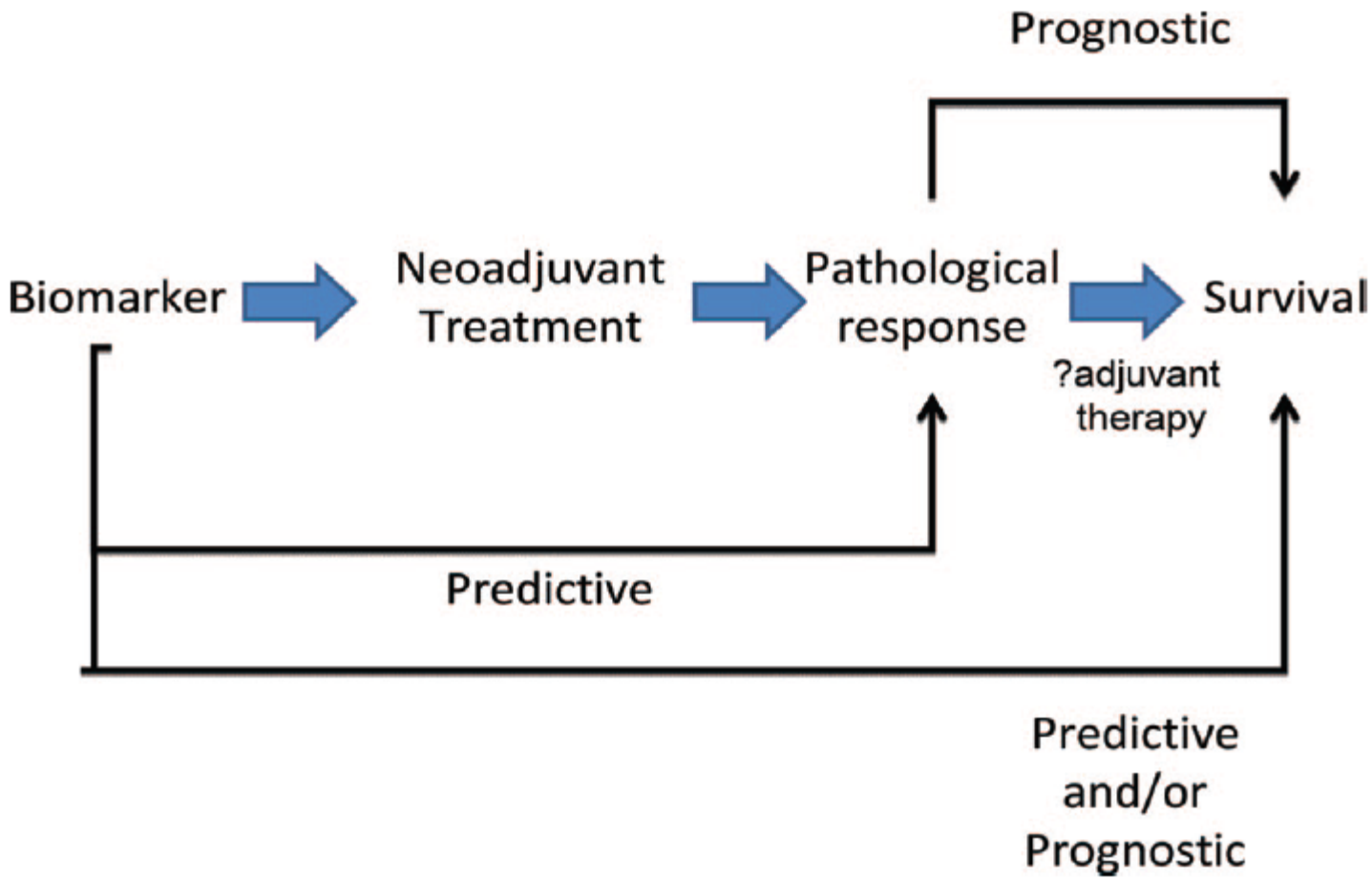
Clonal selection

- Genomic heterogeneity within individual tumors
- Result of clonal evolution during progression

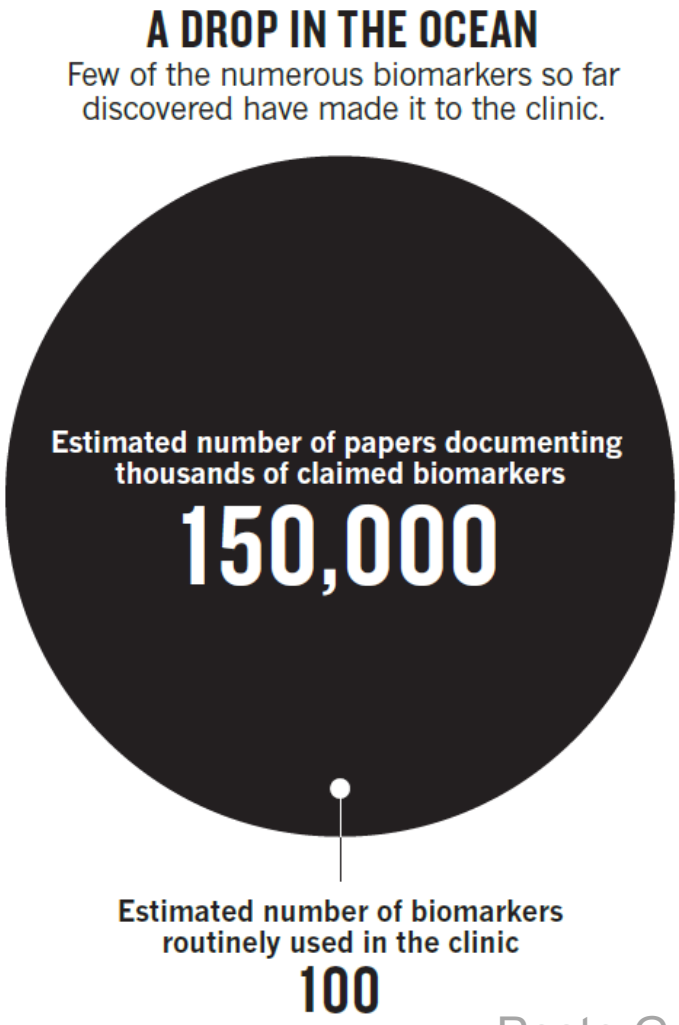


Yates & Campbell, Nature Rev Genet, 2012



Bain GH and Petty RD, The Oncologist 2010

Biomarker discovery



Poste G, Nature 2011

Potential of molecular biomarkers to predict histopathological response

Table 4. Studies demonstrating the potential of molecular markers to predict histopathological response/survival of patients with GEJ adenocarcinoma given neoadjuvant treatment

Type of cellular pathway/factor	Marker/type of change	Timing of measurement	Sample size	Tumor type	Tumor site	Neoadjuvant treatment	Methods	Histopathological response score	Outcome	Study
Transcription factors	NF-κB −ve	Pretreatment	58	A	Esophagus	CRT	Electrophoretic mobility shift assay, western blot, IHC	Other	PathR ↑ ($p = .0001$); survival ↑ ($p < .05$)	Abdel-Latif et al. (2004) [47]
	NF-κB +ve	Pretreatment	37	A/SCC	Esophagus and GEJ	CRT	IHC	Other	PathR ↓ ($p = .05$); OS ↓ ($p = .06$)	Izzo et al. (2006) [48]
	NF-κB +ve	Pretreatment	75	A/SCC	Esophagus and GEJ	CRT	IHC	Other	PathR ↓ ($p = .006$); disease-free survival ↓ ($p = .007$); OS ↓ ($p = .009$)	Izzo et al. (2006) [49]
Growth factor receptors	EGFR ↓	Pretreatment	54	A/SCC	Esophagus and GEJ	CRT	IHC	Other	OS ↑ ($p = .009$)	Gibson et al. (2003) [50]
	EGFR ↓	Pretreatment to resection	22	A/SCC	Esophagus	CRT	PCR	Junker	PathR ↑ ($p = .014$)	Schneider et al. (2005) [51]
	HER-2 ↓	Pretreatment	36	A/SCC	Esophagus	CRT	PCR	Junker	PathR ↑ ($p = .015$)	Miyazono et al. (2004) [52]
Angiogenetic factors	Vascular endothelial growth factor ↓	Pretreatment	56	A/SCC	Esophagus	CRT	IHC	Other	PathR ↑ ($p = .035$); survival ↑ ($p = .021$)	Imdahl et al. (2002) [53]
Tumour suppressor genes	*p53* mutation	Pretreatment	46	A/SCC	Esophagus and GEJ	CRT	PCR, DNA sequencing	Other	OS ↑ ($p = .051$)	Gibson et al. (2003) [50]
	p53 +ve	Pretreatment	48	A/SCC	Esophagus and GEJ	CRT/Chemotherapy	IHC	Other	PathR ↓ ($p = .024$)	Beardsmore et al. (2003) [54]
	p53 +ve to −ve	Pretreatment to resection	23	A	Esophagus and GEJ	Chemotherapy	IHC	Other	PathR ↑ ($p = .003$); OS ↑ ($p = .036$)	Heeren et al. (2004) [55]
Cell cycle regulators	p21 −ve to +ve	Pretreatment to resection	23	A	Esophagus and GEJ	Chemotherapy	IHC	Other	PathR ↑ ($p = .003$); OS ↑ ($p = .036$)	Heeren et al. (2004) [55]
Nucleotide excision repair pathway	*ERCC1* ↓	Pretreatment	36	A/SCC	Esophagus	CRT	PCR	Junker	PathR ↑ ($p < .001$)	Warnecke-Eberz et al. (2004) [56]
	ERCC1 ↑	Pretreatment	84	A/SCC	Esophagus	CRT	PCR	Other	Survival ↓ ($p = .071$)	Joshi et al. (2005) [57]
Apoptotic factors	Survivin ↑	Pretreatment	51	A/SCC	Esophagus	CRT	PCR	Junker	PathR ↔, OS ↑ ($p < .003$)	Warnecke-Eberz et al. (2005) [58]
Chemotherapy associated genes	TS ↑	Pretreatment	69	A/SCC	Esophagus	CRT	PCR	Other	PathR ↓ ($p < .001$); survival ↓ ($p = .007$)	Joshi et al. (2005) [57]
	TS +ve	Pretreatment	118	A/SCC	Esophagus	CRT	IHC	Other	Survival ↓ ($p = .04$)	Harpole et al. (2001) [59]
	TS ↓	Pretreatment to resection	21	A	Esophagus	Chemotherapy	PCR	Becker	PathR ↑ ($p = .028$)	Langer et al. (2007) [60]
	Thymidine phosphorylase ↓	Pretreatment	21	A	Esophagus	Chemotherapy	PCR	Becker	PathR ↑ ($p = .013$)	Langer et al. (2007) [60]
	Dihydropyrimidine dehydrogenase ↓	Pretreatment	21	A	Esophagus	Chemotherapy	PCR	Becker	PathR ↑ ($p = .032$)	Langer et al. (2007) [60]

continued

Bain GH and Petty RD, The Oncologist 2010

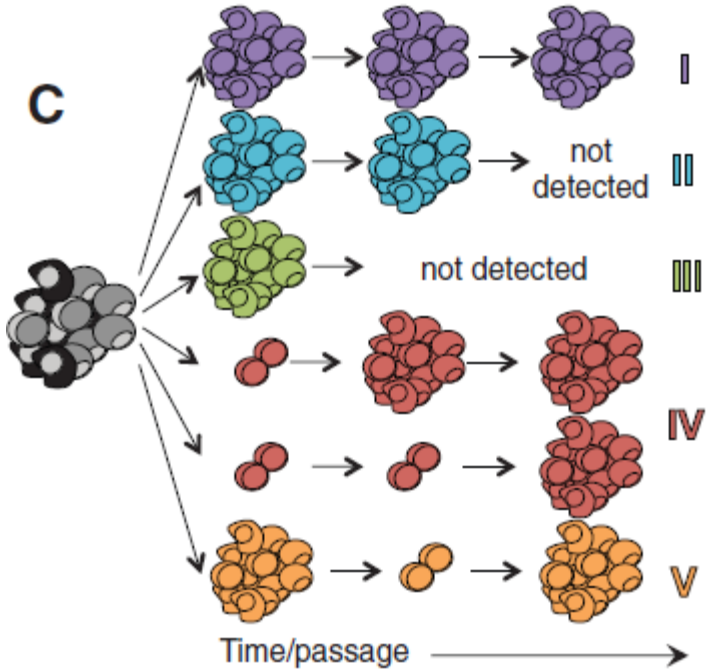
Different settings in GI

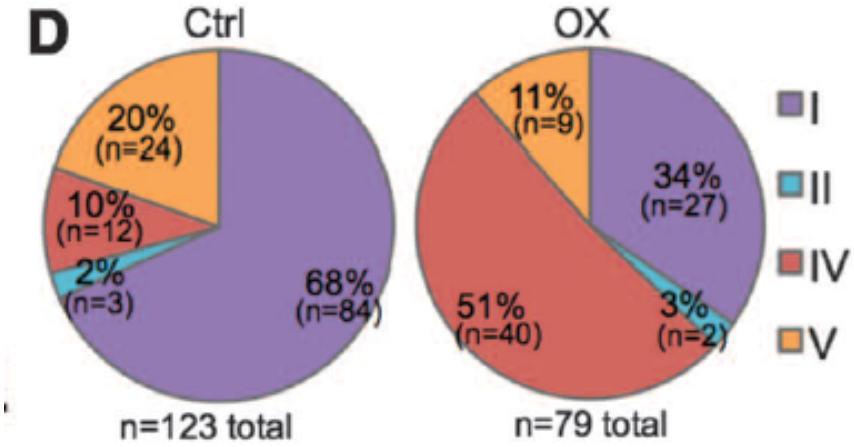
- GEJ
- Pancreas
- Colon
- Rectal

Variable Clonal Repopulation Dynamics Influence Chemotherapy Response in Colorectal Cancer

Antonija Kreso,[1,2]* Catherine A. O'Brien,[1,3]* Peter van Galen,[1] Olga I. Gan,[1] Faiyaz Notta,[1,2] Andrew M. K. Brown,[4] Karen Ng,[4] Jing Ma,[5] Erno Wienholds,[1] Cyrille Dunant,[6] Aaron Pollett,[7] Steven Gallinger,[8] John McPherson,[4] Charles G. Mullighan,[5] Darryl Shibata,[9] John E. Dick[1,2]†

SCIENCE VOL 339 1 FEBRUARY 2013





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Adjuvant therapy, clonal selection, and mCRC

- Adjuvant FOLFOX and improved OS in FOLFIRI/bevacizumab

- CALGB 80405 (not on FOLFOX+targeted, Venook et al., ASCO 2014)
- TRIBE (not in FOLFOXIRI/bevacizumab) (Loupakis et al., NEJM 2014)
- FIRE-3 (Heinemann et al., ESMO 2014)

Neo-Adjuvant therapy, clonal selection, and mCRC

Serial FDG-PET in GEJ adenocarcinoma

- During the course on neoadj

- Early metabolic response and correlation with
  - decrease in tumor size
  - higher rate of curative resections
  - histopathological regression
  - survival

Serial FDG-PET in GEJ adenocarcinoma

- High NPV
- Limited PPV

- Optimization of time and point repeat, plus standardization of protocols

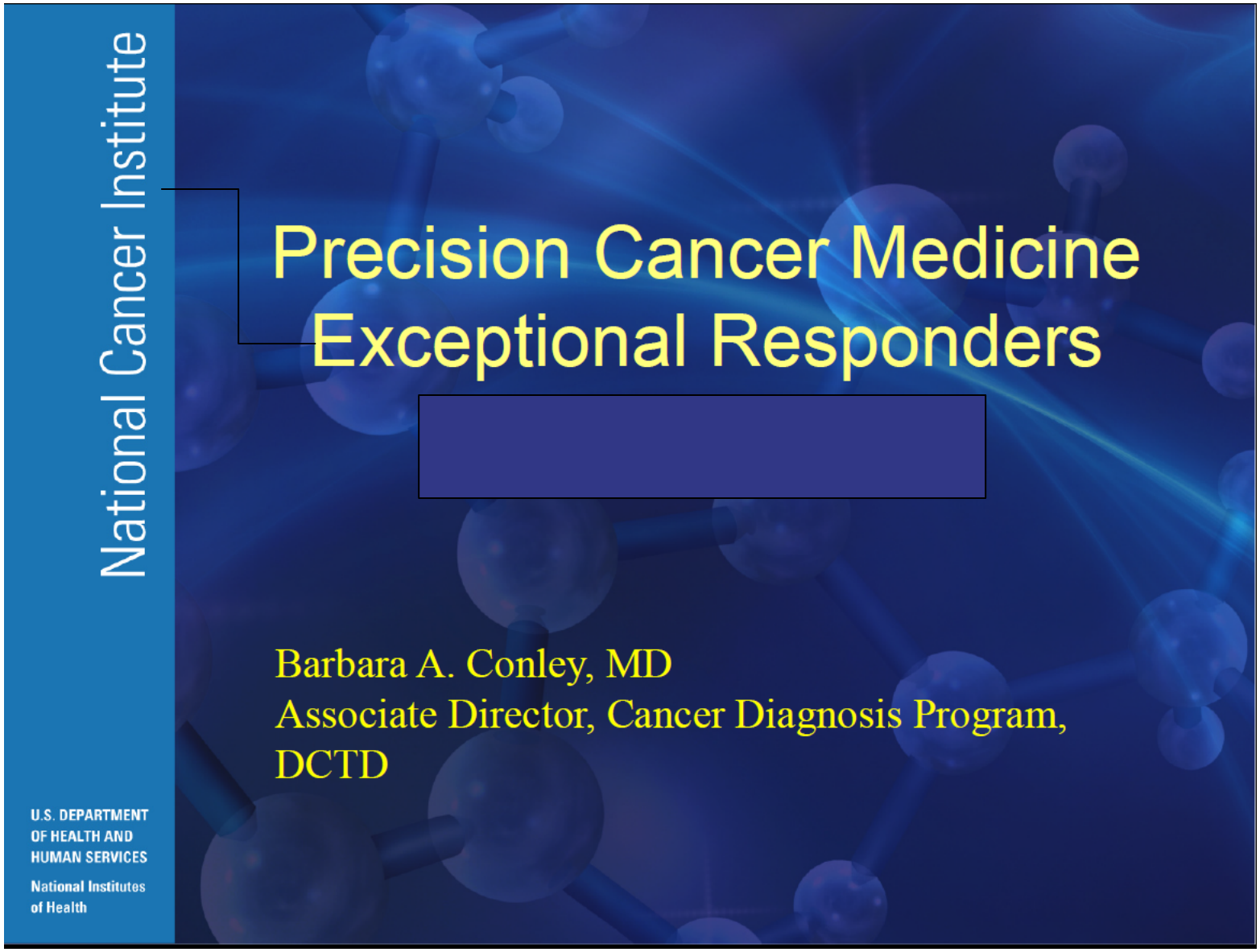
- IMAGE trial

Borderline resectable PDAC

- Node involvement and marginal status predict relapse

- Neoadj (CRT)
  - might improve R0 resection rates
  - select out patients

- Studies not adequately powered
- Utility not fully established yet



Mullard A, Nature Reviews Drug Discovery
13, 803 (2014) Published online 31 October 2014

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NCI Exceptional Responders Initiative

- To understand the molecular underpinnings of exceptional responses to chemotherapy
- Cancer Therapy Evaluation Program phase II trial database over a period of 10 years (2002-2012)
- 100 cases were identified

Definitions of an "exceptional responder"

- Achieved either a complete response or a partial response for >6 months, as defined by RECIST

- Received a treatment in which <10% of patients had either a complete response or partial response for >6 months

NCI Exceptional Responders Initiative

- DNA and RNA will be isolated from tissues submitted to the NCI

- Exome sequencing and/or mRNA sequencing from 100 cases (up to 300 possibly)

Opportunities – neoadj in PDAC

- Ultrasound and FNAs for diagnosis – pre-sample unlikely to be available
- Use of circulating tumor cells
- Stroma predominates in core biopsies

Vitamin D Receptor-Mediated Stromal Reprogramming Suppresses Pancreatitis and Enhances Pancreatic Cancer Therapy

Mara H. Sherman,[1] Ruth T. Yu,[1] Dannielle D. Engle,[2] Ning Ding,[1] Annette R. Atkins,[1] Herve Tiriac,[2] Eric A. Collisson,[3] Frances Connor,[4] Terry Van Dyke,[5] Serguei Kozlov,[6] Philip Martin,[6] Tiffany W. Tseng,[1] David W. Dawson,[7] Timothy R. Donahue,[7] Atsushi Masamune,[8] Tooru Shimosegawa,[8] Minoti V. Apte,[9] Jeremy S. Wilson,[9] Beverly Ng,[10,11] Sue Lynn Lau,[10,12,13] Jenny E. Gunton,[10,11,12,13] Geoffrey M. Wahl,[1] Tony Hunter,[14] Jeffrey A. Drebin,[15] Peter J. O'Dwyer,[16] Christopher Liddle,[17] David A. Tuveson,[2] Michael Downes,[1,*] and Ronald M. Evans[1,18,*]

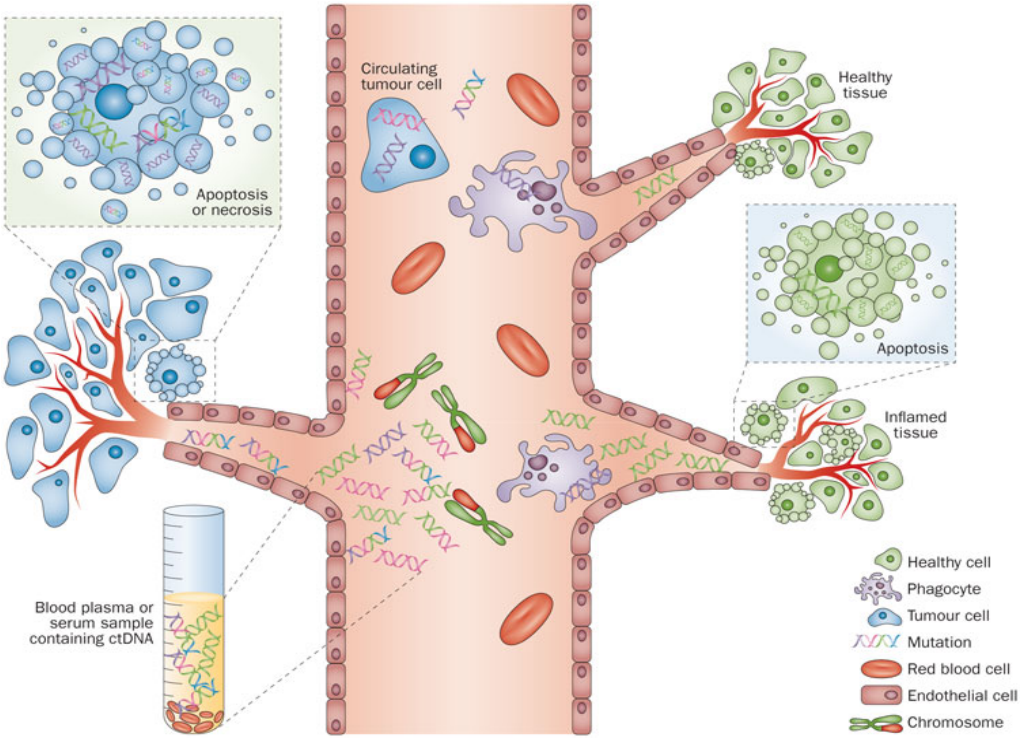
Cell *159*, 80–93, September 25, 2014 ©2014 Elsevier Inc.

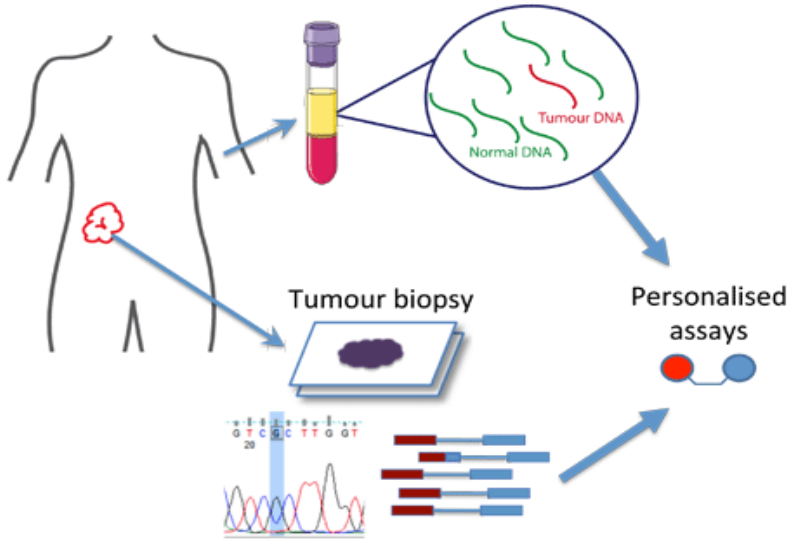
- VDR activation reprograms reactive stroma and reduces inflammation
- Increased gemcitabine concentration
- Reduced tumor volume

Opportunities – neoadj in PDAC

- Rather than stromal ablation or inhibition
- Modality of reprogramming the stromal function
- Prospective testing
- Pre- and post-evaluations of molecular biomarkers

Liquid biopsies





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New York Times

Sidestepping the Biopsy With New Tools to Spot Cancer, Pollack A, April 7th, 2014

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