BigCARE

Big Data & Cancer:
Where are we going?

July 17, 2024

Richard Van Etten, MD PhD
Cancer Center Director

UCI

趙 Chao Family
Comprehensive Cancer Center

UCI Health

Disclosures

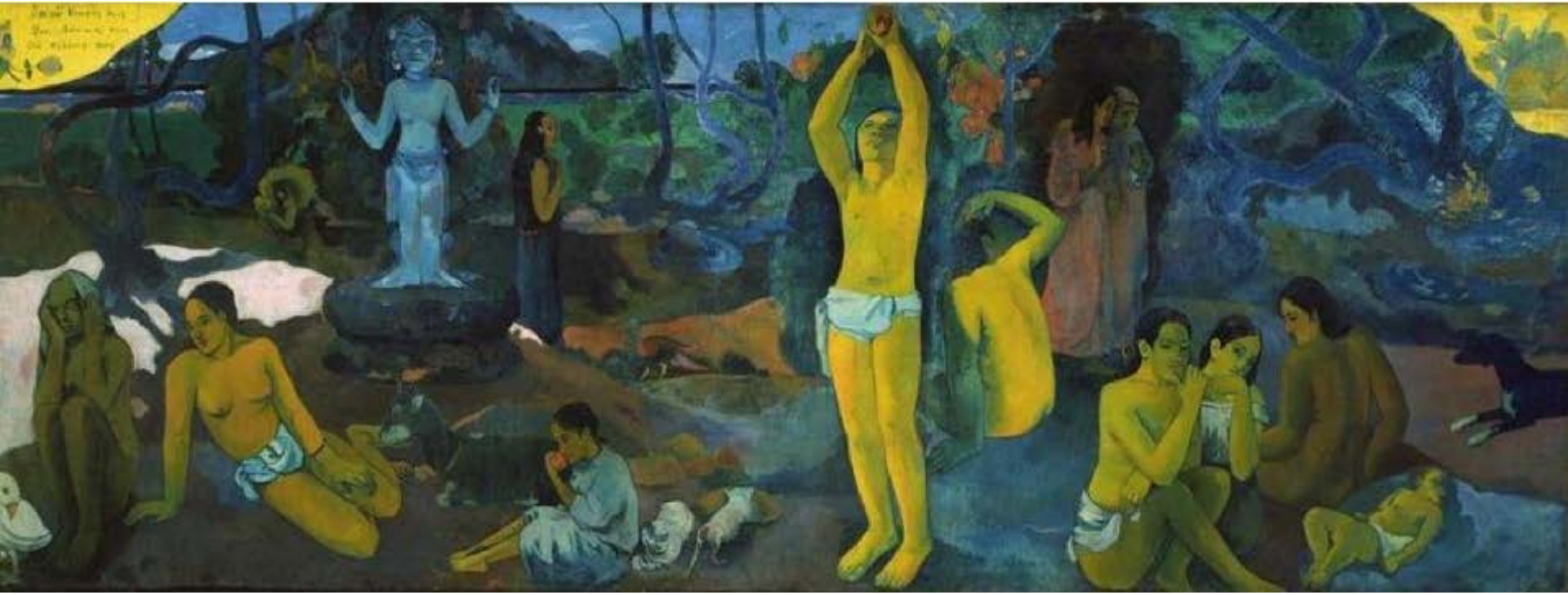
- COI: I am an advisor to Helio Genomics, an early cancer diagnostics company
- I am not an expert in this area, but what follows will be my own opinionated and relatively free-form discourse on this general topic
- If you want to hear from some real experts:

Dr. Eric Stahlberg
NCI Frederick National Laboratory
Around the Corner:
Peering into the Future for Personalized Precision Health
Tue July 23 1:00 pm

Dr. Jill Barnholtz-Sloan
NIH Center for Biomedical Informatics & Information Technology
Utilizing Data to Make Advancements for Cancer
Wed July 24 1:00 pm

D'où Venons Nous / Que Sommes Nous / Où Allons Nous

(Where do we come from? / What are we? / Where are we going?)



Paul Gauguin 1897

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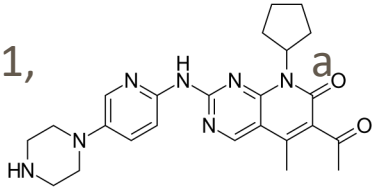
Drug Discovery

A story about rediscovering a targeted cancer drug

- 2000: Dave Fry and Peter Toogood at Parke-Davis synthesize PD-0332991, a selective inhibitor of CDK4/6

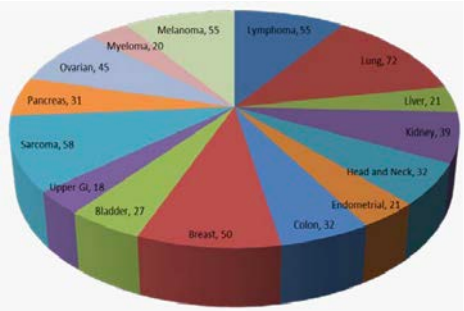


- 2003: Pfizer acquires Parke-Davis. Clinical development of PD-0332991 is de-emphasized

- 2004: A phase 1 clinical trial of PD-0332991 in patients with relapsed/refractory solid tumors shows no major clinical responses, dose-limiting toxicity is myelosuppression

A story about rediscovering a targeted cancer drug

- 2007: Dr. Dennis Slamon at UCLA obtains access to PD-0332991
- 2008: Slamon's Translational Oncology Research Lab analyzes PD-0332991 in a panel of >600 biochemically and genetically defined cancer cell lines in a 6-day proliferation assay



- 2009: Specific activity of PD-0332991 is seen vs. ER^+ breast cancer cells
- 2011: Dr. Richard Finn at UCLA runs a phase 1/2 study in 165 women with advanced ER^+ breast cancer ± letrozole. Median PFS increased from 10 mo to 20 mo.

A story about rediscovering a targeted cancer drug

- 2013: Pfizer launches a randomized phase 3 study of PD-0332991 (now palbociclib) in ER$^+$ HER2$^-$ advanced breast cancer
- 2015: Positive trial results published in NEJM. Palbociclib receives accelerated approval from FDA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

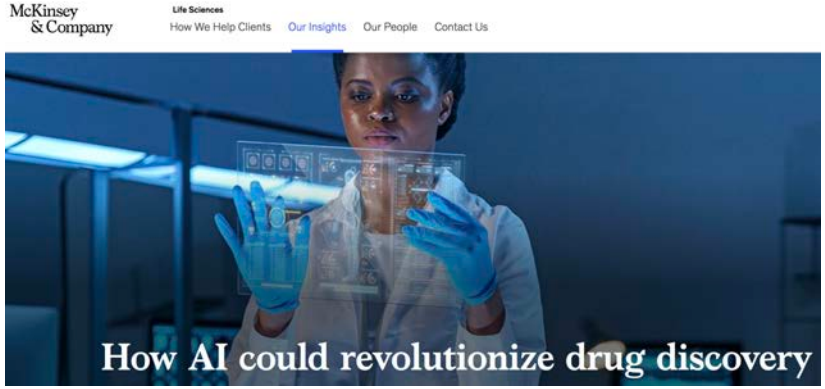
Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer

Authors: Nicholas C. Turner, M.D., Ph.D., Jungsil Ro, M.D., Fabrice André, M.D., Ph.D., Sherene Loi, M.D., Ph.D., Sunil Verma, M.D., Hiroji Iwata, M.D., Nadia Harbeck, M.D., +6, and Massimo Cristofanilli, M.D.

Published July 16, 2015 | N Engl J Med 2015;373:209-219 | DOI: 10.1056/NEJMoa1505270 | VOL. 373 NO. 3

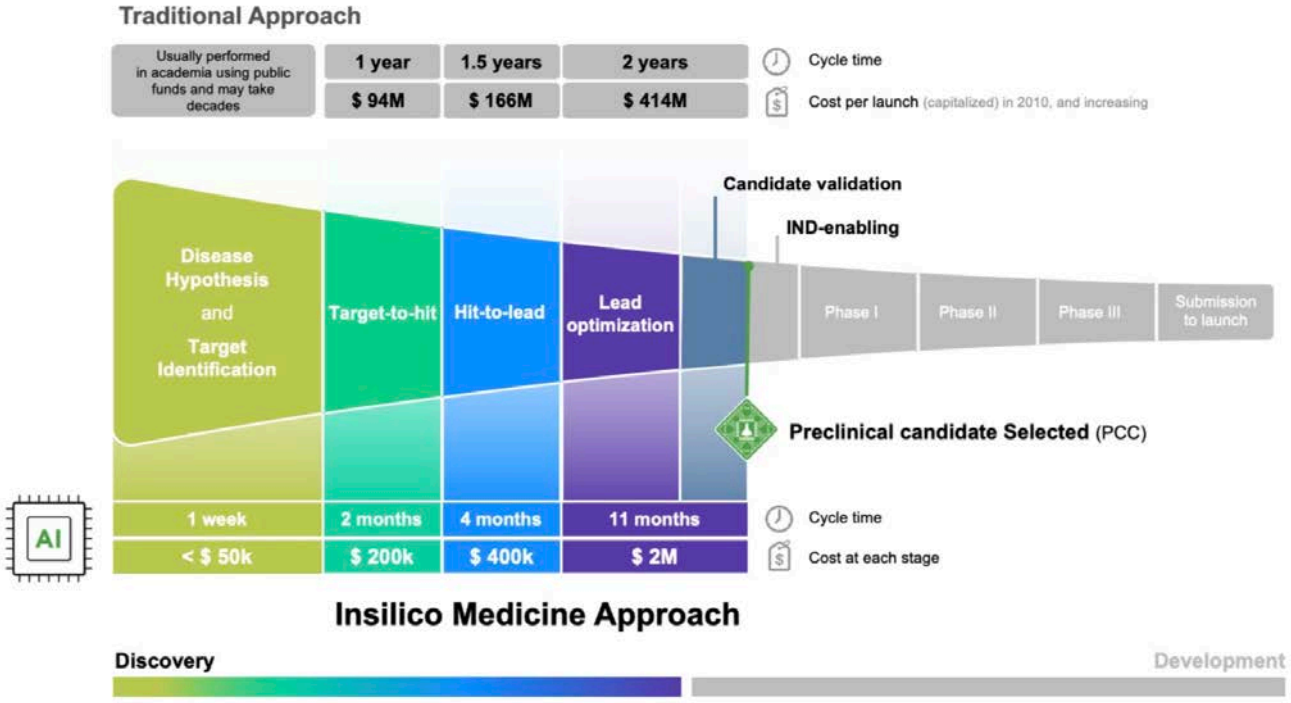
- 2017: Ribociclib (Novartis) approved by FDA for HR$^+$ HER2$^-$ met breast cancer
- 2018: Abemaciclib (Lilly) approved by FDA for HR$^+$ HER2$^-$ met breast cancer
- It took 15 years for the therapeutic potential of CDK4/6 inhibitors to be realized…

Can we do better than this?



An AI-based drug development story: Insilico

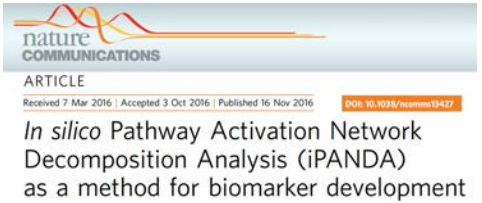
Insilico Medicine

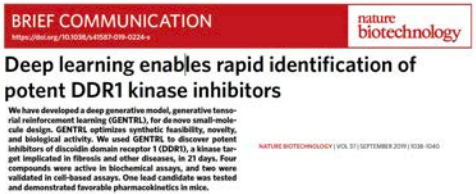


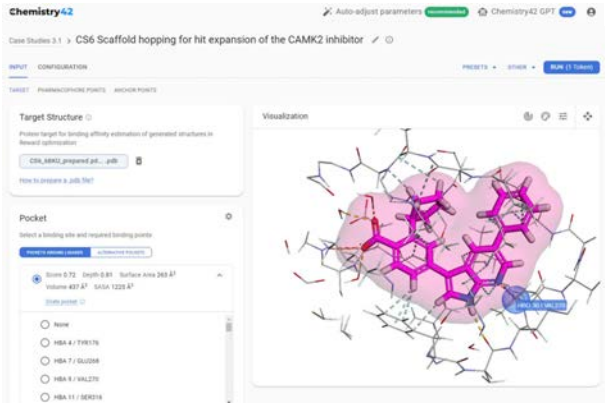
An AI-based drug development story: Insilico

Insilico Medicine

- Identified a potential novel drug target for idiopathic pulmonary fibrosis (IPF)
- AI-generated structure of this (undisclosed) target
- *In silico* selection and optimization of a small molecule inhibitor
- POC testing in a bleomycin-induced mouse pulmonary fibrosis model
- First-in-human PK study in healthy volunteers
- Launched phase 2 in Feb 2024 in IPF (total cost ~$2M)







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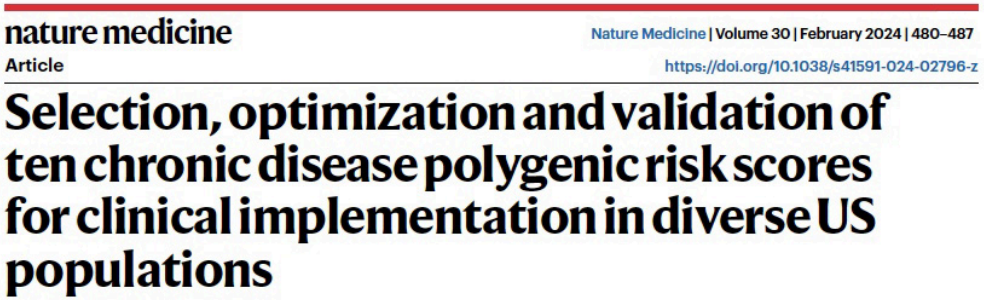
Cancer Prevention & Screening

Cancer risk assessment: polygenic risk scores

ancestry 23andMe

- Cancer risk assessment is straightforward with highly penetrant cancer susceptibility genes (e.g. *BRCA1* in breast cancer: 85% lifetime risk)

- But what about cancers where the incremental impact of multiple genotypes with low individual attributed risk needs to be assessed? (~1 out of 8 women = 13% will get breast cancer in their lifetime)

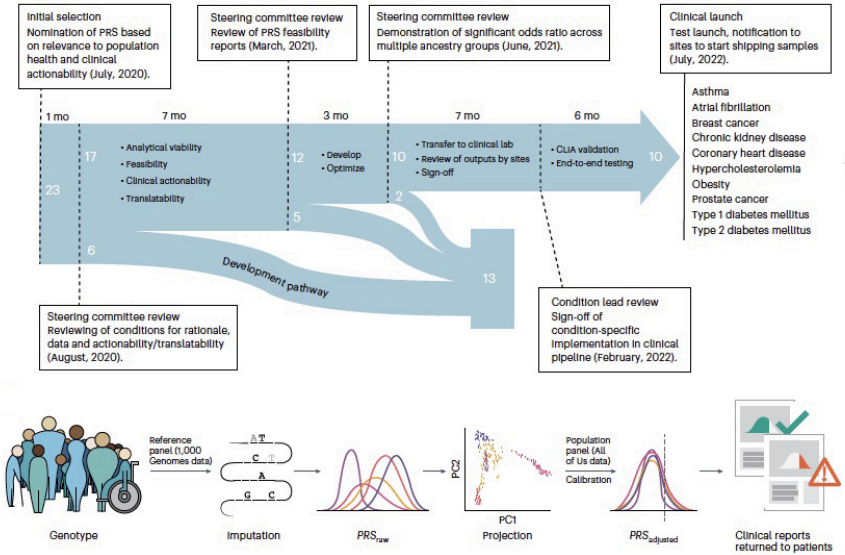


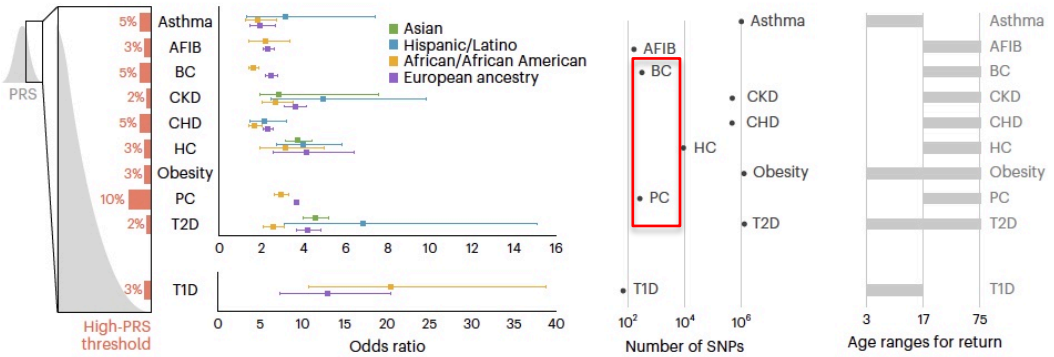
nature medicine
Article
Nature Medicine | Volume 30 | February 2024 | 480–487
https://doi.org/10.1038/s41591-024-02796-z

Selection, optimization and validation of ten chronic disease polygenic risk scores for clinical implementation in diverse US populations

Cancer risk assessment: polygenic risk scores

- Illumina Global Diversity Array (1.8M SNPs)

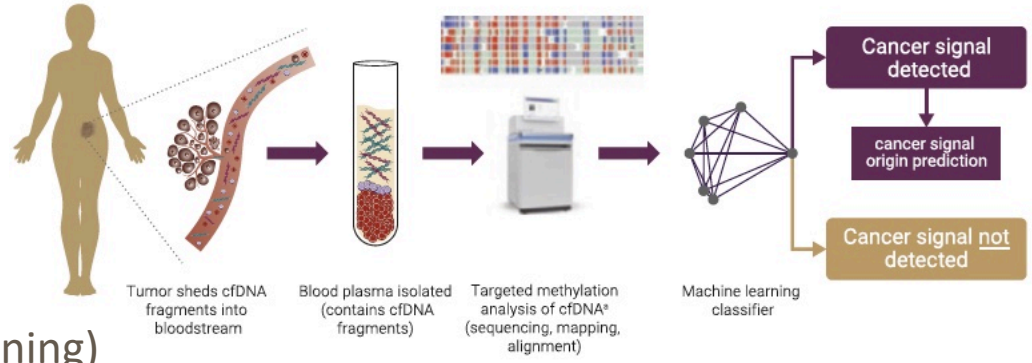


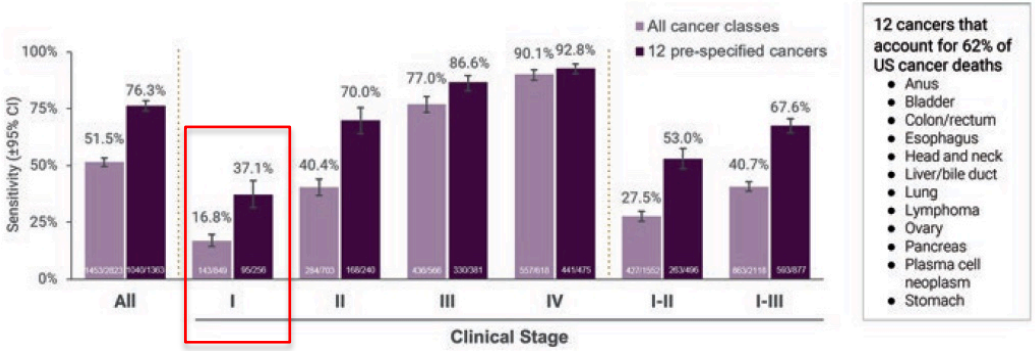


- What to do with the data? (Breast cancer: decrease alcohol consumption, lose weight, avoid HRT, change mammography schedules, prophylactic mastectomy?)

Cancer early diagnosis: Multi-Cancer Early Detection (MCED) Tests

- Galleri detects specific methylated sites in circulating cfDNA
- Test algorithm trained on a “control” group (no h/o cancer, adherent to screening)
- Major issue: low sensitivity for early stage cancer
- Need for specific f/u for positive tests





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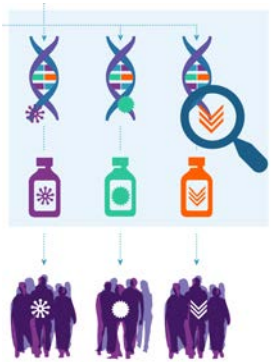
“Precision” Oncology

Multi-Omics data and cancer therapeutics

- Current paradigm: sequence tumor → identify druggable target → try targeted therapy → publish case report of successful response
- Efforts to scale this approach: NCI MATCH, ASCO TAPUR
- UC Data Warehouse: omnibus source of Epic-derived patient data
- What is needed: technology to analyze genomic, epigenomic, transcriptomic, and proteomic patient data that is correlated with outcomes

NIH NATIONAL CANCER INSTITUTE



ASCO TAPUR
Targeted Agent and Profiling Utilization Registry Study

Multi-Omics data and cancer therapeutics

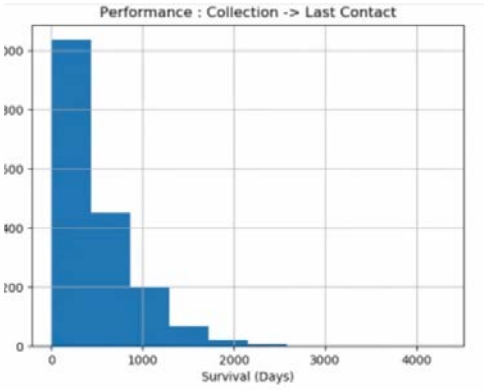
CARIS LIFE SCIENCES

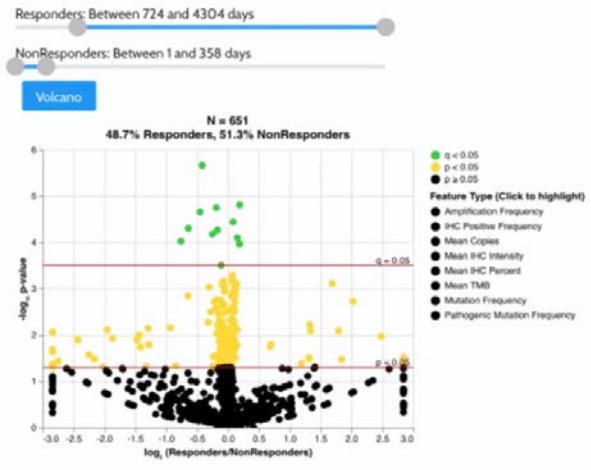
Universe (N=215277)

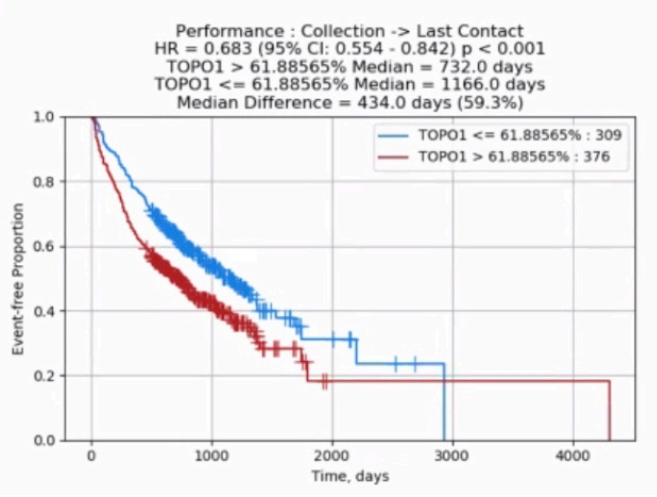
Cancer Types: Lung Non-small cell lung cancer NSCLC (N=38765)

Histology: Adenocarcinoma, NOS, Carcinoma, NOS (N=21122)

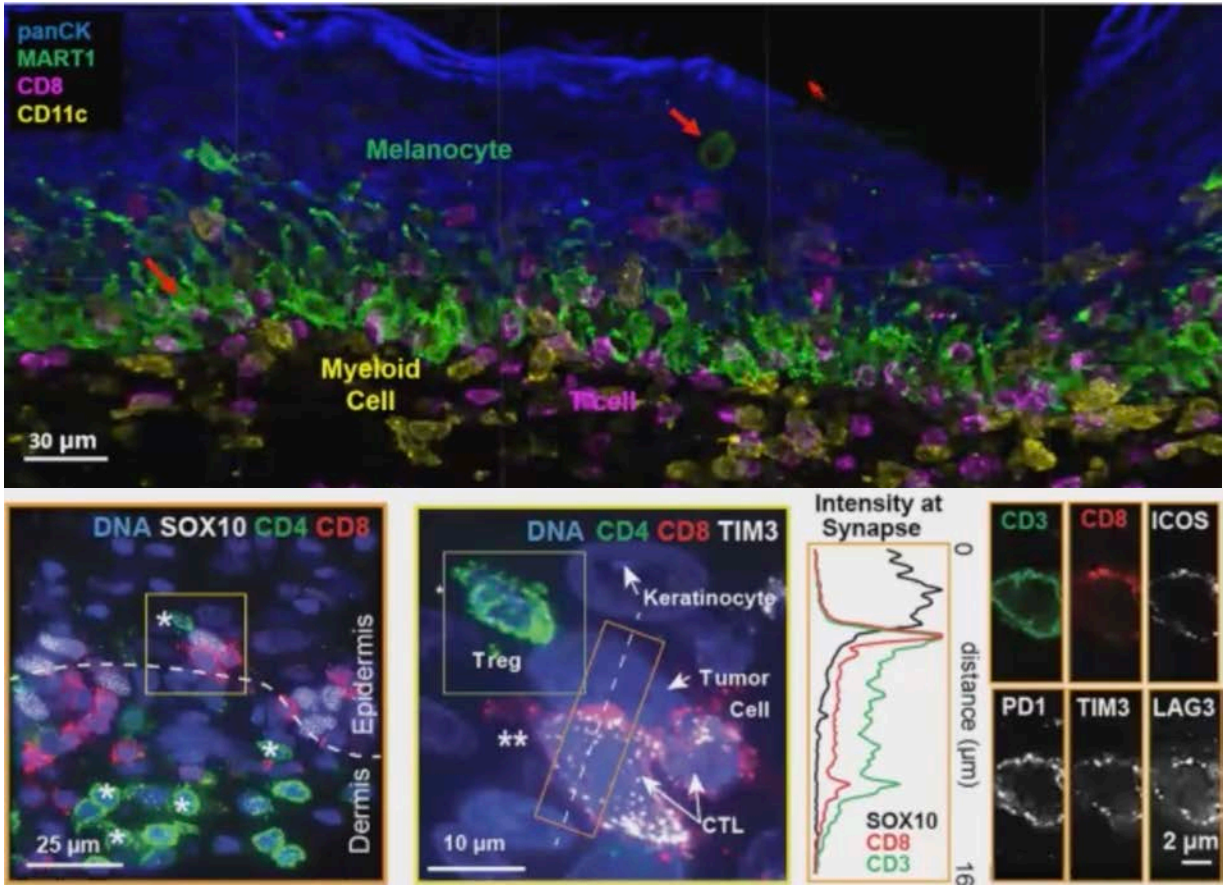
Molecular Subtypes: EGFR Mutated Mutated (N=2040)





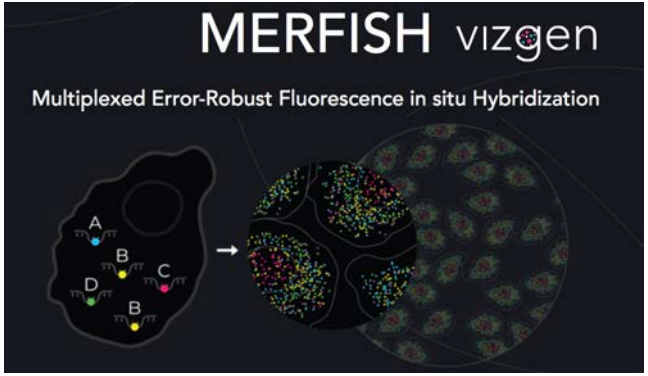


Spatial ‘Omics: the next frontier?



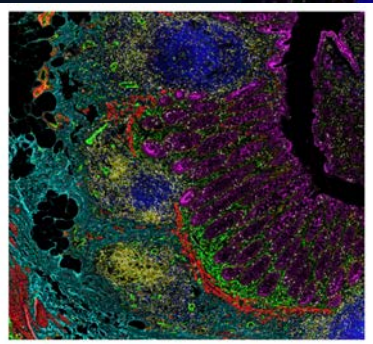
Courtesy Dr. Peter Sorger, MIT

Spatial ‘Omics: Numerous platforms, limited clinical application yet



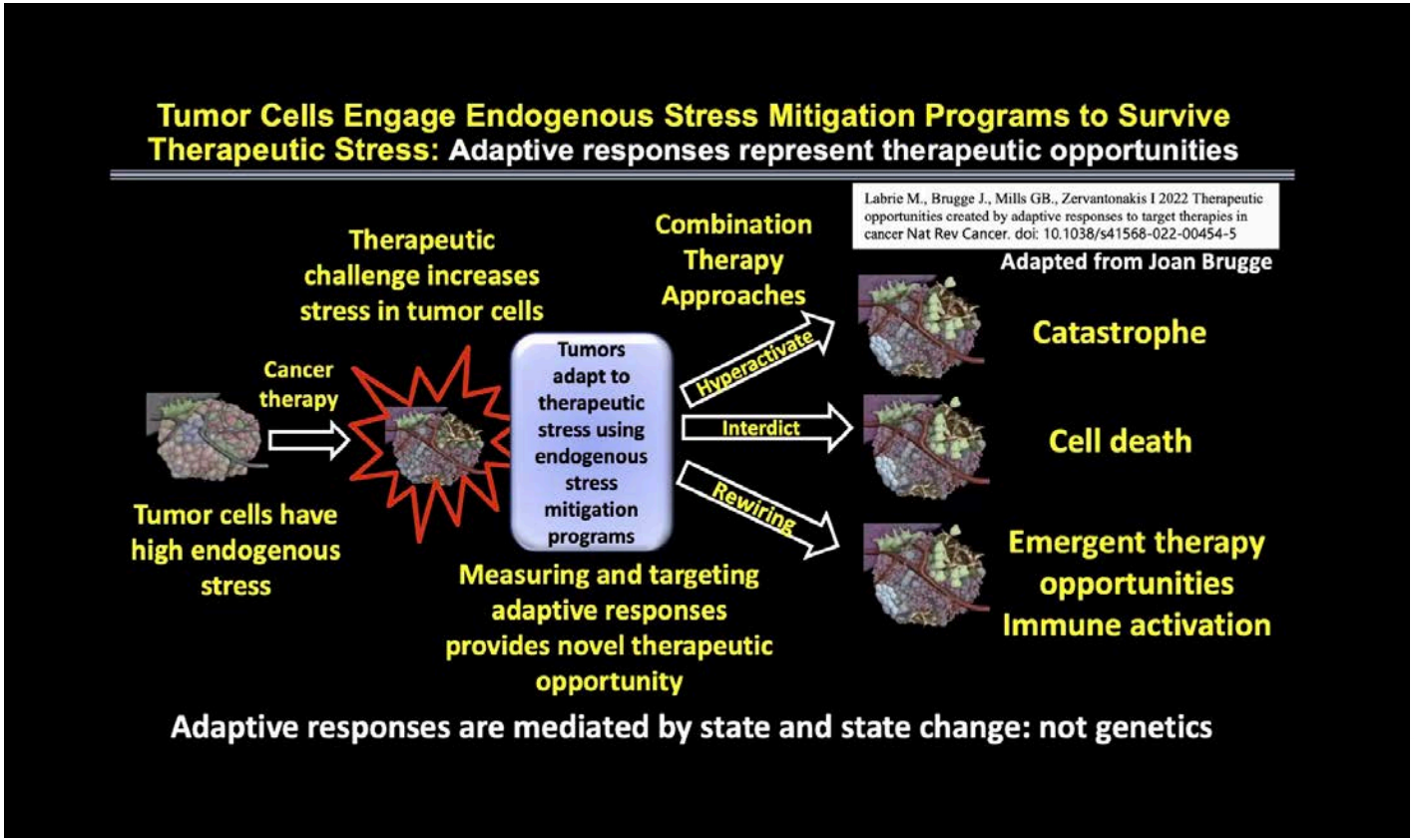
Sirona Dx

Fluidigm Hyperion



The Hyperion™ Imaging Mass Cytometry (IMC) is based on laser ablation technology coupled with time-of-flight (TOF) mass cytometry. This technology allows for a comprehensive understanding of complex cellular phenotypes and their interrelationships in the spatial context of the tissue microenvironment.

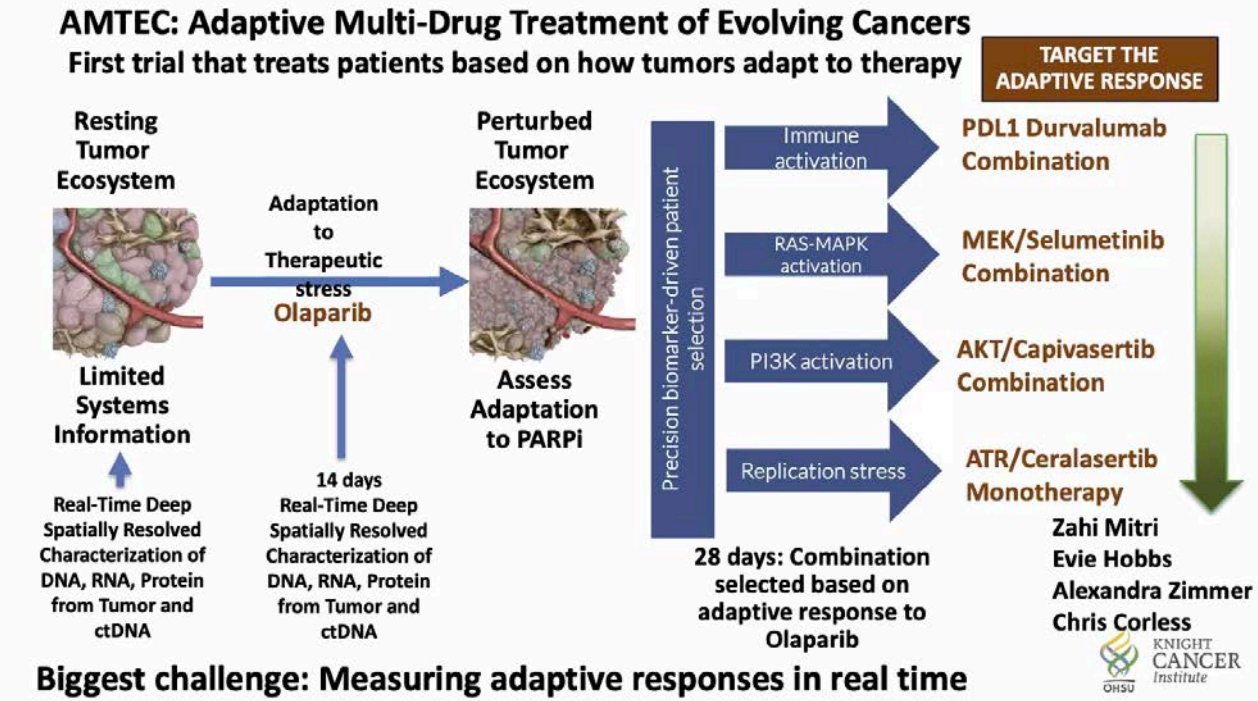
Spatial ‘Omics: An example from Oregon Health & Science Univ.



Courtesy Dr. Gordon Mills, Director of Precision Oncology at Knight Cancer Institute, OHSU

Spatial 'Omics: An example from Oregon Health & Science Univ.

BRCA1/2 WT advanced breast cancer treated with PARP inhibitor



Courtesy Dr. Gordon Mills, Director of Precision Oncology at Knight Cancer Institute, OHSU

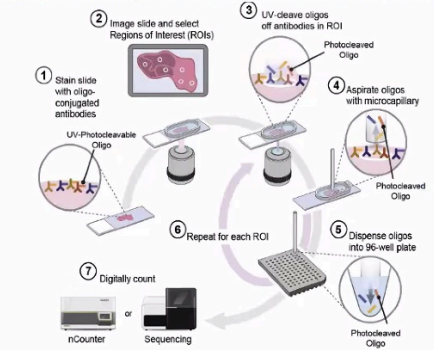
Spatial ‘Omics: An example from Oregon Health & Science Univ.

Digital Spatial Profiling
Spatially oriented ROI

LETTERS
https://doi.org/10.1038/s41587-020-0472-9
nature biotechnology

Multiplex digital spatial profiling of proteins and RNA in fixed tissue

Christopher R. Merritt[1,2], Giang T. Ong[1], Sarah E. Church[1], Kristi Barker[1], Patrick Danaher[1], Gary Geiss[1], Margaret Hoang[1], Jaemyeong Jung[1], Yan Liang[1], Jill McKay-Fleisch[1], Karen Nguyen[1], Zach Norgaard[1], Kristina Sorg[1], Isaac Sprague[1], Charles Warren[1], Sarah Warren[1], Philippa J. Webster[1], Zoey Zhou[1], Daniel R. Zollinger[1], Dwayne L. Dunaway[1], Gordon B. Mills[2] and Joseph M. Beechem[1,2]



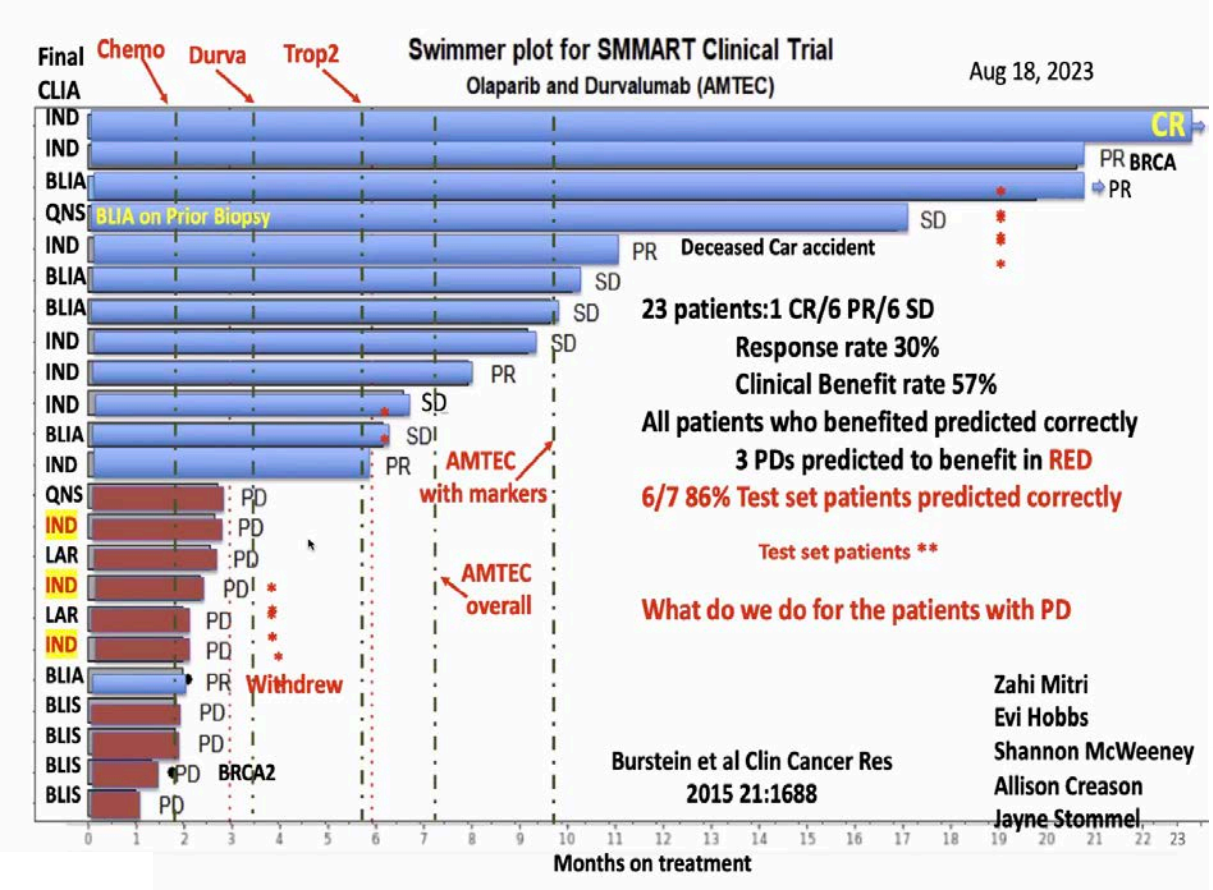
Chris Corless Joanna Pucilowska
<pucilows@ohsu.edu>

Immune Cell Profiling Core	Pan tumor module	Cell Death Module	Oncogenic Signaling - PI3K/AKT	Oncogenic Signaling - RAS.MAPK	DNA damage signaling panel
PD-1	MART1	BAD	PTEN	MET	Cyclin E1
CD68	NY-ESO-1	BCL6	AKT-pS473	p-cMET (Y1234/1235)	ATM_pS1981
HLA-DR	S100B	BCLXL	GSK3ALPHABETA_ pS21/S9	EGFR	ATR_S428
Beta-2-microglobulin	EpCAM	BIM	GSK3_pS9	p-EGFR (Y1068)	c-Myc
CD11c	p21	p53	PRAS40_pT246	Her2	ARID1A
CD20	GAPDH	GZMA	TUBERIN_pT1462	**p-HER2 (Y877)	Cyclin B1
CD3	ER-alpha	CD95/Fas	INPP4B	FGFR1	Cyclin D1
CD4	PR	PARP	PLCG1	Phospho-MEK1 (S217/S221)	AR
CD45	Histone H3	Cleaved caspase 9	Pan-AKT	Phospho-p90 RSK (T359/S363)	p-HER2 (Tyr1248)
CD56	Total Rb	*NF1B	p-4EBP1 (Thr37/46)	p-ERK1/2 (T202/Y204)	p-gammaH2AX (Ser139)
CD8	p-RB (S807)	Mcl-1	S6	p-cMYC	p-Chk2
CTLA4	Ki-67	cleaved PARP	p-S6		p-Histone H3
GZMB	Tumor targets	Bcl-2	IRF1		total ATM
PD-L1	CDK4	Controls			SLFN11
PanCk	CDK6	Rb IgG			
SMA	RRM2	Ms IgG1			
Fibronectin	Trop2	Ms IgG2a			

CLIA Nanostring DSP:90 antibodies on one FFPE slide.
Tumor intrinsic
Immune and tumor microenvironment
ADCs **March 2023**

Courtesy Dr. Gordon Mills, Director of Precision Oncology at Knight Cancer Institute, OHSU

Spatial ‘Omics: An example from Oregon Health & Science Univ.



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AI in Medicine

AI and medicine: hope or hype?

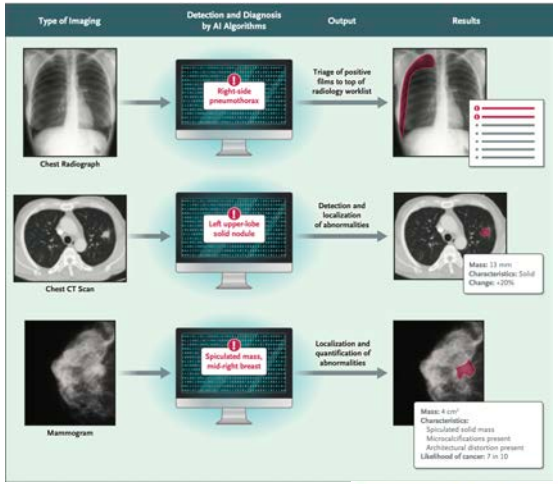
Things AI will <u>definitely</u> be good for:

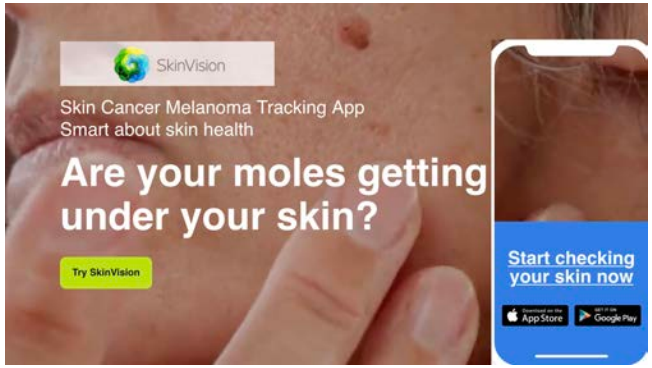
- Interpretation of any images:

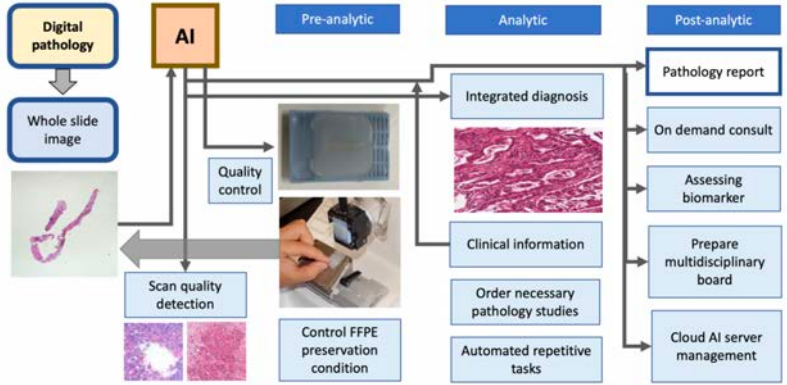
  Radiology

  Pathology

  Dermatology



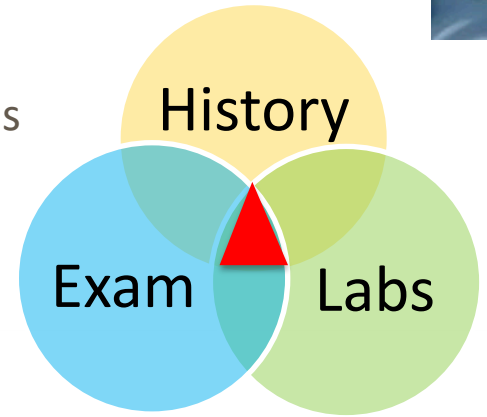




AI and cancer: hope or hype?

Things AI will probably be good for:

- Compilation of medical records/charting
- Differential diagnosis



AI and cancer: hope or hype?

Things AI will might be good for:

- Mining big data sets for novel insights into disease pathogenesis & therapy

Thank you
& Discussion