Complex Adaptive Systems Initiative
Arizona State University

The National Academies of SCIENCES ENGINEERING MEDICINE

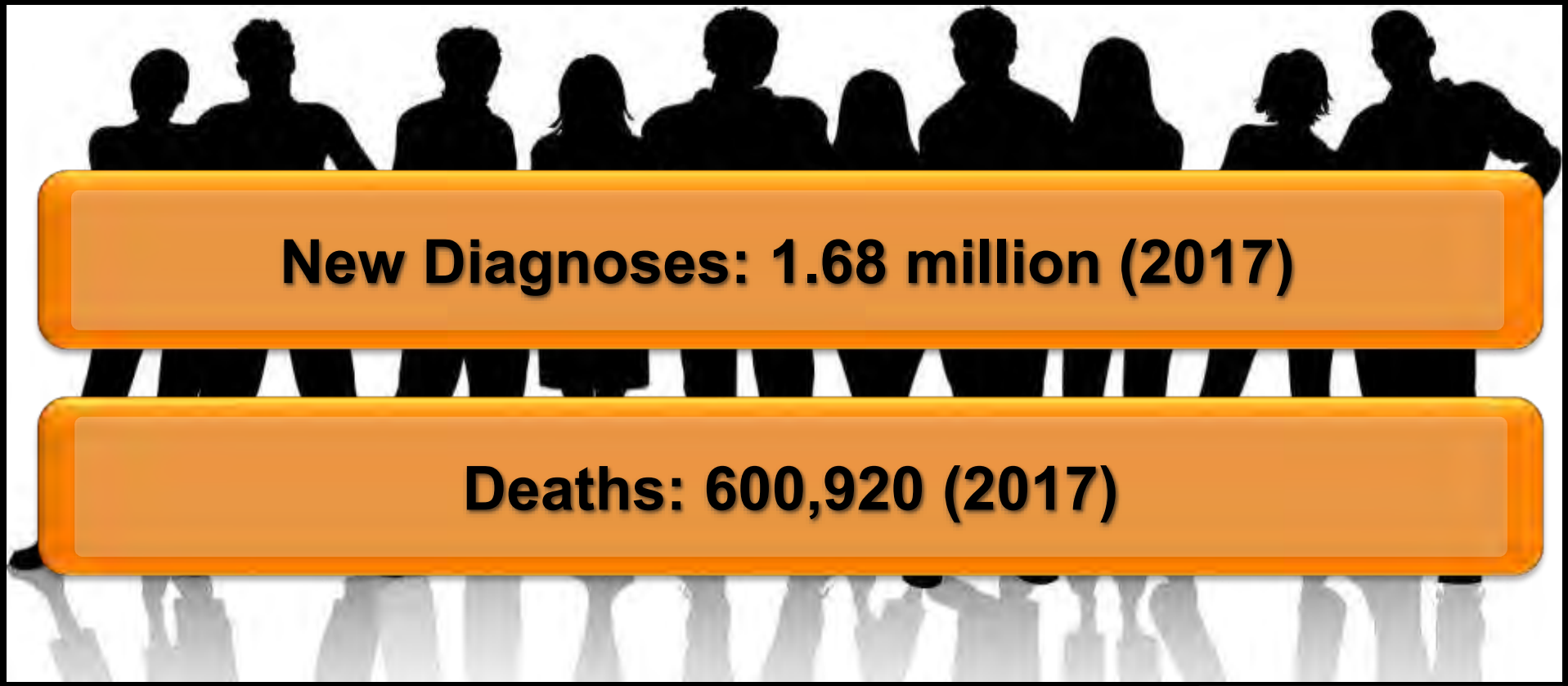
The Challenge of Comprehensive Cancer Control:

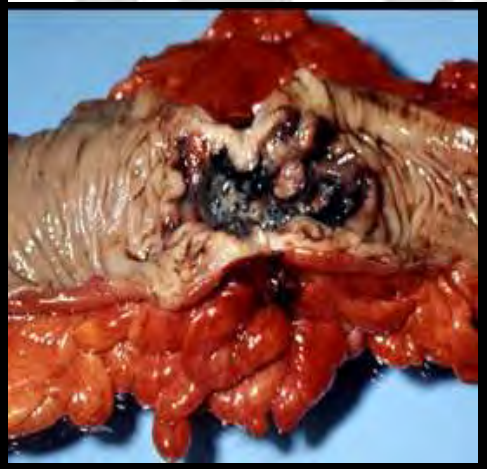
Complexity, Convergence, Cost, Communication, Computing and the Imperative for Radical Change

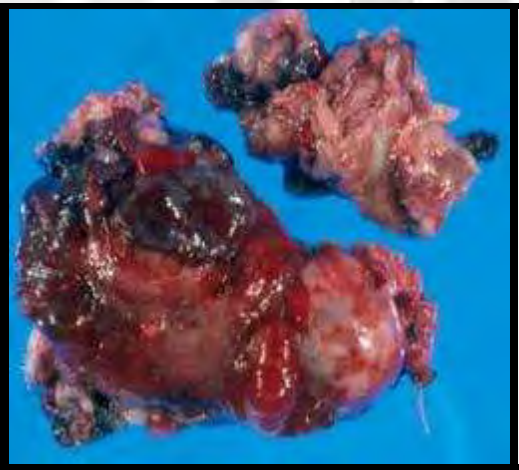
Dr. George Poste
Chief Scientist, Complex Adaptive Systems Initiative
and Regents Professor of Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

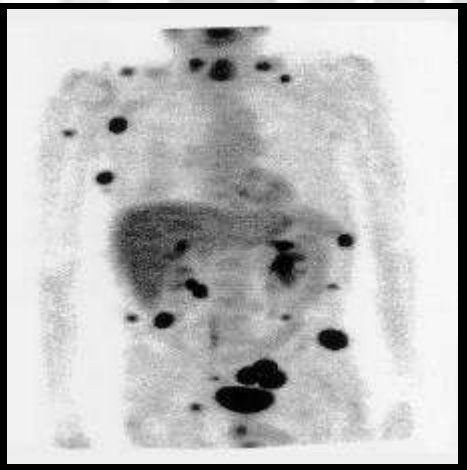
Presentation at:
Committee on National Strategy for Cancer Control in the United States
National Academies of Science, Engineering and Medicine
Washington, D.C. 6 June 2018

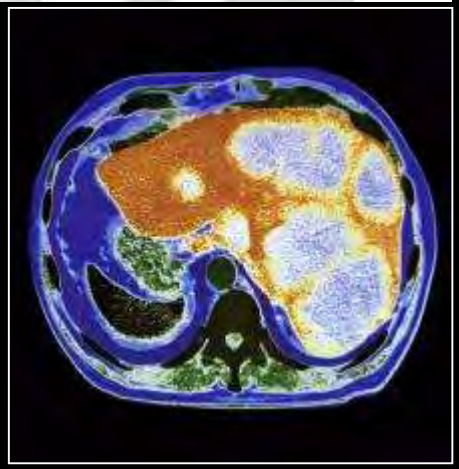
Confronting the Clinical, Economic and Human Toll of Cancer



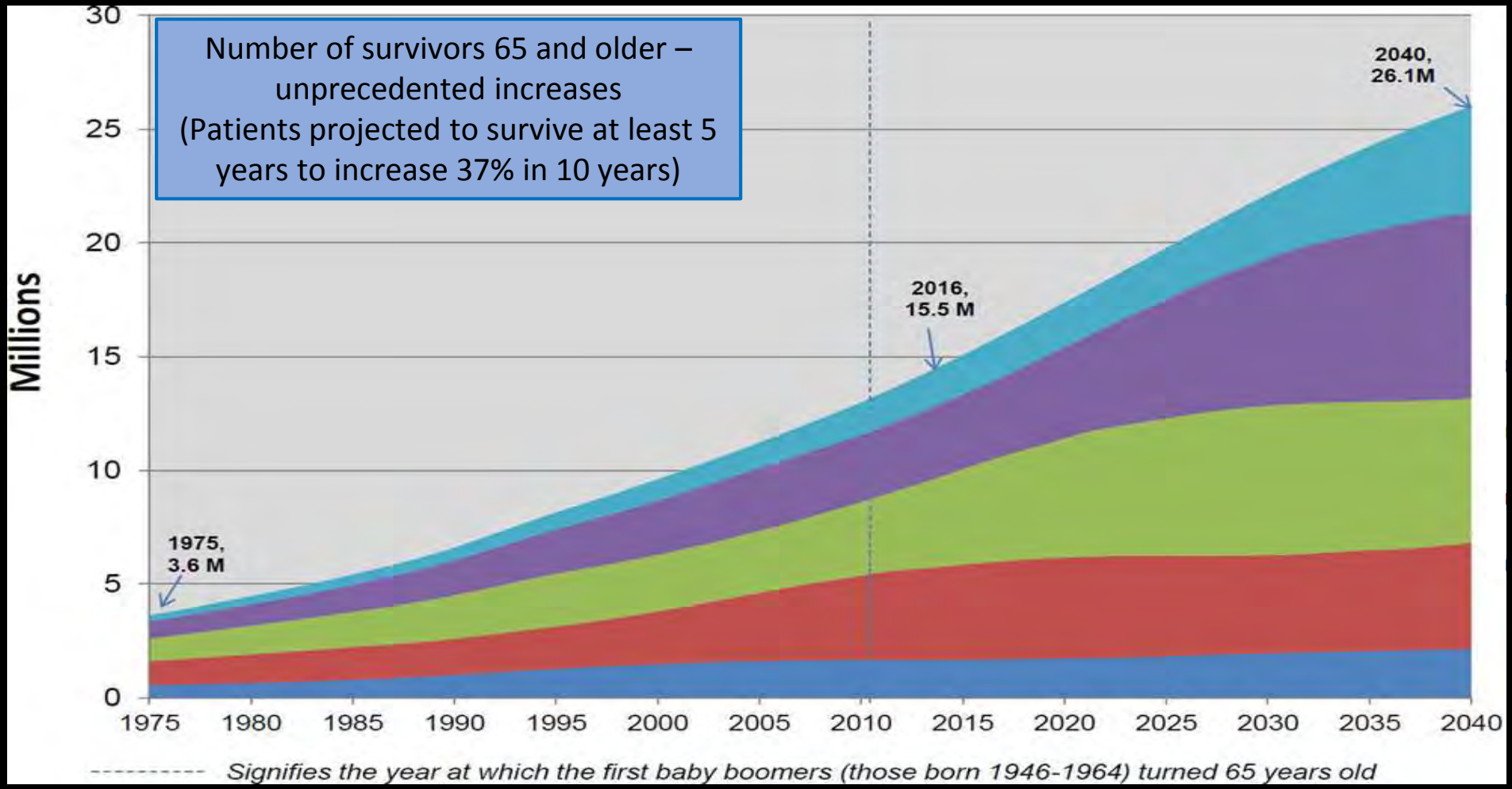








The Pending "Tsunami" of Older U.S. Cancer Survivors

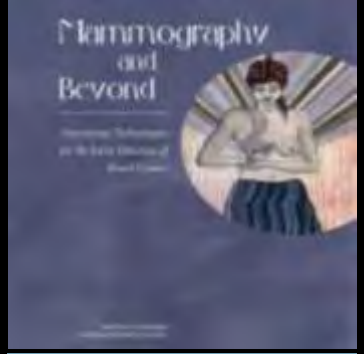


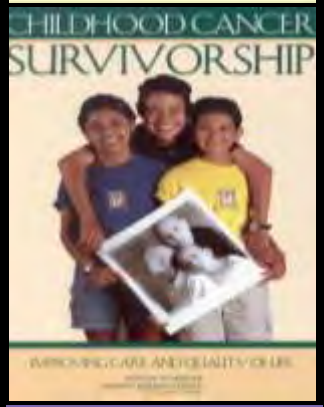
Adapted from Bluethmann et al. Cancer Epidemiol Biomarkers Prev, 2016.


INSTITUTE OF MEDICINE
A Stronger Cancer Centers Program


Ensuring Quality
CANCER Care

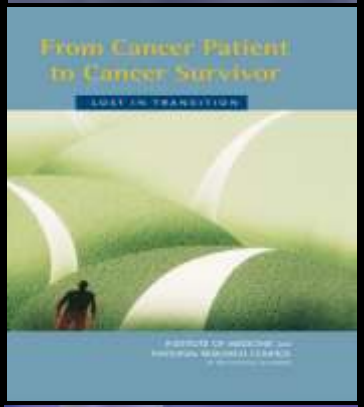

PROMOTING HEALTH
INTERVENTION STRATEGIES FROM SOCIAL AND BEHAVIORAL RESEARCH


Mammography and Beyond

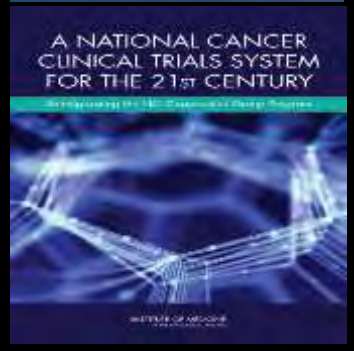

CHILDHOOD CANCER SURVIVORSHIP

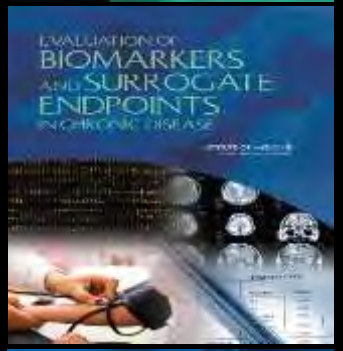

Fulfilling the Potential of
Cancer Prevention and Early Detection


IMPROVING
BREAST IMAGING
QUALITY STANDARDS


From Cancer Patient to Cancer Survivor
LOST IN TRANSITION

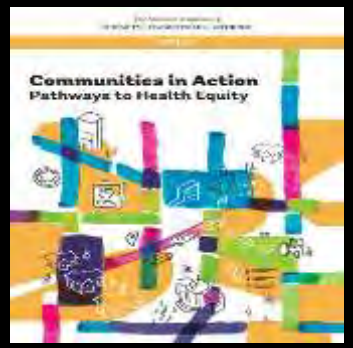

CANCER CONTROL OPPORTUNITIES
IN LOW- AND MIDDLE-INCOME COUNTRIES

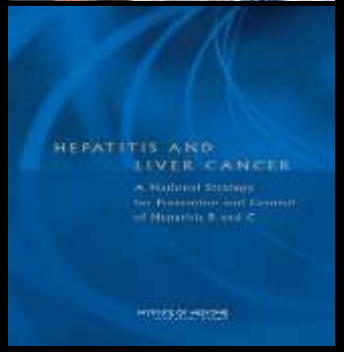

A NATIONAL CANCER CLINICAL TRIALS SYSTEM FOR THE 21st CENTURY


EVALUATION OF BIOMARKERS AND SURROGATE ENDPOINTS IN CHRONIC DISEASE


Relieving PAIN in America
A Blueprint for Transforming Prevention, Care, Education, and Research


Ovarian Cancers


Communities in Action
Pathways to Health Equity


HEPATITIS AND LIVER CANCER
A National Strategy for Prevention and Control of Hepatitis B and C


The Future of the Public's Health

Cancer as a Complex Adaptive System

The Difference Between Complicated Systems and Complex Adaptive Systems

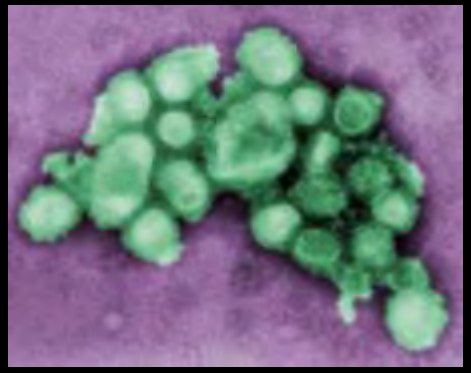
Complicated Systems: Human Design and Engineering

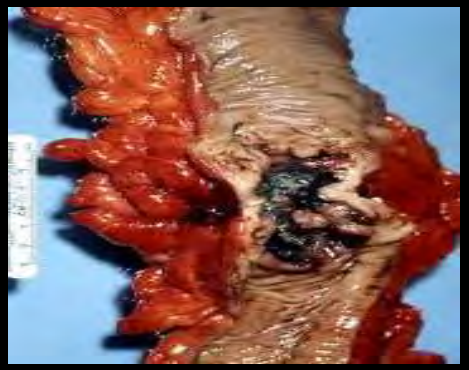


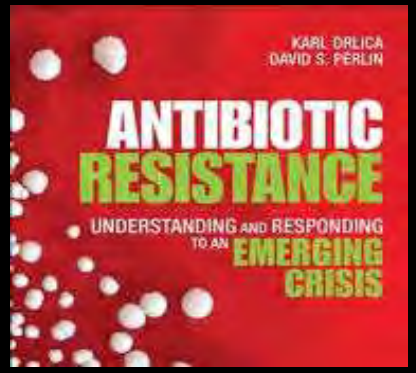

- behavior of the assembled system is predictable from the properties of the components
- proactive awareness of tolerance limits and most likely failure points
- system performance is fixed and not capable of autonomous evolution
- low degrees of design freedom

Complex Adaptive Systems:
Fundamental and Ubiquitous Design Principals of Natural Systems

weather/climate	epidemics/ pandemics	disease pathogenesis	Rx resistance





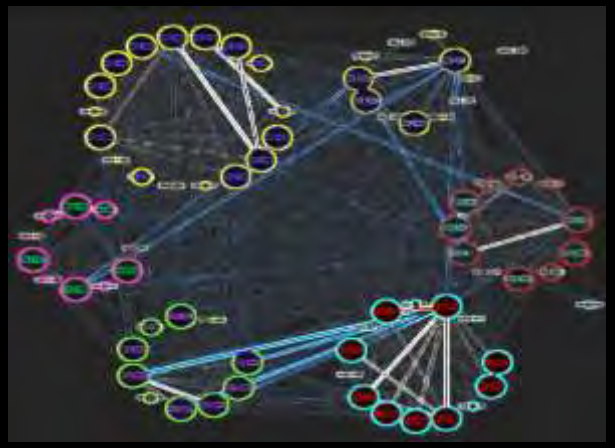


- system behavior not predictable from knowledge of the properties of individual subcomponents
- dynamic behavior defined by constantly changing interactions between components in response to external inputs
- robust, adaptive, evolvable

Complex Adaptive Systems in Biology: Robustness, Adaptation and Evolvability in the Architecture of Molecular (Informatics) Networks

stable networks
(health: physiology)

perturbed networks
(disease: pathophysiology)



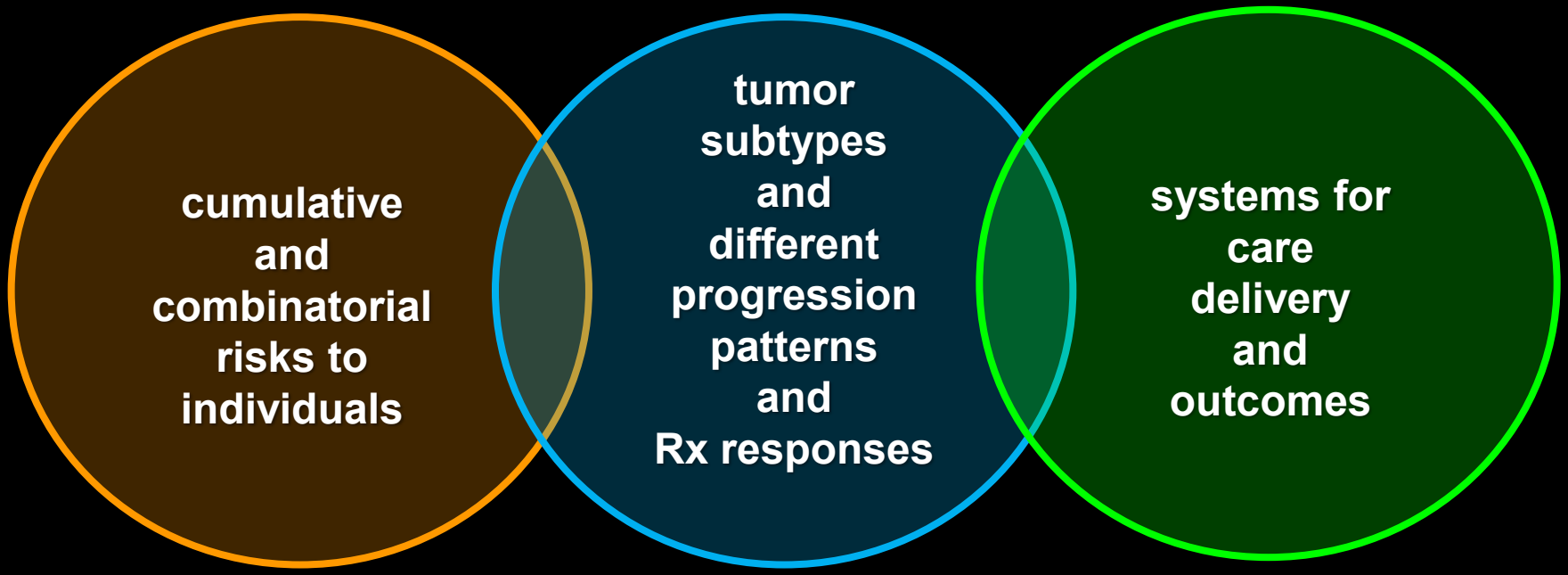
dynamic attractor landscapes of state spaces

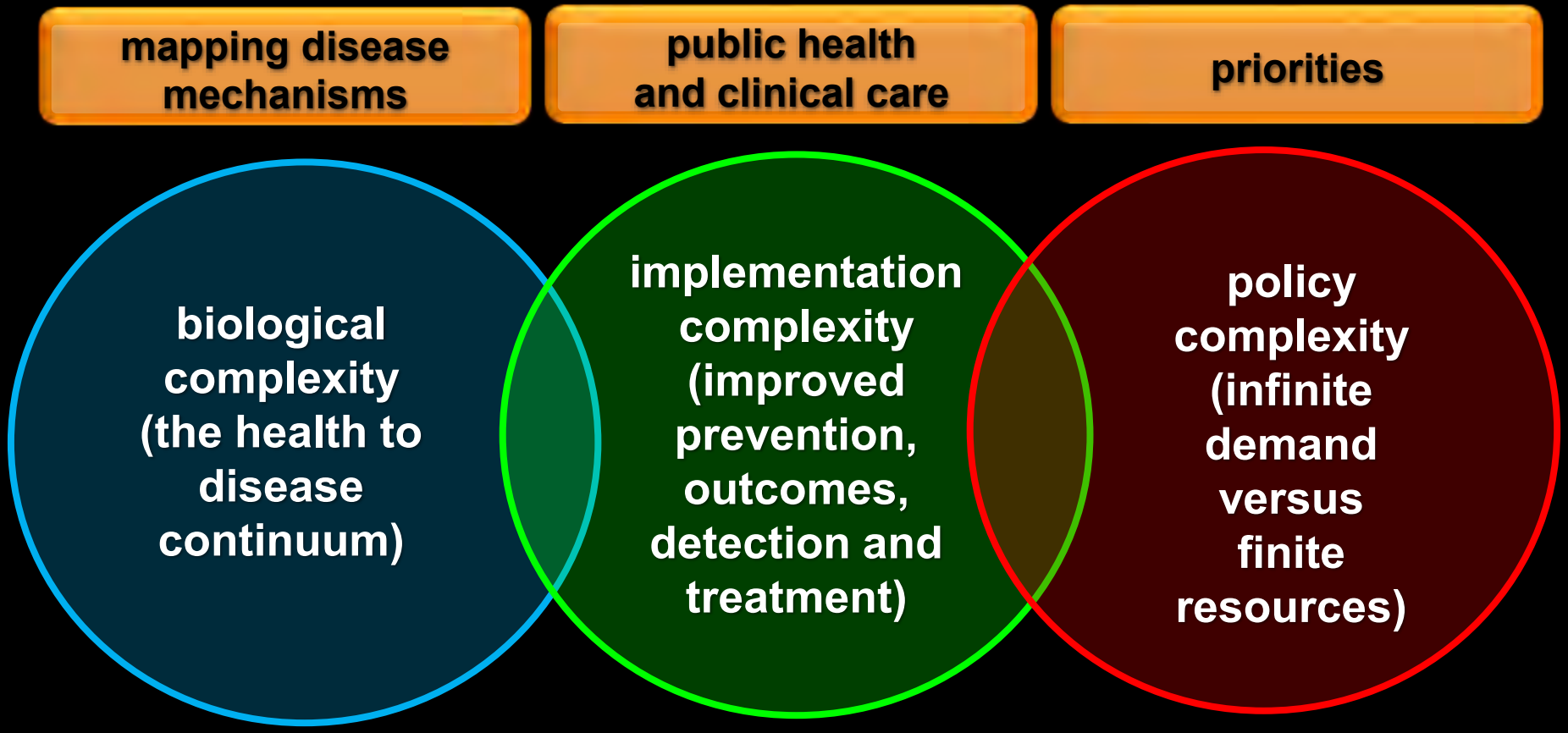
- network structure robust to commonly encountered perturbations (homeostasis)
- fragile to novel perturbations that an trigger major changes in system states (emergence)

The Challenge for Comprehensive Cancer Control

- addressing cancer as a complex adaptive system (CAS)
- cancer is a **biological CAS** embedded within a constellation of multiple other complex adaptive systems (**life style, environmental exposures, patterns of clinical care, rate of innovation, public and payer policies**) whose interactions influence disease risk and the evolutionary dynamics of disease emergence and progression

Cancer as a Multi-Dimensional Dynamic Interaction Between Multiple Complex Adaptive Systems



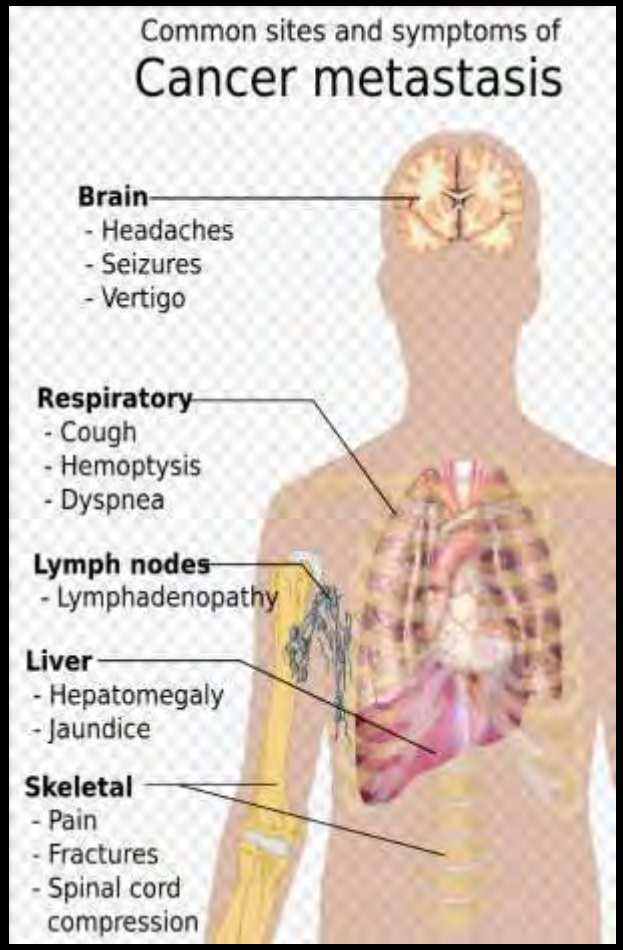


- public and political expectancy of meaningful progress
- aging demographics, escalating disease burden, insufficient clinical infrastructure and economic unsustainability
- political, ethical and legal implications of cost of care and future potential limits on care services

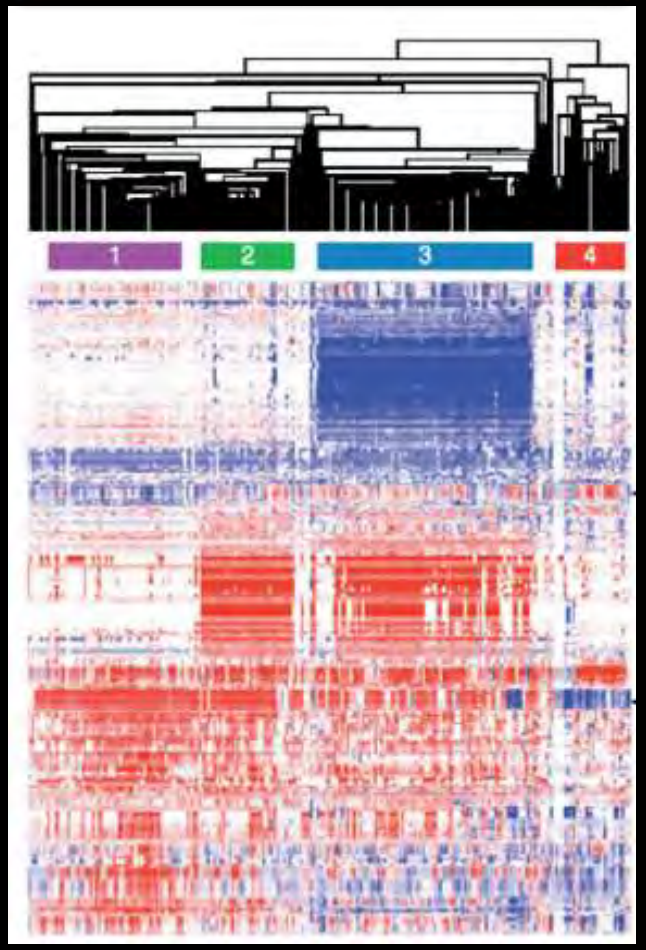
The Path to Precision Oncology:

Superstitions

Symptoms



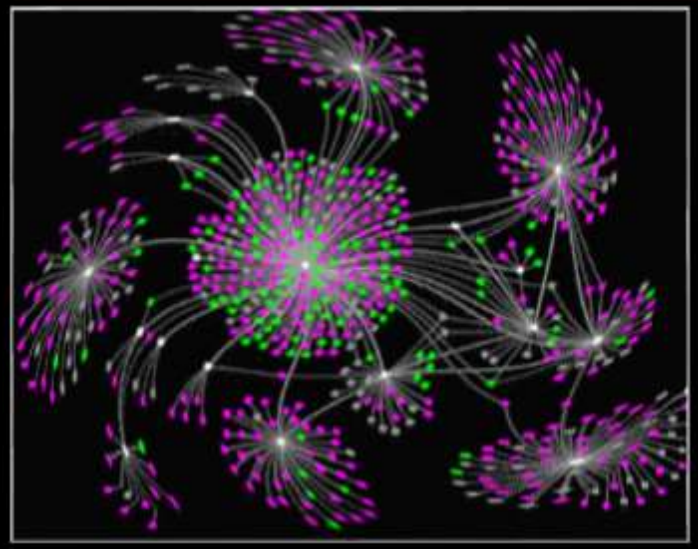
(Molecular) Signatures

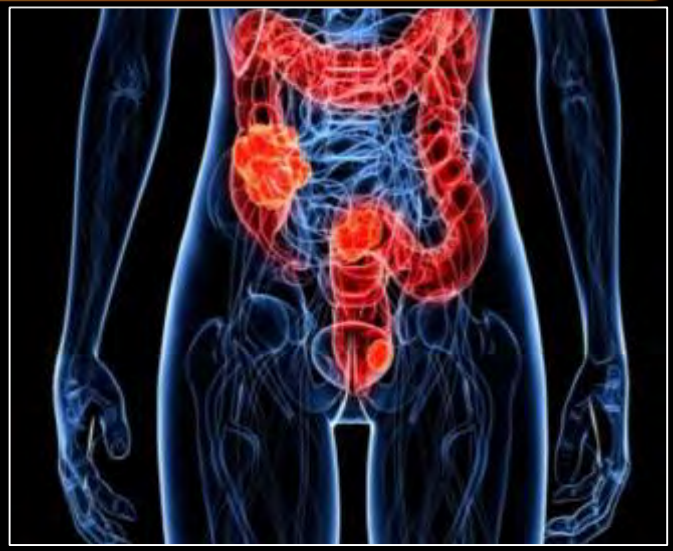


Precision Oncology

(Epi)Genomics

Causal Relationships Between Disruption of Molecular Signaling Networks and Disease





- terabytes per individual
- zettabyte – yottabyte population databases

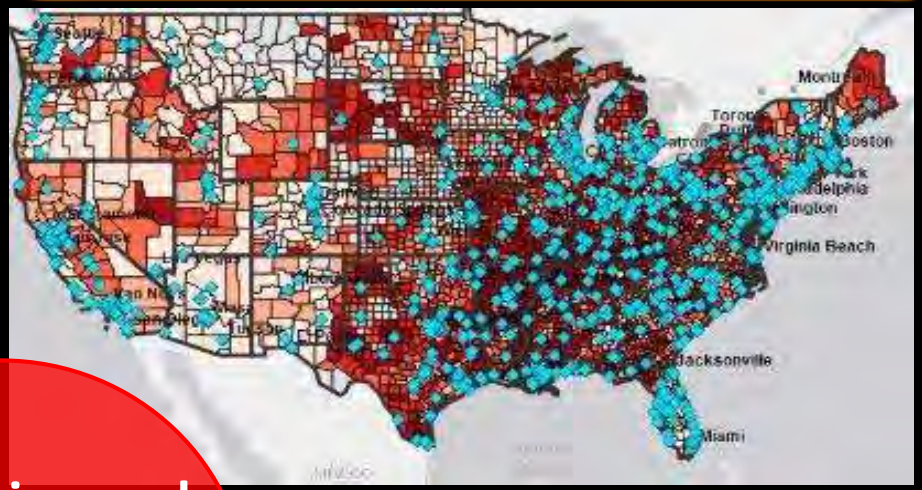
Patient-Specific Signatures of Predisposition to Disease or Overt Disease

Big (Messy) Data

Precision Medicine:
"Computed Phenotypes" and 'Digital Siblings'

Individual Data

Population Databanks



integration and analysis of large scale, diverse data categories

"matching" individuals to 'best match' cohorts using data on similarities of deep phenotyping profiles and treatment outcomes

NIH

NATIONAL CANCER INSTITUTE

Division of Cancer Control & Population Sciences

Division of Cancer Prevention and Control

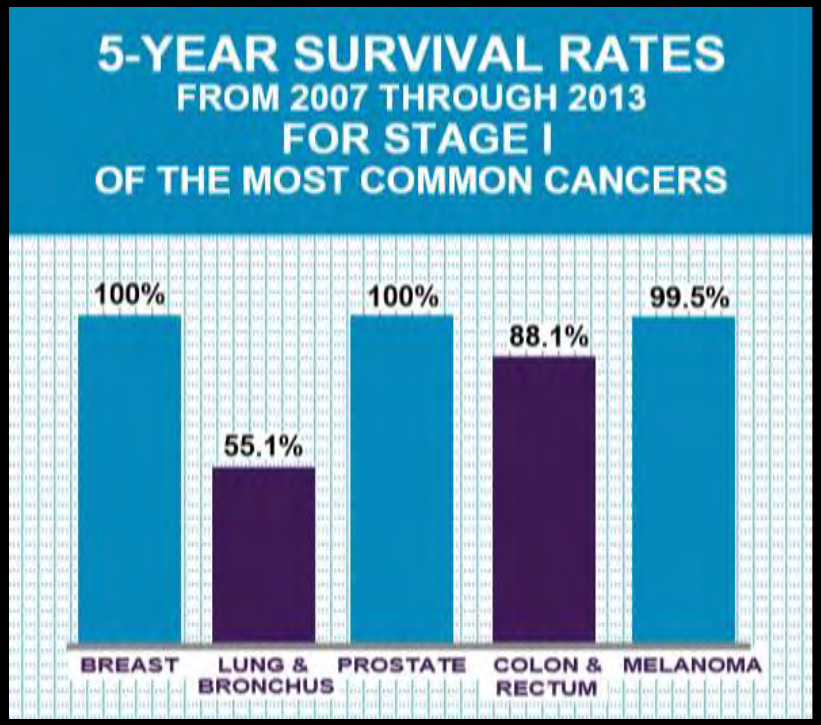
www.cdc.gov/cancer

RELIABLE | TRUSTED | SCIENTIFIC

1992 25 2017

NPCR

NATIONAL PROGRAM of CANCER REGISTRIES



Public Health Approaches to Cancer Prevention and Early Disease Detection

- historical focus on generic risk assessment tools and monitoring
  - sex or age categories
  - specific socio-cultural and environmental exposure risk cohorts
  - limited subpopulation analytics and variable screening intervals
- need for improved assimilation of new molecular insights in risk factor identification to increase precision and sensitivity of existing approaches
  - molecular exposures, including infectious agents
  - social media and behavioral/lifestyle factors

Estimated New Cancer Cases and Deaths – 2018

cases
1,735,350

deaths
609,640

Estimated New Cases

Male			Female		
Prostate	164,690	19%	Breast	[illegible]	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	[illegible]	4%	Kidney & renal pelvis	22,660	3%
All sites	856,370	[illegible]	**All sites**	**878,980**	**100%**

Estimated Deaths

Male			Female		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All sites	**323,630**	**100%**	**All sites**	**286,010**	**100%**

The need for improved diagnosis, treatment, supportive care and survivor care

Large Scale Genome Sequencing as Flagship Projects for Precision Oncology: The Dangers of Reductionism and Ignoring Biological Complexity

NIH National Institutes of Health
All of Us Research Program

All of Us

precisionFDA

U.S. Department of Veterans Affairs

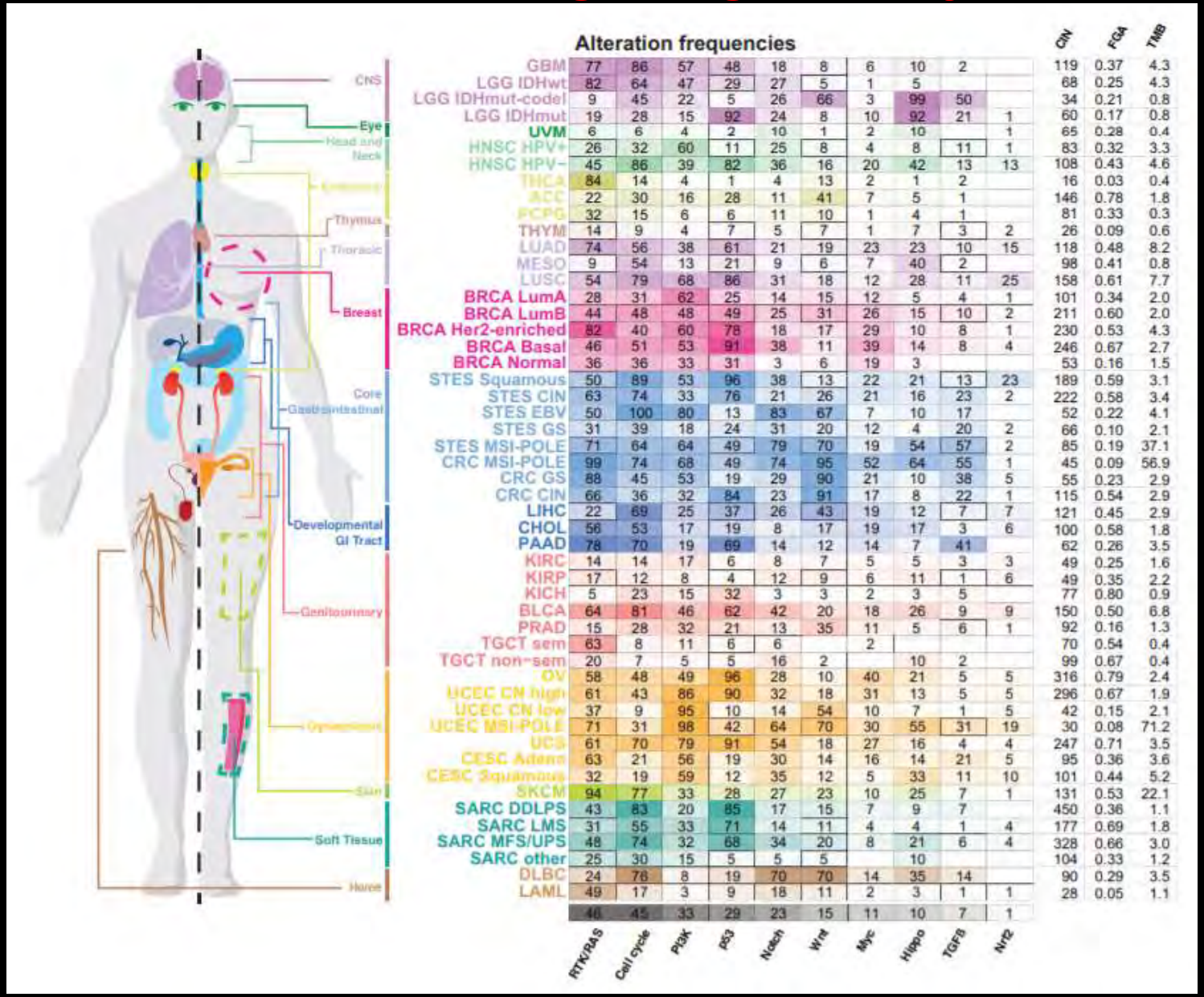
华大基因 BGI

Genomics england

GENOME denmark

GRAIL

Fraction of Tumor Samples with Alterations in 10 Curated Signaling Pathways



	RTK/RAS	Cell cycle	PI3K	p53	Notch	Wnt	Myc	Hippo	TGFB	Nrf2	CIN	FGA	TMB
GBM	77	86	57	48	18	8	6	10	2		119	0.37	4.3
LGG IDHwt	82	64	47	29	27	5	1	5			68	0.25	4.3
LGG IDHmut-codel	9	45	22	5	26	66	3	99	50		34	0.21	0.8
LGG IDHmut	19	28	15	92	24	8	10	92	21	1	60	0.17	0.8
UVM	6	6	4	2	10	1	2	10		1	65	0.28	0.4
HNSC HPV+	26	32	60	11	25	8	4	8	11	1	83	0.32	3.3
HNSC HPV-	45	86	39	82	36	16	20	42	13	13	108	0.43	4.6
THCA	84	14	4	1	4	13	2	1	2		16	0.03	0.4
ACC	22	30	16	28	11	41	7	5	1		146	0.78	1.8
PCPG	32	15	6	6	11	10	1	4	1		81	0.33	0.3
THYM	14	9	4	7	5	7	1	7	3	2	26	0.09	0.6
LUAD	74	56	38	61	21	19	23	23	10	15	118	0.48	8.2
MESO	9	54	13	21	9	6	7	40	2		98	0.41	0.8
LUSC	54	79	68	86	31	18	12	28	11	25	158	0.61	7.7
BRCA LumA	28	31	62	25	14	15	12	5	4	1	101	0.34	2.0
BRCA LumB	44	48	48	49	25	31	26	15	10	2	211	0.60	2.0
BRCA Her2-enriched	82	40	60	78	18	17	29	10	8	1	230	0.53	4.3
BRCA Basal	46	51	53	91	38	11	39	14	8	4	246	0.67	2.7
BRCA Normal	36	36	33	31	3	6	19	3			53	0.16	1.5
STES Squamous	50	89	53	96	38	13	22	21	13	23	189	0.59	3.1
STES CIN	63	74	33	76	21	26	21	16	23	2	222	0.58	3.4
STES EBV	50	100	80	13	83	67	7	10	17		52	0.22	4.1
STES GS	31	39	18	24	31	20	12	4	20	2	66	0.10	2.1
STES MSI-POLE	71	64	64	49	79	70	19	54	57	2	85	0.19	37.1
CRC MSI-POLE	99	74	68	49	74	95	52	64	55	1	45	0.09	56.9
CRC GS	88	45	53	19	29	90	21	10	38	5	55	0.23	2.9
CRC CIN	66	36	32	84	23	91	17	8	22	1	115	0.54	2.9
LIHC	22	69	25	37	26	43	19	12	7	7	121	0.45	2.9
CHOL	56	53	17	19	8	17	19	17	3	6	100	0.58	1.8
PAAD	78	70	19	69	14	12	14	7	41		62	0.26	3.5
KIRC	14	14	17	6	8	7	5	5	3	3	49	0.25	1.6
KIRP	17	12	8	4	12	9	6	11	1	6	49	0.35	2.2
KICH	5	23	15	32	3	3	2	3	5		77	0.80	0.9
BLCA	64	81	46	62	42	20	18	26	9	9	150	0.50	6.8
PRAD	15	28	32	21	13	35	11	5	6	1	92	0.16	1.3
TGCT sem	63	8	11	6	6		2				70	0.54	0.4
TGCT non-sem	20	7	5	5	16	2		10	2		99	0.67	0.4
OV	58	48	49	96	28	10	40	21	5	5	316	0.79	2.4
UCEC CN high	61	43	86	90	32	18	31	13	5	5	296	0.67	1.9
UCEC CN low	37	9	95	10	14	54	10	7	1	5	42	0.15	2.1
UCEC MSI-POLE	71	31	98	42	64	70	30	55	31	19	30	0.08	71.2
UCS	61	70	79	91	54	18	27	16	4	4	247	0.71	3.5
CESC Adeno	63	21	56	19	30	14	16	14	21	5	95	0.36	3.6
CESC Squamous	32	19	59	12	35	12	5	33	11	10	101	0.44	5.2
SKCM	94	77	33	28	27	23	10	25	7	1	131	0.53	22.1
SARC DDLPS	43	83	20	85	17	15	7	9	7		450	0.36	1.1
SARC LMS	31	55	33	71	14	11	4	4	1	4	177	0.69	1.8
SARC MFS/UPS	48	74	32	68	34	20	8	21	6	4	328	0.66	3.0
SARC other	25	30	15	5	5	5		10			104	0.33	1.2
DLBC	24	76	8	19	70	70	14	35	14		90	0.29	3.5
LAML	49	17	3	9	18	11	2	3	1	1	28	0.05	1.1
	46	45	33	29	23	15	11	10	7	1			

From: F. Sanchez-Vega et al. (2018) Cell, 173, 321-337

the myopic, reductionist uni-dimensional
focus on (epi)genome sequencing
(in fact very limited epigenomic data to date)

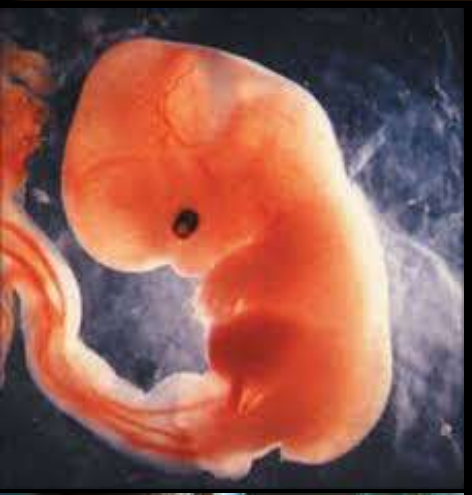
necessary but not sufficient

it's the phenotype (phenomes) that defines
disease risks progression and clinical outcomes

deep phenotyping: longitudinal integration of molecular,
clinical, environmental and socio-cultural data

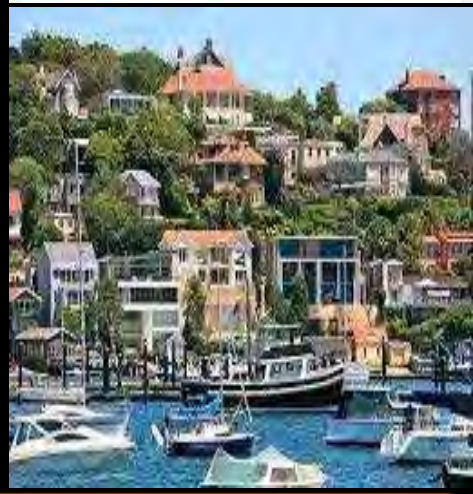
Most Events That Affect Our Health Occur Outside of the Healthcare System And Are Not Monitored

Mapping the Health to Disease Continuum: Womb to Tomb







Behavior

Environment

Large Population Cohorts for Molecular Profiling

Biobank	Region	Start Year	Size	Website
eMERGE	US	2007	105,325	gwas.net
BioVU	US	2007	>247,000	victr.vanderbilt.edu/pub/biovu
UK Biobank	UK	2006	512,000	ukbiobank.ac.uk
Million Veteran Program	US	2011	>580,000 Goal: 1 million	www.research.va.gov/MVP/default.cfm
Kaiser Permanente Biobank	US	2009	240,000	www.rpgeh.kaiser.org
China Kadoorie Biobank	China	2004	510,000	ckbiobank.org
All of Us Research Program	US	2017	Goal: 1 million or more	joinallofus.org
Taiwan Biobank	Taiwan	2005	86,695 Goal: 200,000	www.twbiobank.org.tw
Geisinger MyCode	US	2007	>150,000	

Limited to cohorts exceeding 100,000 individuals with biosamples. Sizes reported are as of 9/2017. eMERGE, Electronic Medical Records and Genomics Network.

Adapted from: J.C. Denny et al. (2018) Clin. Pharm Therap. 103, 409

Consortium for Exome Sequencing of 500,000 UK Biobank Samples by 2020 (Launched Jan. 2018)

REGENERON

biobank uk

abbvie

AstraZeneca

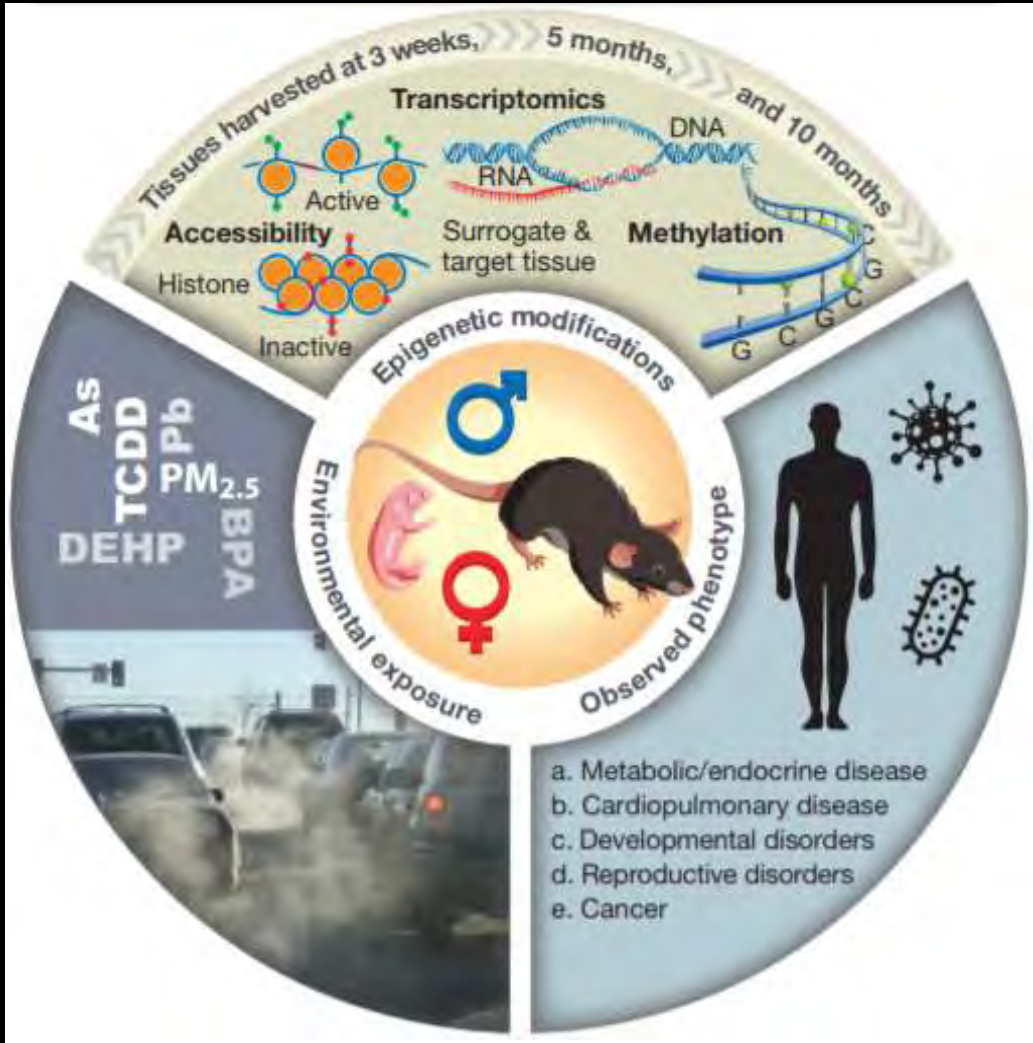
Alnylam PHARMACEUTICALS

Biogen

Pfizer IBM

- **integration with medical records, lab test data and psychological assessments**

The NIEHS Toxicant Exposures by Genomic and Epigenomic Regulators of Transcription (TaRGET) Consortium



T. Wang et al. (2018) Nature Biotechnology 36, 226

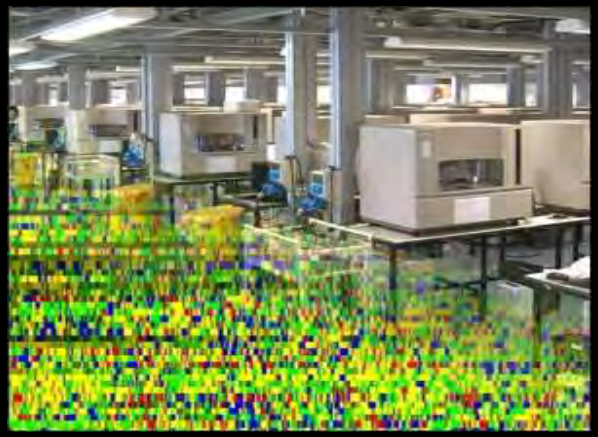
"People Analytics"
Social Activities and Behavior Become Quantifiable

- who knows why people do what they do?
  - the fact is that they do!
- these actions can now be traced and measured with unprecedented precision
- with sufficient data, the numbers reveal increasingly predictable behavior, individual risk patterns and health events
- the confessional of social media and the blurring of private and public spaces
- voluntary vs involuntary data capture
- complex ethical and legal issues
  - consent, privacy, security, surveillance

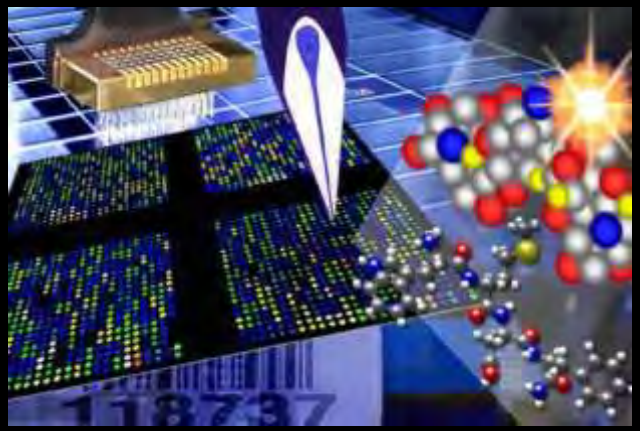
Major Investments in Digital Health by Major Corporations From Within and Outside of Traditional Healthcare Services

The Quest for Precision Oncology:
A New Era of Massive Expansion of Molecular Profiling Data (Multi-Omics)

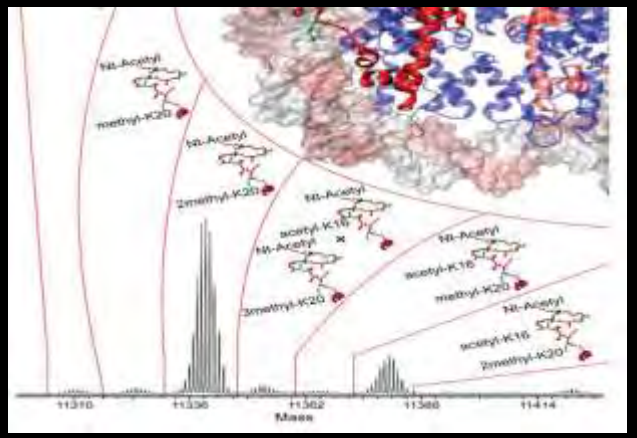
(Epi)Genomics

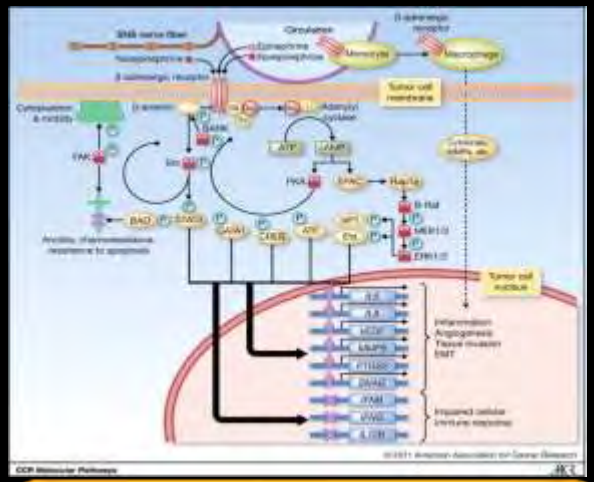


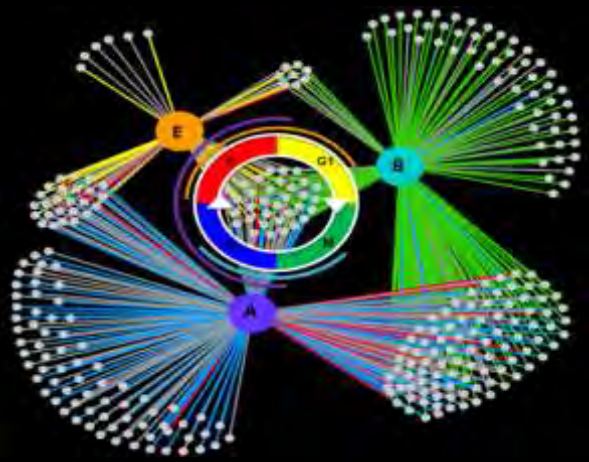
Transcriptomics

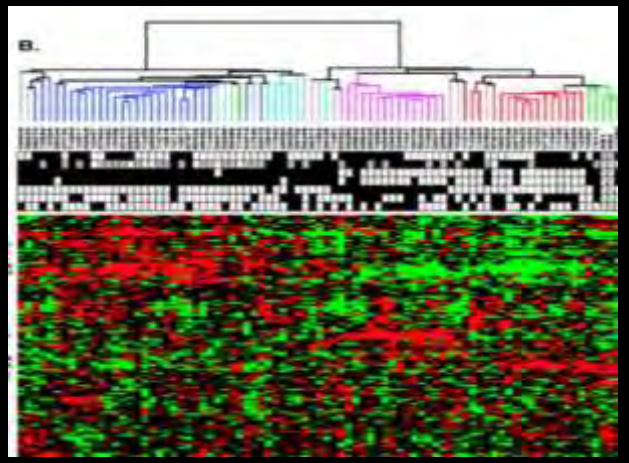


Proteomics







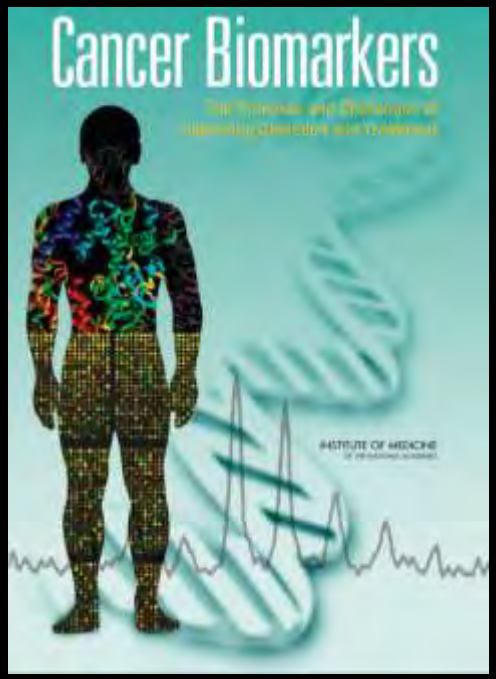


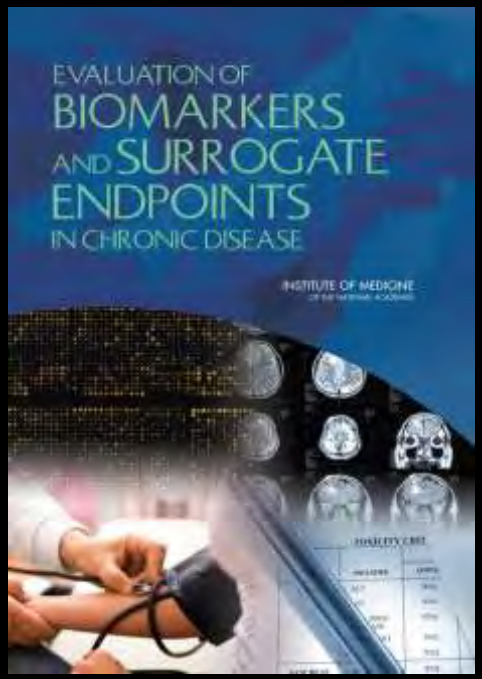
Molecular Interactions and Pathway Analysis

Network Topology and Architecture

Network Perturbation(s) and Disease Subtypes

Biomarkers:
The Core Technology Component of Precision Oncology





- disease predisposition markers
- molecular taxonomy of cancer subtypes
- new clinical trial designs
- companion Dx for target-centric Rx choice
- prediction of Rx response/resistance

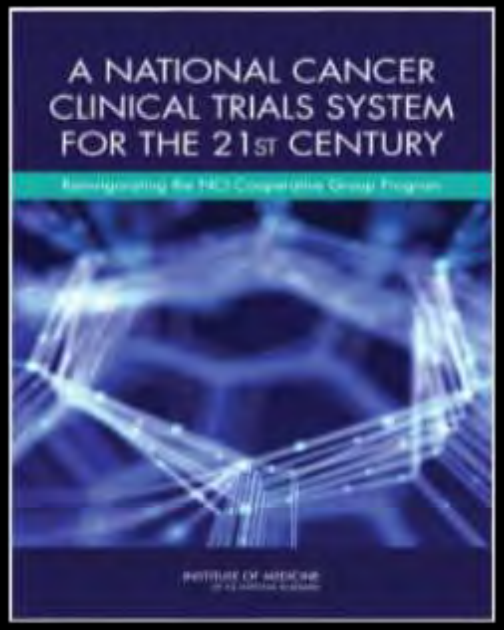
Biomarkers:
The Core Technology Platform in Making Precision Oncology a Reality

- profound mismatch between intellectual rationale and limited availability of validated biomarkers
- poor productivity and reproducibility of biomarker research (publish and vanish)
- insufficient R&D investment (public and private sectors)
- escalating cost of trials for multiplex biomarker validation and reimbursement barriers
- insufficient minimally invasive/imaging technologies for dynamic longitudinal monitoring of health to disease continuum profiling
  - static snapshots of dynamic disease progression
  - promise of liquid biopsy (ctDNA, CTC) not yet validated

Incidence of Biomarkers for Cancer Subtype Profiling for the Selection of Rx Biomarker-Driven Rx Selection (2017)

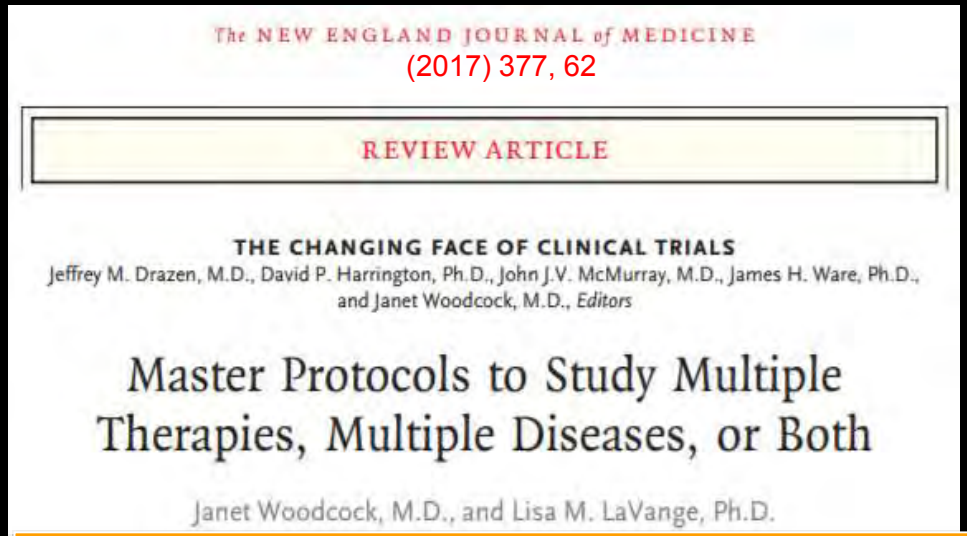
Source: FDA.gov and Drugs@FDA, Apr 2018; IQVIA, ARK R&D Intelligence, Apr 2018; IQVIA Institute, Apr 2018

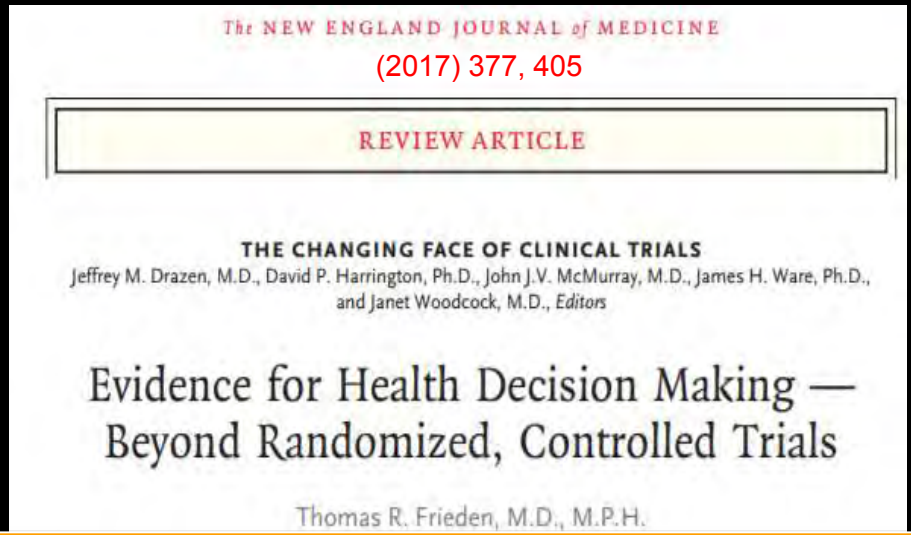
Molecular Biomarkers Classification of Tumor Subtypes and New Clinical Trial Designs



- cost, time and inefficiency (failure) of RCTs
  - test and control arms of large patient cohorts (3000 plus) without biomarker segmentation into subtype cohorts
  - legacy of “one-size-fits-all” Rx strategy
  - economically unsustainable
  - too many trials, too few patients, slow enrollment
  - increased payer requirements for concordance with RWE

Precision Medicine and New Clinical Trial Designs





From RCT to Adaptive, Basket, Umbrella Trials and New Approaches to RWE Observational Trials and Registries

Parallel Co-Development of Companion and Complementary Diagnostics

Tissue-Agnostic Anti-Cancer Drugs in Clinical Trials

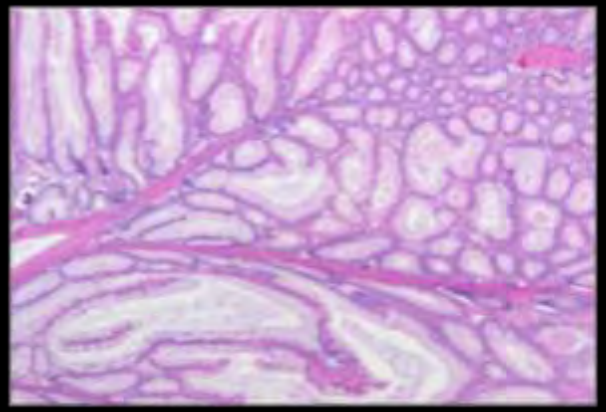
Agent	Company	Target	Indication	Status
Pembrolizumab	Merck & Co.	PD1	MSI-H (MMR-deficient) solid tumours	Approved
Larotrectinib	Loxo Oncology, Bayer	TRK	Solid tumours with NTRK fusions	NDA
Entrectinib	Ignyta, Roche	TRK, ALK, ROS1	Solid tumours with NTRK fusions	Phase II
Merestinib	Eli Lilly	MET, TRK	Solid tumours with NTRK rearrangements	Phase II
Atezolizumab	Genentech/Roche	PDL1	Solid tumours with MSI-H, high mutation burden or alterations in DNA proofreading genes	Phase II
TPX-0005	TP Therapeutics	TRK, ALK, ROS1	Solid tumours with NTRK, ALK and ROS1 rearrangements	Phase I/II
LOXO-195	Loxo Oncology	TRK	Solid tumours with NTRK fusions, including those resistant to larotrectinib	Phase I/II
LOXO-292	Loxo Oncology	RET	Solid tumours with RET rearrangements	Phase I
RXDX-105	Ignyta, Roche	RET	Solid tumours with RET fusions	Phase I
LY3300054	Eli Lilly	PDL1	Monotherapy in MSI-H solid tumours; various combination criteria	Phase I
PLX8394	Plexxikon/Daiichi Sankyo	Mutant BRAF and wild-type CRAF	Solid tumours with BRAF mutation	Phase I/IIa
PLX9486	Plexxikon	KIT	Solid tumours with KIT mutations	Phase I/II

From: K. Garber(2018) Nature Rev. Drug Disc. 17, 228

The Need for Rethinking Therapeutic Strategies to Combat Cancer

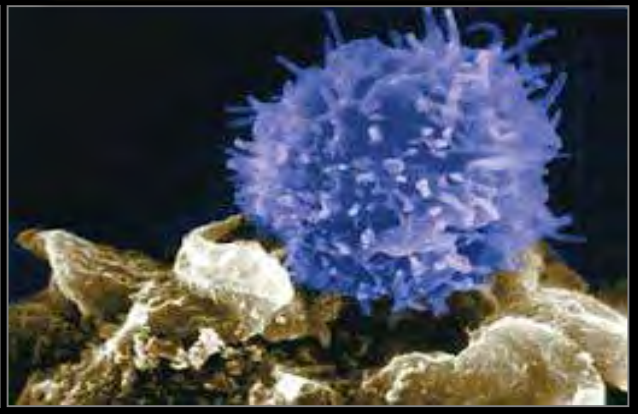
The Complex Biology of Cancer Progression and Treatment Resistance

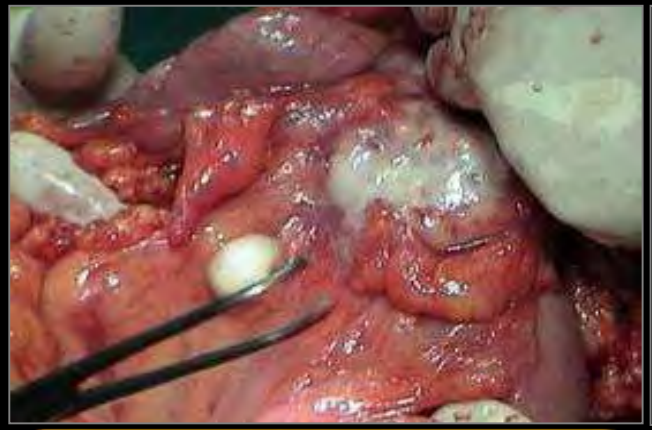
Escape From Controls for Normal Tissue Architecture

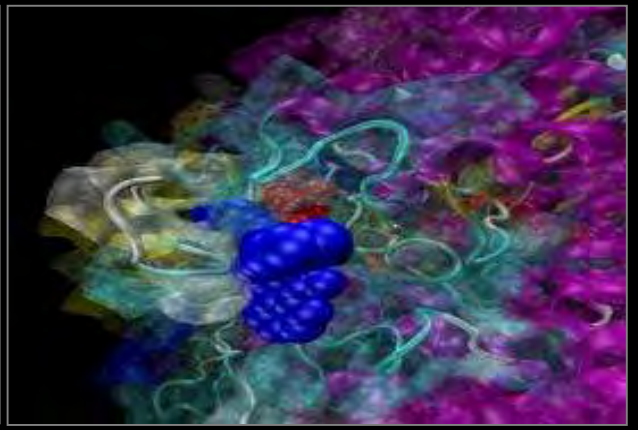


Genome Instability and Emergence of Clonal Variants

Evasion of Detection/ Destruction by Host Immune System







Use of Host Systems to Promote Progression

Invasion and Metastasis

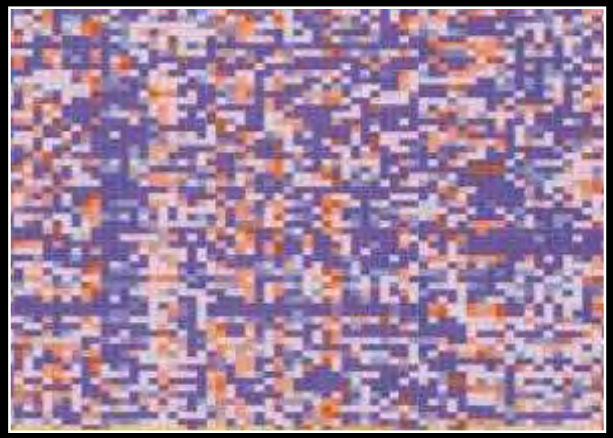
Emergence of Drug-Resistant Clones

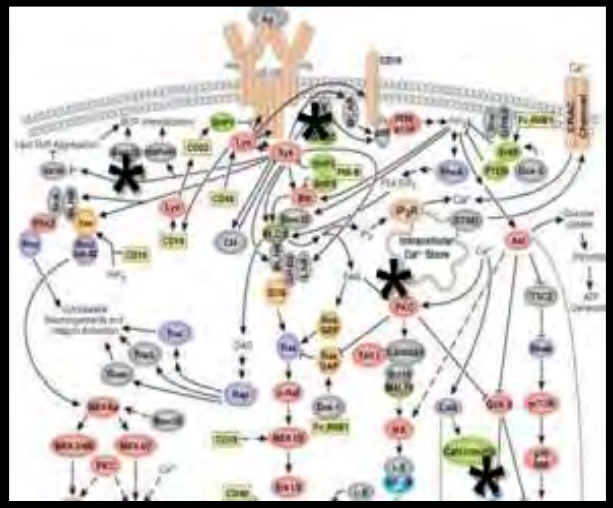
Targeted Therapeutics and the Omnipresent Problem of R_x Failure Due to Emergence of Drug Resistance Clones

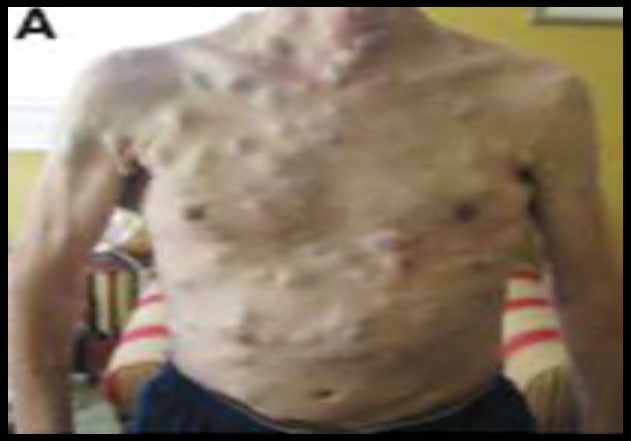
Molecular Subtyping and R_x Targets

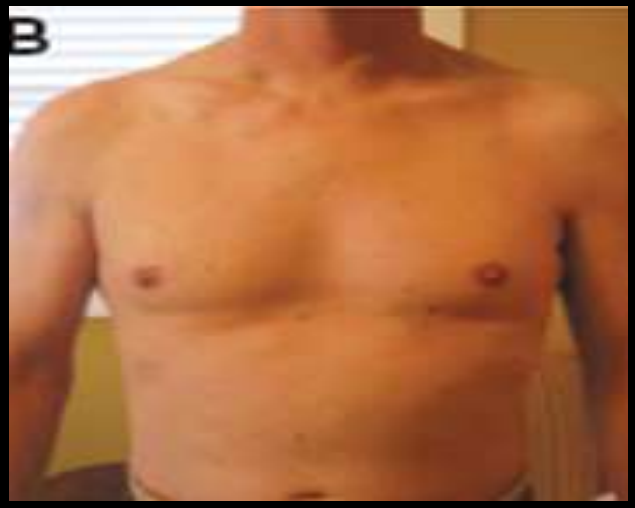
Initial R_x - Response to Targeted R_x

R_x - Resistance via Redundant Molecular Pathways









B = 15 weeks R_x (vemurafenib)

C = 23 weeks R_x and emergence of $MEK1^{C121S}$ mutant

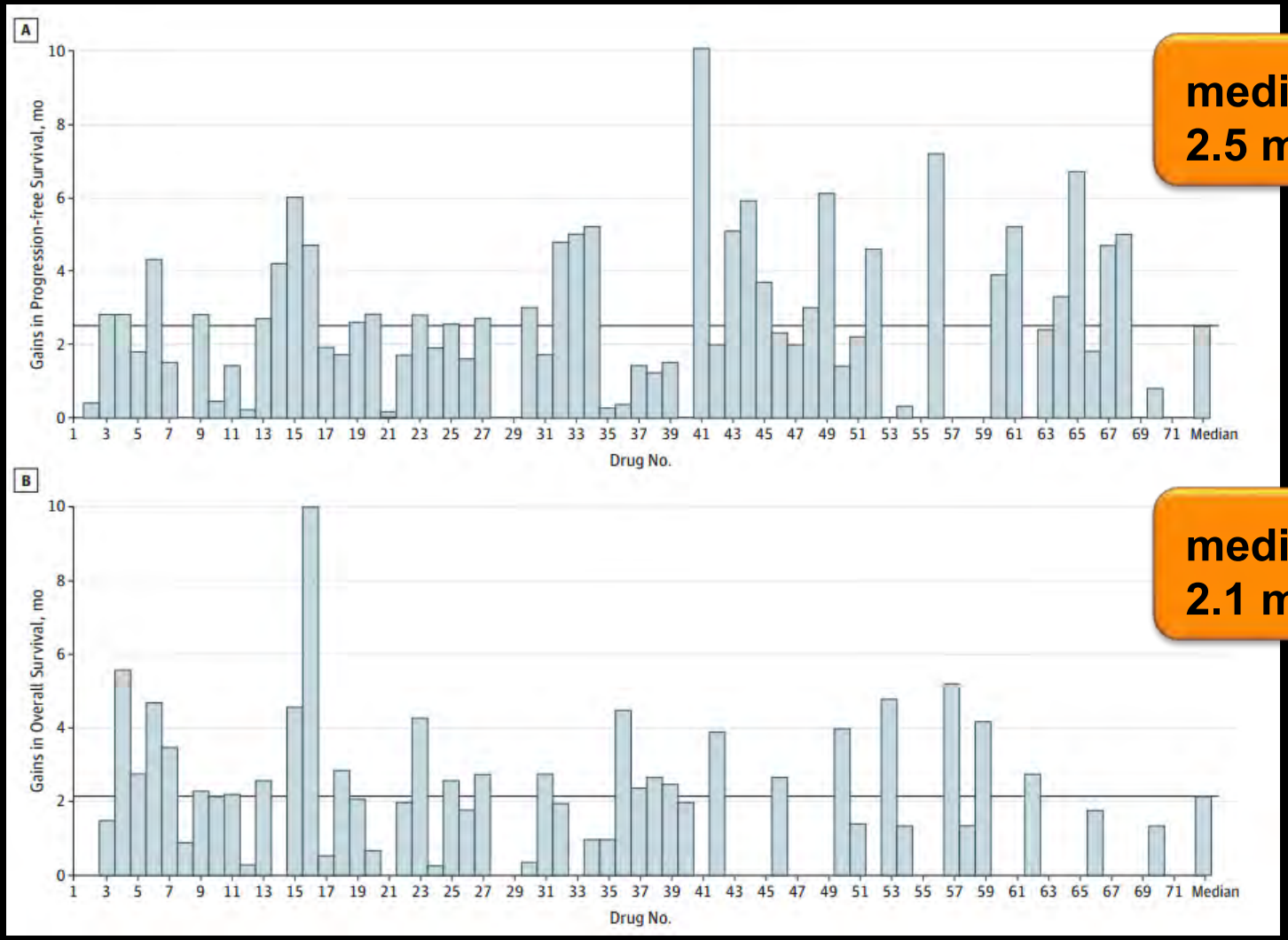
Wagle N, et al. *J Clin Oncol*. 2011;29(22),3085-3096.

Cancer R_x: Ugly Realities

- in the majority of cancers the efficacy of R_x therapies (except immunotherapies) is either short-lived or completely ineffective
- mutations that confer R_x resistance may pre-exist prior to treatment (intrinsic resistance) or arise during treatment (acquired resistance)
- mutations are typically present in multiple pathways
- intrinsic and/or acquired mutations in non-targeted pathways can enable 'by-pass' signaling circuits that ensure tumor cell survival and ever-broadening resistance R_x spectrum

Performance Comparison for New Anti-Cancer Drugs Approved 2002-2014 for Top Ten Pharmaceutical Companies

Gains in Progression-Free Survival (PFS) and Overall Survival (OS) for 71 Drugs Approved by the FDA From 2002 to 2014 for Metastatic and/or Advanced and/or Refractory Solid Tumors



median 2.5 months

median 2.1 months

From: T. Fojo et al. (2014) JAMA Otolaryngology–Head & Neck Surgery 140, 1225

What Is a Meaningful Clinical Outcome (Benefit)?

- performance (outcomes) of FDA-approved anti-cancer drugs (excluding immunotherapy)
- 71 Rx for solid tumors 2002 to 2012[a]
  - median PFS (2.1 months) and OS (2.3 months)
- 47 Rx 2014-16[b]
  - only 19% met ASCO modest OS benefit criterion
- ESMO analysis of 226 randomized trials[c]
  - only 31% met meaningful benefit criteria

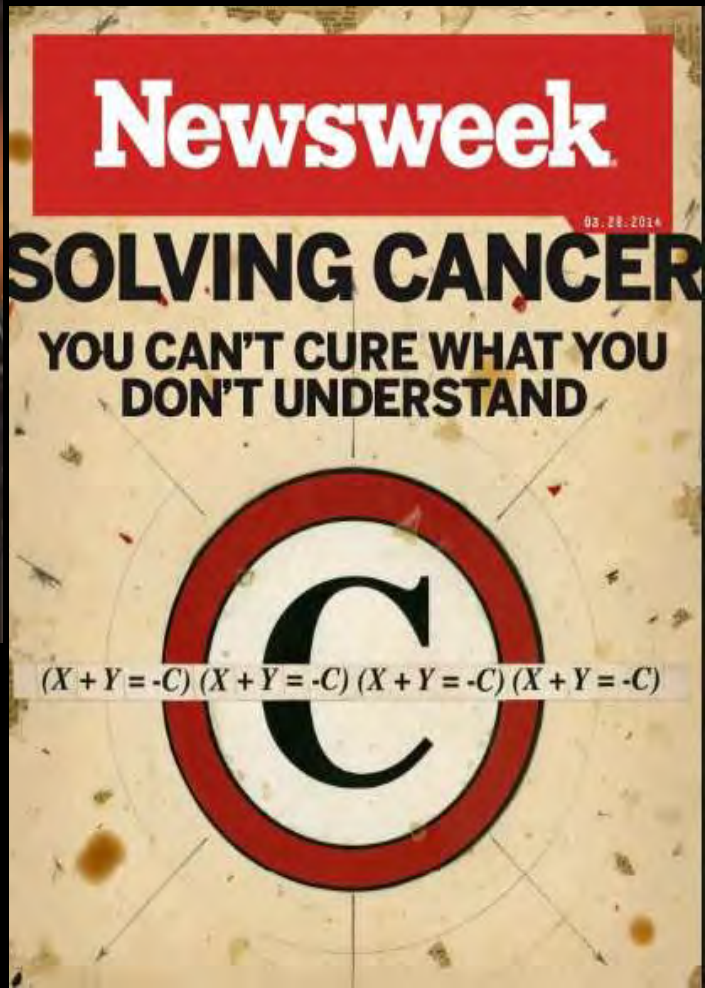
a = T. Fojo et al. (2012) JAMA Otolaryngol. Head Neck Surg. 140, 1225
b = H. Kumar et al. (2016) JAMA Oncology 2, 1238
C = J. C. Del Paggio et al. (2017) Ann. Oncol. 28, 157

Aspirations for Improved Cancer Treatment

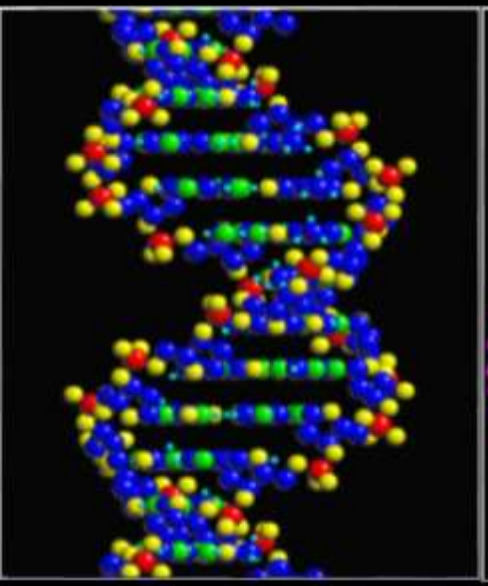
- how to maximize the efficacy and safety of therapeutic interventions against advanced (metastatic) disease
  - circumventing variability in tumor cell clones to the selected R_x regimen (overcoming the heterogeneity problem)
  - dynamic monitoring of changing clonal dynamics during treatment for faster detection of drug-resistant clones and more agile, anticipatory shifts in R_x regimen
  - mobilization (reactivation) of immune defenses to detect and destroy all clones

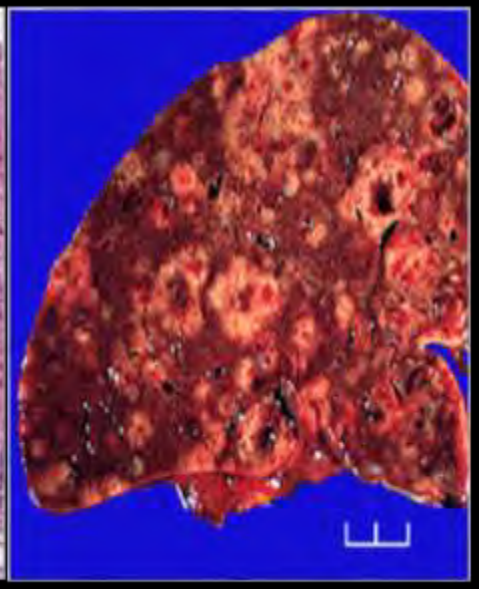
Hope and Hype

Reality



Precision Oncology: Understanding the Disruption of Molecular Information Networks in Cancer





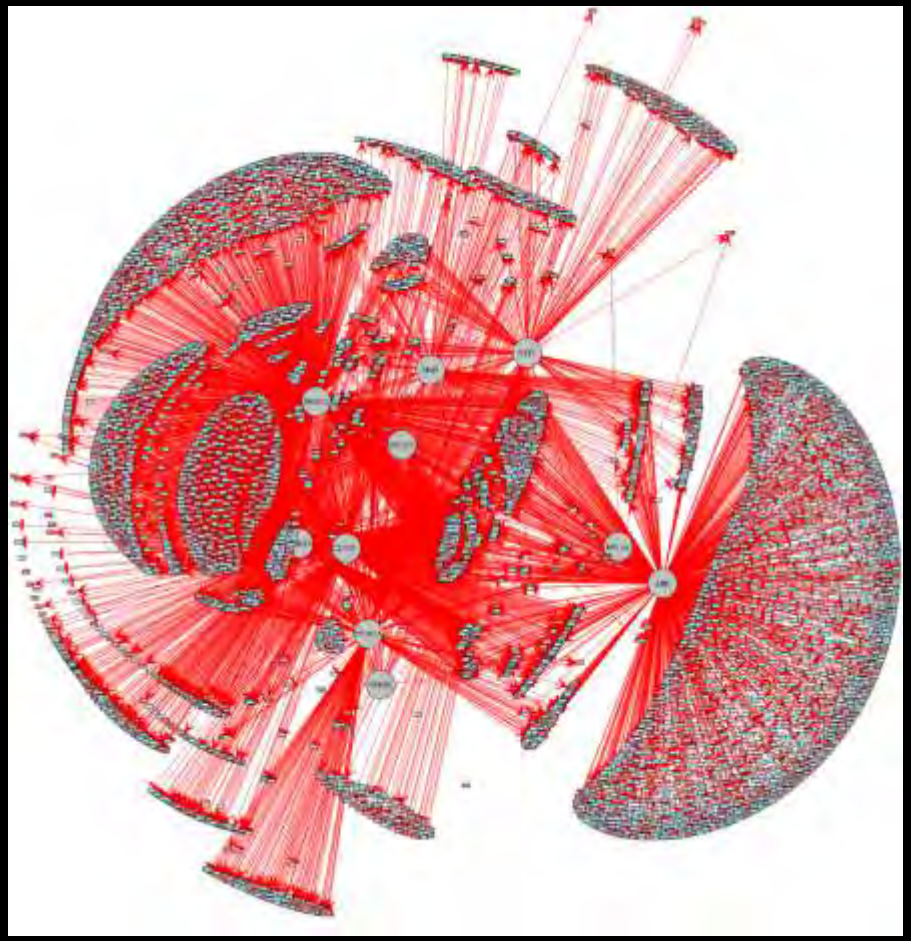
encoded information and expression as cell-specific signaling networks

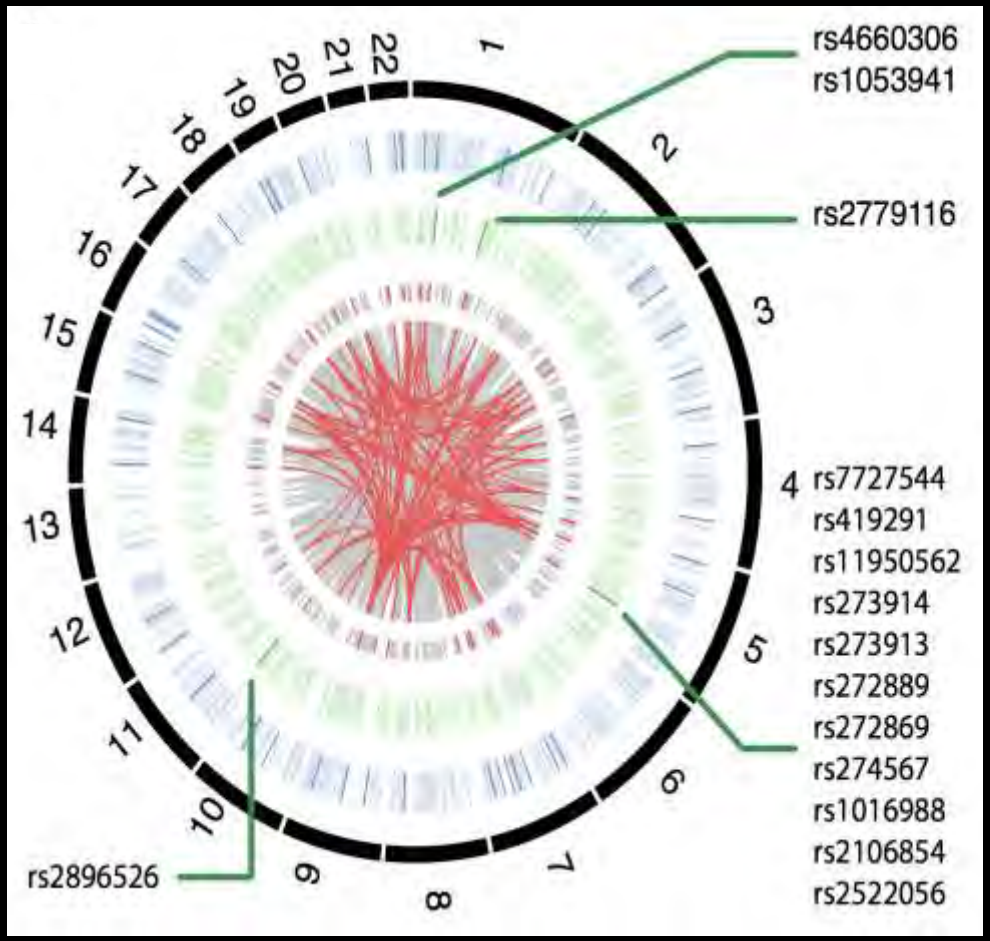
patterns of information flow within signaling networks (network topology)

stable networks and information fidelity (health)

dysregulated networks and altered information patterns (disease)

Integrative Gene Expression Network Models and Classification of Functional Modules (Communities) That Span Multiple Chromosomes



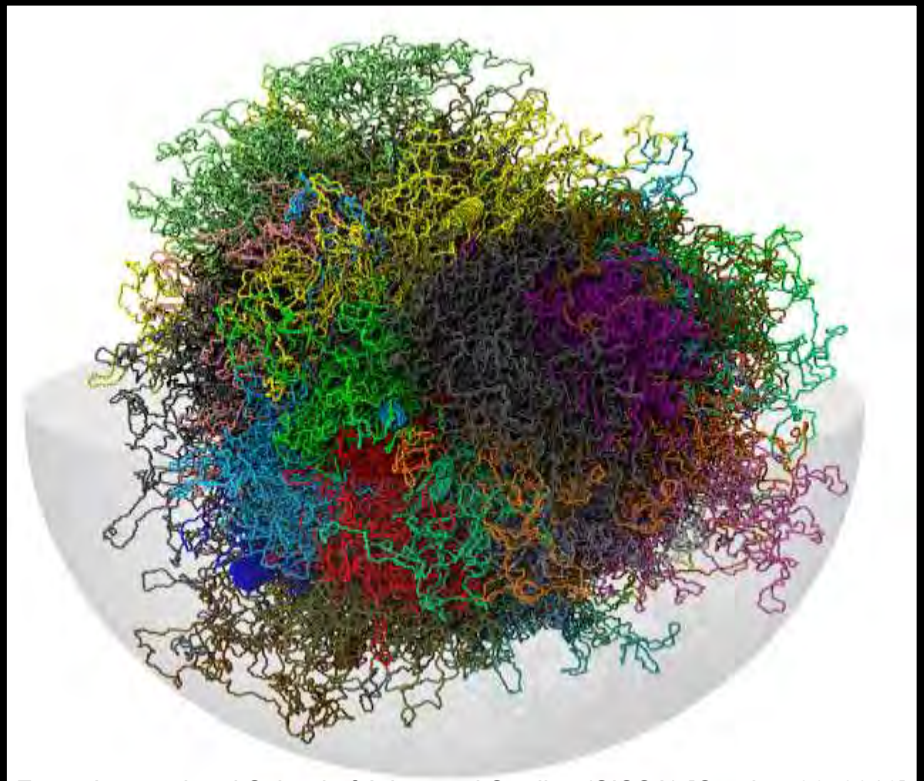


Courtesy of Dr. J. Quackenbush, Dana Farber Cancer Center

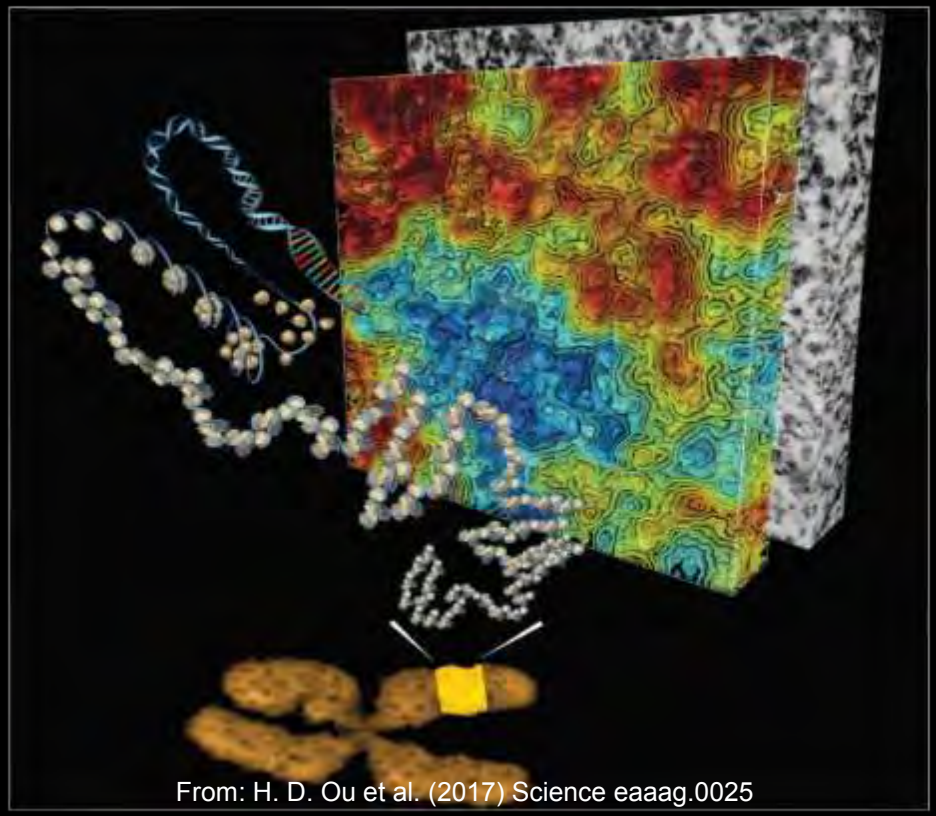
Defining Short- and Long-Range Cis- and Trans- Regulation of Gene Networks

Chromosomal Neighborhoods: Understanding the 3-D and 4-D Genome

ChromEMT Mapping of Chromatin Ultrastructure and DNA Packing



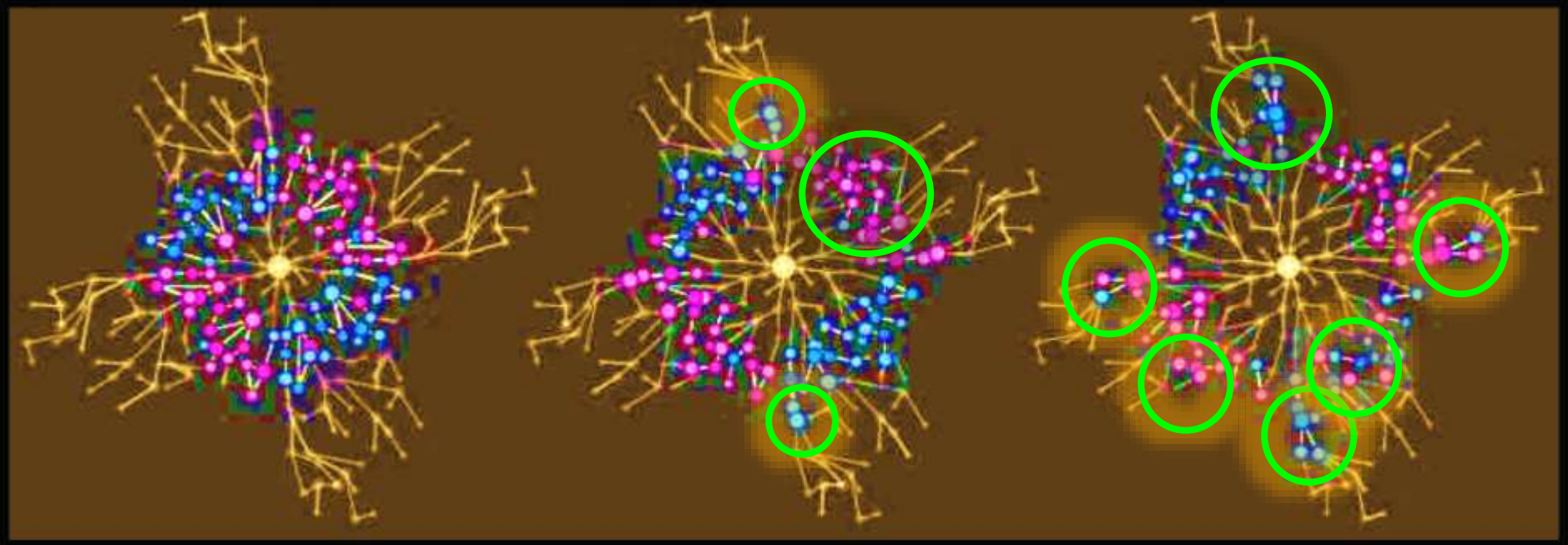
From: International School of Advanced Studies (SISSA) [October 26, 2016]



From: H. D. Ou et al. (2017) Science eaaag.0025

- spatial and temporal regulation of topological association domains (TADs)
- intra and inter-chromosomal cis- and trans- juxtaposition of TFs, promoters and enhancers

Understanding System State Shifts (Phenomes) and Emergent Perturbations in Molecular Signaling Networks in the Health to Disease Continuum

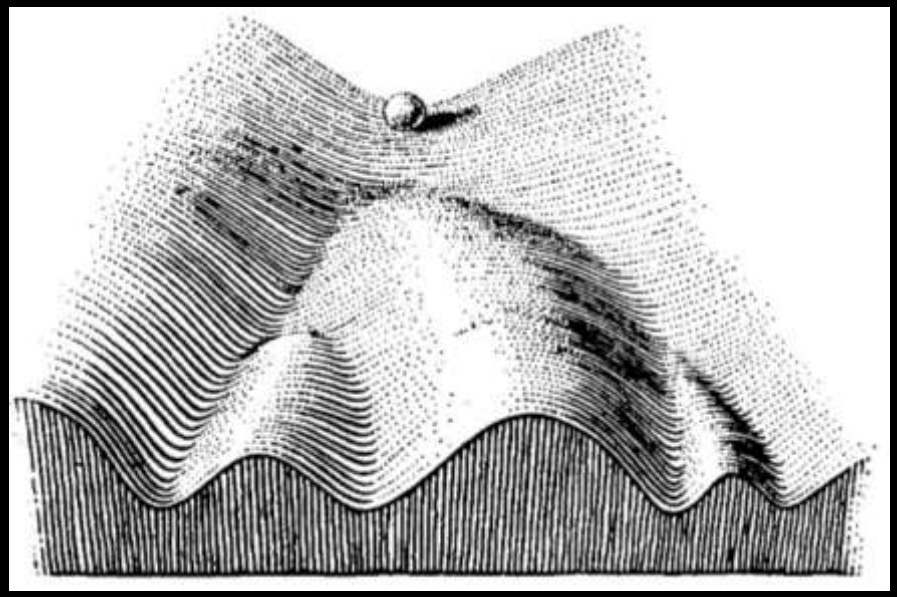


$T_{1(n)}$ health

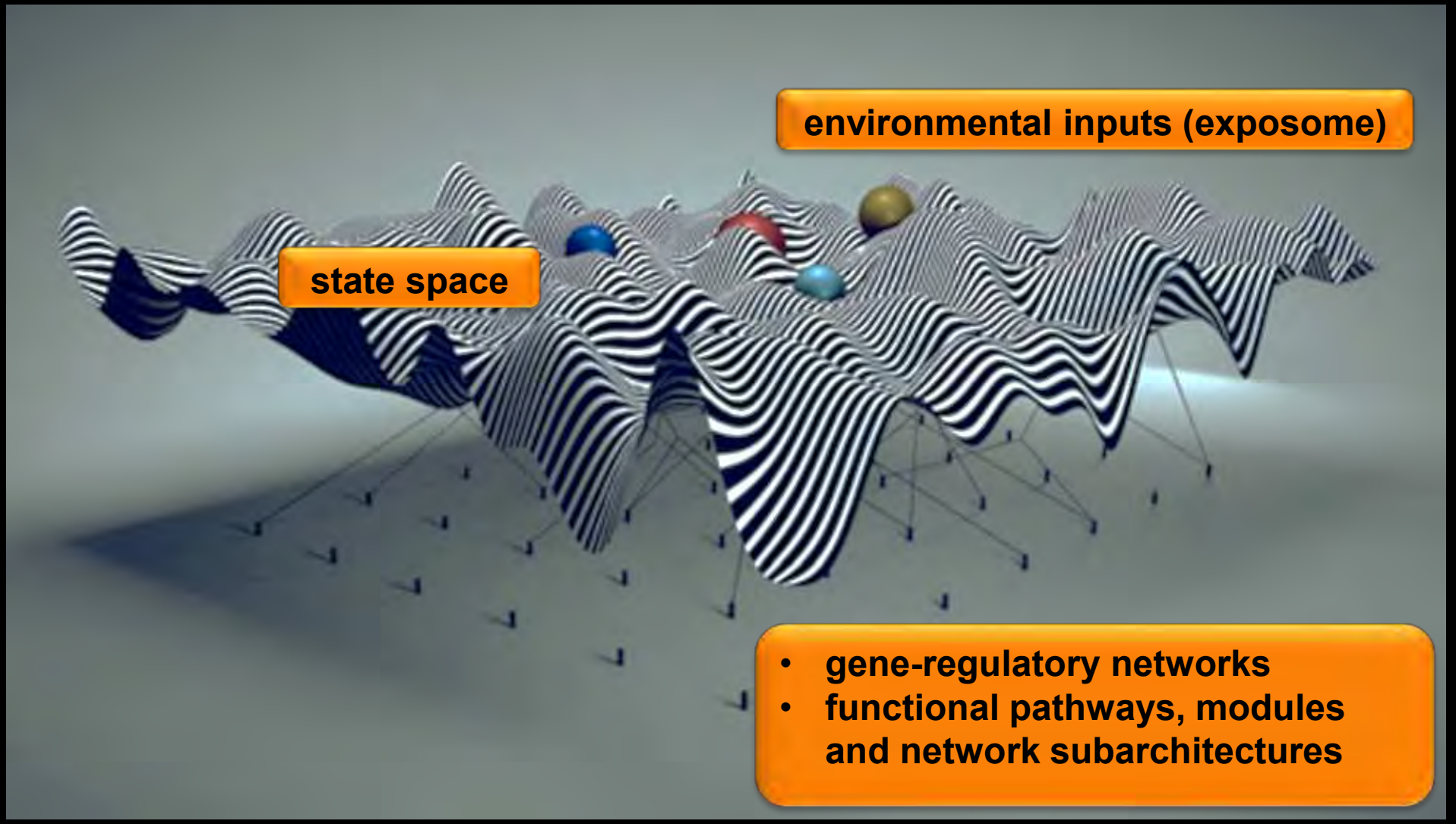
$T_{2(n)}$ subclinical disease

$T_{3(n)}$ overt disease

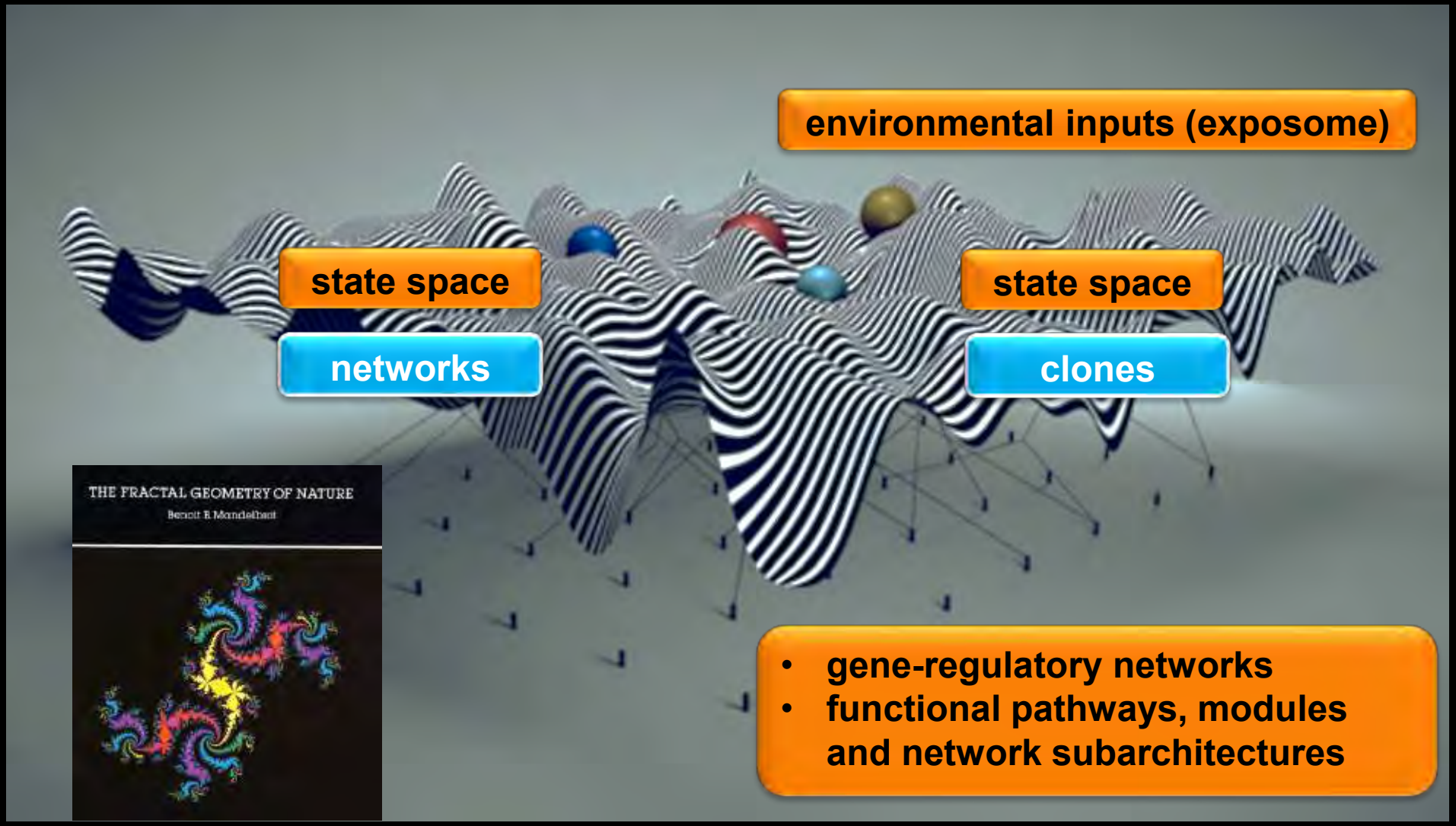
Multi–Attractor Landscapes and System State Space Occupancies in Biological CAS (After Haldane 1957)



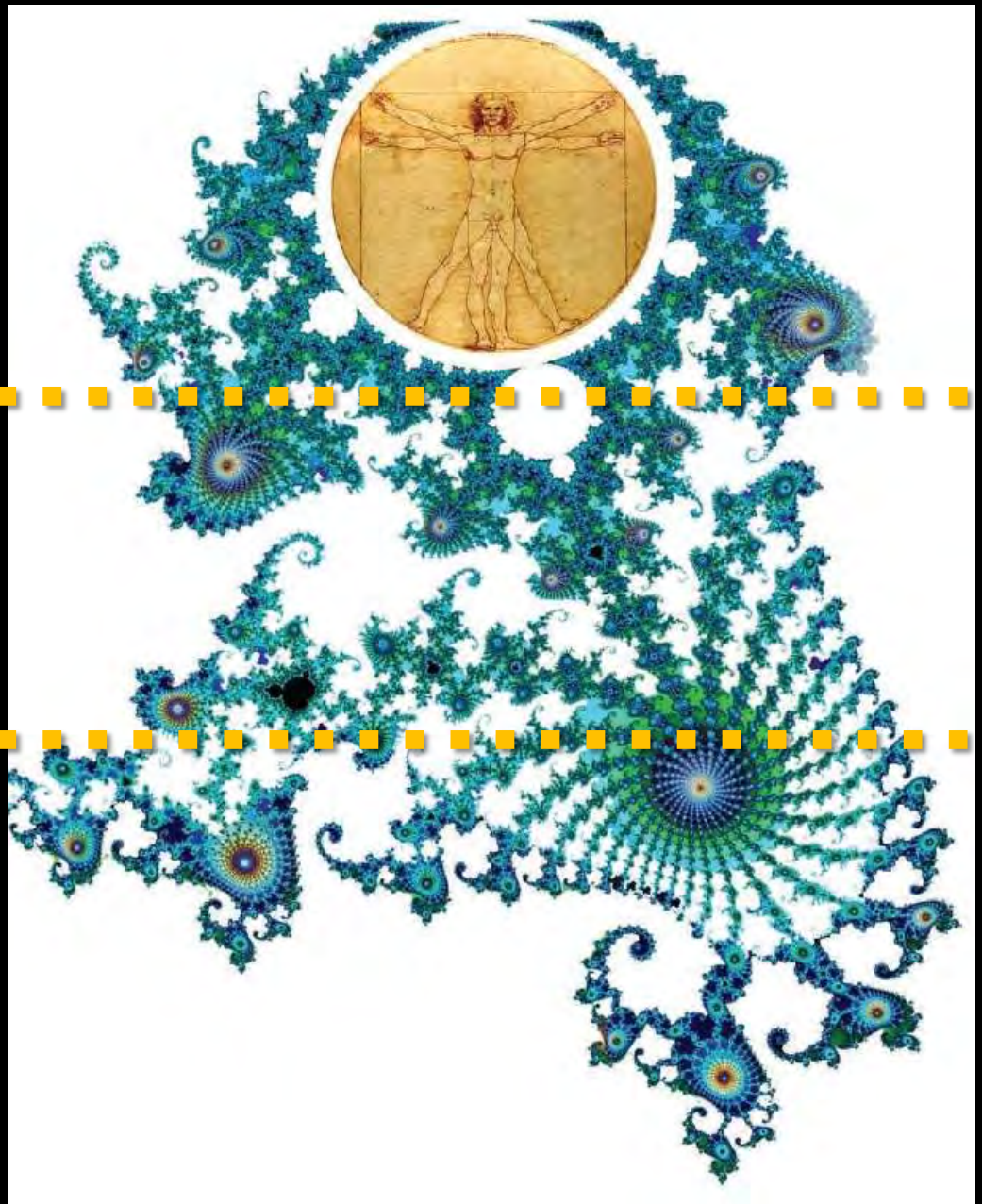
Multi–Attractor Landscapes and State Space Occupancies in CAS



Multi–Attractor Landscapes, State Space Occupancies, and Adaptive, Evolutionary Pathways in CAS



Multi-Attractor CAS Landscapes and State-Space Occupancies in the Health to Disease Continuum



physiology
(homeostasis)

- graded perturbations
- disease predisposition and/or subclinical disease

clinical disease
(pathology)

- disease subtypes and phenotypes

Nature (2018) 556, 463

https://doi.org/10.1038/s41586-018-0040-3

Identification of the tumour transition states occurring during EMT

Ievgenia Pastushenko[1], Andrey Brisebarre[1], Alejandro Sifrim[2,3], Marco Fioramanti[1], Tatiana Revenco[1], Soufiane Boumahdi[1], Alexandra Van Keymeulen[1], Daniel Brown[2,4], Virginie Moers[1], Sophie Lemaire[1], Sarah De Clercq[1], Esmeralda Minguijón[5], Cédric Balsat[6], Youri Sokolow[7], Christine Dubois[5], Florian De Cock[1], Samuel Scozzaro[1], Federico Sopena[8], Angel Lanas[8], Nicky D'Haene[5], Isabelle Salmon[5,9], Jean-Christophe Marine[6,10], Thierry Voet[2,3], Panagiotis A. Sotiropoulos[1,12] & Cédric Blanpain[1,10,11,*]

Nature (2018) 556, 457

https://doi.org/10.1038/s41586-018-0024-3

Intra-tumour diversification in colorectal cancer at the single-cell level

Sophie F. Roerink[1,13], Nobuo Sasaki[2,11,13], Henry Lee-Six[1,12], Matthew D. Young[1], Ludmil B. Alexandrov[3,4,5], Sam Behjati[1,6], Thomas J. Mitchell[1,7], Sebastian Grossmann[1], Howard Lightfoot[1], David A. Egan[8,12], Agnello Pronk[9], Niels Smakman[9], Iwest van Gorp[10], Elizabeth Anderson[1], Stephen J. Gamble[1], Chris Alder[1], Marc van de Wetering[2], Peter J. Campbell[1], Michael R. Stratton[1,6] & Hans Clevers[2,*]

Cell (2018) 173, 595

Deterministic Evolutionary Trajectories Influence Primary Tumor Growth: TRACERx Renal

Samra Turajlic,[1,2,26] Hang Xu,[1,26] Kevin Litchfield,[1,26] Andrew Rowan,[1,26] Stuart Horswell,[3,26] Tim Chambers,[1,26] Tim O'Brien,[4,26] Jose I. Lopez,[5,26] Thomas B.K. Watkins,[1] David Nicol,[6] Mark Stares,[1] Ben Challacombe,[4] Steve Hazell,[7] Ashish Chandra,[8] Thomas J. Mitchell,[9,10] Lewis Au,[2] Claudia Eichler-Jonsson,[1] Faiz Jabbar,[1] Aspasia Soultati,[11] Simon Chowdhury,[11] Sarah Rudman,[11] Joanna Lynch,[2] Archana Fernando,[4] Gordon Stamp,[12] Emma Nye,[12] Aengus Stewart,[3] Wei Xing,[13] Jonathan C. Smith,[13] Mickael Escudero,[3] Adam Huffman,[13] Nik Matthews,[14] Greg Elgar,[14] Ben Phillimore,[14] Marta Costa,[14] Sharmin Begum,[14] Sophia Ward,[1,14,19] Max Salm,[3] Stefan Boeing,[3] Rosalie Fisher,[1] Lavinia Spain,[2] Carolina Navas,[1] Eva Grönroos,[1] Sebastijan Hobor,[1] Sarkhara Sharma,[1] Ismaeel Aurangzeb,[1] Sharanpreet Lall,[11] Alexander Polson,[8] Mary Varia,[8] Catherine Horsfield,[8] Nicos Fotiadis,[15] Lisa Pickering,[2] Roland F. Schwarz,[16] Bruno Silva,[13] Javier Herrero,[17] Nick M. Luscombe,[18] Mariam Jamal-Hanjani,[19] Rachel Rosenthal,[17,19] Nicolai J. Birkbak,[1,19] Gareth A. Wilson,[1,19] Orsolya Pipek,[20] Dezso Ribli,[20] Marcin Krzystanek,[21] Istvan Csabai,[20] Zoltan Szallasi,[21,22] Martin Gore,[2] Nicholas McGranahan,[19] Peter Van Loo,[23,24] Peter Campbell,[9] James Larkin,[2,*] Charles Swanton,[1,19,25,27,*] and the TRACERx Renal Consortium

Cell (2018) 173, 581

Tracking Cancer Evolution Reveals Constrained Routes to Metastases: TRACERx Renal

Samra Turajlic,[1,2,26] Hang Xu,[1,26] Kevin Litchfield,[1,26] Andrew Rowan,[1,26] Tim Chambers,[1,26] Jose I. Lopez,[2,26] David Nicol,[4,26] Tim O'Brien,[2,26] James Larkin,[2,26] Stuart Horswell,[3] Mark Stares,[1,2] Lewis Au,[2] Mariam Jamal-Hanjani,[1] Ben Challacombe,[4] Ashish Chandra,[5] Steve Hazell,[6] Claudia Eichler-Jonsson,[1] Aspasia Soultati,[26] Simon Chowdhury,[7] Sarah Rudman,[10] Joanna Lynch,[2] Archana Fernando,[5] Gordon Stamp,[11] Emma Nye,[11] Faiz Jabbar,[1] Lavinia Spain,[2] Sharanpreet Lall,[10] Rosa Guarch,[12] Mary Falzon,[13] Ian Proctor,[13] Lisa Pickering,[2] Martin Gore,[2] Thomas B.K. Watkins,[1] Sophia Ward,[1,6] Aengus Stewart,[1] Renzo DiNatale,[14] Maria F. Becerra,[14] Ed Reznik,[15] James J. Hsieh,[15] Todd A. Richmond,[17] George F. Mayhew,[17] Samantha M. Hill,[16] Catherine D. McNally,[16] Carol Jones,[16] Heidi Rosenbaum,[17] Stacey Stanislaw,[16] Daniel L. Burgess,[17] Nelson R. Alexander,[16] Charles Swanton,[1,2,19,25,*] PEACE, and the TRACERx Renal Consortium

Cell (2018) 173, 611

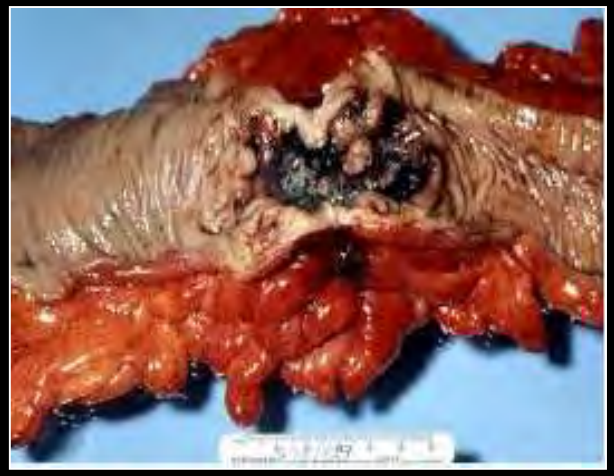
Timing the Landmark Events in the Evolution of Clear Cell Renal Cell Cancer: TRACERx Renal

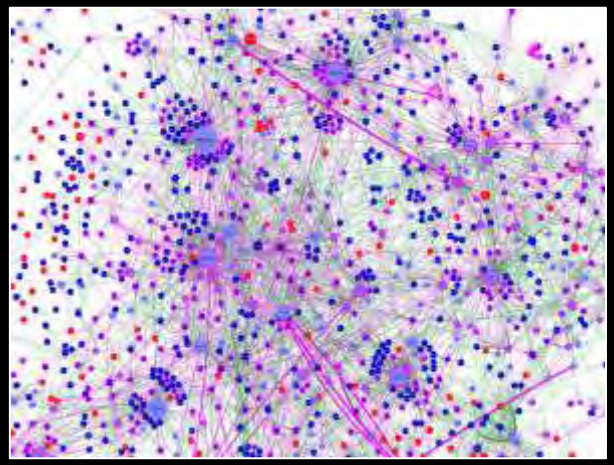
Thomas J. Mitchell,[1,2,27] Samra Turajlic,[2,4,27] Andrew Rowan,[2,27] David Nicol,[4,27] James H.R. Farmery,[4] Tim O'Brien,[5] Inigo Martincorena,[1] Patrick Tarpey,[1] Nicos Angelopoulos,[1] Lucy R. Yates,[1,6] Adam P. Butler,[1] Keiran Raine,[1] Grant D. Stewart,[2] Ben Challacombe,[6] Archana Fernando,[6] Jose I. Lopez,[7] Steve Hazell,[8] Ashish Chandra,[9] Simon Chowdhury,[6] Sarah Rudman,[6] Aspasia Soultati,[6] Gordon Stamp,[6] Nicos Fotiadis,[6] Lisa Pickering,[6] Lewis Au,[6] Lavinia Spain,[6] Joanna Lynch,[6] Mark Stares,[6] Jon Teague,[1] Francesco Maura,[1] David C. Wedge,[10] Stuart Horswell,[11] Tim Chambers,[2] Kevin Litchfield,[2] Hang Xu,[2] Aengus Stewart,[11] Reza Elaidi,[12] Stéphane Oudard,[13] Nicholas McGranahan,[2,14] Istvan Csabai,[15] Martin Gore,[2] P. Andrew Futreal,[16] James Larkin,[2] Andy G. Lynch,[2,17] Zoltan Szallasi,[2,18] Charles Swanton,[2,19,20,*] Peter J. Campbell,[1,20,21,*] and the TRACERx Renal Consortium

Dynamic Modeling of Signaling Pathways and Networks in Complex Systems

- what parts of the system and the subsystem networks are the most/least sensitive to perturbation?
- what part(s) of the network(s) are most/least influential on the rest of the network when perturbed?
- exploitation to identify new R_x targets and prediction of most likely trajectories of R_x resistance

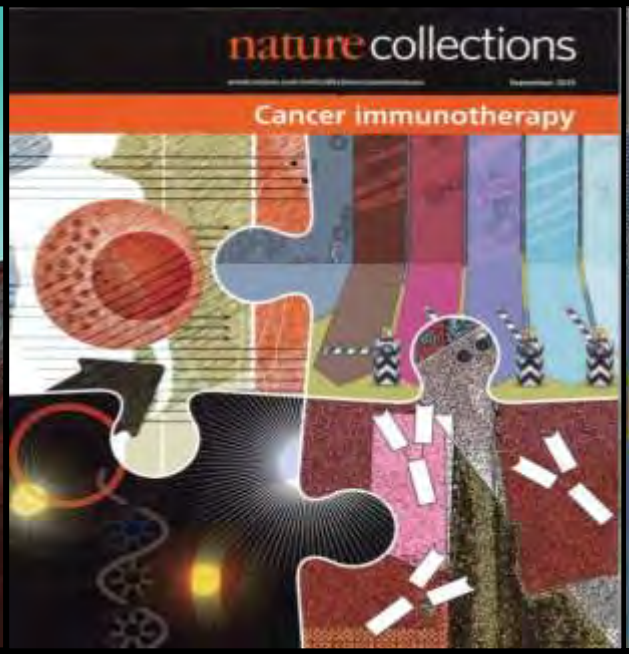
A Disturbing Question:
Is Unifocal R_x Modulation of Complex Network Dysregulation in Advanced Chronic Diseases Feasible or a Delusion?

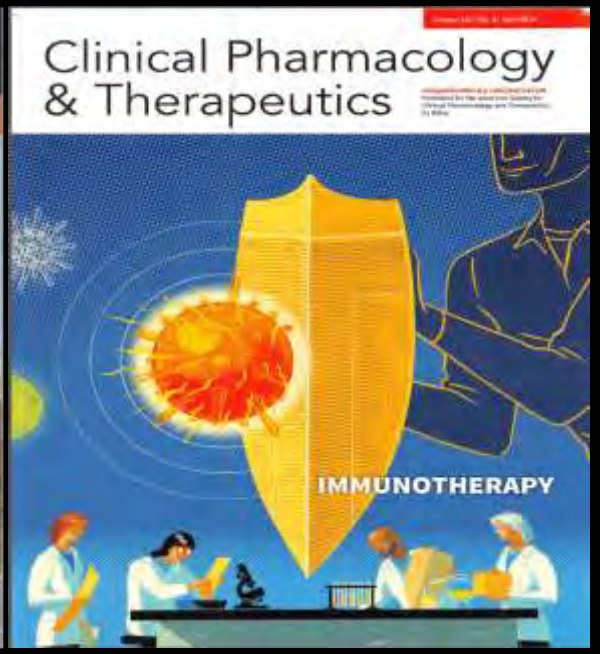




- "too disrupted to restore"? (homeostatic reset) ?
- multi-node/multi-module/ multi-subnetwork dysregulation
- low feasibility of multi-R_x intervention against multiple dysregulated targets ?
- even lower feasibility of design of promiscuous multi-target single R_x ?

The Promise of Cancer Immunotherapy





Cancer Immuno-Oncology (I/O) Therapies in Clinical Trials (4/18)*

- over 300 investigational therapies and 1700 clinical trials
- late stage Phase II/III pipeline dominated by agents with 4 MOAs
  - anti-CTLA4, anti-PDI, anti-PD-LI, CD19 modulation (CAR-T cells)
- enthusiasm for indoleamine-pyrole-2, 3 dioxygenase (INDO/IDO) inhibitors dashed and recent corporate withdrawals (4/18)
- additional 52 immune-targets under investigation

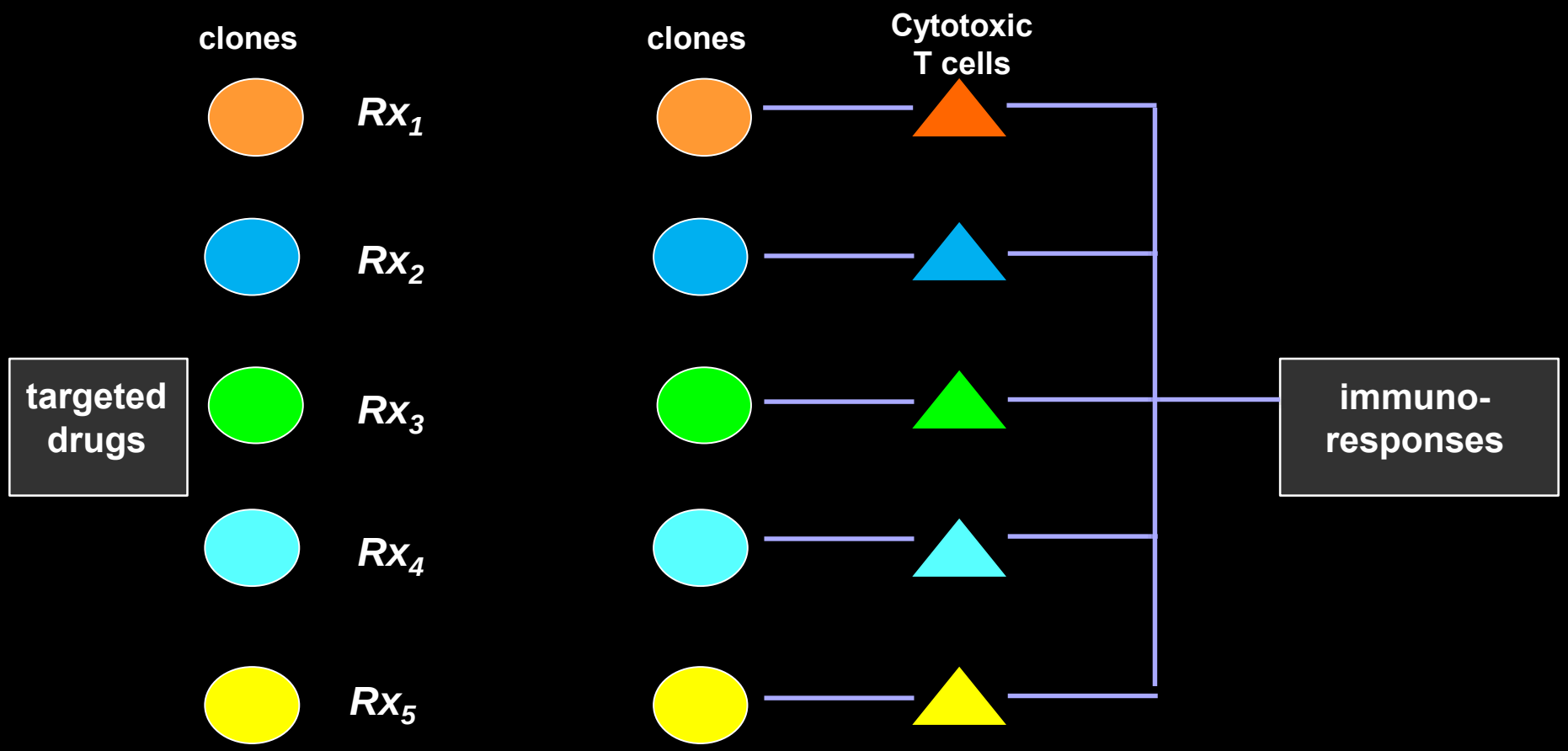
*Source: Clarivate Analytics Coretllis; IQVIA Institute

Host Immune-Tumor Interactions and the Tumor-Immune Microenvironment (TIME)

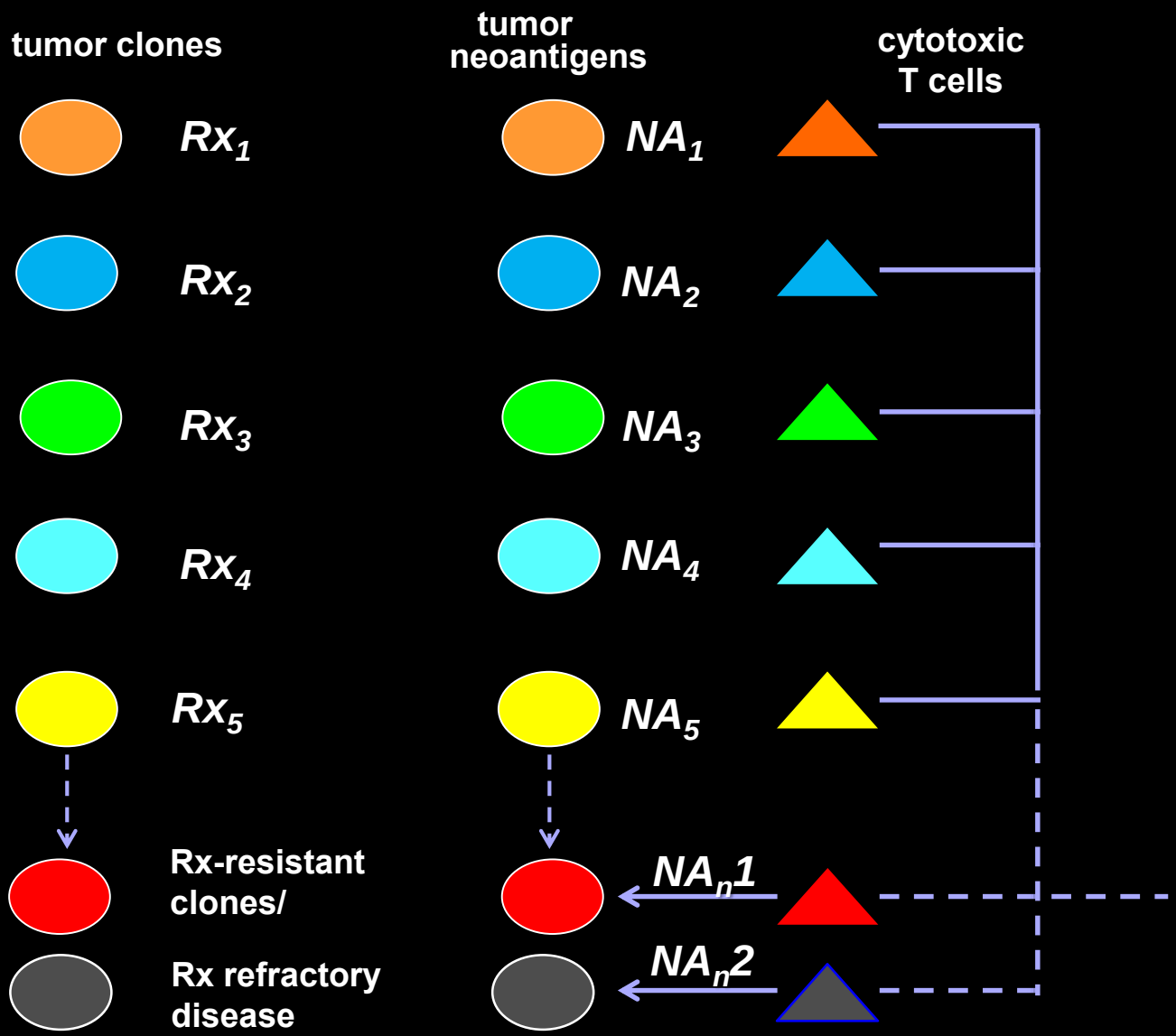
Clone Wars

Relentless Emergence of New Tumor Cell Clones During Tumor Progression and Immune Evasion
versus
Activation of Host T Lymphocyte Clones to Kill (Neo)Antigen-Specific Tumor Clones

Therapeutic Strategies for Circumvention of Clonal Diversity in Malignant Tumors: Single Target Drugs (Rx) versus Immunotherapeutics (Irx)



Circumventing the Inevitable Drug Resistance Problem in Targeted Rx Therapy versus Therapeutic Restoration of Effective Immune Surveillance

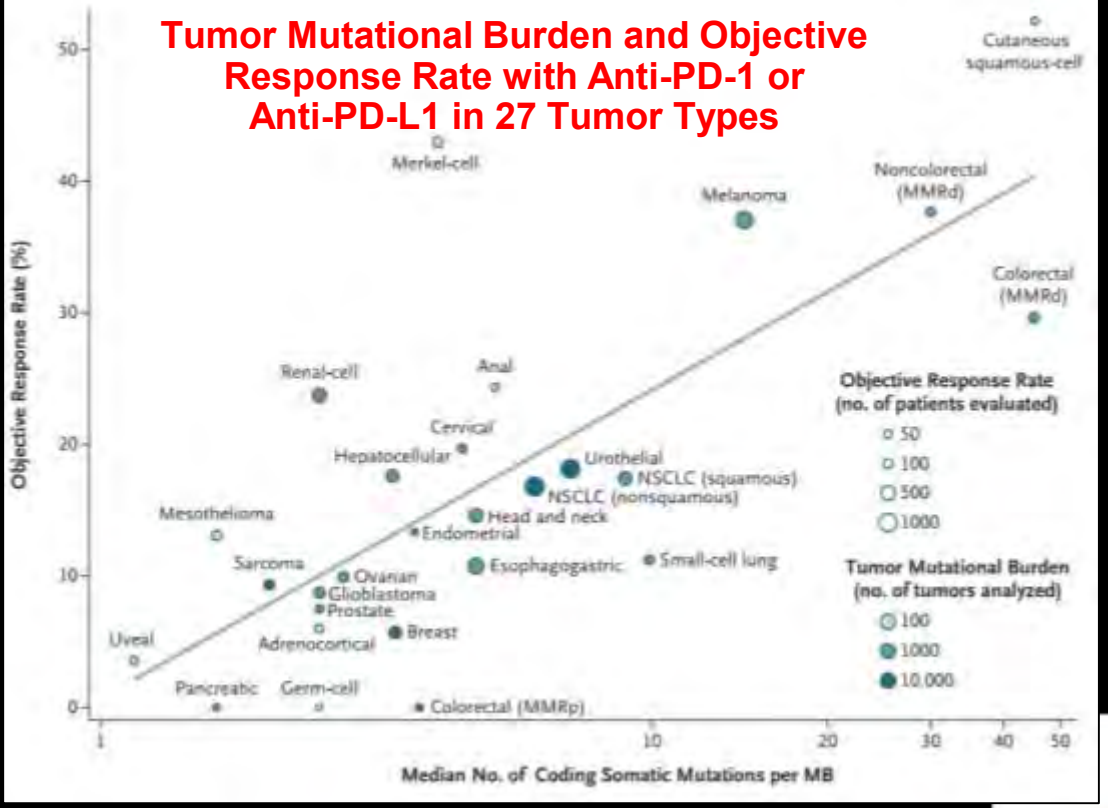


adaptive evolution of immune response and expanded cytotoxic T cell responses

Realizing The Promise of Cancer Immunotherapy

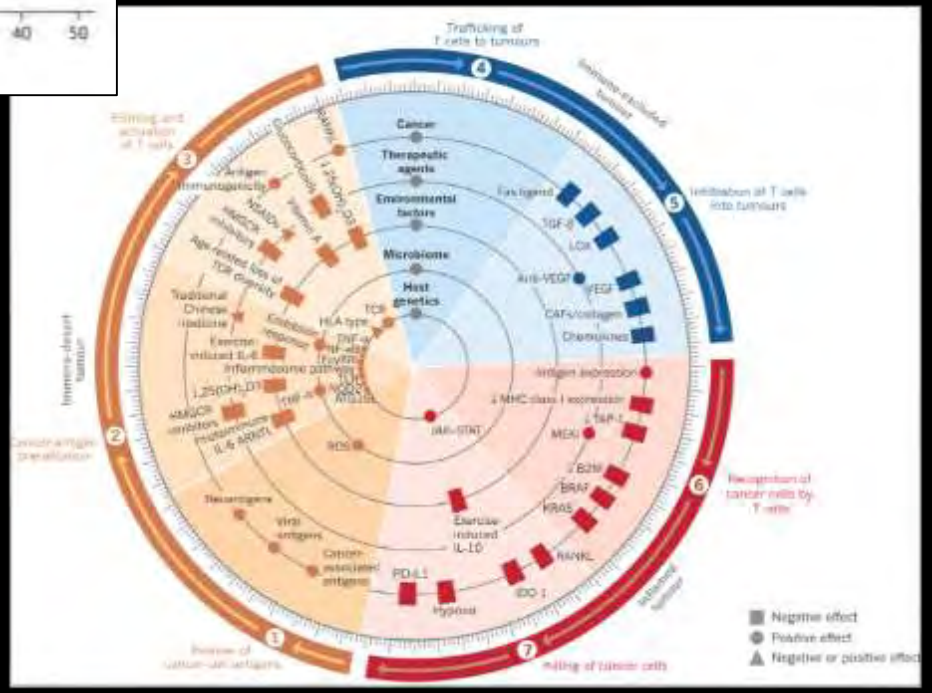
- wide variation in R_x response rates
  - only 20 - 40% positive responses even in the most responsive tumors
- lack of diagnostic tests to reliably predict responder vs. non-responder patients
- improving response rates across all malignancies and all stages
- will I/O combinations increase response rates?

Tumor Mutational Burden and Objective Response Rate with Anti-PD-1 or Anti-PD-L1 in 27 Tumor Types



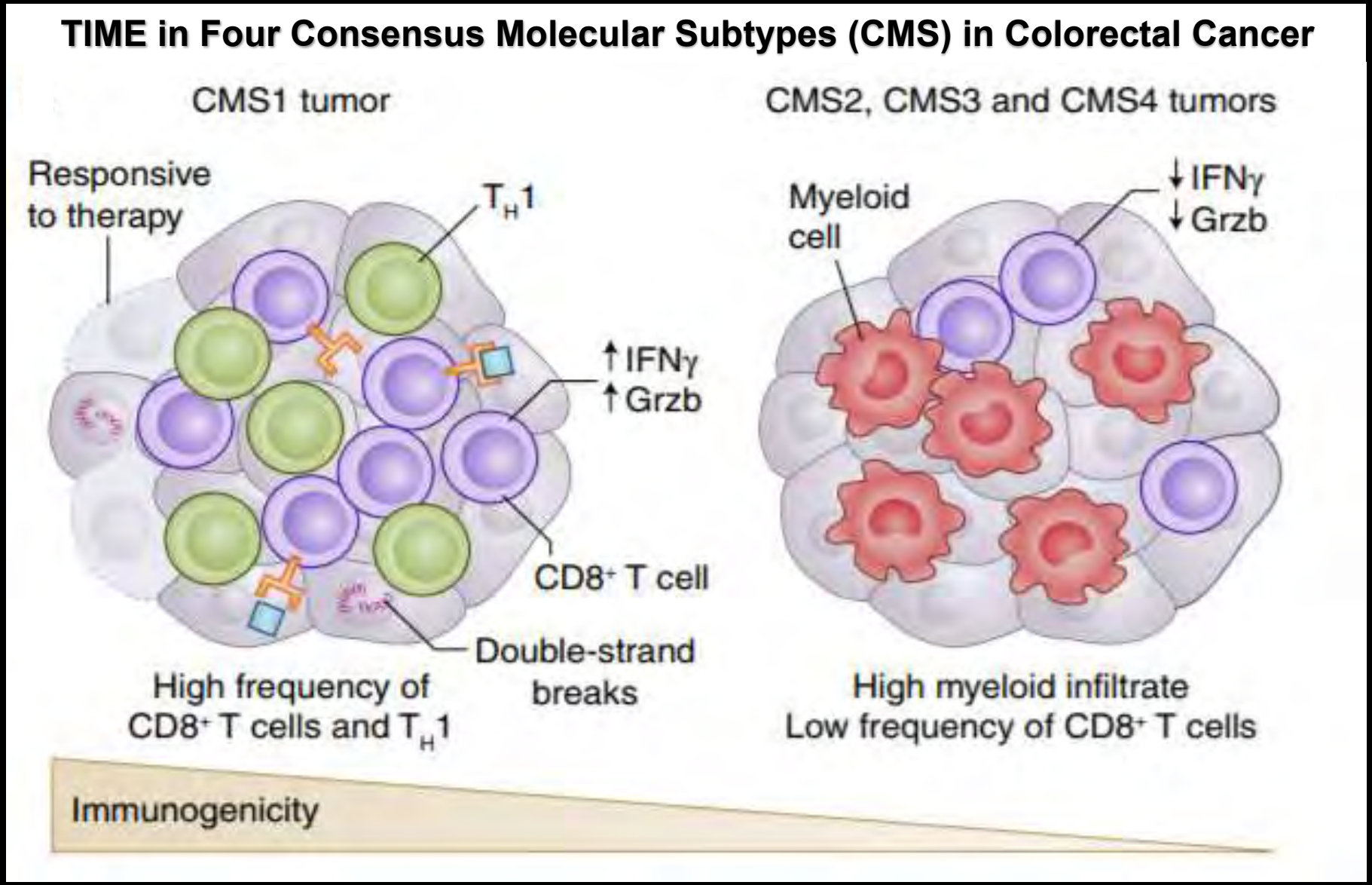
From: M. Yarchoan et al. (2017) NEJM 377, 2501

The Complexity of Cancer-Immune Phenotypes



From: D. S. Chen and I. Mellman (2017) Nature 541, 321

Development of Multi-parameter 'Immunoscore' Assays to Predict Responsiveness to Immunotherapy



From: M. Binnewies et al. (2018) Nature Med. 24, 541

The lasting health toll of chemical warfare *p. 20*

Hidden impacts of air pollution *p. 39*

Flying through Saturn's ionosphere *p. 66*

Science

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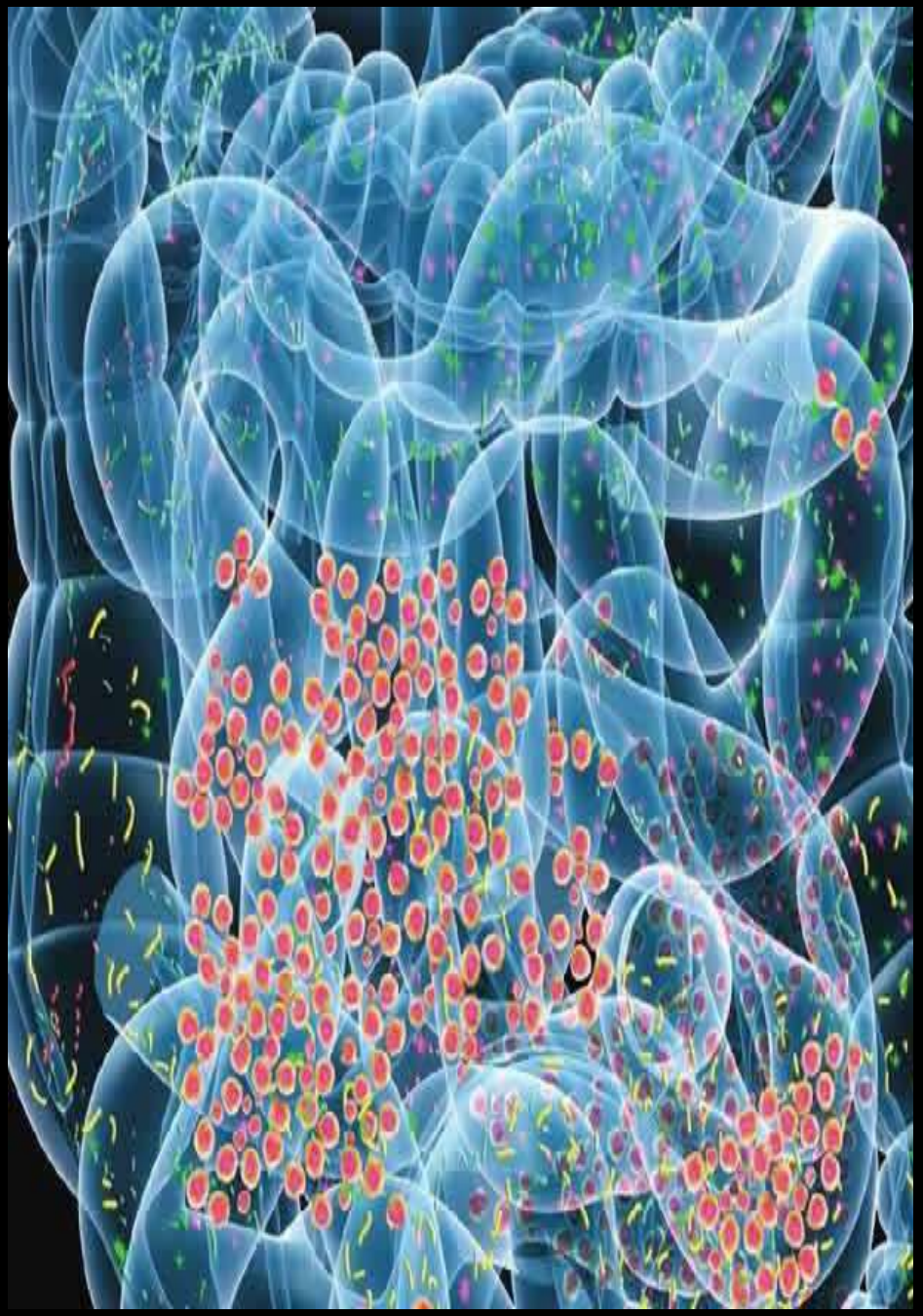
GUT MICROBES AND CANCER

The microbiome influences patient response to immunotherapy

pp. 32, 91, 97, & 104



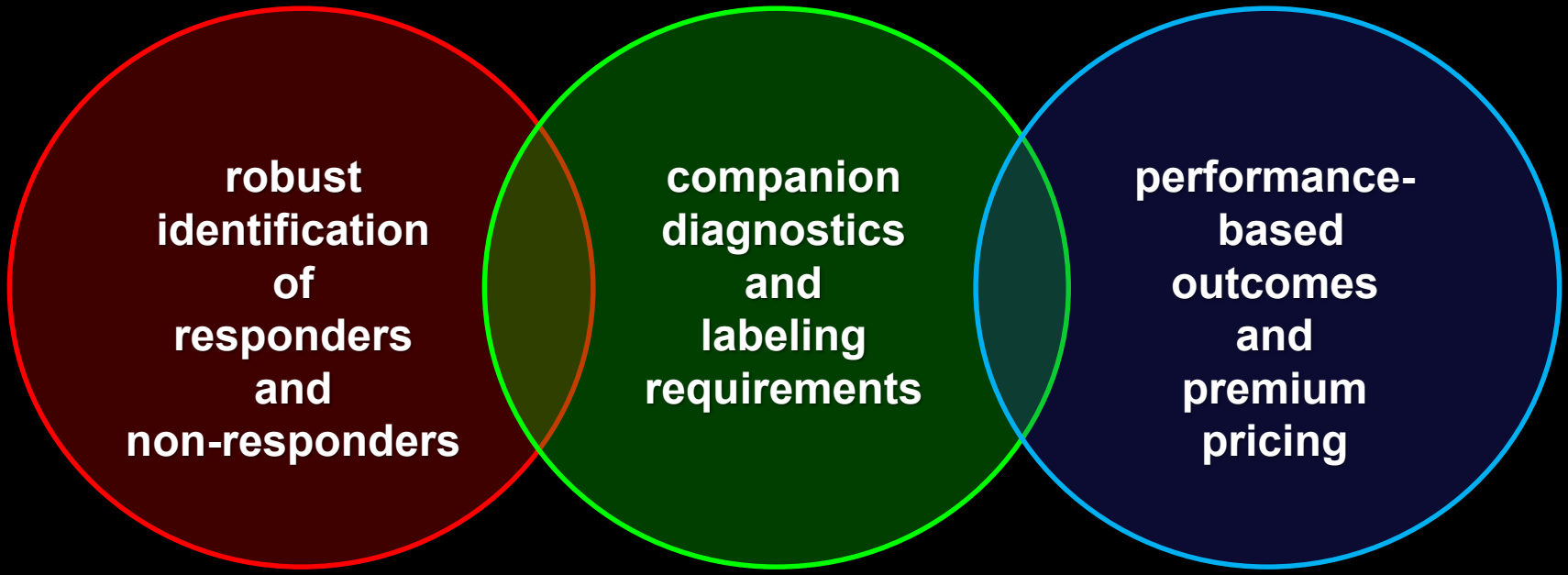
The Promise of Immunotherapy: Is Widespread Adoption Economically Feasible?

- unit Rx cost ($100 - 400K)
- indirect care cost
- escalating cost of combination Rx regimens
- extravagant cost of cell-based therapies ($500K - $1.5 million)
- complex clinical management challenges and compatibility with community oncology services?

Understandable Enthusiasms But With Risk of Considerable Waste in Patient Resources and Cost

- proliferation of I/O combination trials absent biological rationale for dose selection, sequence, timing, number of cycles and duration
  - I/O : I/O
  - I/O : chemo -
  - I/O : targeted Rx
  - I/O : oncolytic viruses
- patient expectations
  - informed consent vs informed risk
- market saturation and performance-based pricing?

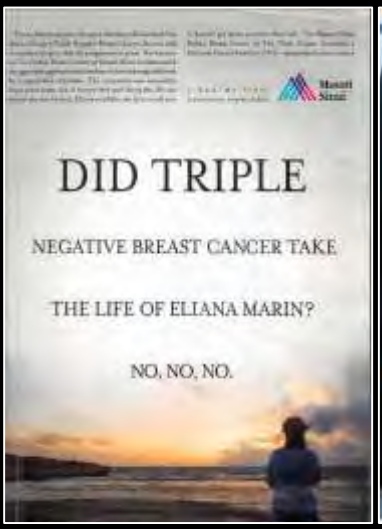
Performance-Based Contracts and Pricing: The Inevitable Future Landscape for Cancer Therapy?



integration of R:NR phenotypes into clinical trials and registration dossier

risk sharing

Hype Versus Hope- A Delicate Ethical Balance: Come and Be Cured by Us: (Go Elsewhere at Your Peril) !



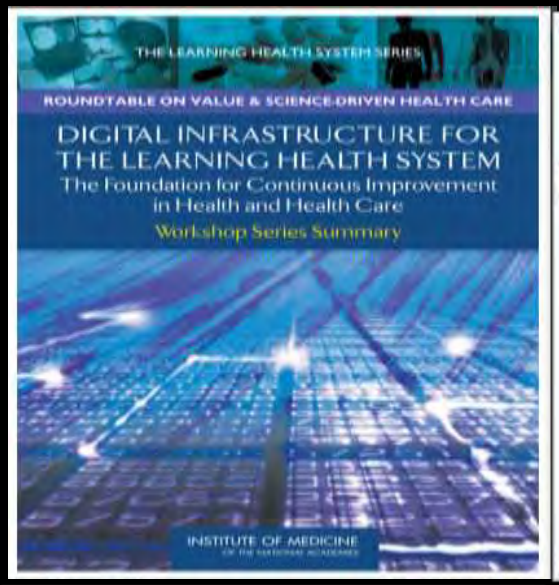
H.R. 5427: “Right to Try” Legislation Signed by President D. Trump 30 May 2018

Now Comes the Really Hard Part!

Building a Learning Healthcare System

Robust Data as the Core Element in Improved Cancer Control and Outcomes

Building a Learning Health Care System and a National Cancer Data Ecosystem



Making Precision Oncology a Reality

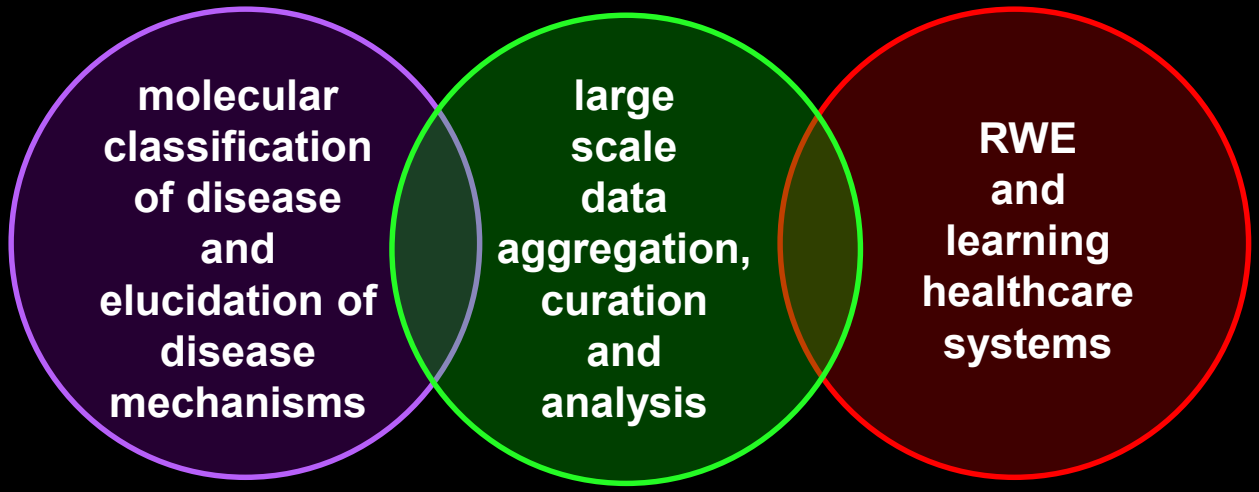
deep phenotyping

integration of molecular, clinical,
social and environmental data

longitudinal, dynamic data capture
versus
isolated static snapshots

managing the data deluge

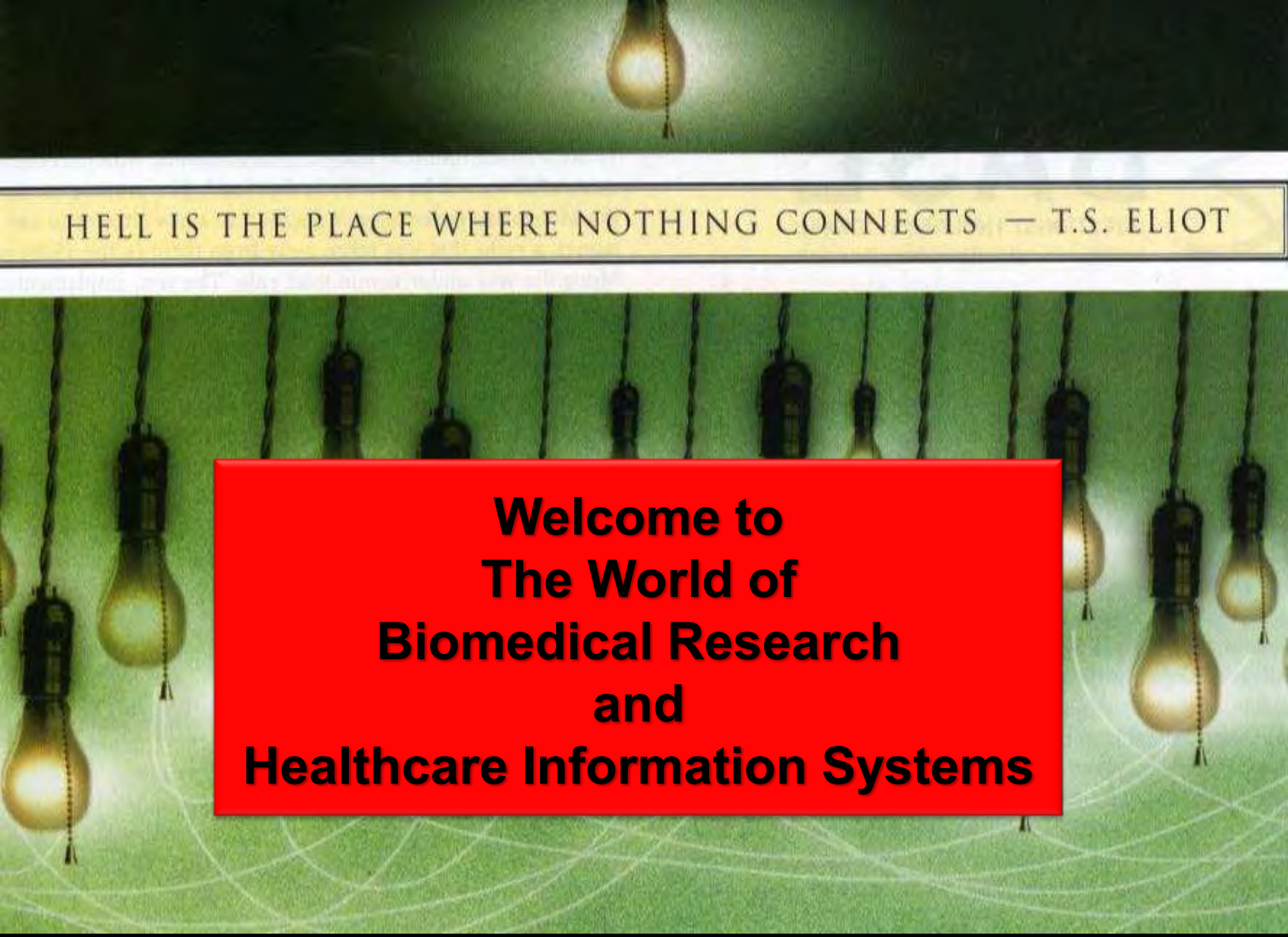
Precision Medicine and Computational Medicine: Evolving Inter-dependencies



The Big Data Challenge
V6: volume, variety, velocity, veracity, virtualization, value
D3: distributed, dynamic, decision support
I3: infrastructure, investment, intelligent systems

Population Health Research and Precision Oncology: Blurring the Boundaries Between Daily Life and Interactions with the Healthcare System

- every encounter (clinical and non-clinical) is a data point
- every individual is a data node
- every individual is a research asset
- every individual is their own control



Welcome to The World of Biomedical Research and Healthcare Information Systems

The Democratization of Healthcare Information and Data

- m (mobile) health apps
- wearables/sensors/implanted devices and wireless technologies
- social media analytics
- geospatial sensors
- IoT

Integration of Molecular Profiling, Clinical and Social Datasets for Computable Disease Phenotypes

- need for generalizable computational infrastructure for diverse deep phenotyping data classes
  - HL7 Fast Healthcare Interoperability Resources (FHIR)
  - integration of cTAKES, SMART, SHARP, TIES, OBO
- ONC requirements for EHR interoperability
- payer requirements for RWE
  - new trial protocols and registries

Data Sharing in Oncology

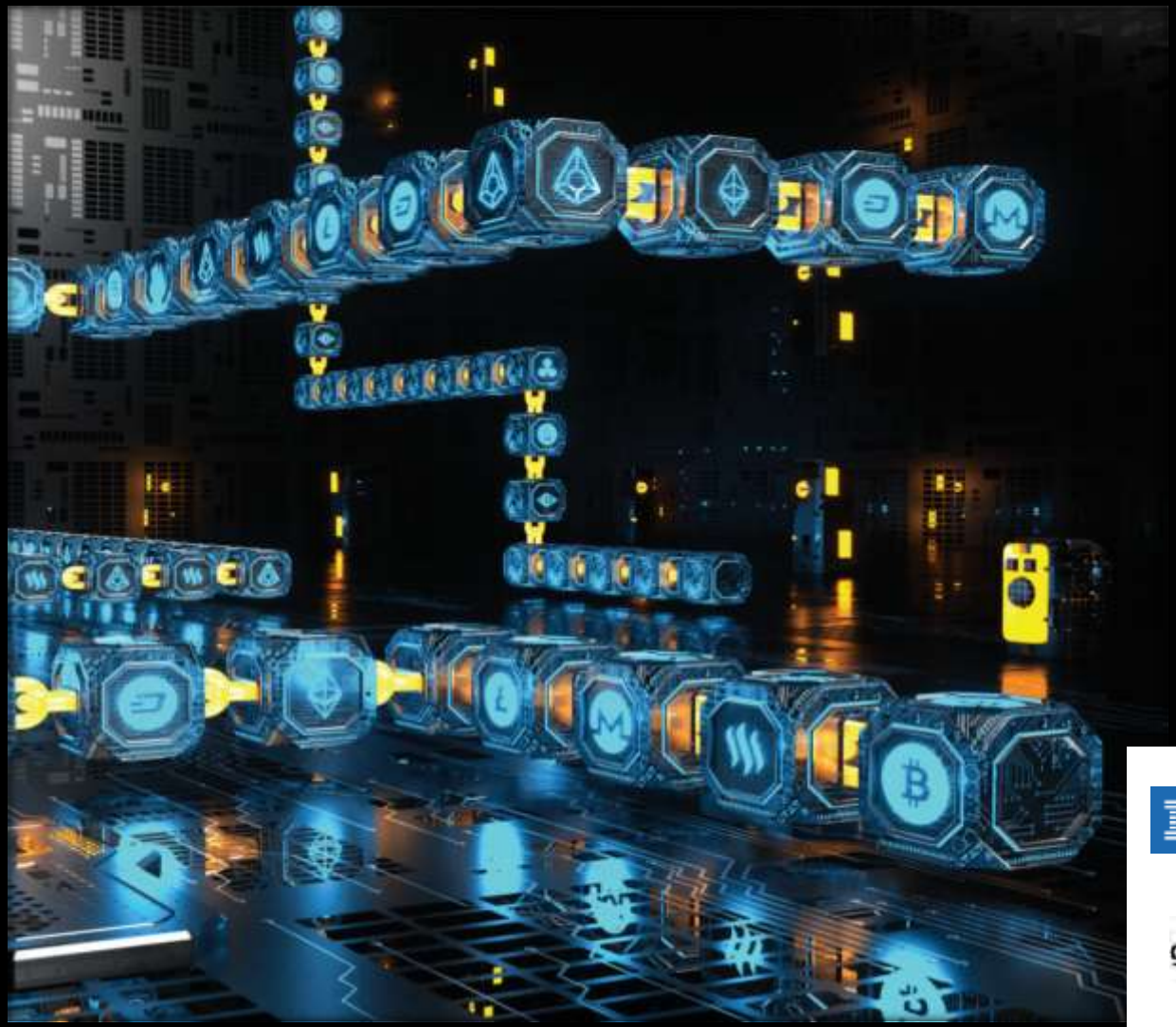
- TCGA (The Cancer Genome Atlas)
- GENIE (Genomics, Evidence, Neoplasia, Information Exchange – AACR)
- ASCO CancerLinQ
- NIH Genomic Data Commons
- Global Alliance for Genomics and Health (GA4GH)
- Molecular Evidence Development Consortium
- ORIEN (Oncology Research Information Network)
- TARGET (Therapeutically Applicable Research to Generate Effective Treatments – NCI)

- NIH Big Data to Knowledge
- NIH ClinGen and ClinVar

Issues in Open Data Initiatives and Data Sharing

- HIPPA and protected health information (PHI)
- tracking data provenance in aggregated data/meta-analysis
- voluntary or imposed data deposition
- credits: researchers versus trialists versus informatician versus patient interests
- IP and regulatory policies for analytical algorithms for machine learning/artificial intelligence
- ownership, privacy, EU-GDPR

Early Entrants Into The Use of Blockchain for Secure Healthcare Data



IBM Microsoft Google GE

guardtime pokitdok Gem

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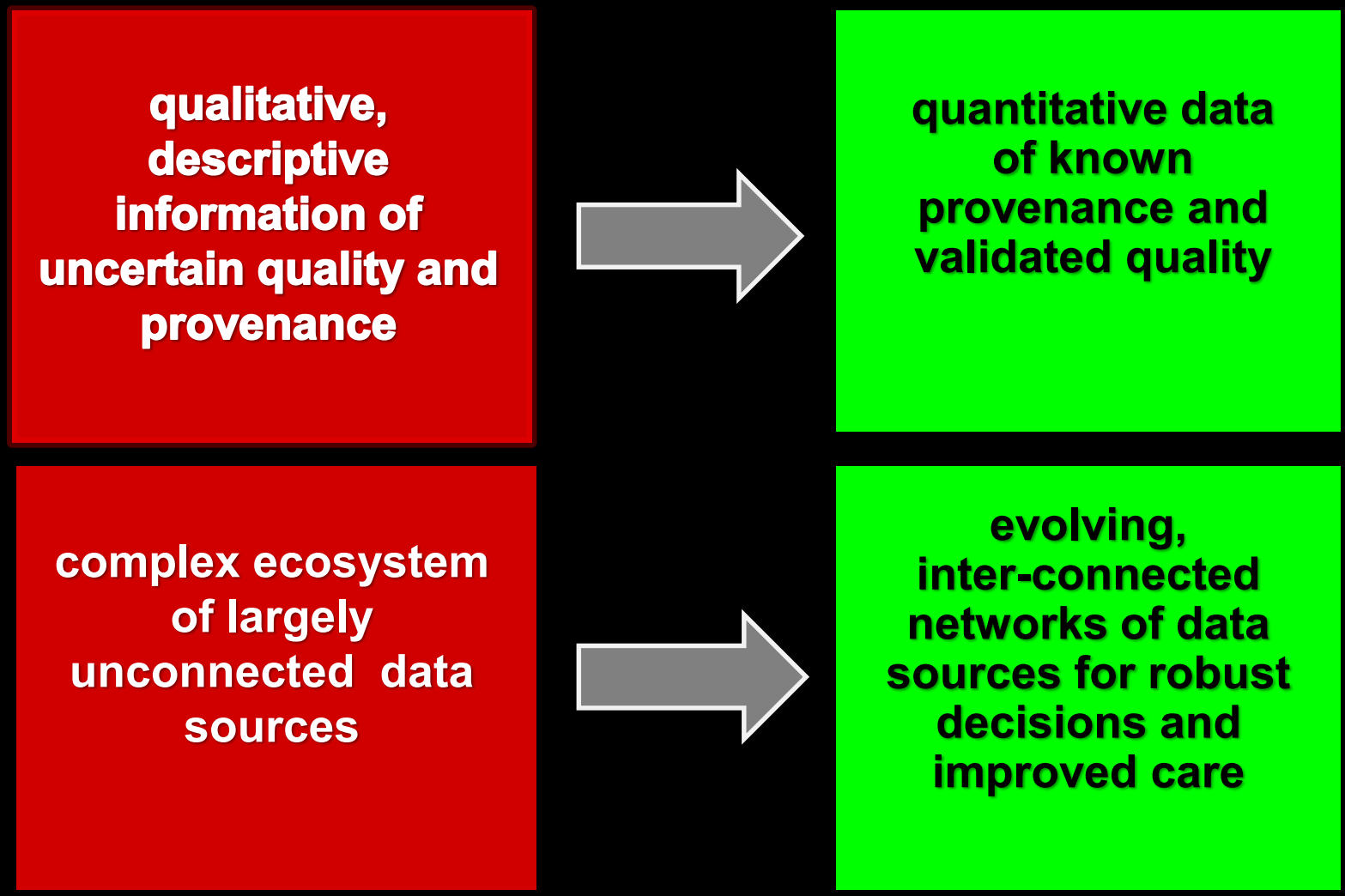
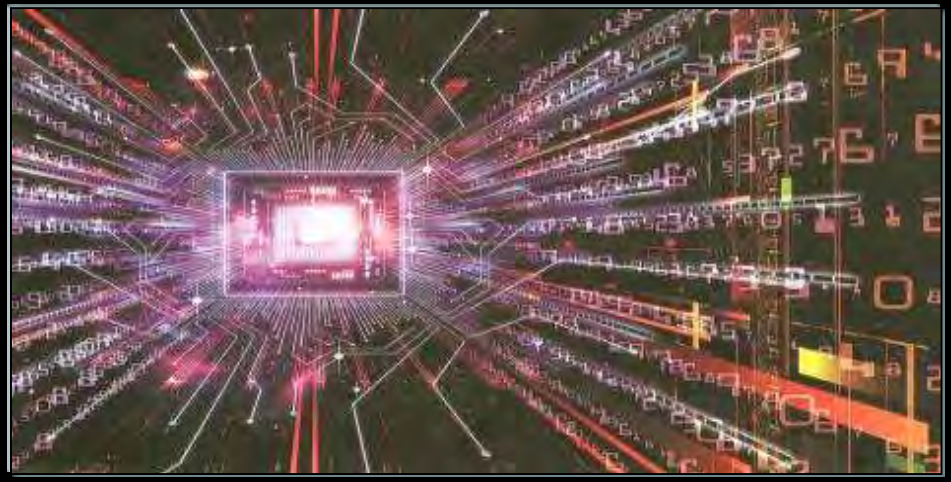
Precision Medicine and Digital Health: Building a Learning Healthcare System



Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Medical Education

Data Deluge

Cognitive Bandwidth Limits



Automated Analytics and Decision Support

Facile Formats for Actionable Decisions

Artificial Intelligence, Pattern Analysis and Medical Practice

Incorporation of AI could transform cancer diagnosis in UK - PM May

NHS

May 21, 2018

Br Dr Ananya Mandal, MD

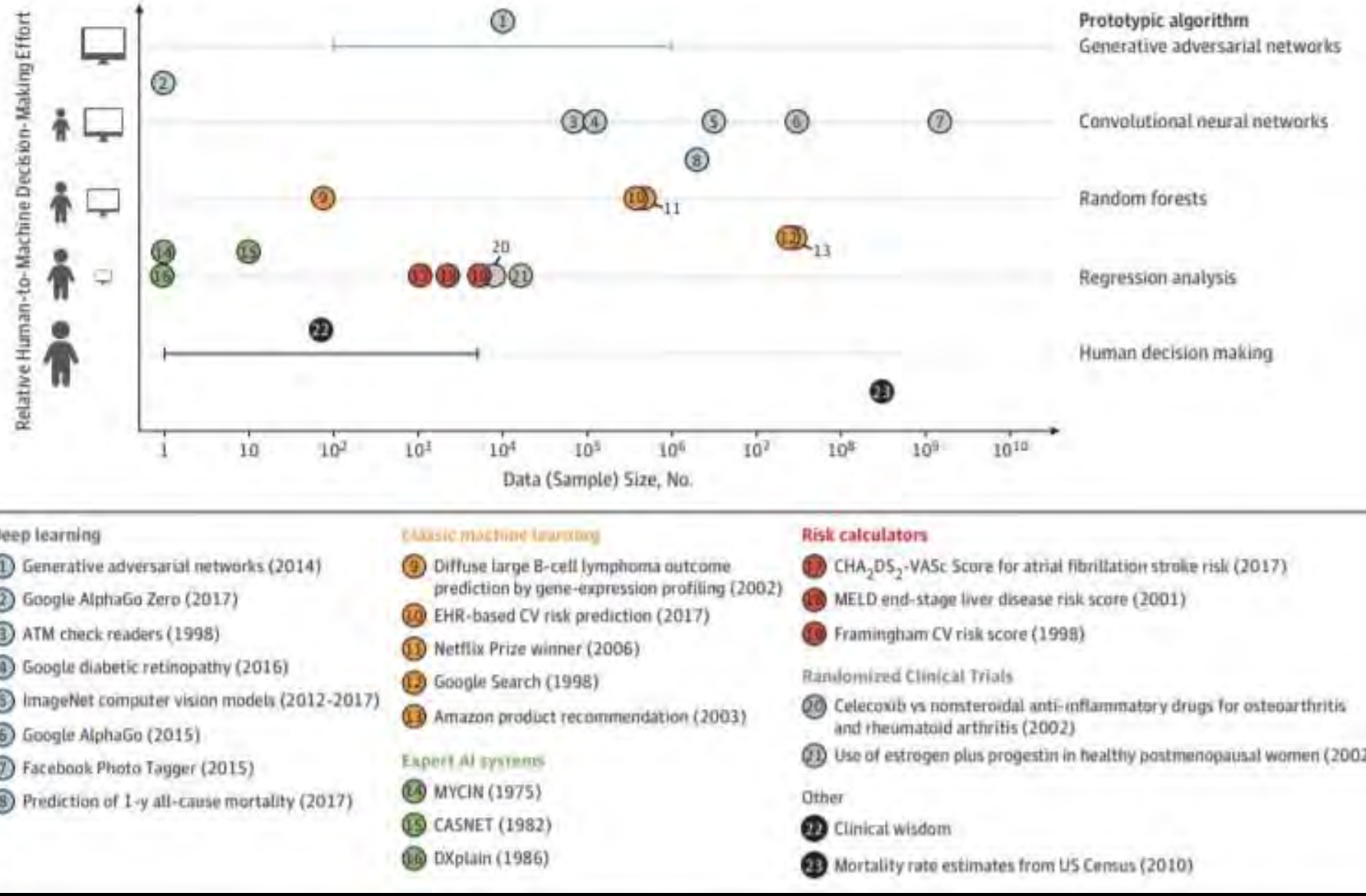
According to Prime Minister Theresa May, Artificial Intelligence (AI) is soon to change the scene in cancer and other disease diagnosis. She is to speak today in Macclesfield where she would acknowledge AI as a "new weapon" that is being used by the NHS and technology companies in research.

"I don't think any physician today should be practicing without artificial intelligence assisting in their practice.

It's just impossible otherwise to pick up on patterns, to pick up on trends to really monitor care."

Bernard J. Tyson
CEO, Kaiser Permanente
Cited in Forbes: The Future of Work
1 March 2017

Machine Learning and Big Data



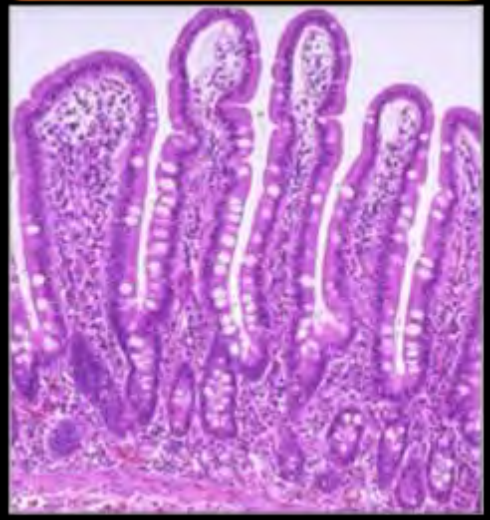
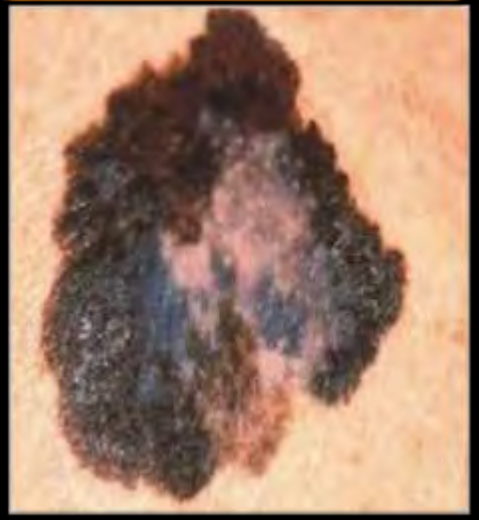
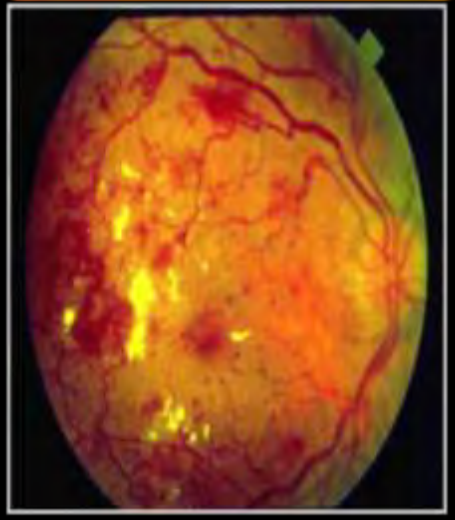
Adapted from: A.L. Beam and I.S. Kohane (2018) JAMA 319,1317

Just What the Data Ordered

Black Box Medicine:

Machine Intelligence and Algorithms for Clinical Diagnosis and Treatment Decisions

Machine Learning and Image Analysis in Clinical Medicine

pathology	radiology	dermatology	ophthalmology
			

- large scale training sets and classification parameters
- standardized, reproducible and scalable
- 260 million images/day for $1000 GPU

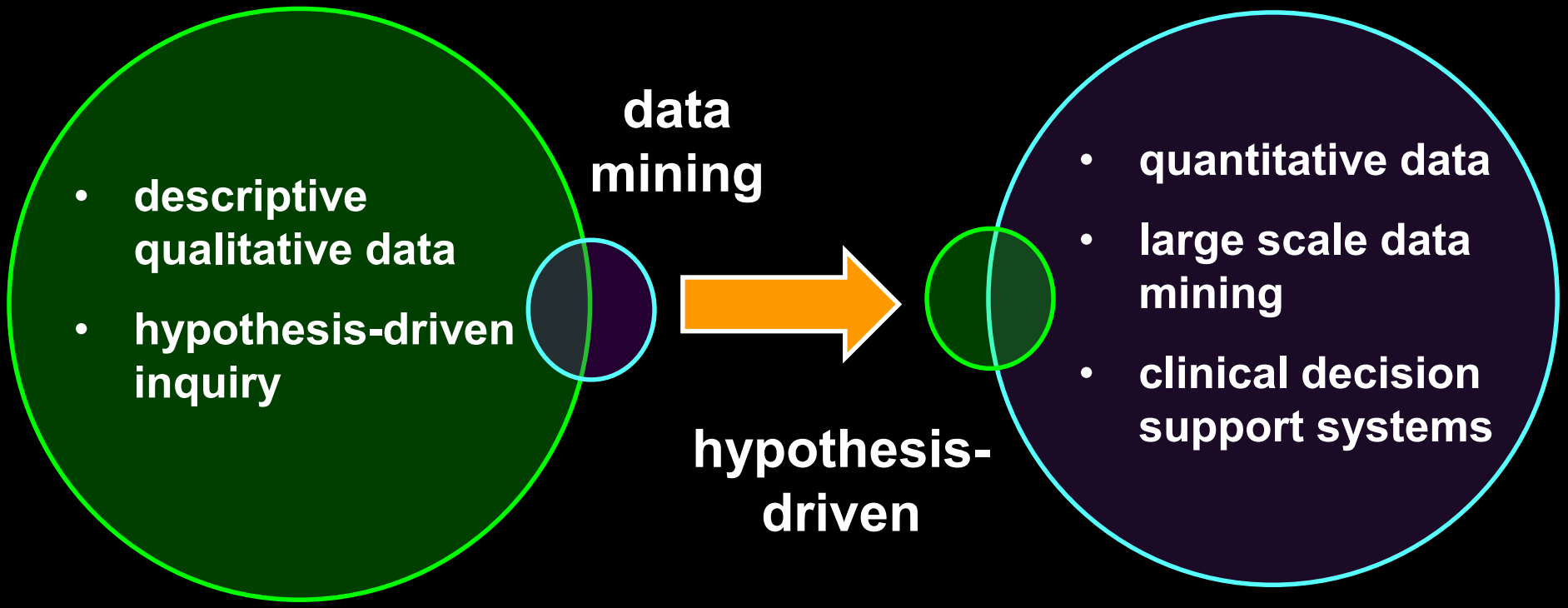
Critical Questions in the Application of ML/AI Platforms in Profiling Large Scale Biomedical Data

- overfitting and bias in datasets used in training
  - error propagation versus automated recognition and exclusion of questionable data
- scale and layered datasets
  - impact of accretion by incorporation of legacy systems of uncertain quality/provenance?
- “black box” effects versus “explainable AI”
  - algorithm evolution neither predicted nor understood by original coders?
  - generative adversarial networks (GANs)

Artificial Intelligence (AI) and Healthcare

- will physicians, payers and patients trust AI?
- how will AI tools be integrated into current work flow or will radical reorganization/re-training be required?
- how will AI platforms alter payment schemes?
- how will AI algorithms/decision analytics be regulated?
- which clinical specialities/processes be at risk of replacement by AI and when?
- how will professional competencies in using AI decision-support tools be defined?
  - MD curriculum, CME
- what new malpractice liabilities will emerge by failure to use/interpret AI platforms

A Pending Transition in Biomedical Research and Clinical Care Decisions?



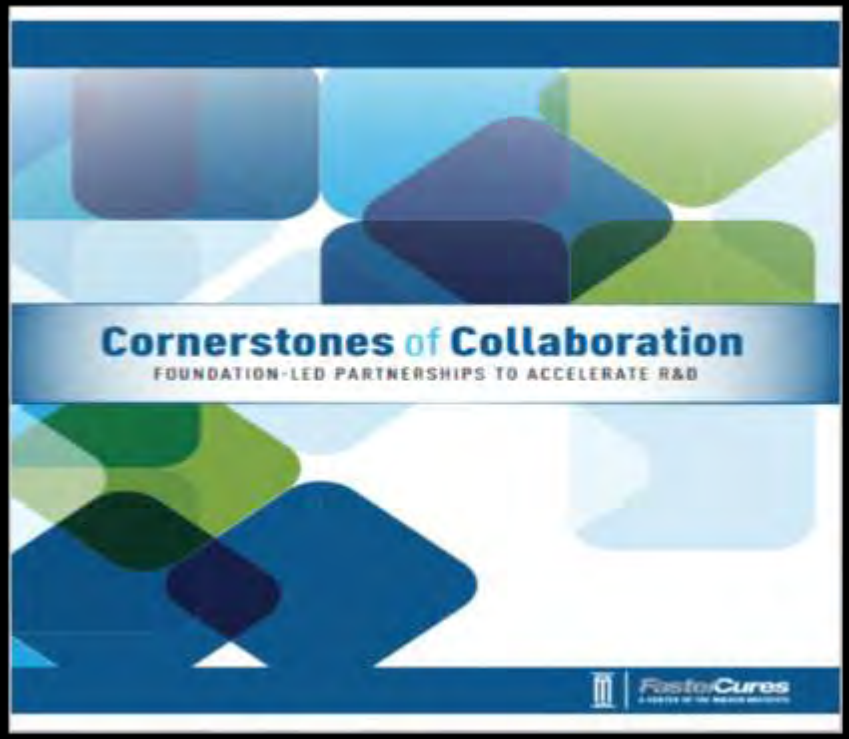
Science Translational Medicine
(2014, 6, 242cm6)

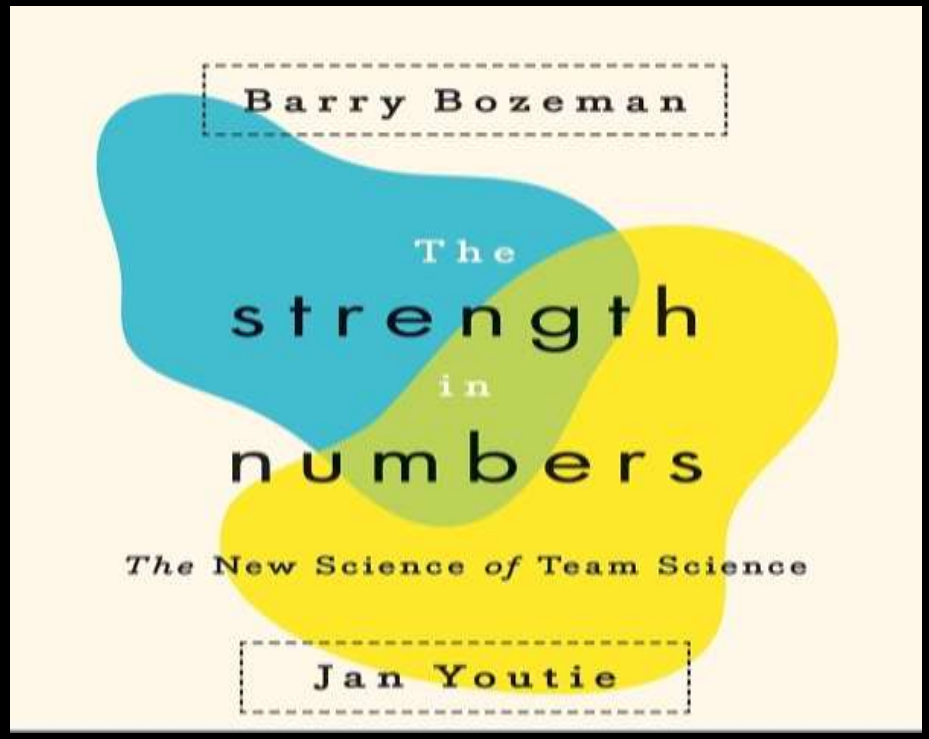
COLLABORATIVE ENVIRONMENTS

Consortium Sandbox: Building and Sharing Resources

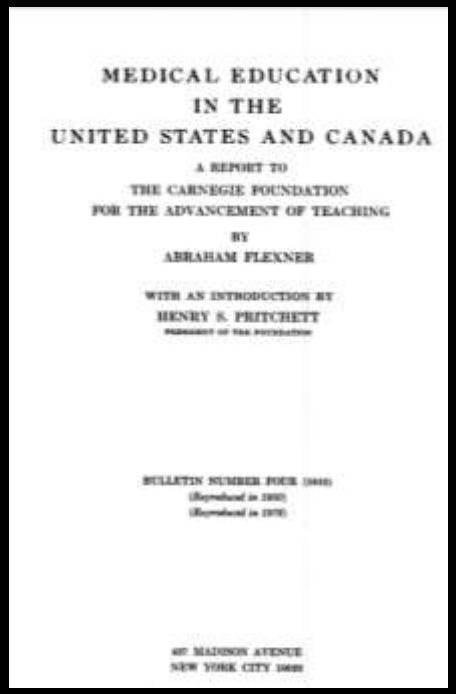
Mark D. Lim

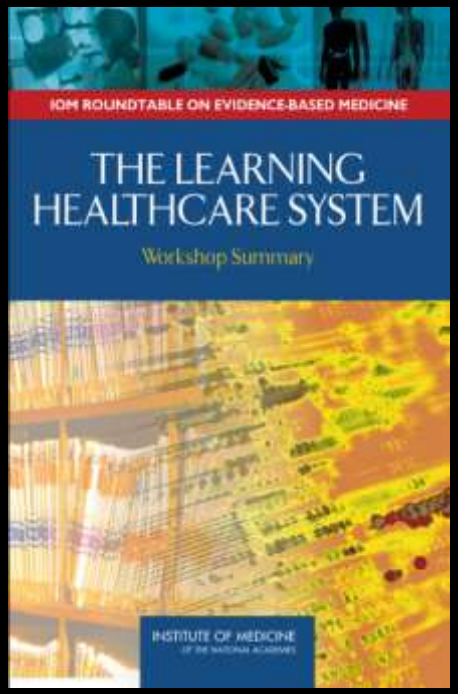
Some common challenges of biomedical product translation—scientific, regulatory, adoption, and reimbursement—can best be addressed by the broad sharing of resources or tools. But, such aids remain undeveloped because the undertaking requires expertise from multiple research sectors as well as validation across organizations. Biomedical resource development can benefit from directed consortia—a partnership framework that provides neutral and temporary collaborative environments for several, oftentimes competing, organizations and leverages the aggregated intellect and resources of stakeholders so as to create versatile solutions. By analyzing 369 biomedical research consortia, we tracked consortia growth around the world and gained insight into how this partnership model advances biomedical research. Our analyses suggest that research-by-consortium provides benefit to biomedical science, but the model needs further optimization before it can be fully integrated into the biomedical research pipeline.

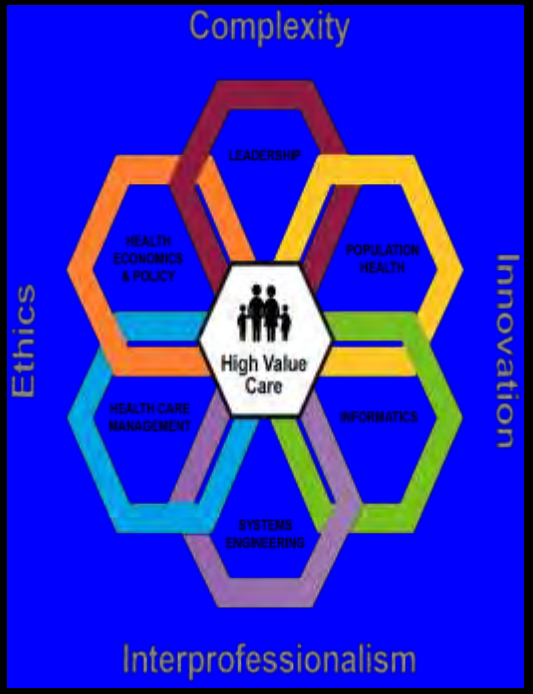




Major Transitions in Medical Education and Healthcare







1910-present

(science-centric)

2000 - present

healthcare as a learning system (data-centric)

2015 - ?

network topologies and dynamics in complex adaptive systems (network-centric): major disruptions in education, R&D and care delivery

Imbalances in Strategies for Comprehensive Cancer Control

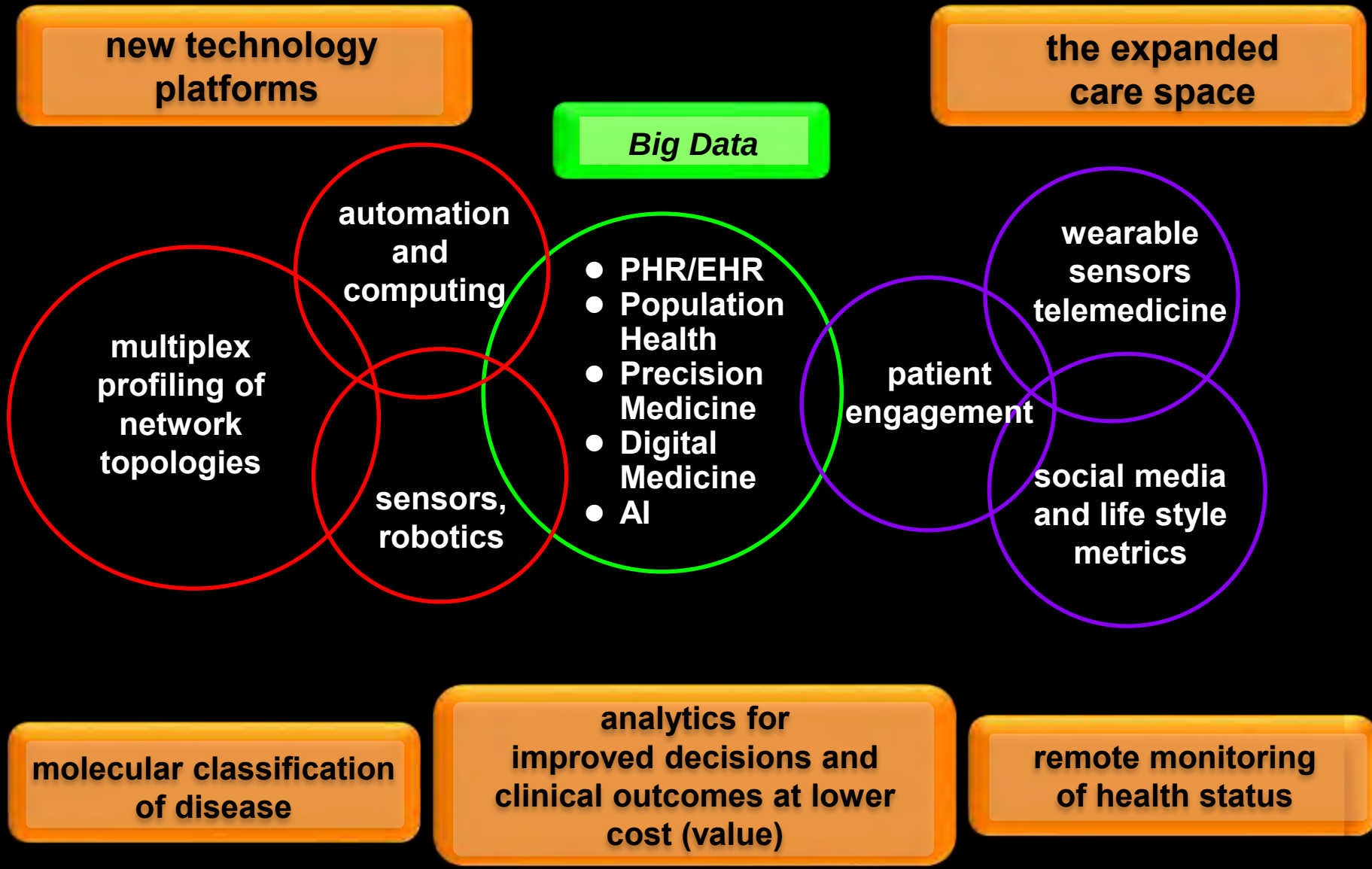
- between investment in cancer prevention versus treatment
- between aggressive non- I/O treatment regimens with curative intent but limited efficiency versus supportive care and palliation
- between cost of therapeutics versus meaningful clinical outcomes and QOL (value)
- between cancer control in HIC and MIC/LIC

Imbalances in Strategies for Comprehensive Cancer Control

between the intellectual rationale of precision oncology and translation into routine clinical practice

between limited availability, analysis and use of population-based of RWE versus comprehensive, data-driven analysis, and robust decision-support systems

The Evolution of Cancer Care: Precision Oncology and Digital Medicine



Cancer As a Complex Adaptive System: Legacy of 32 Years of Prescient Perspectives Still Alarmingly Ignored

"It may also be necessary to re-evaluate how cancer is perceived, not only as a disease but as a biological system."

E.D. Schwab and K.J. Pienta
Medical Hypotheses (1996) 47, 235

"The cancer biology community by itself is unprepared to solve the difficult transdisciplinary problems such as biological complexity, information transfer and tumor cell evolution."

Ann Barker (2008)
NCI PSOP Meeting Summary

"Learning to manage cancer is learning to manage the evolutionary process."

Dr. Richard L. Schilsky
CMO, ASCO
Oncology Times 25 June 2014

Slides Available @ http://casi.asu.edu/presentations