ASU Complex Adaptive Systems Initiative
Arizona State University

BIO 302: 23 April 2018

Cancer: A Multi-Dimensional Problem
Science, Medicine, Economics, Ethics, Fear & Emotion

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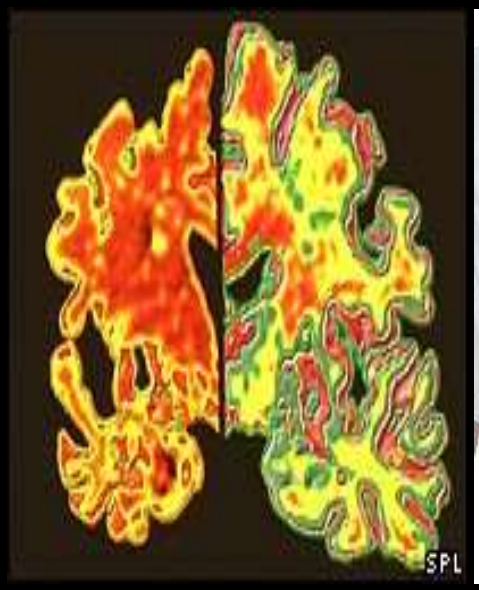
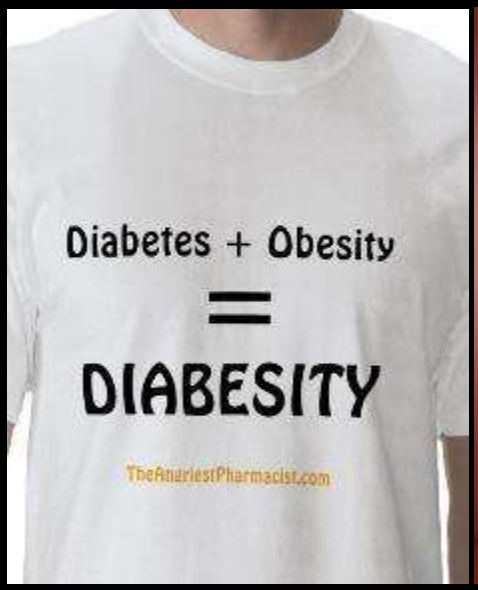
Infinite Demand Versus Finite Resources (Clinical and Economic)

- public expectancy for unlimited care and access to latest advances

Disease Burden:
Confronting the Largest Clinical Economic Disruptions and Threats to Sustainable Healthcare





cancer

neurodegeneration

cardio-vascular/ metabolic disease

mental illness

health versus illness

value versus volume

integrated systems versus disconnected silos in access and effectiveness of care delivery

Demographics and the Clinical and Economic Challenges to U.S. Healthcare

wellness with longevity and high QOL

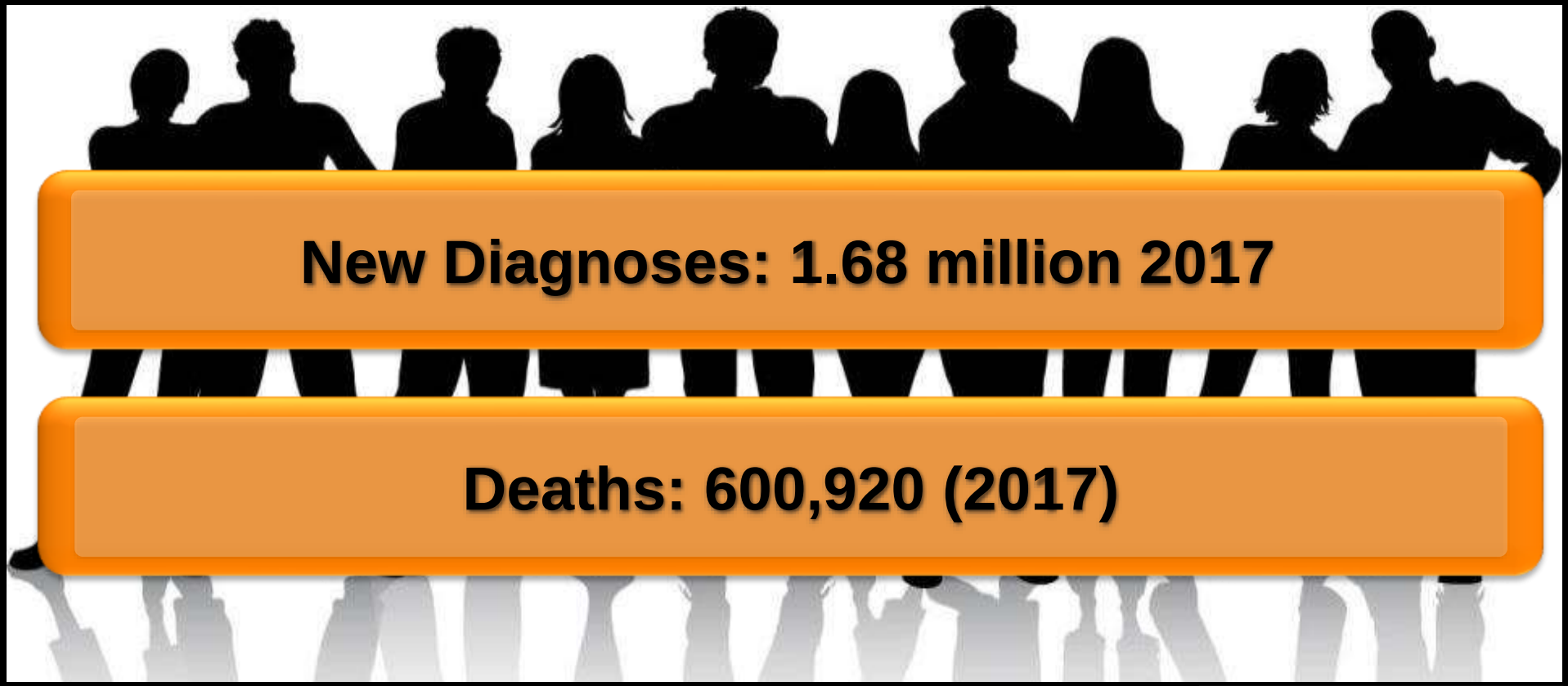
OR

multiple co-morbidities and low QOL

?

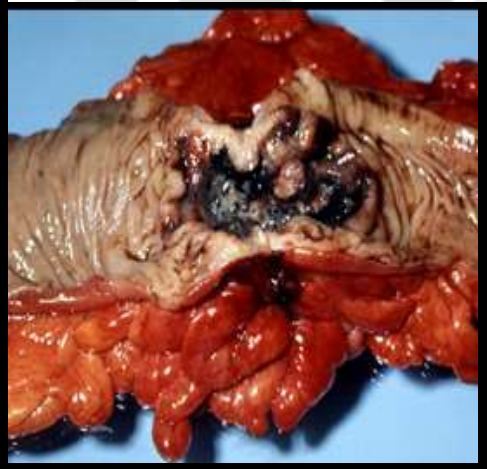
?

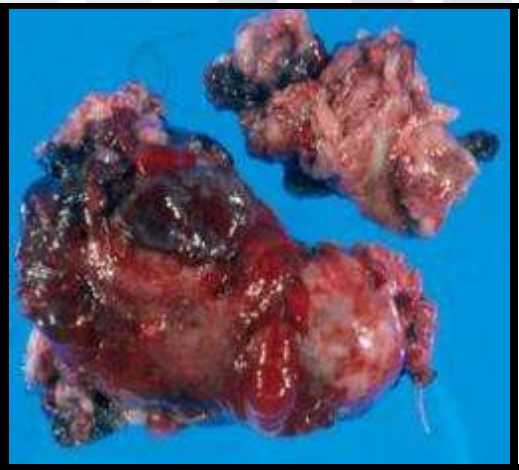
Confronting the Clinical, Economic and Human Toll of Cancer

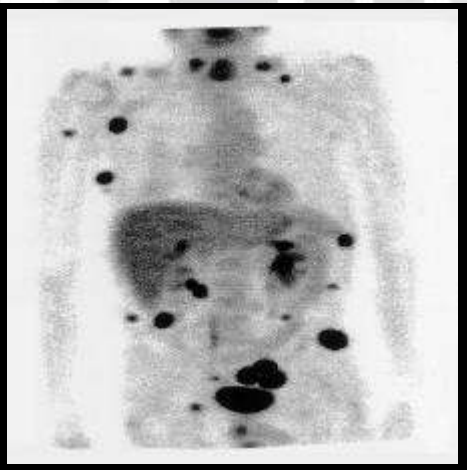


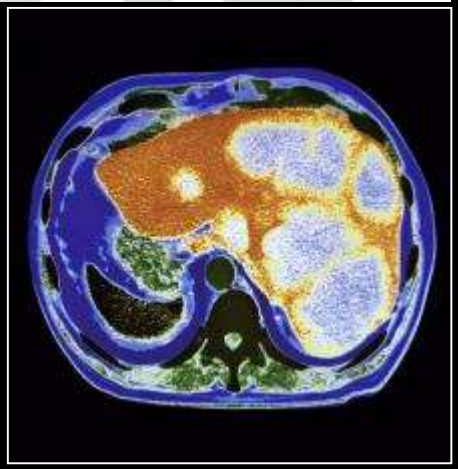
New Diagnoses: 1.68 million 2017

Deaths: 600,920 (2017)









Cancer Care: 7 C's

- clonal heterogeneity (cancer biology)
- clinical care (outcomes)
- consistency of care (guidelines)
- communication (patient-physician relationships)
- choice (intervention versus palliation)
- cost (sustainability and value)
- culture (expectations, motivations, incentives)

Cancer Care: 7 C's

- clonal heterogeneity (cancer hi
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- sation (r sician
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- (expectations, motivations, incentives)

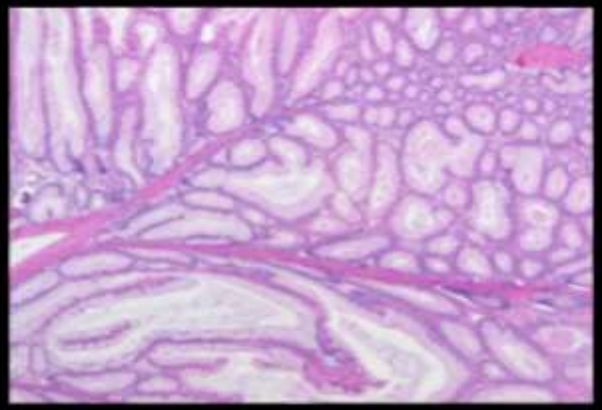
complexity

data and decisions

value

The Complex Biology of Cancer Progression and Treatment Resistance

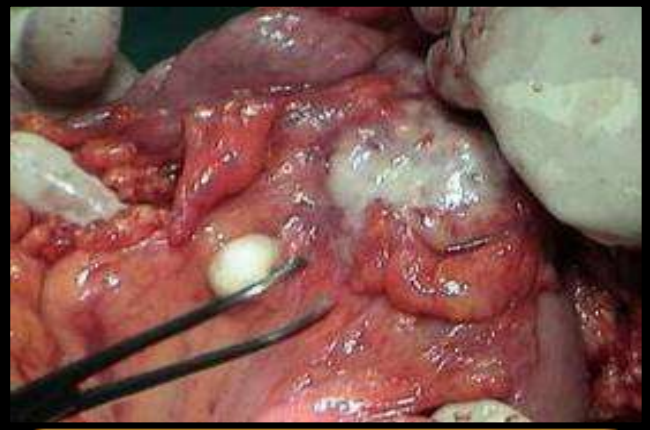
Escape From Controls for Normal Tissue Architecture



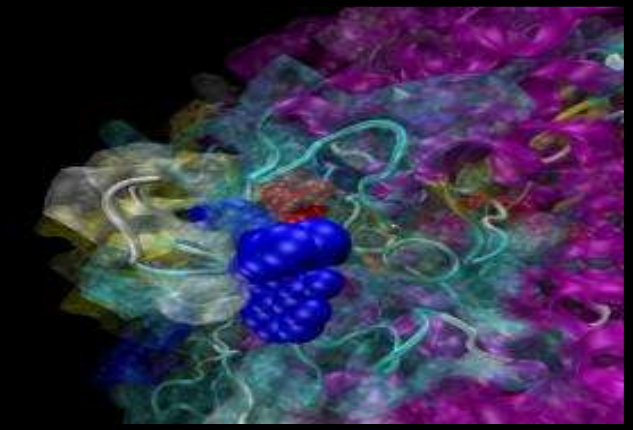
Genome Instability and Emergence of Clonal Variants

Evasion of Detection/ Destruction by Host Immune System

Use of Host Systems to Promote Progression



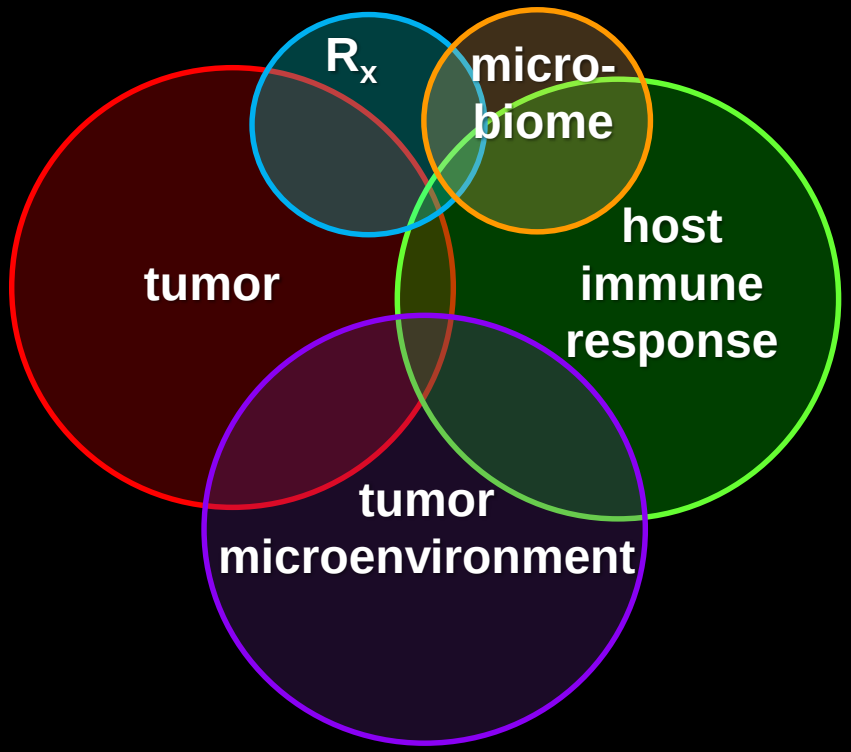
Invasion and Metastasis



Emergence of Drug-Resistant Clones

Understanding the Complex Ecosystem of Constantly Changing Tumor and Host Interactions

- lineage and subtype
- clonal heterogeneity
- mutagen burden
- neoantigen profile

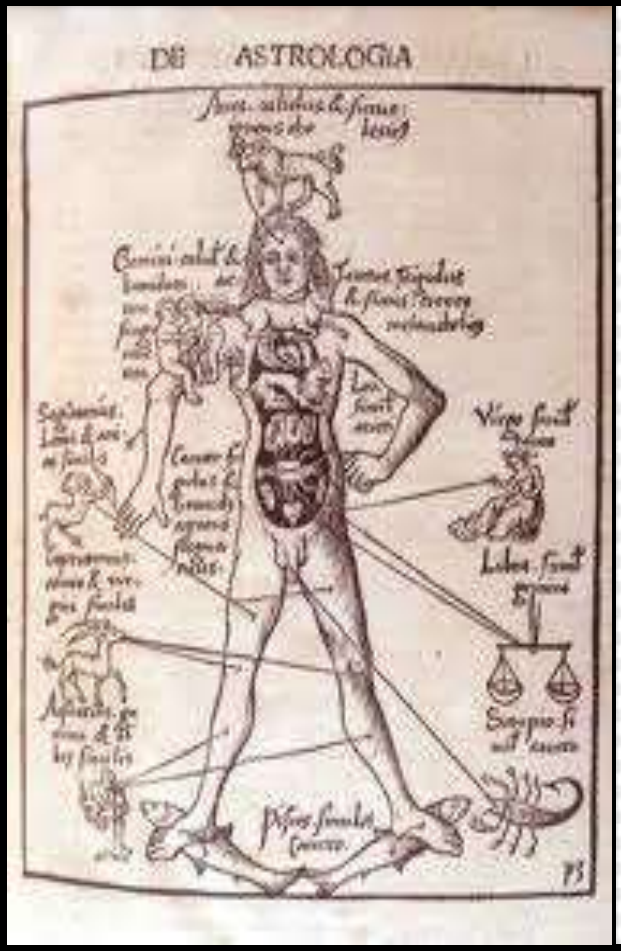


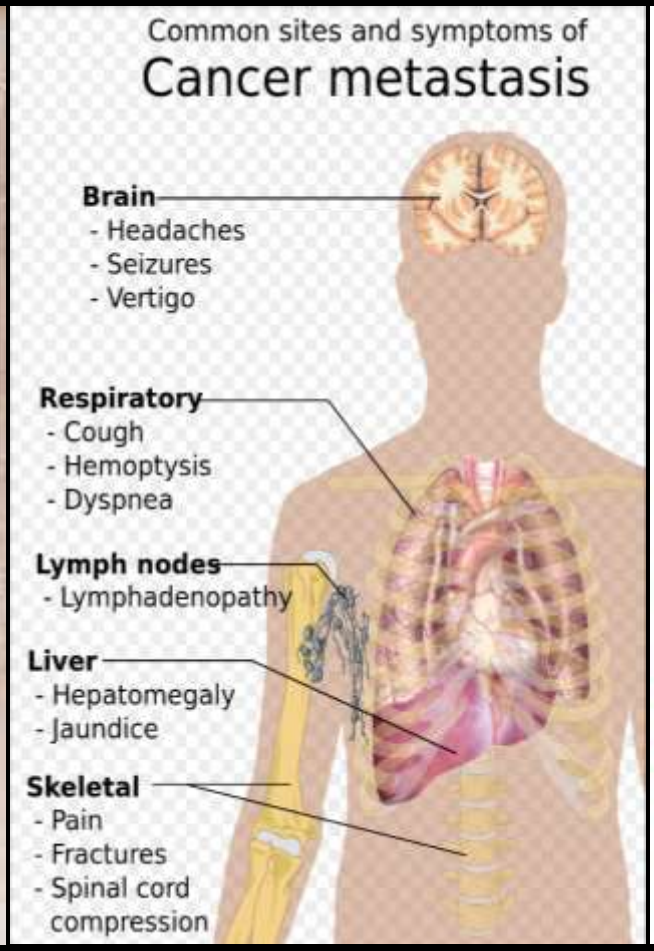
balance of stimulatory and suppressive factors

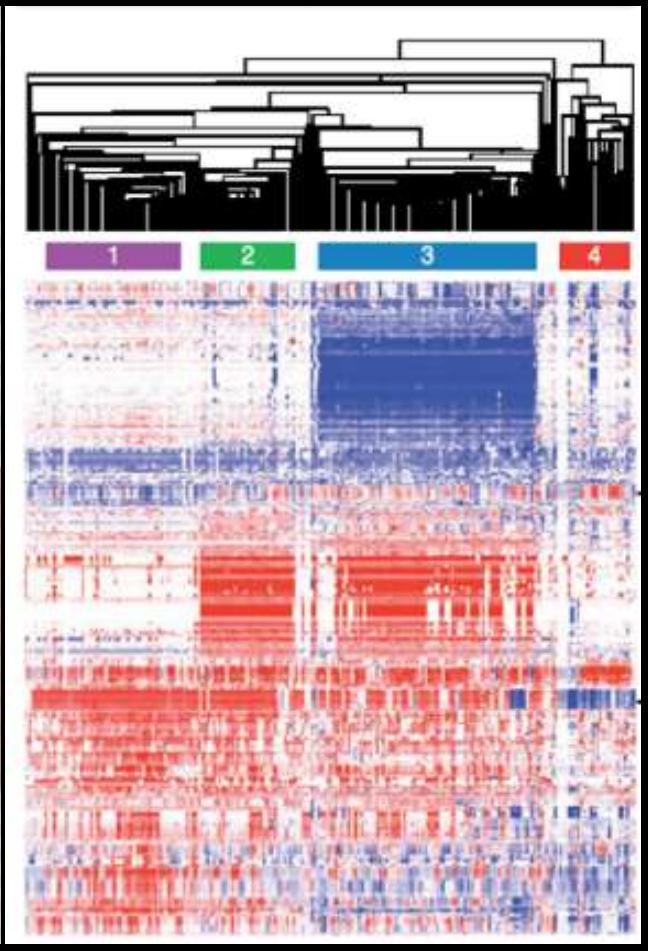
localization of immune cells/soluble mediators and impact of R_x

The Path to Precision Oncology:

Superstitions	Symptoms	(Molecular) Signatures



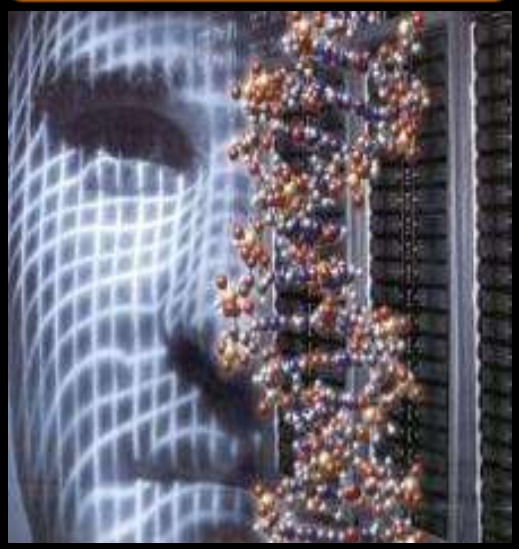


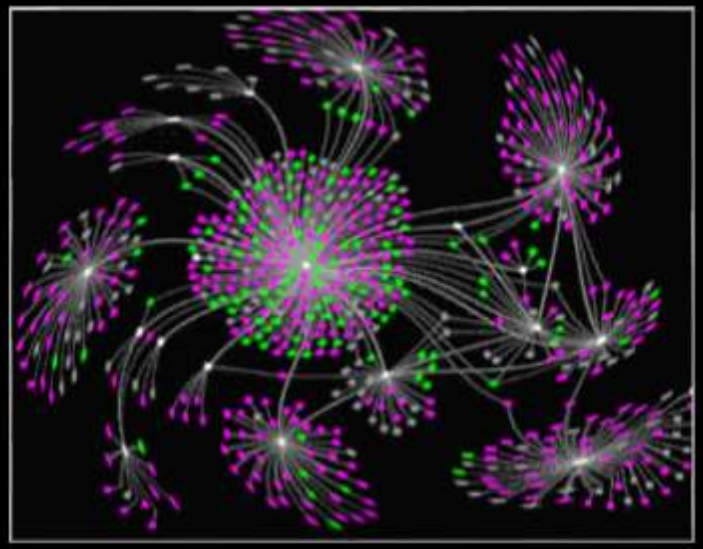


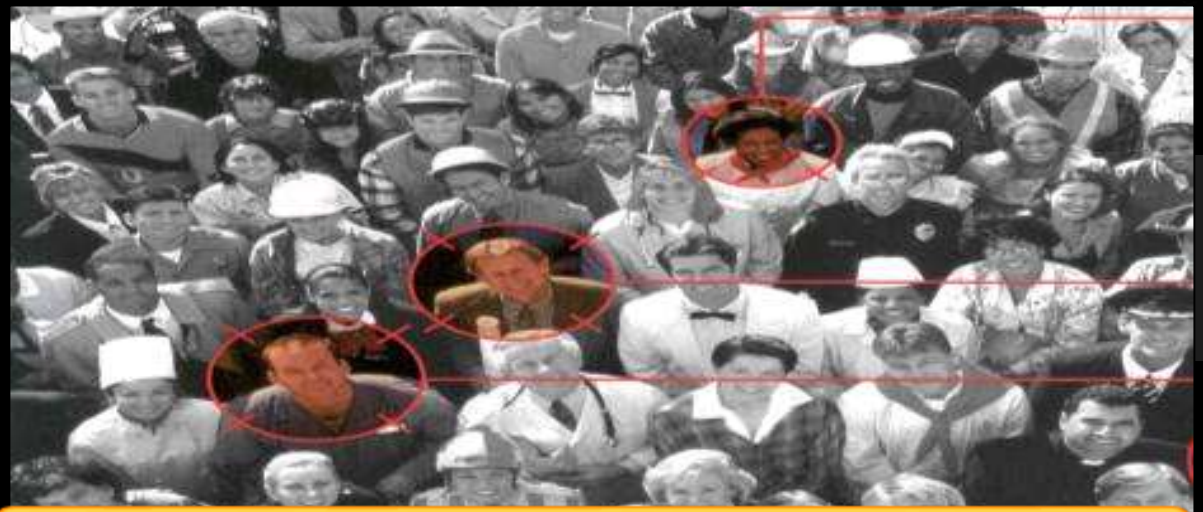
Precision Oncology:

(Epi)Genomics

Causal Relationships Between Disruption of Molecular Signaling Networks and Disease







- terabytes per individual
- zettabyte – yottabyte population databases

Patient-Specific Signatures of Disease or Predisposition to Disease

Big (Messy) Data

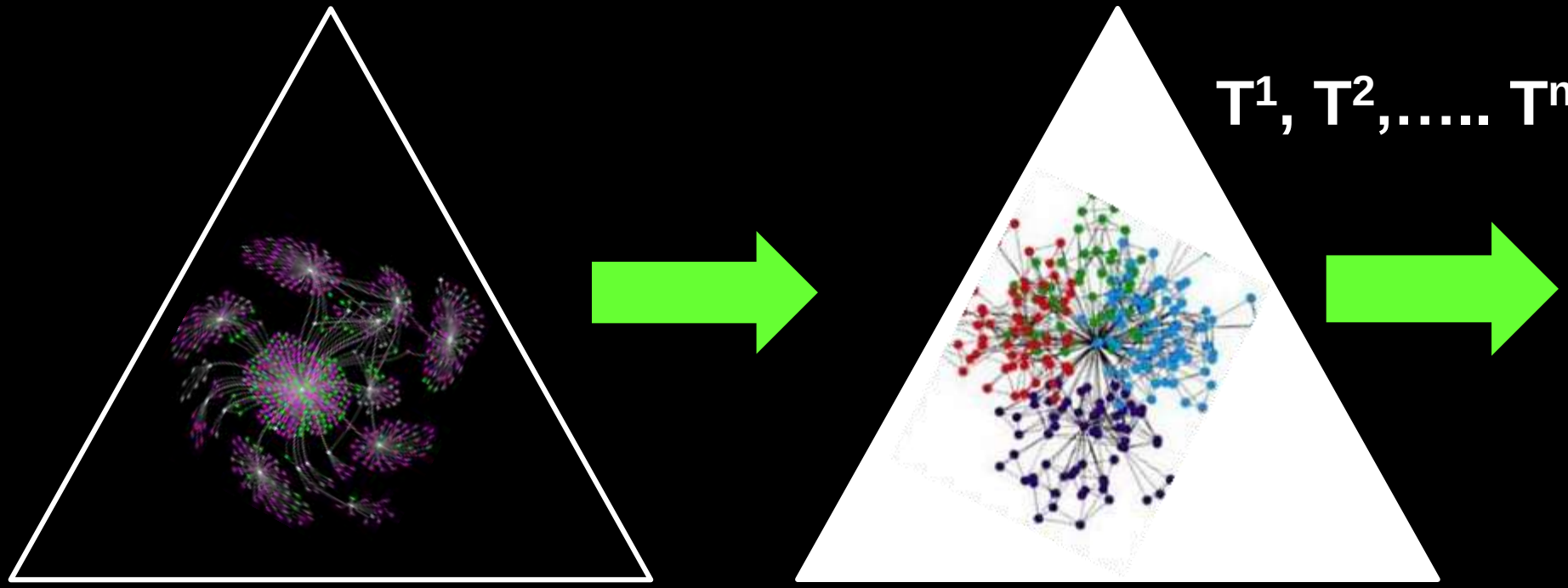
Molecular Diagnostics and Biomarkers as the Intellectual Drivers of Precision Medicine

- disease predisposition risk
- increased accuracy of disease classification (molecular subtypes) and staging
- more rational treatment selection based on presence/absence of specific molecular targets for R_x action
- pharmacogenetic profiling to avoid R_x adverse events
- monitoring R_x efficacy
- detection of emergence of R_x resistance (microbiology; oncology)
- earlier alert of pending relapse and detection minimal residual disease

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

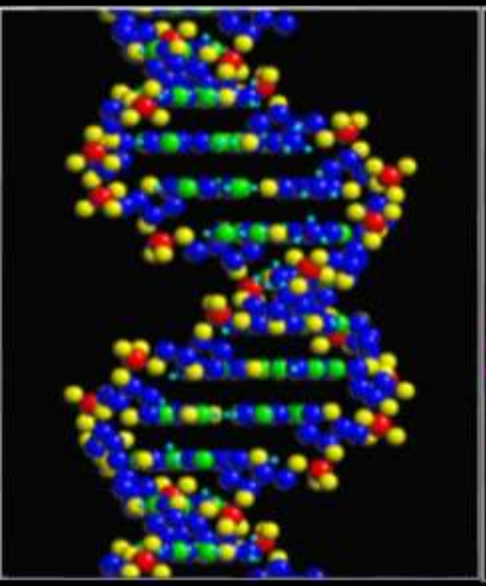
network topology

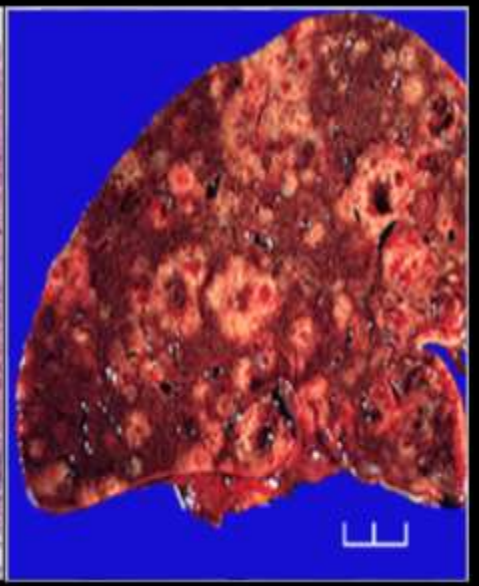
evolution of new network topologies and 'state spaces'



- (epi) genomic, transcriptomic and protein expression networks
- gene-gene interactions (epistasis)
- multi-omic network- environmental interactions
- context: multicellular signaling interactions across multiple levels of biological scale

Precision Medicine: Understanding the Disruption of Molecular Information Networks in Disease





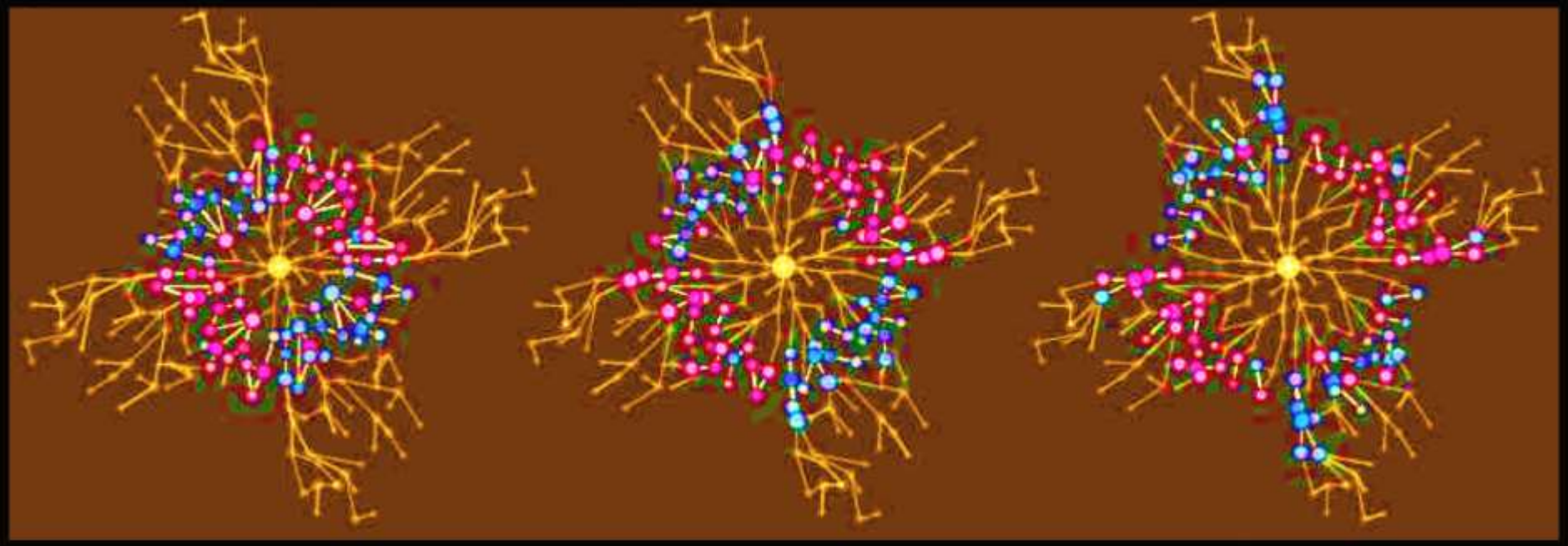
encoded information and expression as cell-specific signaling networks

patterns of information flow in signaling networks (network topology)

stable networks and information fidelity (health)

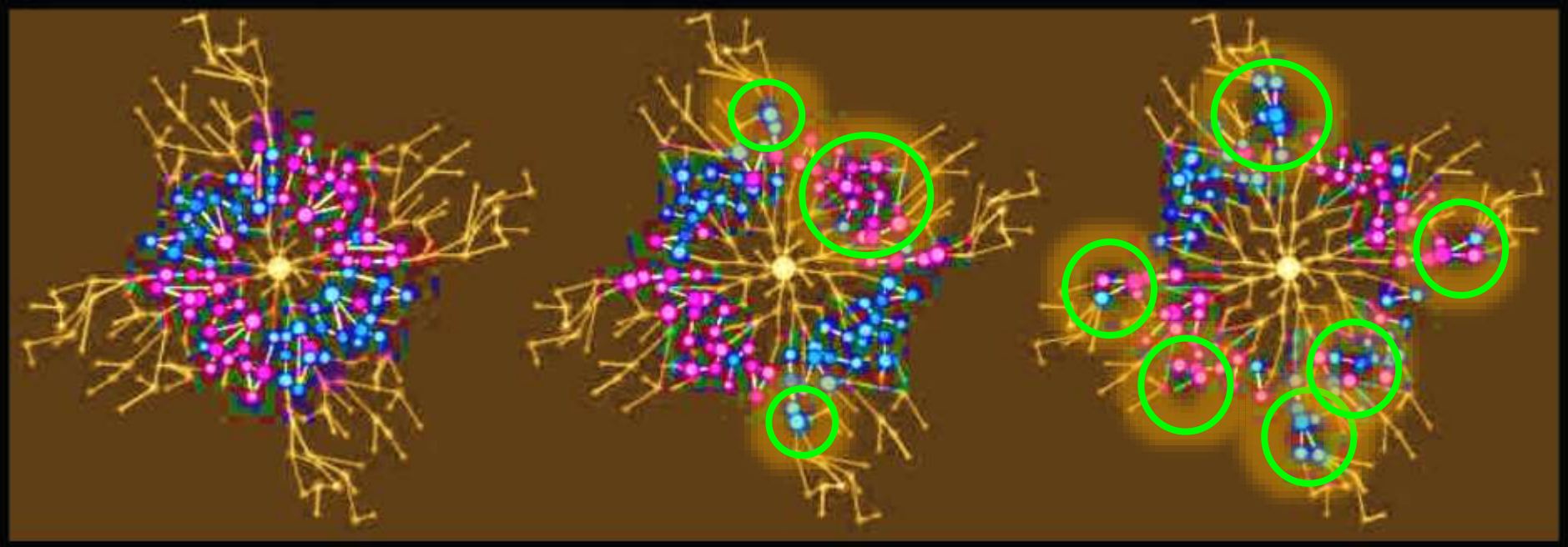
dysregulated networks and altered information patterns (disease)

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



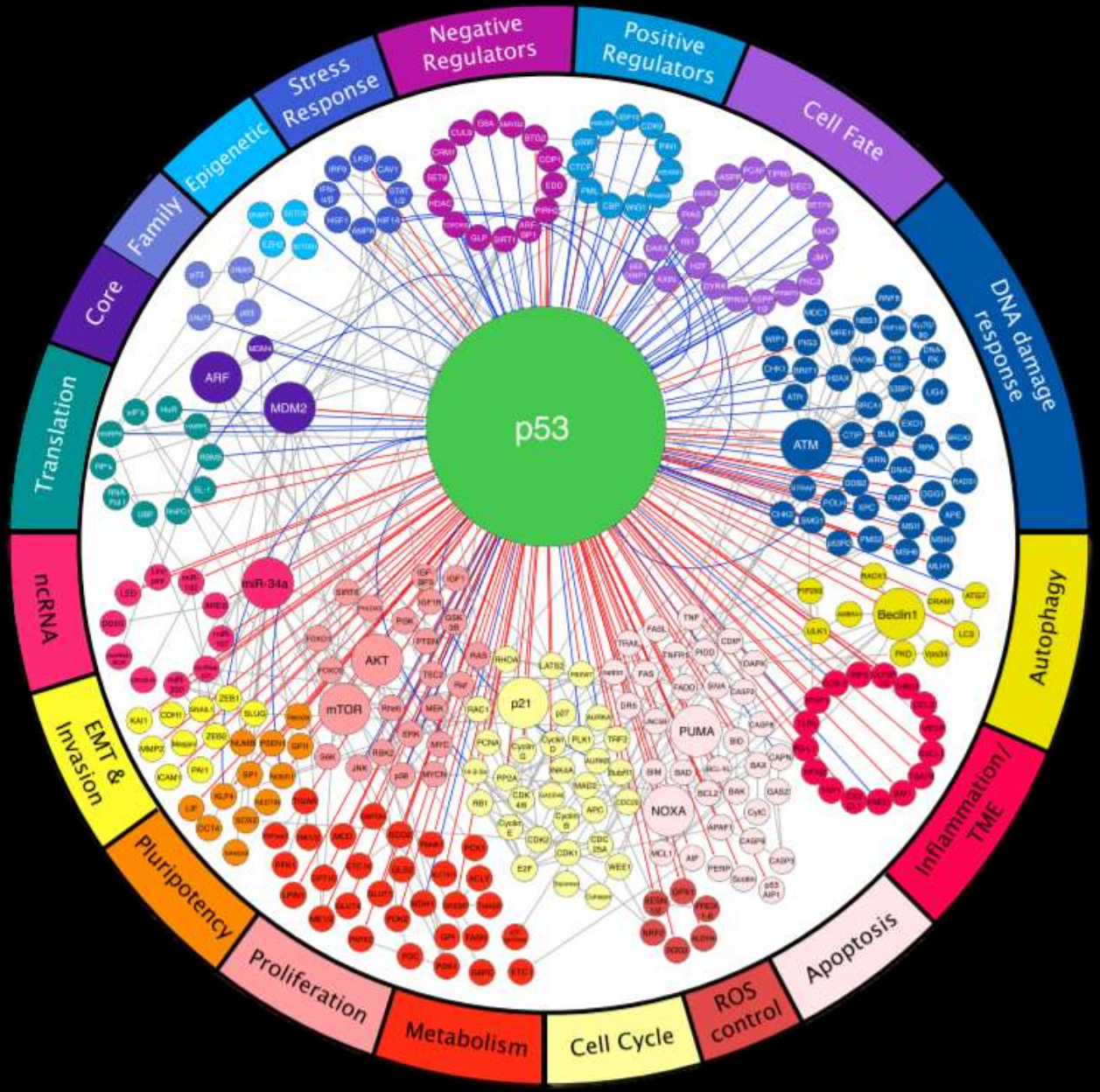
T_1 T_2 T_3

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



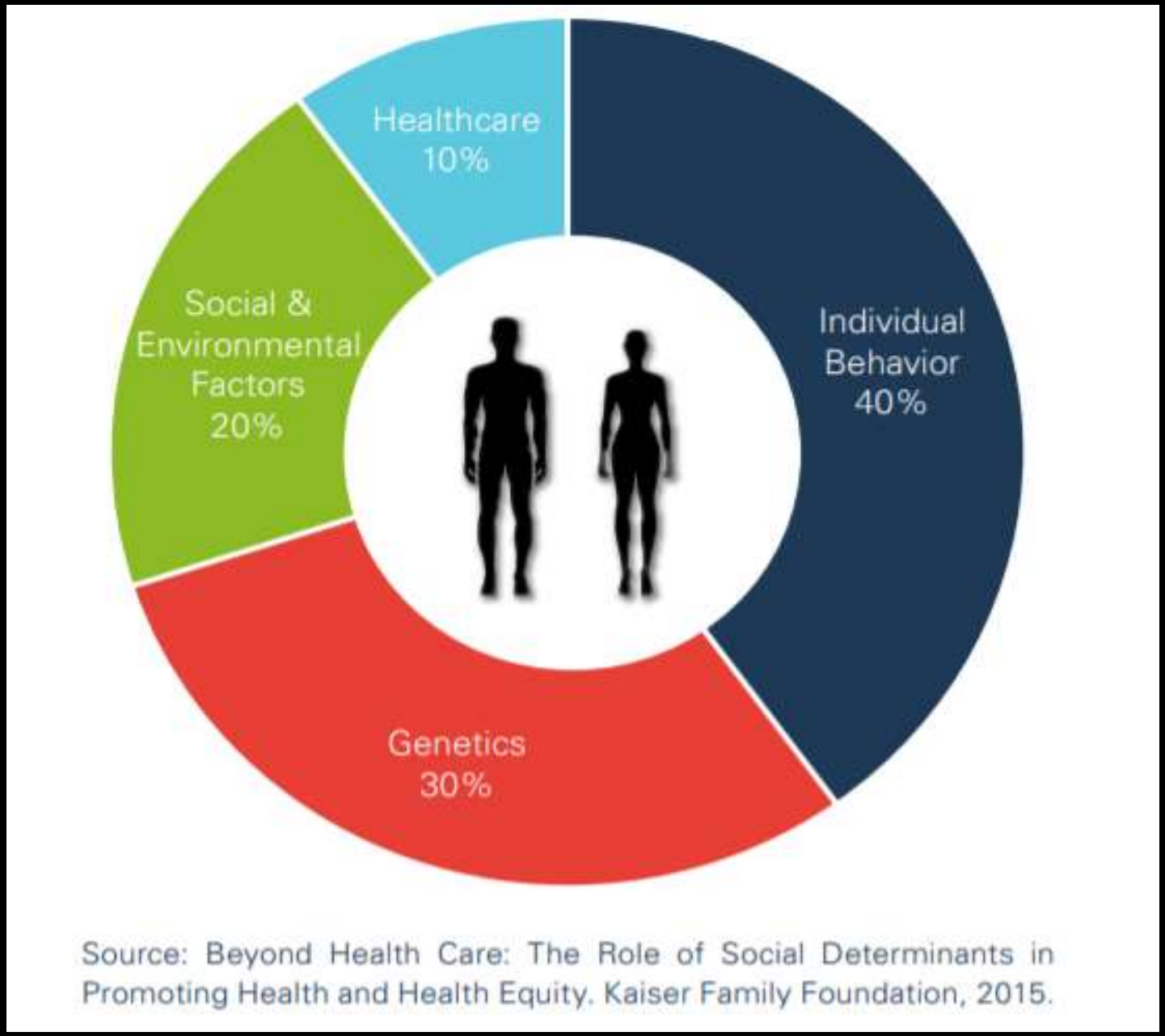
T_1	T_2	T_3
health	subclinical disease	overt disease

The p53 Network



From: E. R. Kastenbuber and S.W. Lowe (2017) Cell 170, 1062
http://www.cell.com/cell/pdf/S0092-8674(17)30953-4.pdf

Impact of Different Factors On The Risk of Premature Death



Source: Beyond Health Care: The Role of Social Determinants in Promoting Health and Health Equity. Kaiser Family Foundation, 2015.

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

Hidden impacts of air pollution *p. 39*

Flying through Saturn's ionosphere *p. 66*

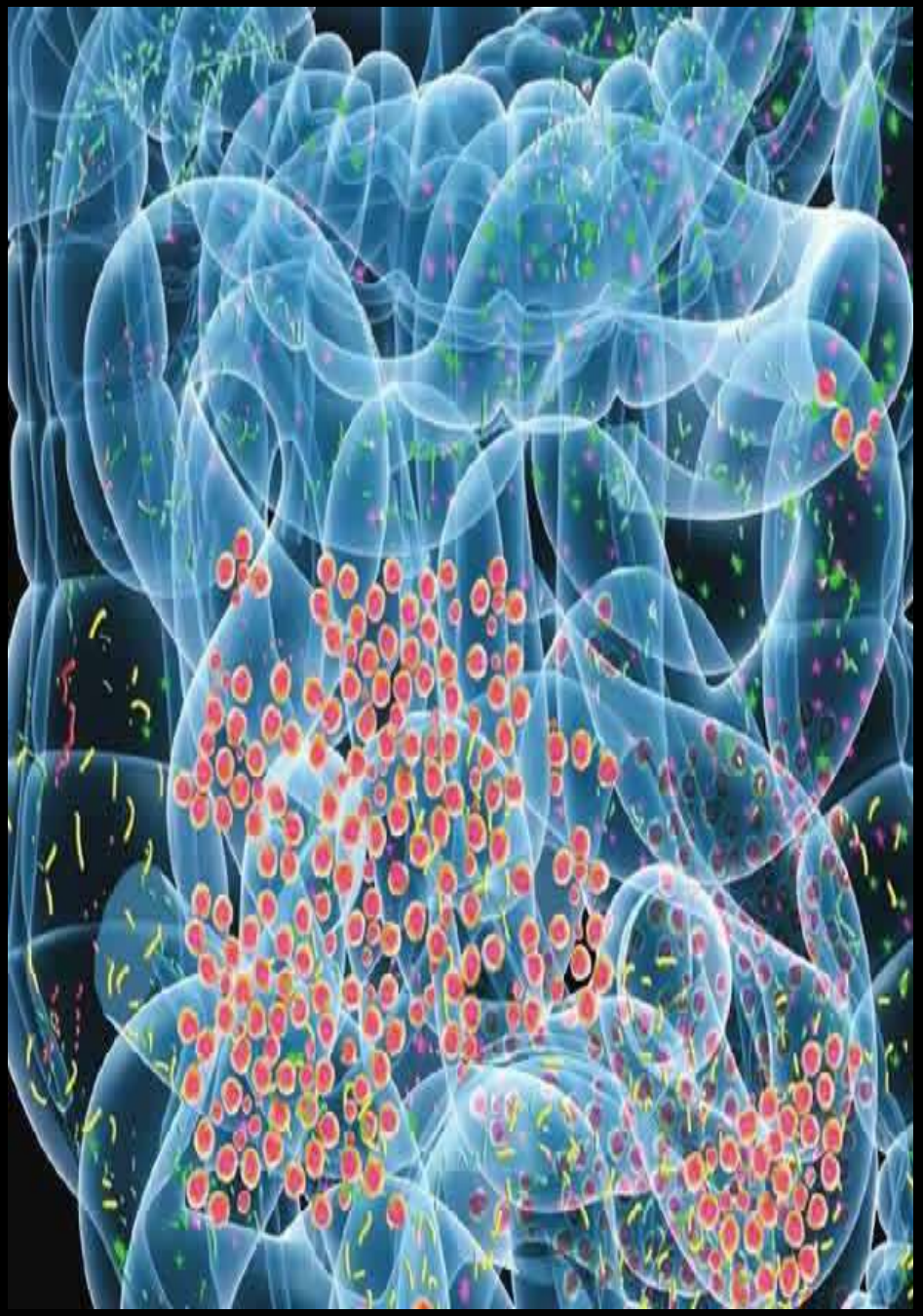
Science

$15
5 JANUARY 2018
sciencemag.org
AAAS

GUT MICROBES AND CANCER

The microbiome influences patient response to immunotherapy

pp. 32, 91, 97, & 104



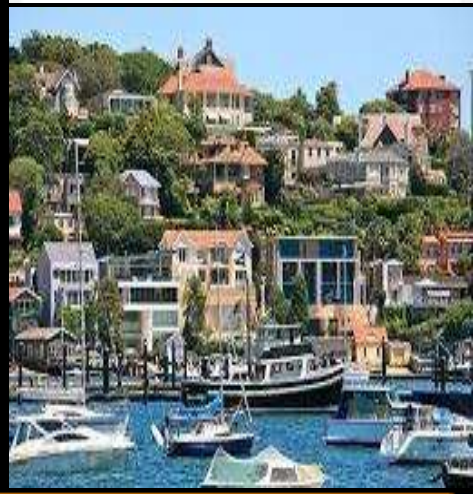
Most Events That Affect Our Health Occur Outside of the Healthcare System And Are Not Monitored

Need for Continuity of Care Record: From Womb to Tomb







Behavior

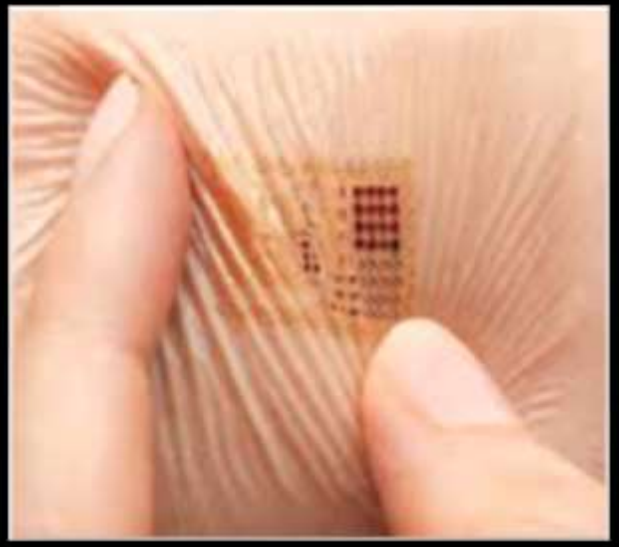
Environment

“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 and individual risk patterns
- the confessional of social media
- the blurring of private and public spaces
- complex ethical and legal issues
  - consent, privacy, security, surveillance

Wellness Apps for Fitness, Diet and Exercise

Remote Monitoring of Health Status



Gray Technologies and Ageing in Place: The Rapid Expansion of Telemedicine for Remote Health Monitoring

Rx adherence

cognitive stimulation

in home support and reduced readmissions

reduced office visits

Chatbots and Support Robots in Healthcare

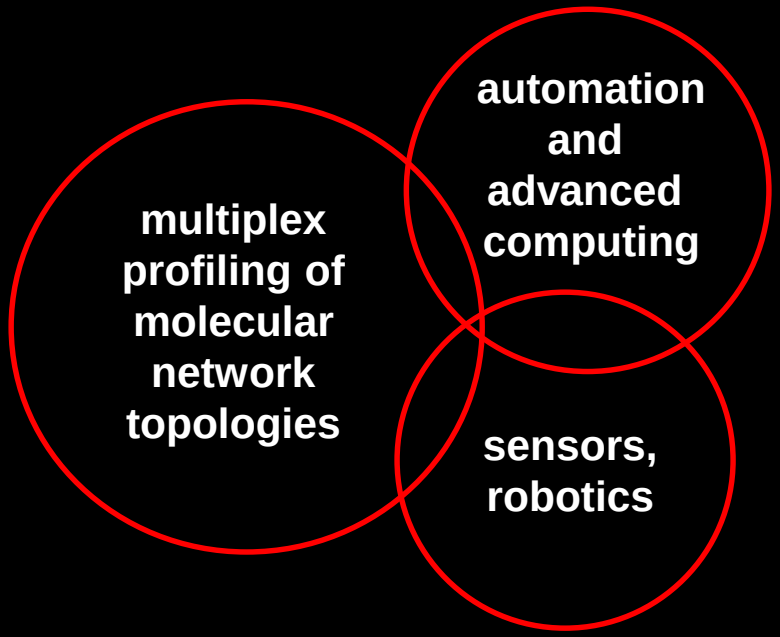
Mobile Apps, Wearables, Sensors and Continuous Health Status Monitoring

- who sets the standards?
- who integrates and interprets the data?
- who pays?
- who consents?
- who owns the data?


Epic ail

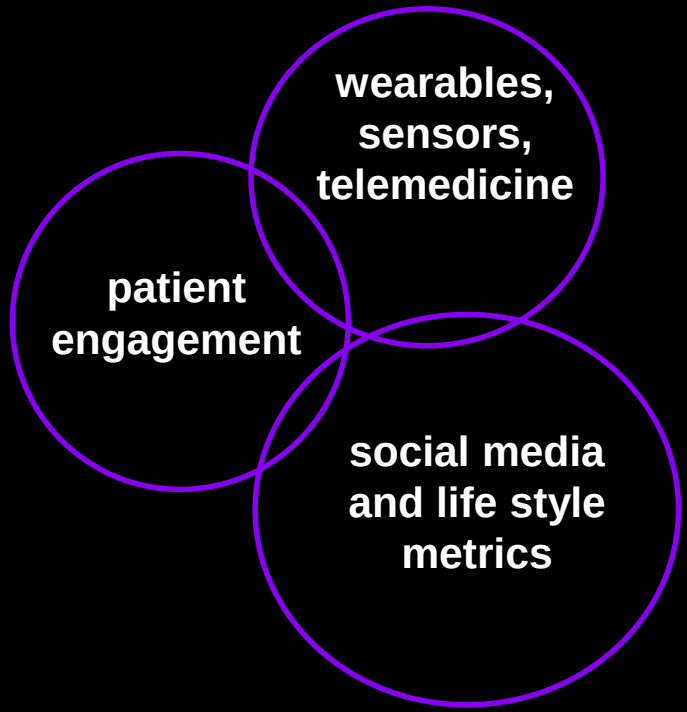
The Future of Healthcare: Precision Medicine and Digital Medicine

new technology platforms



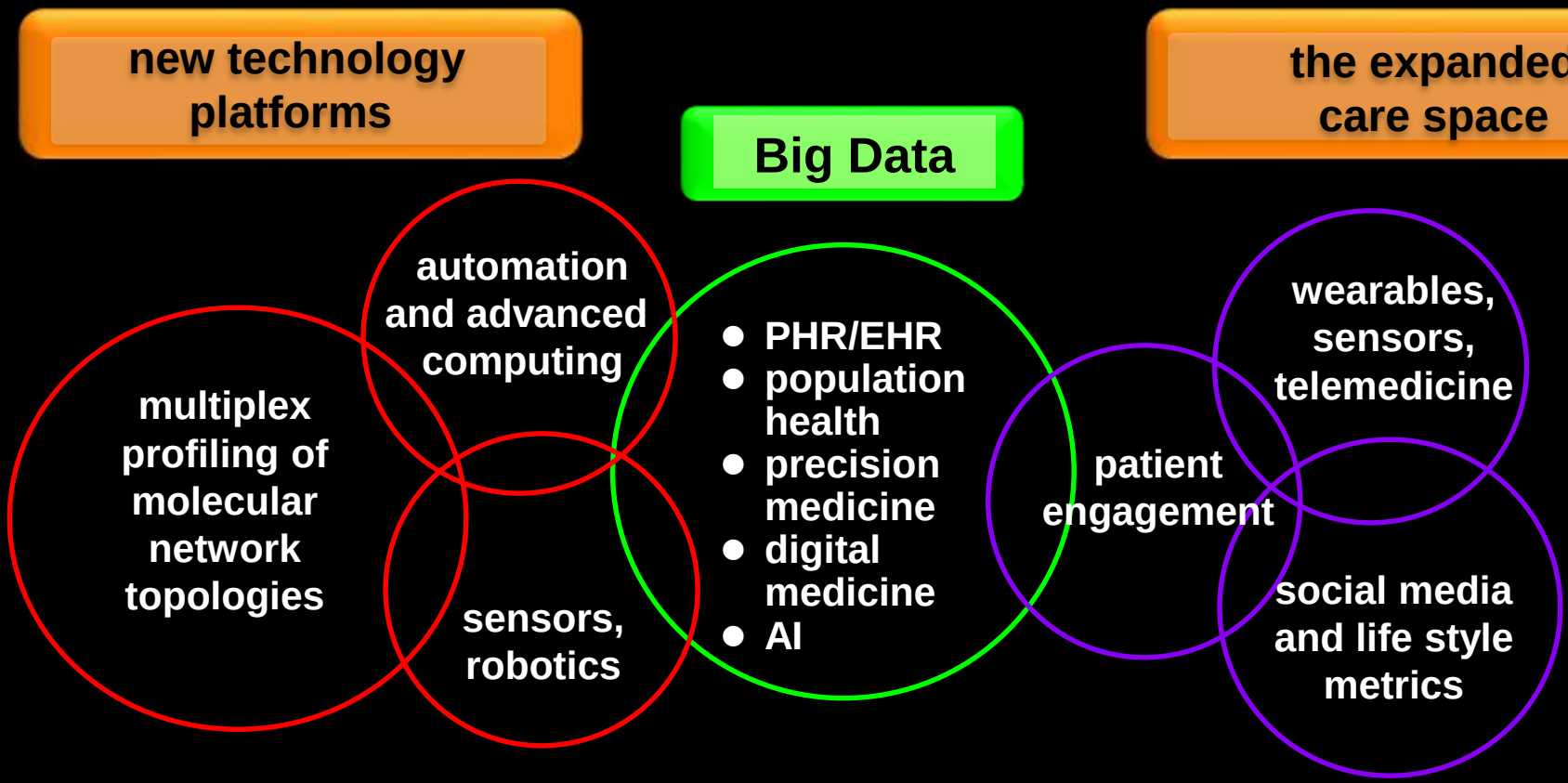
molecular classification of disease

the expanded care space



remote monitoring of health status

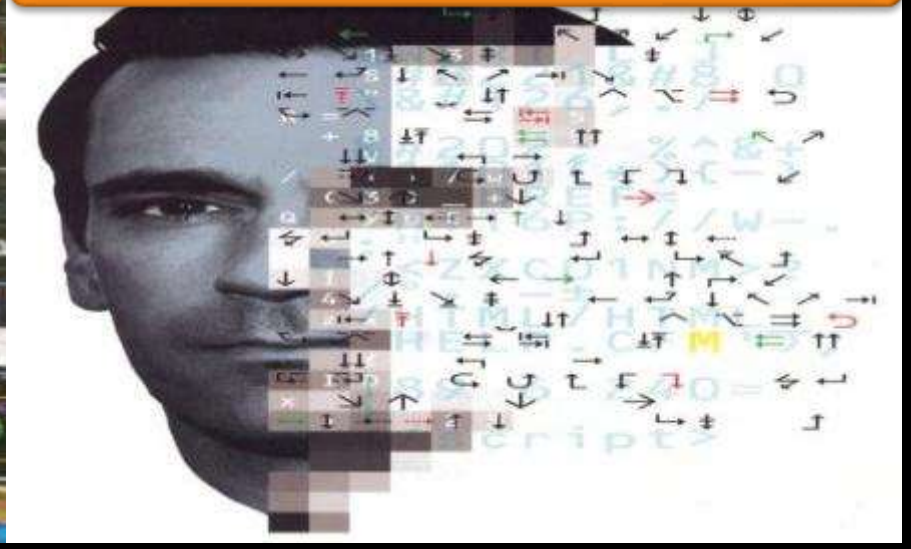
The Future of Healthcare: Precision Medicine and Digital Medicine



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

Data Deluge

Cognitive Bandwidth Limits

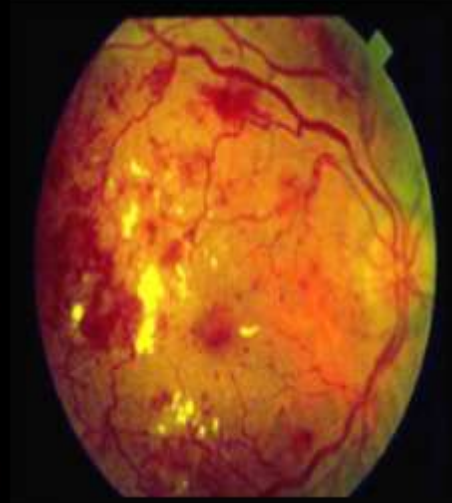


Automated Analytics and Decision Support

Facile Formats for Actionable Decisions

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

Complexity: Delivery of Care

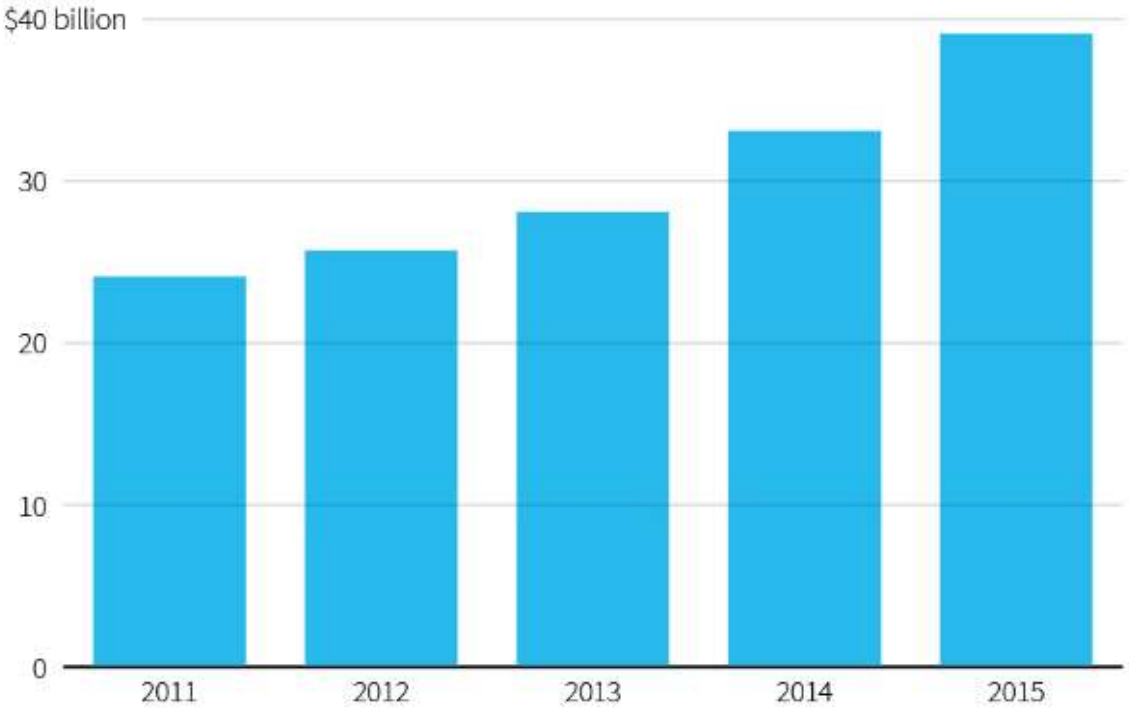
- multiple clinical specialties
  - pathology, radiology, surgery, clinical oncology,
  - lab testing
  - supportive care clinical services
- multiple delivery sites
  - hospital (OP, IP, ICU), nursing home, at home, hospice
  - academic medical centers (20%), community practice (80%)
- multiple participants
  - academia, industry regulators, providers
  - pharmacy benefit management companies
  - payers: private (insurance companies) and public (governments)


CANCER STARTED IN MY CELLS, BUT QUICKLY SPREAD TO MY WALLET, LIVELIHOOD, AND PSYCHE.
A cancer diagnosis affects every part of your life. Which is why the American Cancer Society does much more than breakthrough research. We also provide free rides to chemo, a live 24/7 helpline, and free lodging near hospitals. Beating cancer takes more than medicine, which is why we're attacking from every angle.
Please give what you can today at cancer.org.
American Cancer Society®
Attacking From Every Angle™

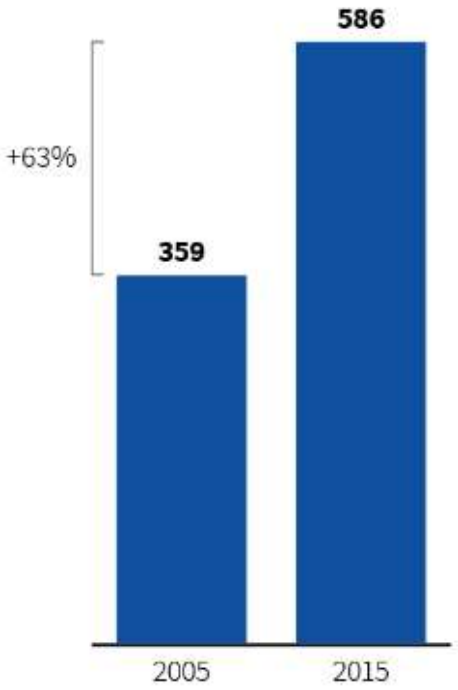
Complexity: Moral, Ethical and Legal Issues

- access to care
- cost of care
- outcomes of care
- limits to care
- transparency in care decisions
- end-of-life care
- assisted death
- public policy from prevention to EOL
- personal responsibility for risk reduction

U.S. SPENDING ON ONCOLOGY MEDICINES



NUMBER OF CANCER DRUGS IN CLINICAL DEVELOPMENT



PD1/PDL1 CHECKPOINT INHIBITOR PRICES

Estimated average per month*

Opdivo	Keytruda	Bavencio**	Tecentriq
BRISTOL-MYERS SQUIBB	**MERCK**	**PFIZER**	**ROCHE HOLDING**
$13,100	$13,000	$13,000	$12,500

* Drug price is based on the milligrams of medicine used and varies with the weight of the individual patient.
** Bavencio's price is the wholesale acquisition cost for an average patient.

Sources: QuintilesIMS Institute ; Reuters

Monthly and Median Costs of Cancer Drugs at FDA Approval 1965-2016

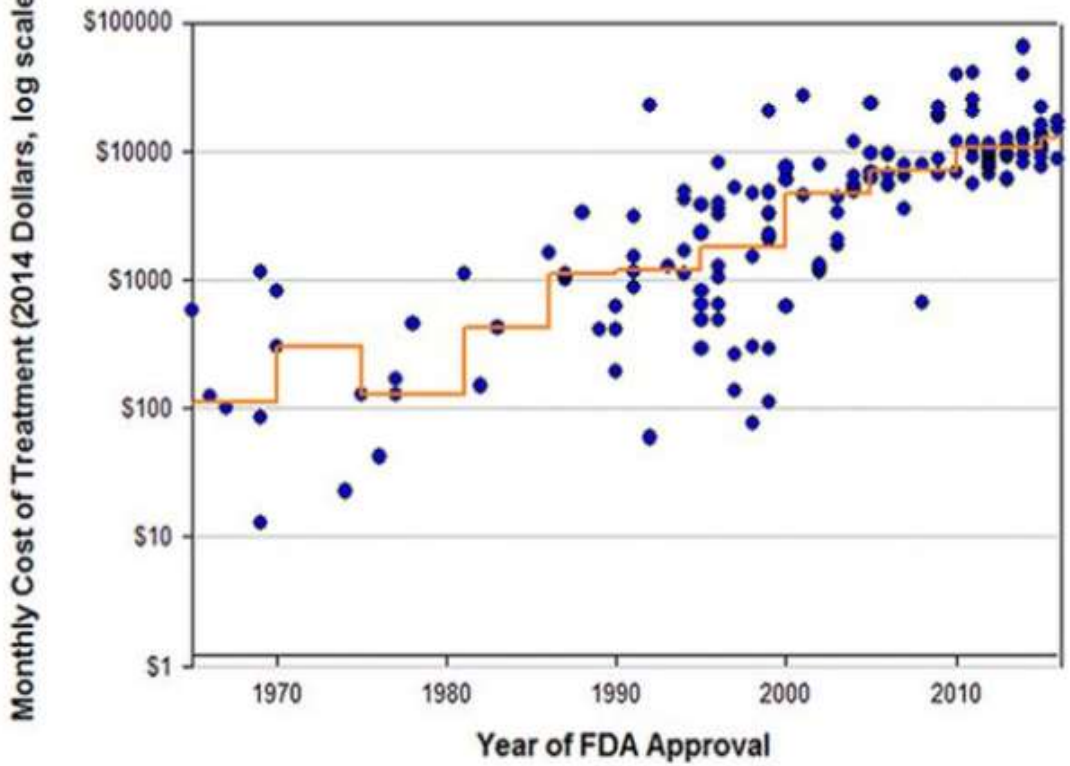
Navigating the Coverage Experience and Financial Challenges for Cancer Patients:

Affordable Care Act Brings Improvements, But Challenges Remain

By JoAnn Volk and Sandy Ahn

Cancer Action Network™ American Cancer Society

CENTER ON HEALTH INSURANCE REFORMS



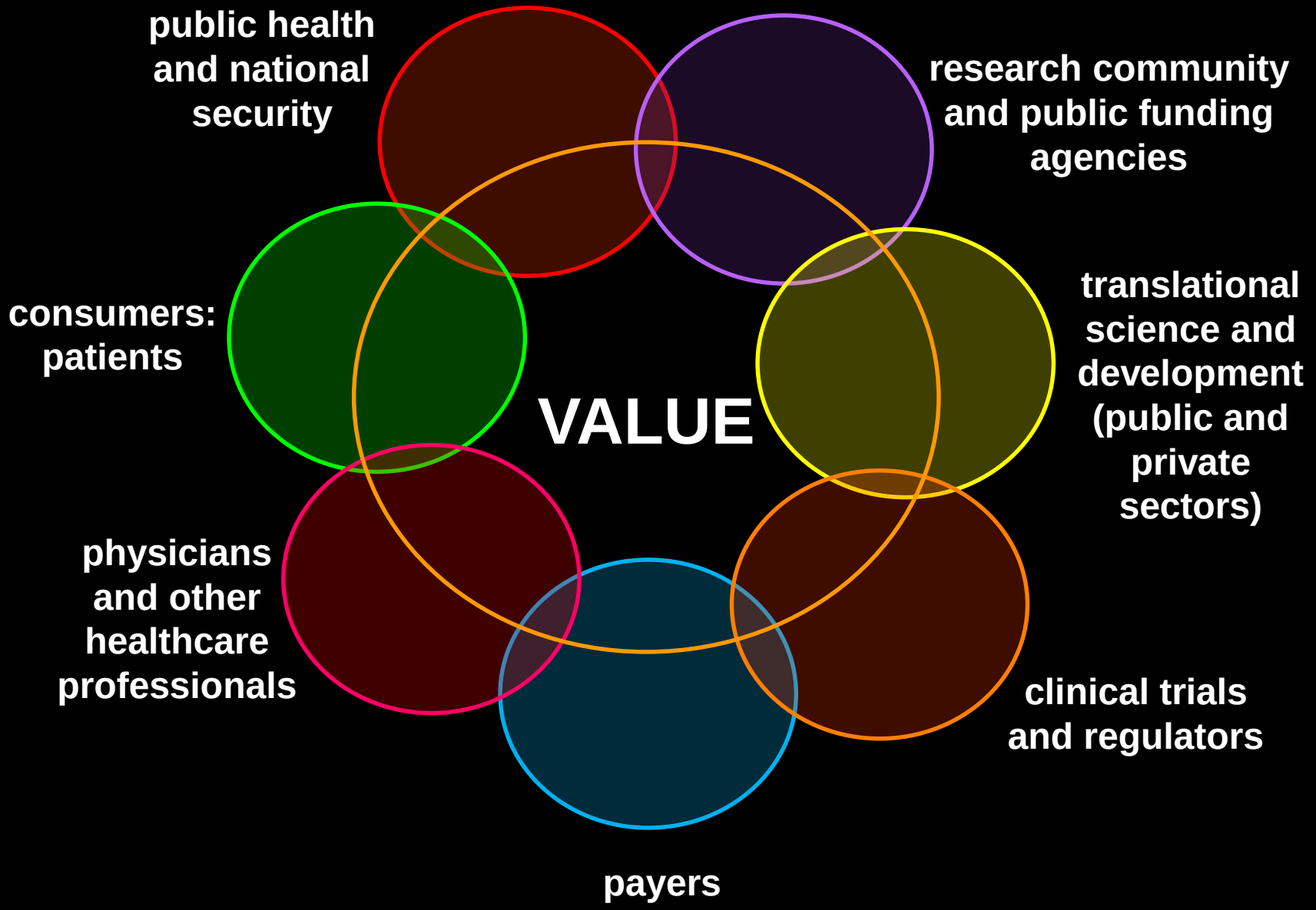
Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center

What Constitutes a Meaningful Clinical Benefit?

“Price is what you pay.
Value is what you want.”

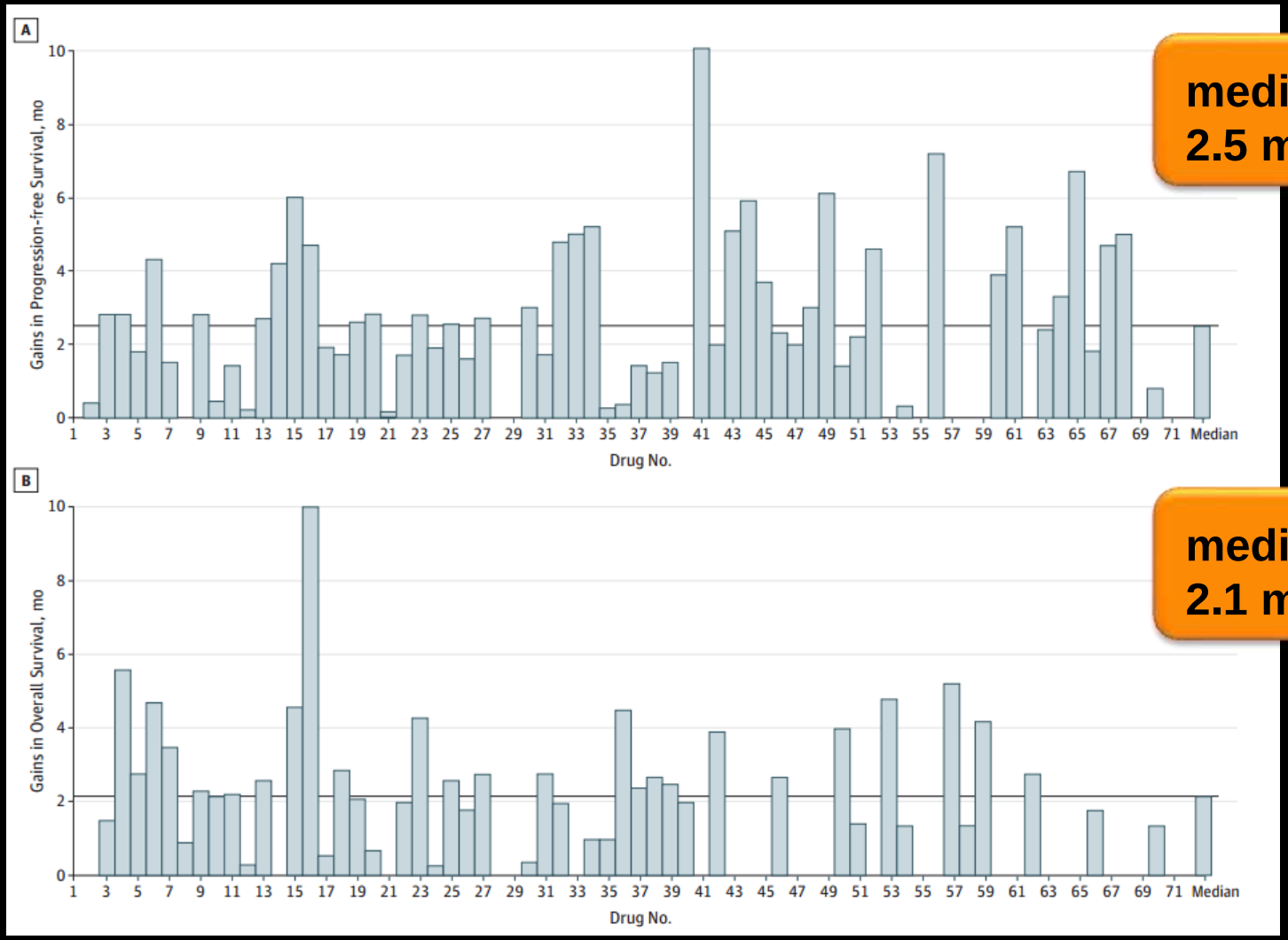
Warren Buffet

The Complex Ecosystem of Biomedical Research and Clinical Care: Different Perceptions of Value By Different Constituencies



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

When 340B Hospitals Buy Oncology Practices Prices Go Up

- price for oncology drugs administered in hospital versus typically double price paid for community clinic
- Herceptin
  - hospital/hospital outpatient $5,350
  - independent clinic $2,740
- Avastin
  - clinic ($6,620), hospital ($14,100)
- incentive for trend for purchase of community clinics by hospital systems and reclassification as ‘hospital outpatient clinics’ and eligible for 340B discounts

Treatment At All Costs:
How Far Should Treatment Go?

"Why do they put nails in coffin lids?
To stop oncologists having one last try….."

C. Chatfield
Prospect July 2012, p.16

Are Oncologists' Financial Incentives Aligned with Quality Care?

Are Oncologists Financial Incentives Misaligned with Optimum Treatment?

- uncritical payer acceptance of high cost of new oncology drugs (US)
  - $50K-120K/year
- estimated 80% annual income for community oncologists tied to R_x use
- no incentives to select less expensive R_x or palliative care
- physician/payer refuge in slow pace of change in SOC guidelines to incorporate obligate molecular diagnostic profiling for R_x selection
- unacceptable levels of use of new R_x regimen(s) in last two weeks of life

Choosing Wisely®

An initiative of the ABIM Foundation

American Society of Clinical Oncology

ASCO

American Society of Clinical Oncology

Five Things Physicians and Patients Should Question - 2013

The Evolving Trajectory for Payer Policy for Cancer Therapeutics

- performance – based pricing
- indication – based pricing
- reference – based pricing

Hypothetical Scenarios for Indication-Based Drug Pricing

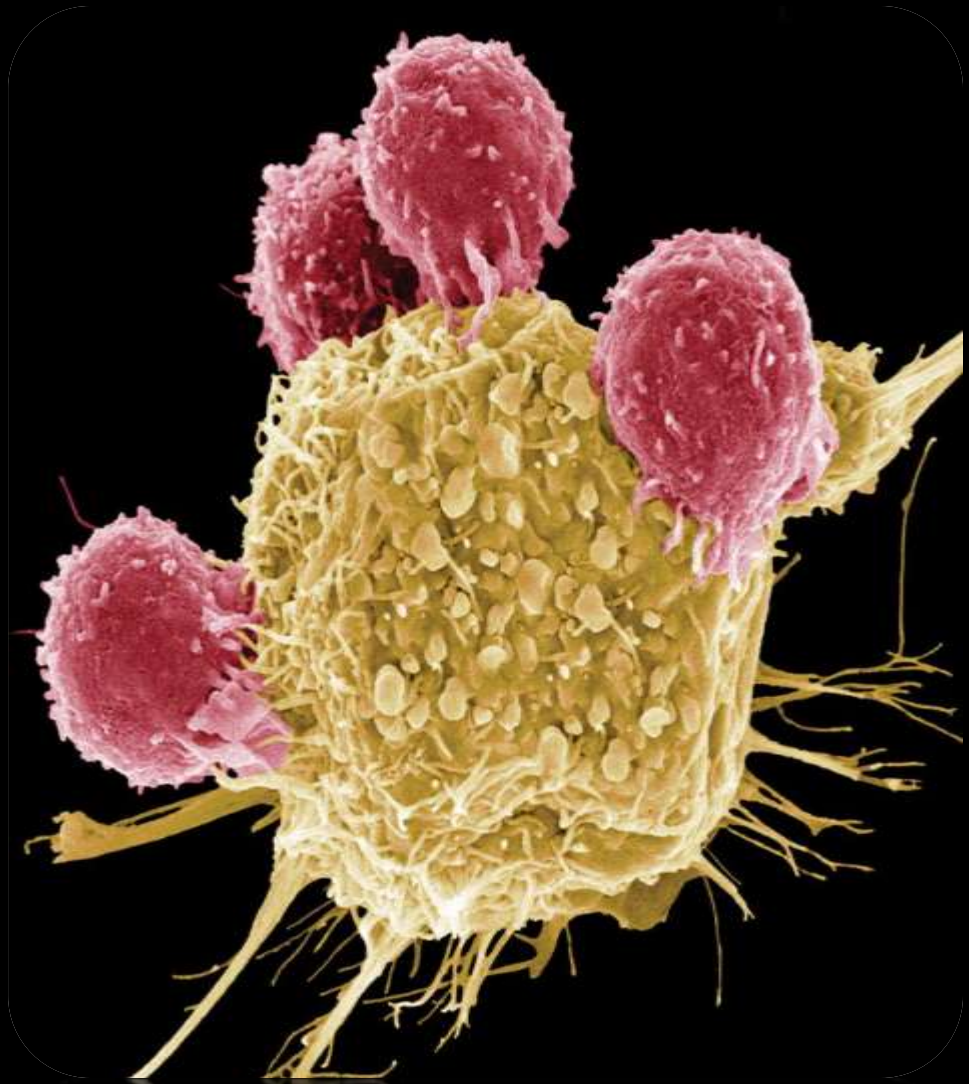
Drug and Indication	Median Survival Gain In Years	Current Monthly Price	Price Based On Indication With Most Value
Abraxane (Celgene)			
Metastatic breast cancer	0.18	$6,255	$6,255
Non-small cell lung cancer	0.08	$7,217	$2,622
Pancreatic cancer	0.15	$6,766	$448
Tarceva (Roche/Astellas)			
First-line treatment metastatic non-small cell lung cancer	0.28	$6,292	$6,292
Pancreatic cancer	0.03	$5,563	$1,556
Erbitux (BMS/Lilly)			
Locally advanced squamous cell carcinoma of head/neck	1.64	$10,319	$10,319
First-line treatment recurrent or metastatic squamous cell carcinoma of head/neck	0.23	$10,319	$471
Herceptin (Roche)			
Adjuvant treatment breast cancer	1.99	$5,412	$5,412
Metastatic breast cancer	0.40	$5,412	$905

Source: JAMA article by Peter Bach, Oct. 3, 2014

Adapted from: P. B. Bach JAMA (2014) 312, 1629 Pink Sheet 20 Oct. 2014

The Need for Rethinking Therapeutic Strategies to Combat Cancer


A sobering view of our energy future p. 1322
Maternal care alters newborn mouse genomes pp. 1330 & 1396
Wet route to phosphorus fine chemicals pp. 1350 & 1353
Science
$15
23 MARCH 2018
sciencemag.org
AAAS
SPECIAL ISSUE
CANCER IMMUNOTHERAPY
Engineered & personalized



A Very Expensive DTC Campaign

The Promise of Immunotherapy: Is Widespread Adoption Economically Feasible?

- unit Rx cost (> $100K)
- indirect care cost
- escalating cost of combination Rx regimens (> $200K)
- extravagant cost of cell-based therapies ($500K - $1.5 million)
- complex clinical management challenges and compatibility with community oncology services

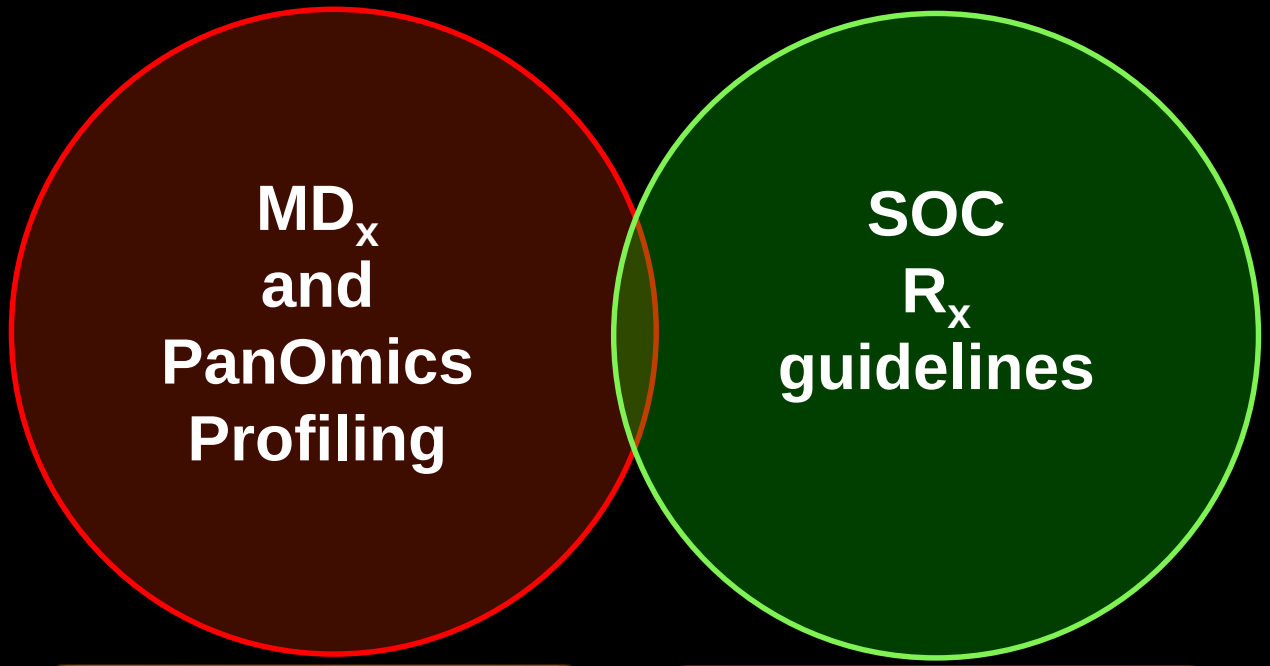
40-80% patients fail to respond even with I/O – I/O combinations

A Pricing and Reimbursement Dichotomy

D_x

R_x

Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MD_x) and Therapeutics (R_x) in Oncology



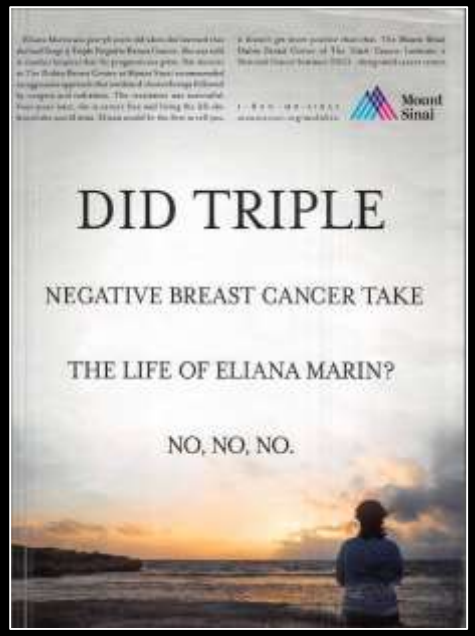
Disease Subtyping and ID of Rx-Responsive Cohorts

Precision Diagnosis and Rational Treatment Selection

High Cost Rx Without Subset Profiling

Propagation of Therapeutic Regimens With Limited Response Rates

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



The Emotional Impact of Terminal Disease


Family

"The Right to Try"
Early Access to Unapproved Investigational Drugs for Patients with Life-Threatening Illness

- "nothing to lose" principle
- "False hope": companies aren't required to provide the drug
- complex risk: benefit analysis
- Phase 1 data insufficient to understand the full efficacy/safety profile
- unexperienced adverse events due to advancement disease status of eligible patients
  - cannot be considered by FDA in assessing the drug for the intended patient population
- liability protections for drug company and physicians

Hype versus Hope

Physician (HCP): Patient Communications in Chronic and/or Terminal Illness

- clinical challenge of balance between ethical transparency and empathy
- the vulnerability of patients: "trust and surrender" to presumed "authoritative knowledge"
- physicians/HCPs are rushed and stressed
- oncologists know but often deny the limited efficacy of many interventions
  - when to move from continued aggressive intervention to palliative care?
  - why do so many physicians chose to go gently into the night with their own terminal illness (WSJ)
- the syntax of survival (JAMA 2013 310, 1027)
  - complex interplay between fear, hope, optimism and reality
  - verbal content, tone, facial expression and body language

Physician- Patient Comminutions About Terminal Disease

- the 15 minute per patient barrier
- demonstrated taxing emotional discourse for all parties
- value of advanced directives durable power of attorney to transfer third party
- value of end – of – life conversations in advanced cancer
  - switch from intervention to palliation
  - higher QOL
  - more and earlier hospice care

Palliative Care:
Treatment With No Longer a Curative Intent

Economic (Payors) and Evidence-Based Pressure for Increased Use of Palliation versus Repeated Aggressive Cycles of Different Rx Without Clinical Benefit and Major Impact on QOL

Palliative Care in Advanced Cancer Clinical Practice Guidelines J. Clin. Oncol. (2017) 35, 96

- palliative care available to ALL patients with advanced cancer
- alleviate pain and suffering
- discussion of bad news
- advanced care planning
- end- of- life (EOL) care

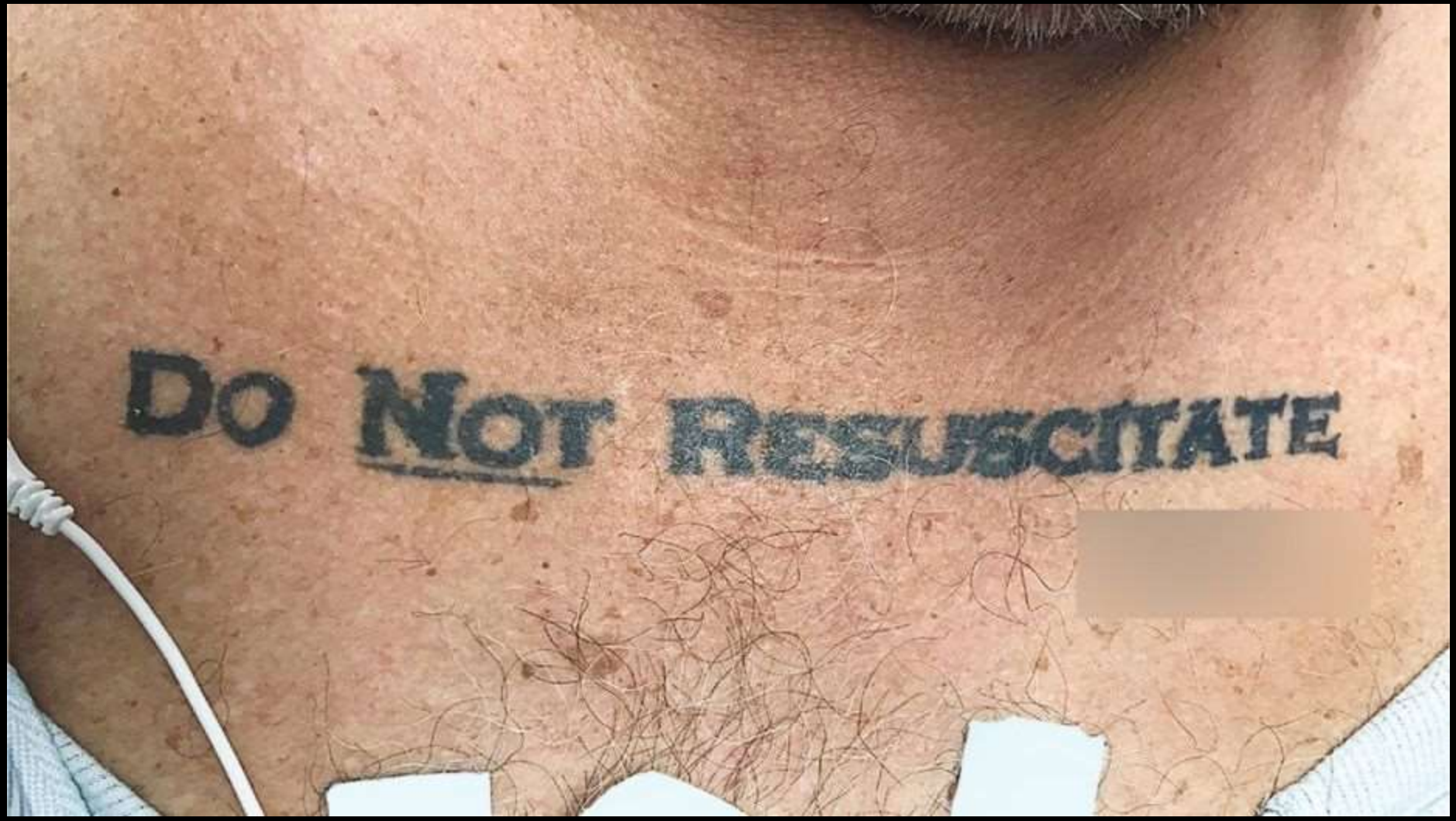
Increased Emphasis on Training HCPs to Engage in End-of-Life Preparation Discussions

- scripts to guide the conversation
- AMA Serious Illness Conversation Guide
- Center to Advance Palliative Care
  - allocate the time!
  - in general settings MDs let patients on average 18 seconds before interrupting them
  - minimum of 30-60 min discussion
- emerging role of trainers/ counselors to disseminate these activities

Advance Directives

- discussions of death and dying largely avoided in patient management
- fewer than half cancer patients who died in 2011 had documented preferences
  - end-of-life care, resuscitation
  - durable power of attorney for health decisions
- typically only discussed in last 30 days of life or even less
- less than 15% ambulatory patients with advanced cancer have advanced directives
- see J.H. Von Roden (2013) JCO, 31, 663

An Unconscious Patient with DNR Tattoo
University of Miami



N Engl J Med 2017; 377:2192-2193November 30, 2017DOI: 10.1056/NEJMc1713344

Advance Directive Registry (Arizona)

ARIZONA SECRETARY OF STATE'S OFFICE

ARIZONA ADVANCE DIRECTIVE REGISTRY

GEORGE H POSTE

User ID:

Password:

The person named on the front of this card has an advance health care directive registered at:

www.azsos.gov/adv_dir/

To access this directive please go to the above site and enter the User ID and Password.

If you have any questions please call (602) 542-6187 or toll-free (800) 458-5842.

Approaching Death: Care At End of Life

Dying with Dignity

New Expectations for the Level of Intervention(s) in Late Stage Terminal Illness

http://mentalfloss.com/article/77544/most-distinctive-obituary-euphemism-died-each-state

Physician-Assisted Death

Medical Aid in Dying (MAID)

Physician-Assisted Death

Dr. Jack Kevorkian

Al Pacino portraying
Dr. Kevorkian
in
You Don't Know Jack

Dr. Jack Kevorkian arrested


CENTRUM
EUTHANASIE

Physician-Assisted Death

- use of life-ending medications under physician's supervision
- Oregon's Death with Dignity statuted passed over 20 years ago
- more recently CA, CO, DC, MT, VT and WA passed similar legislation

Physician-Assisted Death

- complex moral ethical and legal issues
- voluntary euthanasia vs. involuntary euthanasia
- adequacy of protections against abuse
  - physician certification
- patient advocacy
  - incurable pain, loss of autonomy, QOL and dignity
- patient consent
  - assessment of cognitive compresence
  - patients unable to advocate for themselves (coma, severe intellectual disabilities)

Summary and Key Points

Infinite Demand Versus Finite Resources (Clinical and Economic)

- public expectancy for unlimited care and access to latest advances
- prioritized care
  - what works and what doesn't (outcomes)?
  - what is the cost/benefit/risk calculus (value) ?
- rationed care
  - who decides?
  - what are the criteria and cut-off thresholds?
  - risk of multi-tier economic discrimination or utilitarian, equalization, equality

Cancer Care: 7 C's

- clonal heterogeneity (cancer biology)
- clinical care (outcomes)
- consistency of care (guidelines)
- communication (patient-physician relationships)
- choice (intervention versus palliation)
- cost (sustainability and value)
- culture (expectations, motivations, incentives)

Cancer Care: 7 C's

- clonal heterogeneity (cancer bi
- clinical care (outcom
- consisten (guideli
- ation (n sician
- lationshi
- tervention ualiation)
- cost (su and value)
- (expectations, motivations, incentives)

complexity

data and decisions

value

The Most Important Missing 'C' Word in Cancer

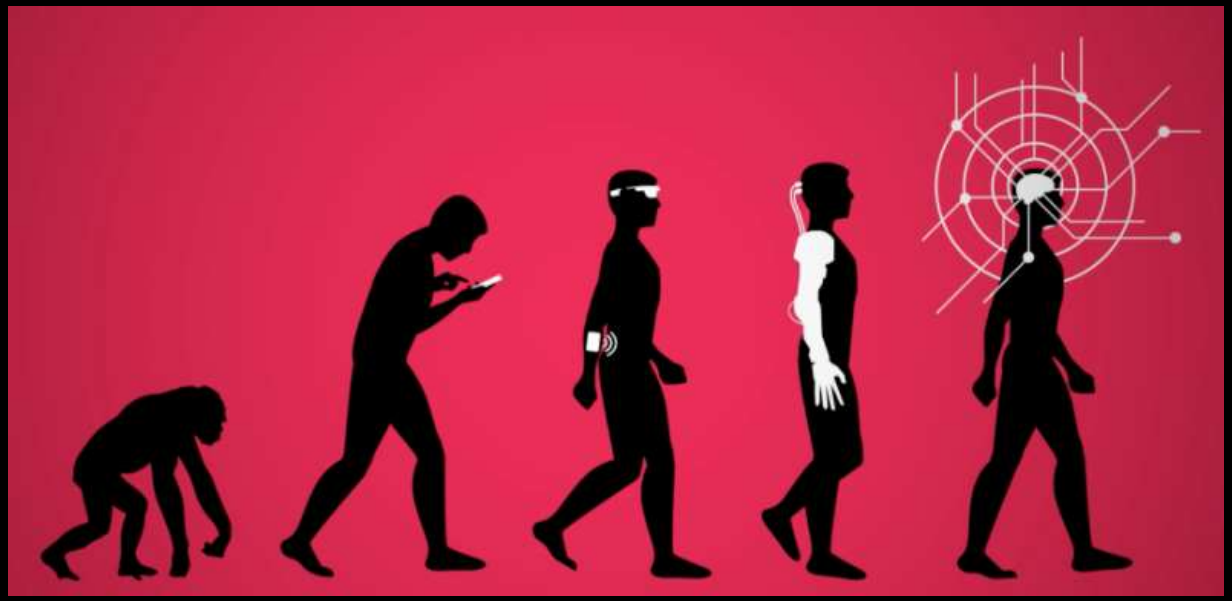
- "Cure"
- progress but the morbidity and mortality statistics tell the story of how much remains to be done
- the promise of immunotherapy (IR_X)
  - hematopoietic cancers versus solid tumors
  - will IR_X – resistant clones create longer term relapse?
- major gaps in our understanding of the biology of cancer as obstacle to rational treatment

Careers

Careers

- limitless opportunities
- academia, industry, government
- entrepreneurial startup companies

The Co-evolution of Augmented Humans, Robotics and Human-Machine Interactions



Careers

- convergence
  - science, medicine, engineering, computer, law, ethics, public policy
- acceleration
  - continuous learning
- automation
  - will a robot or a computer replace you?
- differentiation
  - adding value: employment, satisfaction, impact