ASU Complex Adaptive Systems
ARIZONA STATE UNIVERSITY

BIO 302:
APRIL 28, 2015

WEEK 15, LECTURE 1:
THE FUTURE OF CANCER CARE: ECONOMIC OUTLOOK; CARE DELIVERY SYSTEMS; TECHNOLOGICAL INNOVATION; PREVENTION; PATIENT PARTICIPATION

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The Future of Cancer Care

Faces Many of the Same Challenges As US Healthcare At Large

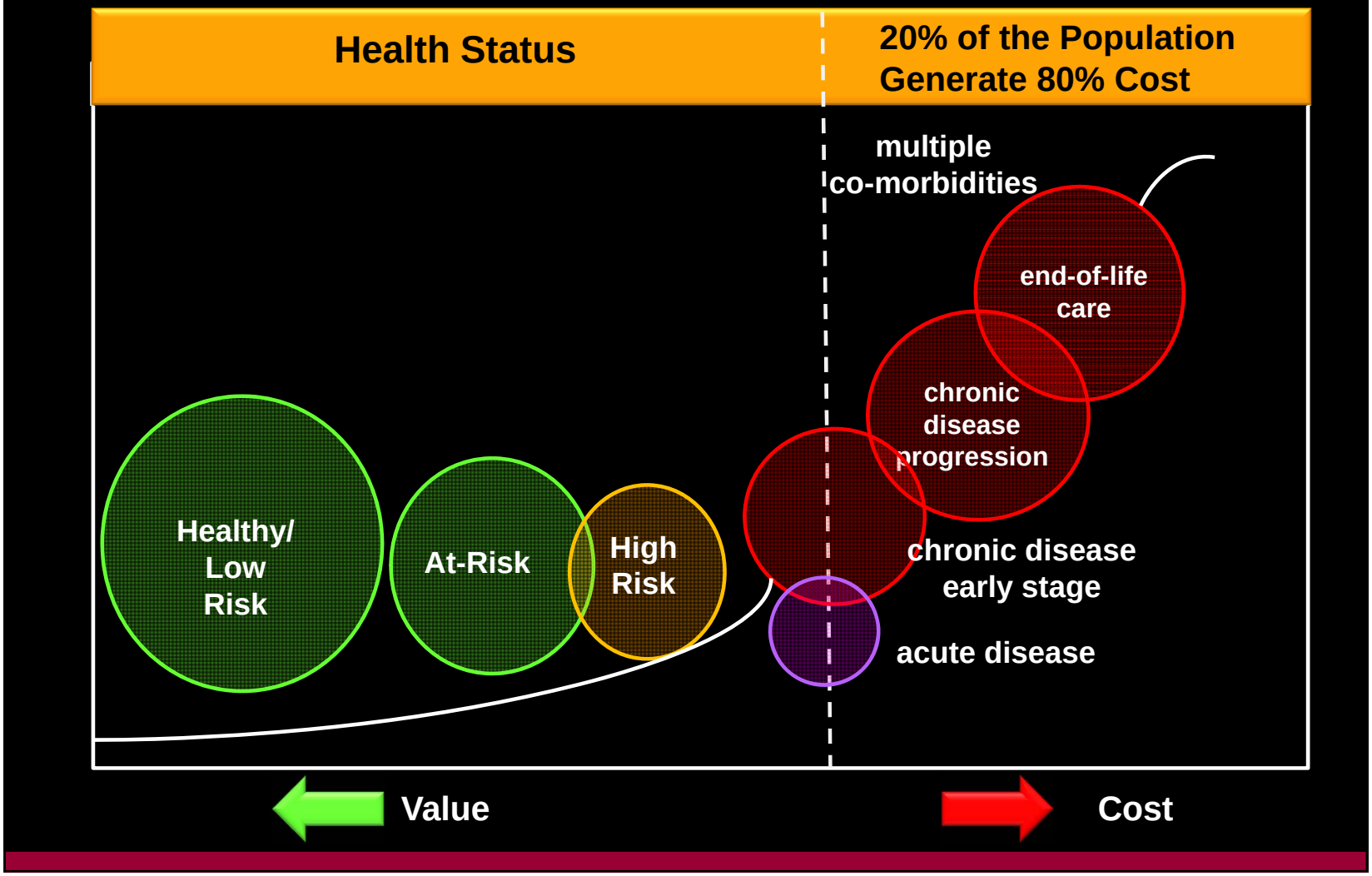
Healthcare: An Expensive Menu Without Prices

Managing the Demands of an Aging Society and Chronic Disease Burden in an Era of Economic Constraint

Shift From a "Do More, Bill More" Healthcare System to Managing Individual Risk to Improve Health Outcomes and Control Cost

Sustainable Health: Societal (Economic) and Individual (Wellness)

The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities



US Healthcare (2015)

- $2.9 trillion enterprise (15% GDP) destined to grow to $5 trillion by 2020
- reactive ‘sickness’ system versus optimizing health (wellness)
- episodic ‘incident-based’ care versus integrated continuity of care
- multiple participants and stakeholders with divergent interests, aspirations and expectations
- passive consumers
- healthcare only industry in which new technologies constantly drive up the cost of care
- inefficient capture and use of information for improved continuity of care and assessment of clinical outcomes

The Socio-Economic and Political Issues at the Core of the Healthcare Debate

- infinite demand versus finite resources
- individual expectations for “cure” exceed technical capabilities or cost-effectiveness rules set by payers
- inadequate information systems to generate robust evidence to evaluate improvements in clinical care and cost management
- polarizing national political debates with emotionally loaded sound-bites
  - rationing, denial of care, “like-Canada” , inequities, ‘death panels’

The Real World

- innovation in science and technology alone is necessary but not sufficient
- adoption requires overcoming multiple barriers
  - current practices/standard of care guidelines
  - cultural conservatism
  - loss of income and other financial disincentives
  - regulatory and reimbursement policies
- wide variation in speed of adoption of new technologies by different sectors
  - healthcare (10-30 years)
  - engineering (1-10 years)
  - computing (1-2 years)

The Principal "'ics" in the Future Evolution of US Healthcare

- 'omics (profiling technologies)
- geriatrics (aging populations and chronic disease burden)
- informatics (big data and analysis)
- economics (value)
- ethics (societal)

The Principal "'ics" in the Future Evolution of US Healthcare

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Politics:
Slick Lobbies, Big Bucks, Quick Fixes, Ducking the Hard Questions and Long Term Impact of Indecision and Flawed Policies

The Key Objectives of Healthcare

Improving Clinical Outcomes

Health (Wellness) vs. Illness

The Key Objectives of Healthcare

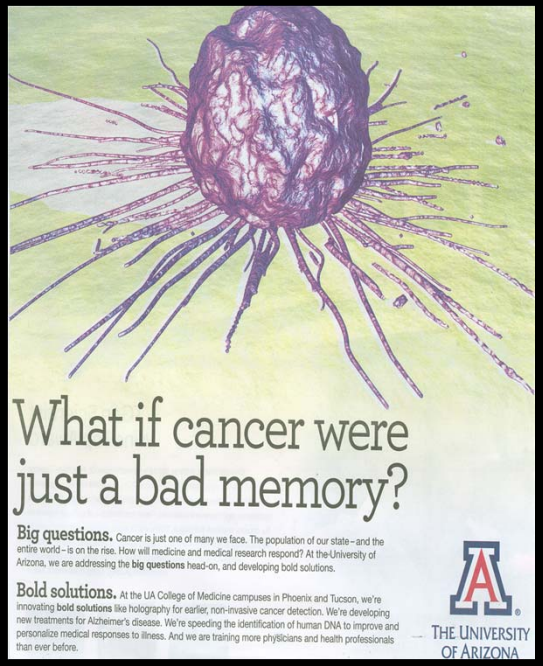
Improving Clinical Outcomes

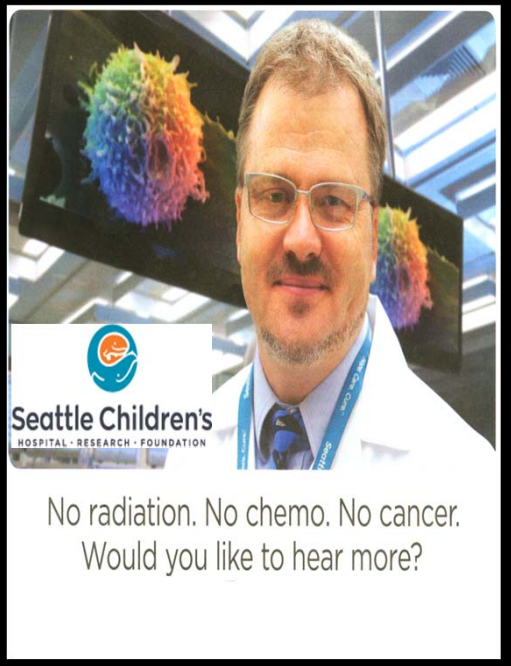
Health (Wellness) vs. Illness

VALUE

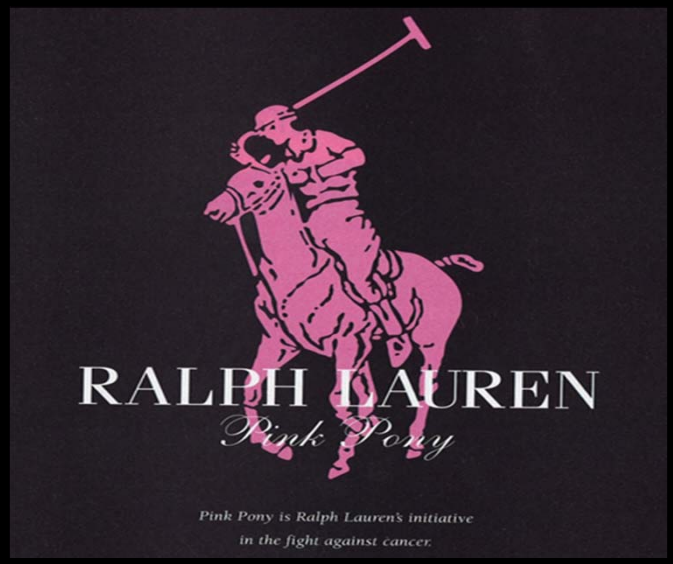
Confronting Cancer: Changing Outcomes to Reduce the Massive Clinical, Economic and Personal Impact of a Devastating Disease

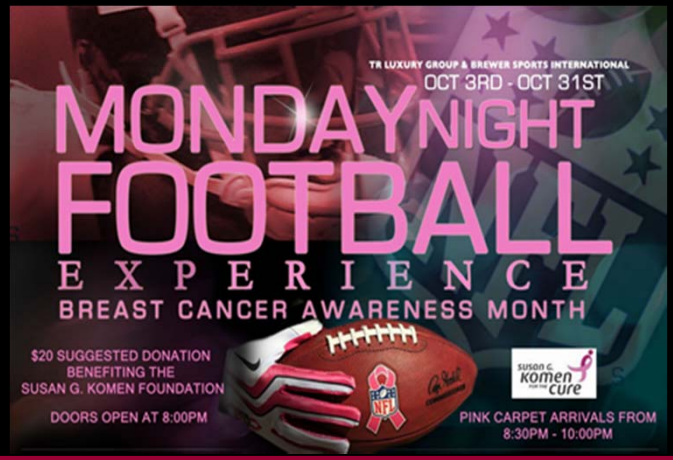
Hope, Hype and Hubris





Sincere Advertising and Advocacy or Cynical Hijacking of Public Generosity?





Choices

- celebrity populism and belief that more money will solve everything

versus

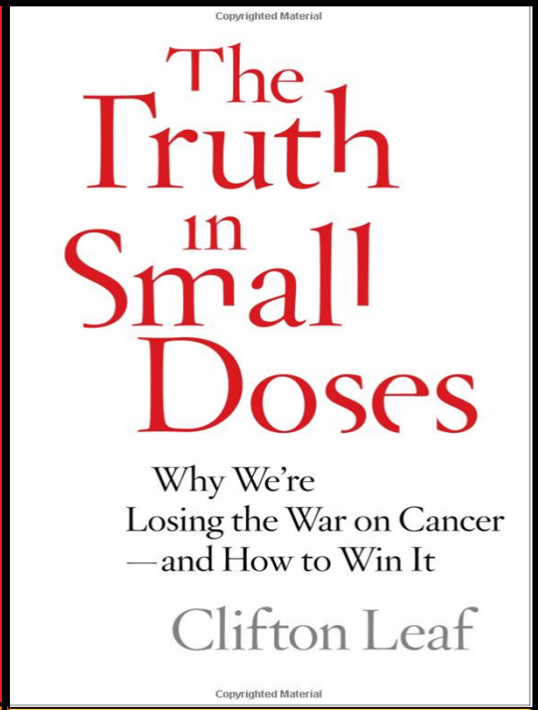
- fundamental reassessment of why therapeutic success for metastatic solid tumors remains so elusive

plus

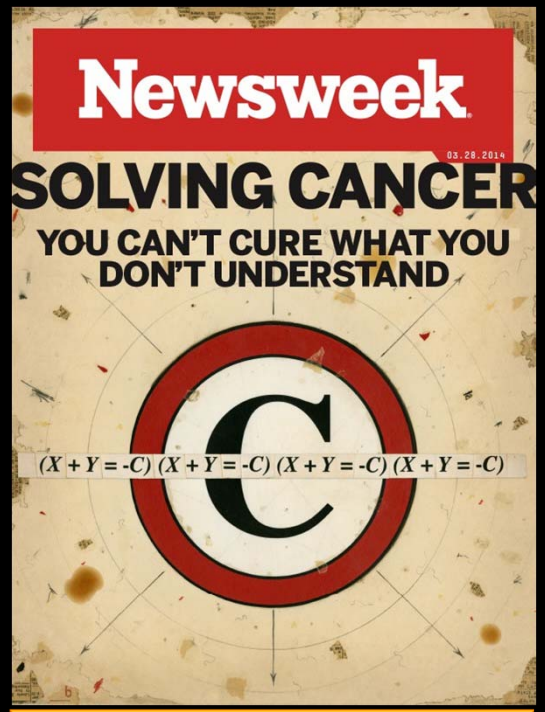
- recognition that cancer is a complex adaptive system demands major changes in current approaches to cancer research and clinical oncology

Conflicting Messages

Hype



Critique

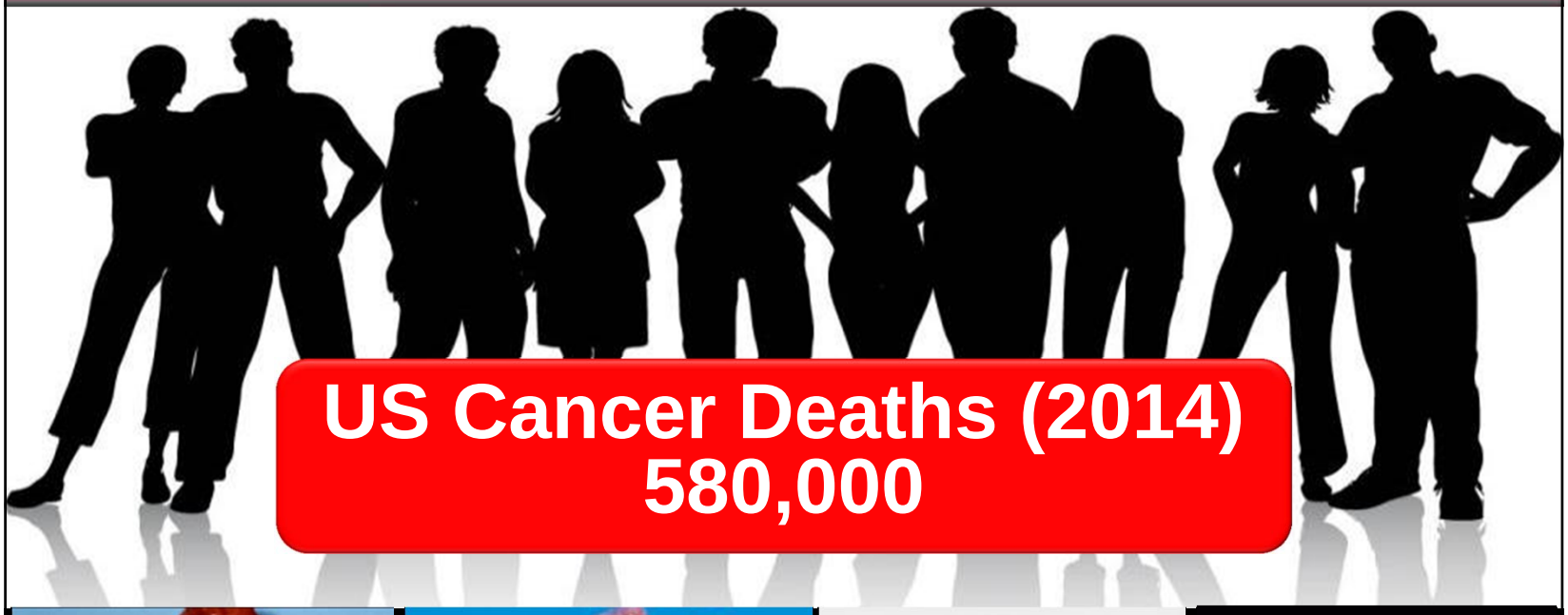


Reality

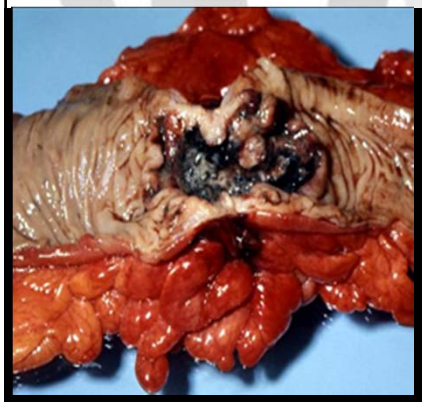
“The War on Cancer”

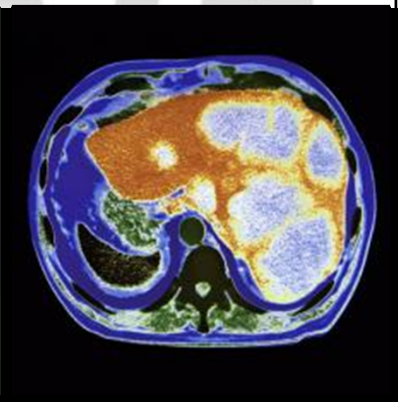
President Richard Nixon signs the National Cancer Act December 23, 1971

Ugly Realities!
Confronting the Clinical, Economic and Human Toll of Cancer

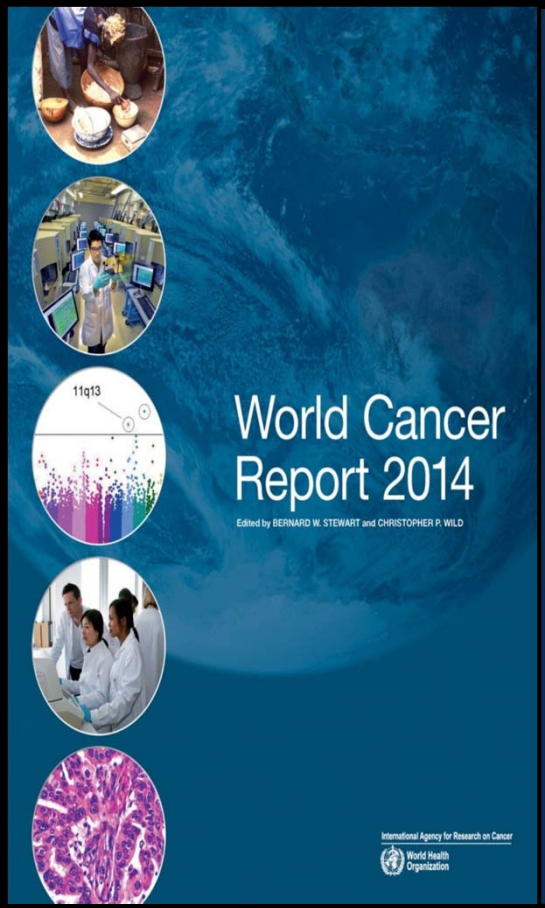


US Cancer Deaths (2014)
580,000






AACR CANCER
PROGRESS REPORT
2014
TRANSFORMING LIVES THROUGH RESEARCH
AACR American Association for Cancer Research
FINDING CURES TOGETHER™
CancerProgressReport.org // AACR.org // #CancerProgress14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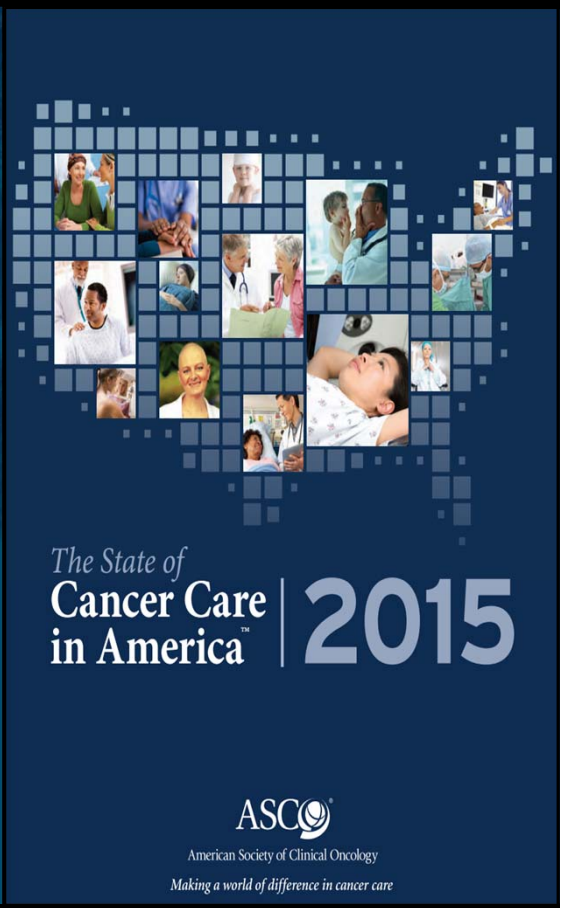
World Cancer Report 2014
Edited by BERNARD W. STEWART and CHRISTOPHER P. WILD
International Agency for Research on Cancer
World Health Organization


The State of
Cancer Care in America™
2015
ASCO
American Society of Clinical Oncology
Making a world of difference in cancer care

Progress in Reducing Disease Burden Mortality 1970 – 2008*

- cerebrovascular disease — 74% ↓
- heart disease — 63% ↓
- accidents — 33% ↓
- cancer — 12% ↓
  - major impact of leukemia/lymphoma success and early detection of colon/breast cancers

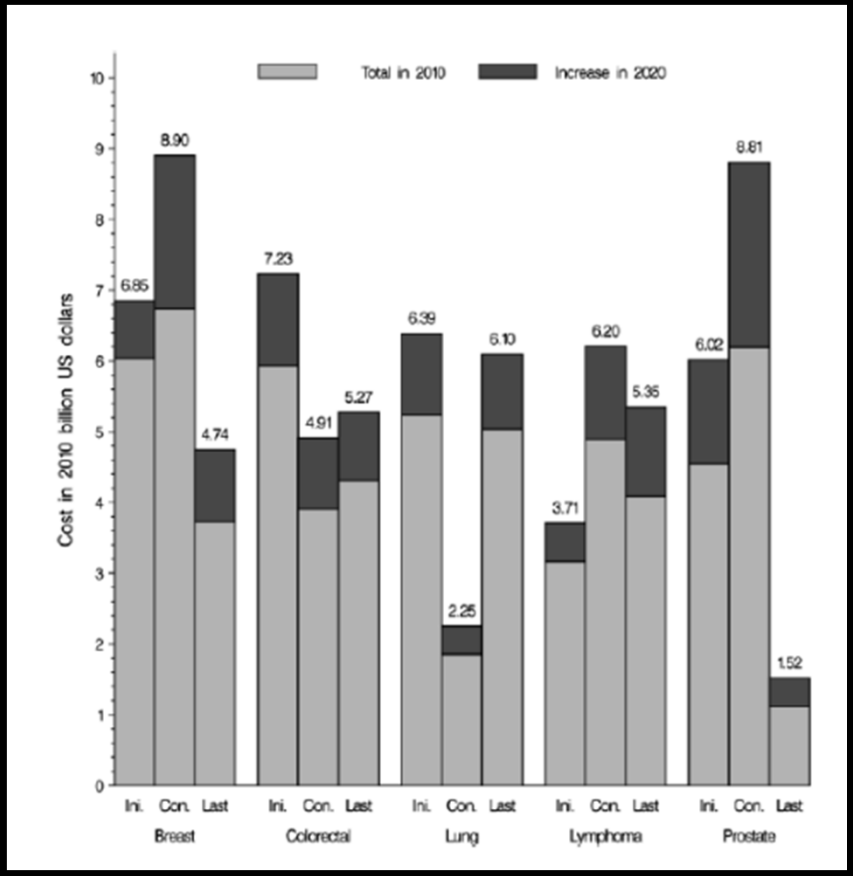
*S. Soneji et al (2014) JCO 32, 444

US Cancer Prevalence Estimates 2010 and 2020

Site	# People (thousands) 2010	2020	% change
Breast	3461	4538	31
Prostate	2311	3265	41
Colorectal	1216	1517	25
Melanoma	1225	1714	40
Lymphoma	639	812	27
Uterus	588	672	15
Bladder	514	629	22
Lung	374	457	22
Kidney	308	426	38
Leukemia	263	240	29
All Sites	13,772	18,071	32

From: A.B. Mariotto et al. (2011) J. Nat. Cancer Inst. 103, 117

Estimates of U.S. National Expenditures for Cancer Care 2010



$124 billion and projected to rise to $207 billion (66% increase) by 2020

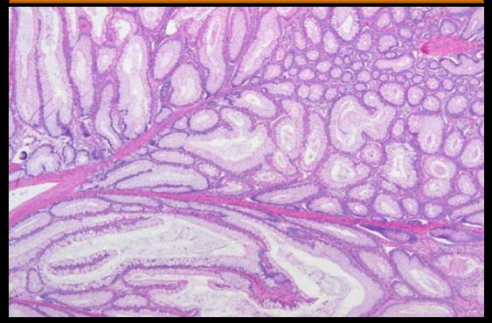
Ini. = within 1 year of Dx; Con = continuing; Last = last year of life
From: A. B. Mariotto et al. (2011) J. Nat. Cancer Inst. 103, 117

Seeking Cancer Cures

- the balance between hope and hype
- the balance between desperation and delusion
- the balance between continued aggressive intervention versus palliative care and QOL
- asking tough questions about the adequacy of current scientific and clinical strategies

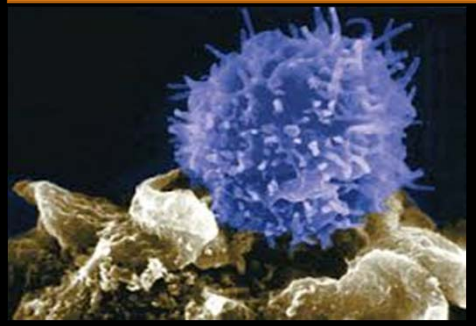
Cancer as a Complex Adaptive System: Emergent Phenomena and Tumor Progression (System State Shifts)

Escape From Controls for Normal Tissue Architecture

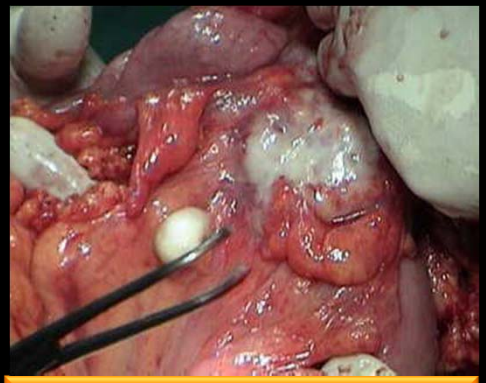


Genome Instability and Emergence of Clonal Variants

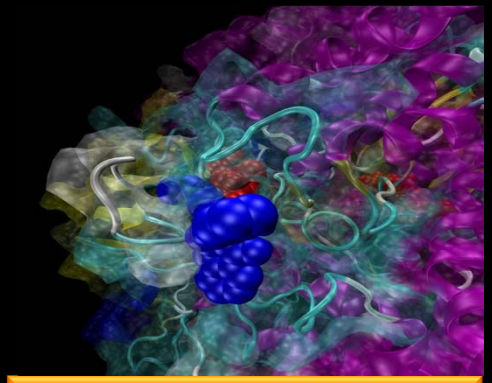
Evasion of Detection/Destruction by Host Immune System



Use of Host Systems by the Tumor to Promote Progression

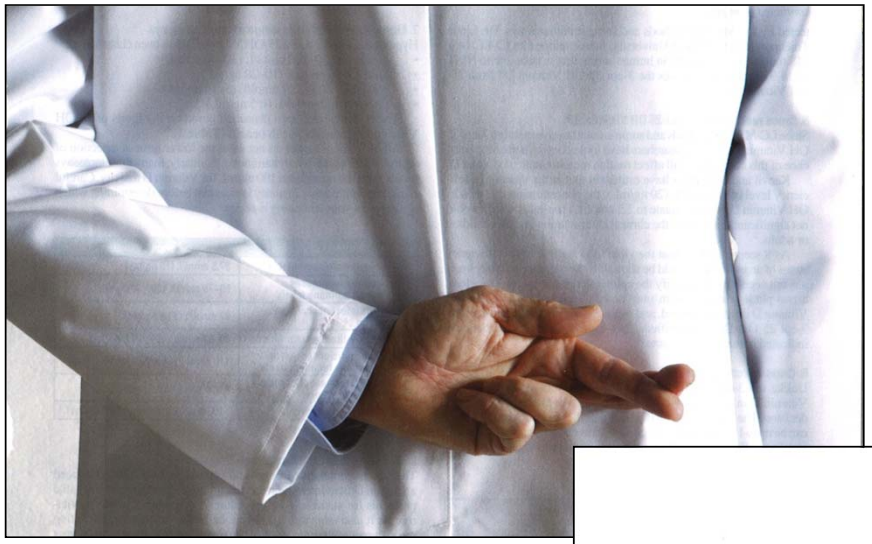


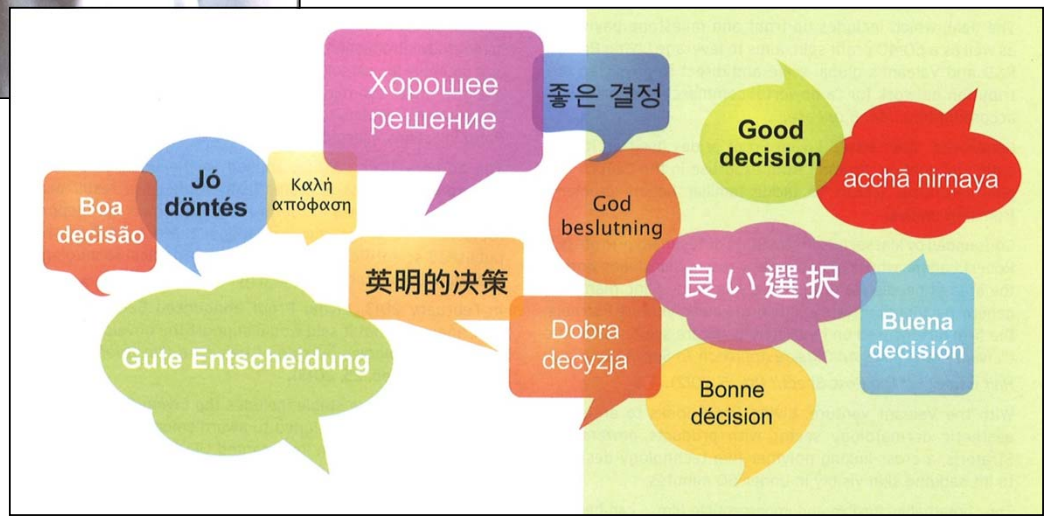
Invasion and Metastasis



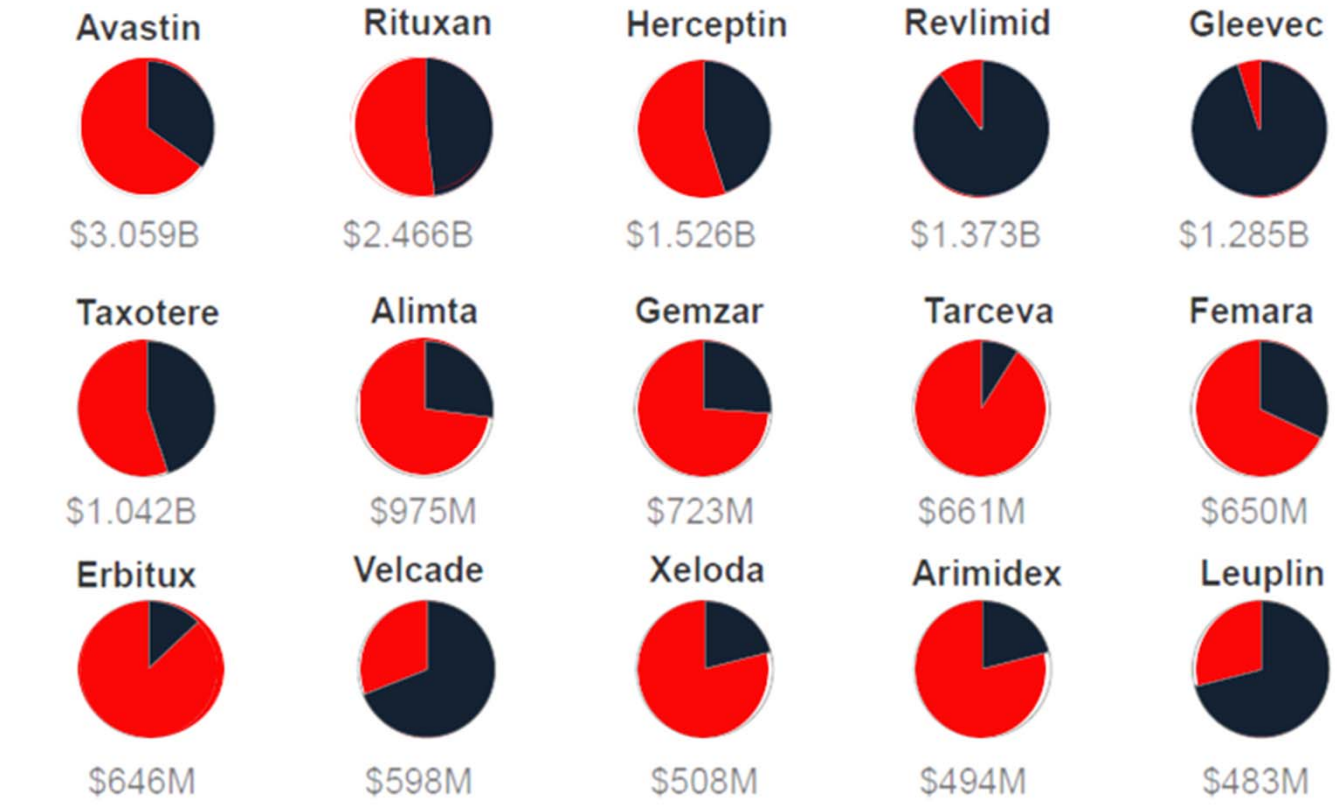
Emergence of Drug-Resistant Clones

The Foundation of Rational Healthcare: Better Decisions for Better Outcomes



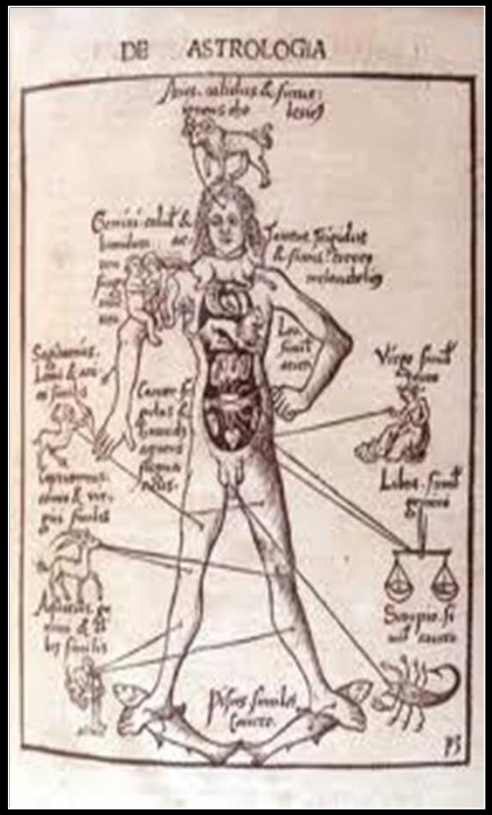


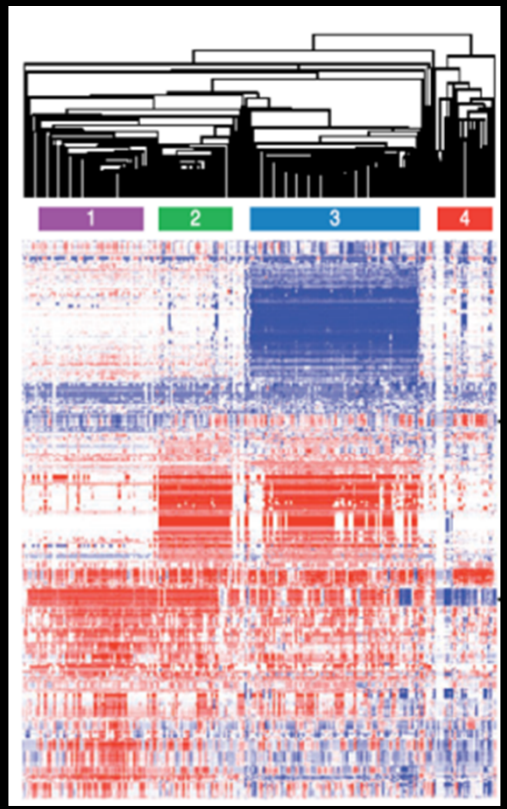
Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly



Sources: Individual Drug Labels. US Food and Drug Administration. www.fda.gov
Market and Product Forecasts: Top 20 Oncology Therapy Brands. DataMonitor, 2011.

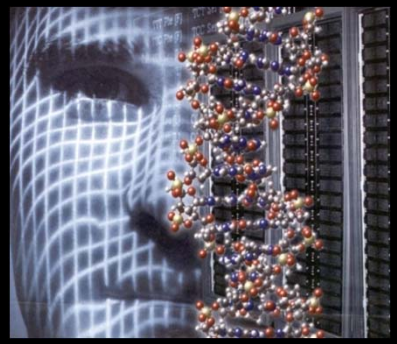
Medical Progress:
From Superstitions to Symptoms to Signatures



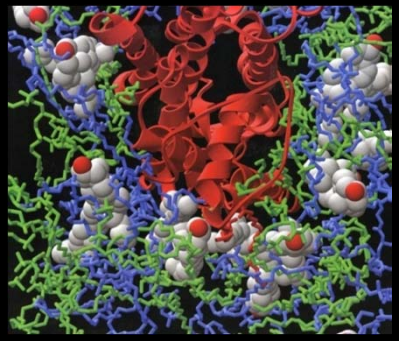


Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

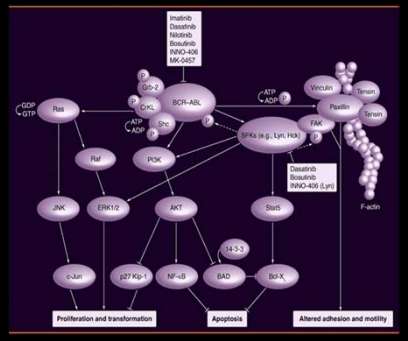
(Epi)Genomics



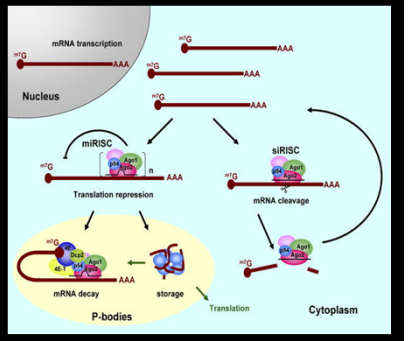
Proteomics

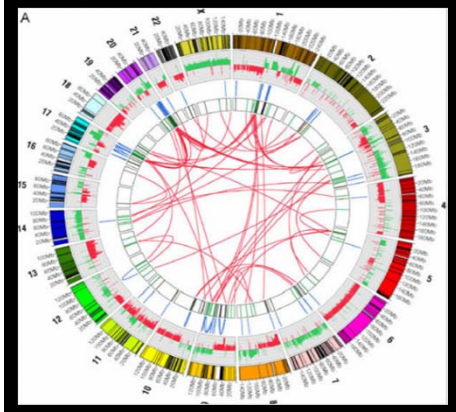


Molecular Pathways and Networks



Network Regulatory Mechanisms



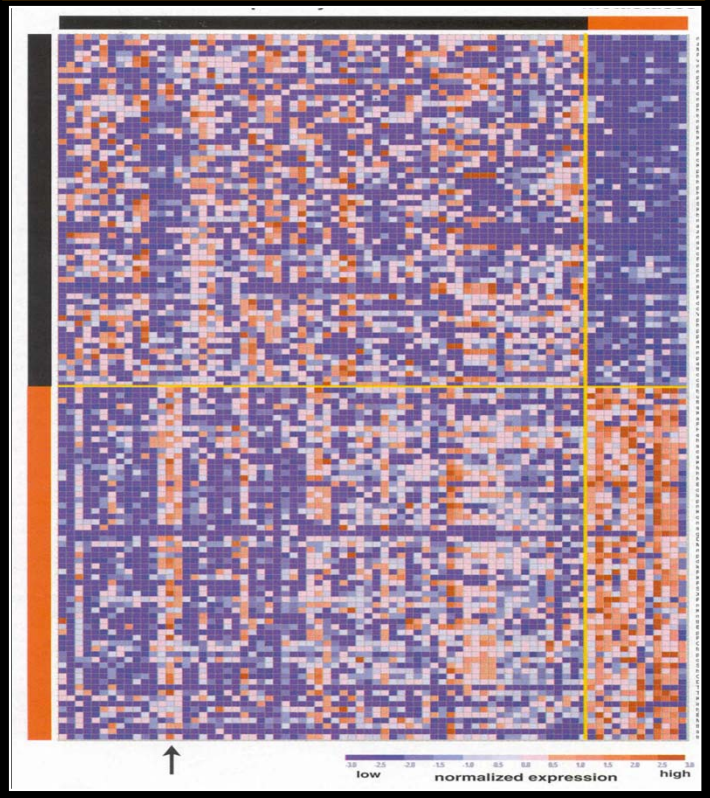


ID of Causal Relationships Between Network Perturbations and Disease

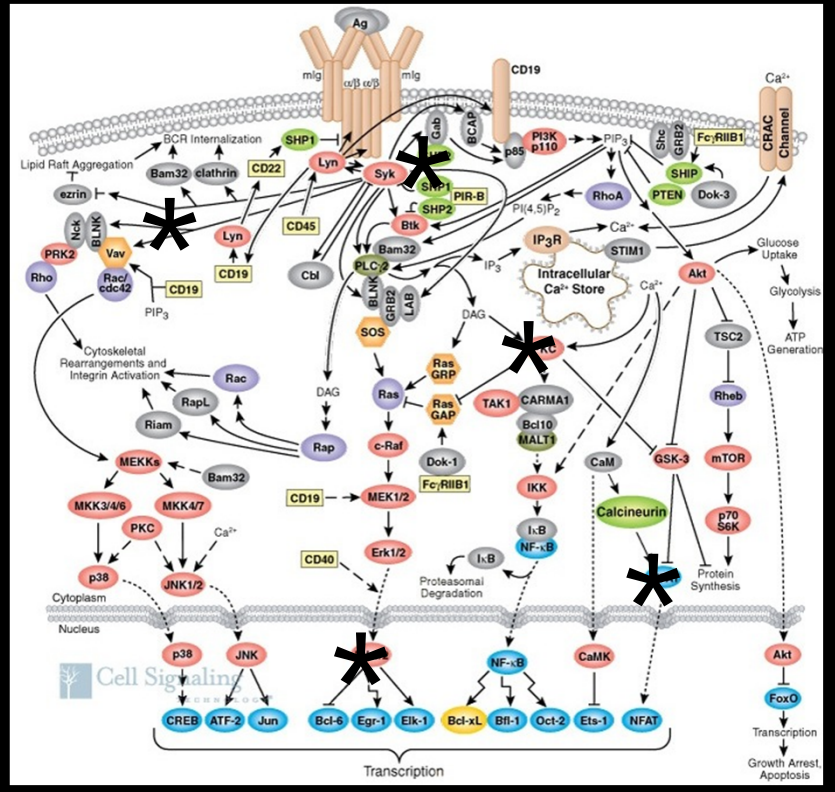
Patient-Specific Signals and Signatures of Disease or Predisposition to Disease

Mapping Dysregulation of Biological Networks in Disease

Disease Profiling to Identify Subtypes (+ or - Rx Target)

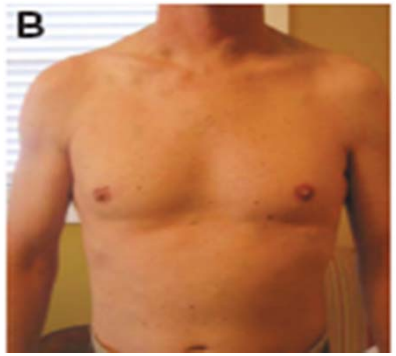


ID Molecular Targets for Rx Action and Blockade of Compensatory "By pass" Pathways



Emergence of Drug Resistance to Targeted Therapy in Melanoma

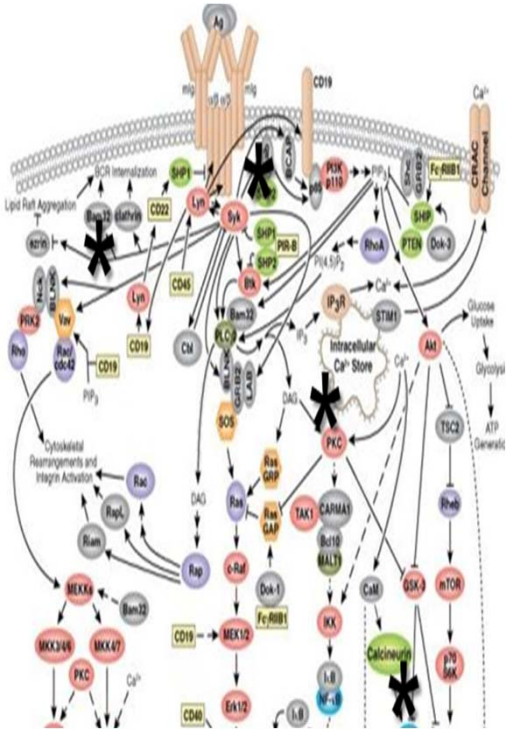
Initial Rx-Response to Targeted Rx



Rx-Resistance via Alternate Molecular Signaling Pathway (Network Redundancy)

B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)

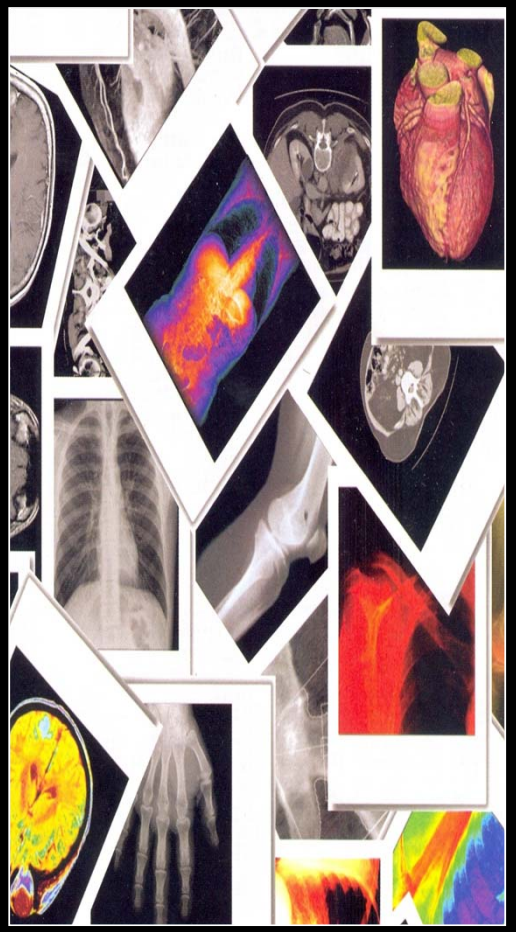
Circumvention of Rx-Resistance Requires Multi-site Blockade of Connected Signaling Pathways

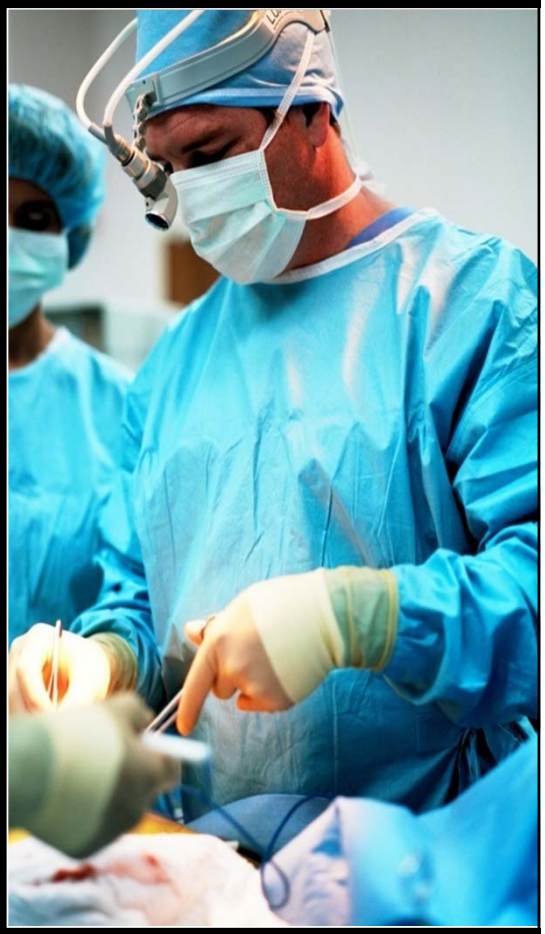


Challenges in Cancer Therapy and Precision Oncology

- genomic heterogeneity
- clonal diversification
- drug-resistance phenotypes
- inadequate tools for dynamic monitoring of treatment responses and risk of tumor recurrence
- limited knowledge on use of drug combinations and immunotherapeutics

How Much New Technology Can We Afford?





The Difficult but Largely Ignored Central Questions in Oncology and Cancer Care Delivery

What is a meaningful advance in Rx effectiveness?

Can we continue to afford the high cost of anti-cancer drugs for modest gains in PFS/OS and limited QOL?

Cost of Recently Approved Anti-Cancer Drugs

- brenfuximab (Adcetris) $216,000/course
- ipilimab (Yervoy) $123,000/year
- cabazitaxel (Jevtana) $96,000/year
- sipuleucel-t (Provenge) $93,000/year
- vismodegib (Erivedge) $75,000/course
- petuzumab (Perjeta) $70,800/year
- vemurafenib (Zelboraf) $61,000/year
- abiraterone (Zimiga) $60,000/year
- premetrexed (Alimta) $30,000/course

Oncology Drugs Are Not Alone in Potentially Breaking the Bank

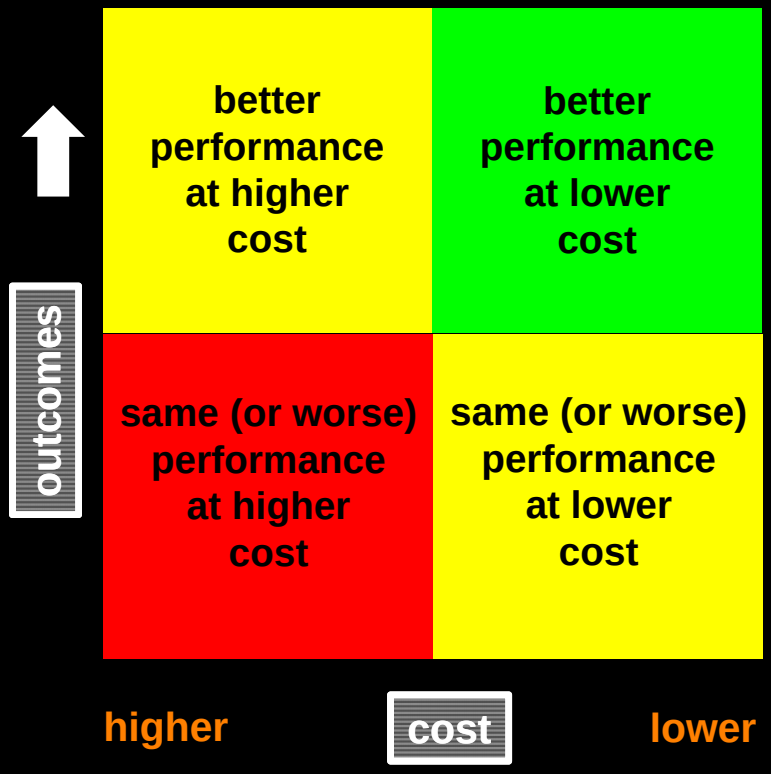
Drug	Indication	Cost
Cerdelga	Gaucher's disease	$310,250/year
Kalydeco	Cystic Fibrosis	$294,000/year
Solvadi	Hepatitis C	$84,000/12 weeks

Health Technology Assessment (HTA)

Defining What Works (and What Doesn't)

Defining Value

Defining Value in Healthcare: A Complex Technical, Economic and Social Calculus



Regulatory Criteria for Drug Approval

FDA

- safety
- efficacy

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- safety
- efficacy
- cost-effectiveness
- separate review for regulatory approval (EU wide) and pricing (national)

“I would like someone to declare war on cancer.
The NCI is an agency that is perpetuating
the old cancer establishment.
The FDA should not be approving drugs
that have only shown a three month survival benefit.”

Dr. James D. Watson
Nobel Laureate
2012 Celebration of Science
Washington, DC 7-9 Sept. 2012
cited in Scrip Intelligence 10 Sept. 2012

Are Regulatory Approval Hurdles Too Low for New Anti-Cancer Treatments?

Are Empathic and Political Considerations Diluting the Definition of "Breakthrough"

UK National Institute for Health and Care Excellence (NICE)

NHS
National Institute for Health and Clinical Excellence

NICE
National Institute for Health and Care Excellence

Cost Per Quality-Adjusted Life-Year (QALY)

Switch to an aromatase inhibitor for early-stage breast cancer vs. continued tamoxifen	$22,900
Implant a cardioverter-defibrillator (primary prevention) vs. continued medical management	$37,400 to $77,200
Perform fusion surgery for degenerative spondylolisathesis with spinal stenosis vs. conservative management	$120,000
Prescribe trastuzumab for metastatic breast cancer vs. standard chemotherapy	$150,000
Prescribe erlotinib for advanced pancreatic cancer vs. gemcitabine alone	$370,000 to $500,000
Perform helical computed tomographic screening for lung cancer in 60-year old former heavy smokers vs. no screening	$2,300,000
Avoidance of end-organ damage by ERT therapy in Fabry disease	$8-10,000,000*

From: G. Lyman (2013) The Oncologist 18, 752

*S. M. Rombach et al. (2013) Orphanet Journal of Rare Diseases 8, 29

What Are We Willing to Pay for Added Months of Survival in Cancer?

Lifetime cost above standard care	If cancer is on par with other diseases ($150,000 per life year gained), months of added overall survival benefit needed	Treating cancer as worthy of much higher reimbursement ($250,000 per life year gained), months of added overall survival benefit needed
$50,000	4 months	2.4 months
$100,000	8 months	4.8 months
$150,000	12 months	7.2 months
$200,000	16 months	9.6 months
$250,000	20 months	12 months
$300,000	24 months	14.4 months
$350,000	28 months	16.8 months
$400,000	32 months	19.2 months
$450,000	36 months	21.6 months
$500,000	40 months	24 months

Source: Pink Sheet 13 Sept. 2010. Adapted from S. Ramsey FHCRC, ASCO 2010

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 Current Status of Cancer Care Delivery

Doing More, But Not Necessarily Doing Better

Oncologists' Financial Incentives Are Not Aligned With Quality of Care

The Unacceptable Status of Cancer Care

- unwarranted practice variation
  - cancer outcomes vary regionally, nationally and internationally
- fragmented and poorly coordinated multi-speciality services
  - PCP, oncologists, pathologists, surgeons
  - inconsistent supportive care and survivorship care
- lack of proficient data migration and QA systems aligned across different elements of the healthcare system

Uneven and More Expensive Cancer Care

- Medicare payments up to 50% higher for Rx therapy given in hospital outpatient facilities versus Rx in community cancer clinics
- hospital patients also more likely receive more expensive drugs versus generic Rx
- I.V. drugs requiring infusion clinics used disproportionally versus oral drugs

The Unacceptable Status of Cancer Care

- failure to keep pace with advances in the molecular biology of cancer and integrate into SOC guidelines
  - community oncologists/HCPs versus academic medical centers
  - regulatory and reimbursement policies
- refuge in anachronistic SOC guidelines and "one-size-fits all" Rx strategies based on outdated histologic profiling taxonomy (anatomic pathology)
  - slow pace of adoption of molecular profiling and tumor subtyping for Rx selection
  - insufficient enrollment of stratified patients into investigational Rx trials

Overcoming Heterogeneity in Tumor Cell Rx Responses: The Omnipresent Challenge in Cancer Treatment

Molecular Profiling and Rx Selection in Cancer Treatment

- should molecular profiling be conducted on all patients as SOC?
- should patients receive SOC if profiling indicates absence of molecular targets for the SOC regimen?

Why Should Oncology Adopt Different Considerations for Rx Selection Than Other Clinical Disciplines?

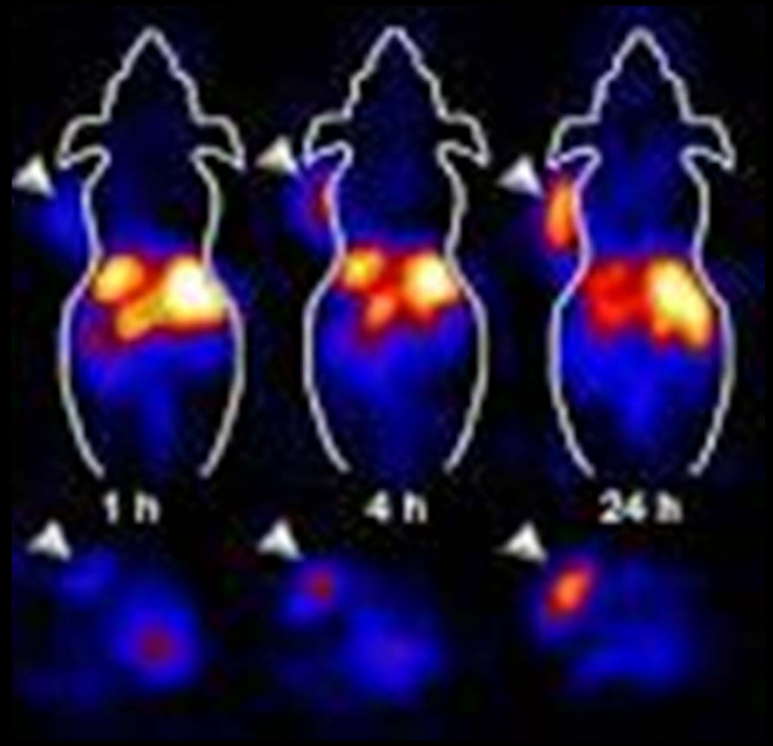
- antibiotics aren't given to patients with a known antibiotic resistant bacterial infection
- HIV-positive patients are routinely profiled for Rx-resistance before Rx starts
- blood transfusions aren't given to people with incompatible blood groups
- influenza vaccines are designed to combat the current circulating influenza strains versus historical strains no longer circulating

Assessing Tumor Cell Rx Sensitivity and Resistance: Selection of the Right Rx for the Right Patient

Assessing Tumor Rx Sensitivity and Resistance: Selection of the Right Rx for the Right Patient

- inter- and intra-patient heterogeneity of clones with different Rx vulnerabilities
- moving beyond 'one-size-fits-all' Rx regimens to select Rx based on expression (or absence) of molecular targets on which the Rx acts (molecular profiling)
- challenge of how to achieve the most representable molecular profile to guide Rx choice
  - static versus dynamic profiling (liquid biopsy) to reflect tumor progression
  - value of patient-specific tumor xenografts to test Rx responsiveness

Human Tumor Xenografts and Drug Screening



Grafting of Patient's Tumor Specimen Into Mice and Evaluation of Rx Responsiveness

To develop a PDX mouse model, a researcher grafts a bit of a tumor into a handful of mice. Tumor sections from a successful graft expand, then are harvested, divided, and regrafted into many more mice, providing a large number of animals on which to test a variety of drugs or drug combinations.

Patients Often Do Not Understand the Goals of Cancer Treatment

Cancer Care

- patients often do not understand goals of cancer treatment
- 70-80% believe treatment is curative and do not understand they have incurable disease (NEJM 2012, 367, 1616)
- patient ‘shut down’ and ‘denial’
- how to best communicate difficult information and engage patients (and families) in care decisions?

Empowered Patients (and Families)

Access to Information Previously Limited to MDs/HCPs Courtesy of the Internet and Patient Advocacy Groups

The Vital Role of Patients and Patient Advocacy Organizations in Demanding Information on Best Care Options

Clinician-Patient Communication in Progressive and Terminal Disease

Patients' Need to Know and Need to Feel Known

The Need for Change in Physician-Patient Relationships

From Medical Paternalism in Decision-Making to More Inclusive Roles for Other Healthcare Professionals, Patients and Families

Certain Death in Uncertain Time: Balancing Hope and Harsh Reality in Terminal Illness

"I respect the seriousness of death
I've had many occasions to meditate on its intrusions.
….the way the message was delivered.
Frankly, it made me furious."

Sen. Edward Kennedy
True Compass. A Memoir. 2009

Cancer Therapeutics: Some Perplexing Emerging Questions

- are oncologists sufficiently transparent in discussing prognosis/options and role of palliative care for patients with advanced disease?
  - failure of two prior chemotherapies
  - estimated less than 40% patients receive full information
- why are less than 5% cancer patients enrolled in investigational trials for new drugs?

The Too Often Overlooked Communication Interaction Gap in Healthcare and Patient Safety

- "do you understand"
  - MD paternalism and patient timidity: a dangerous combination
- limited time for in-depth discussion with patients
  - time = money but also significant cultural dimension to in-depth discussion
- the sociology of medical training and practice
  - hierarchical, authoritarian, paternalistic
- oncologists and patients often hold different perception of priorities
- positive impact of discharge counseling by RNs and other non-MD health personnel on complications/readmissions
- inadequate focus on team-based care and services and family engagement

Patient Communications in Chronic and/or Terminal Illness

- clinical challenge of balance between ethical transparency and empathy
- the vulnerability of patients: "trust and surrender" and presumed "authoritative knowledge" of MD/HCPs
- 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 (WSJ)".

The Syntax of Survival (JAMA 2013, 310, 1027)

- impact of physician/HCP behavior and language on patient's psyche/family attitudes
- does the rushed physician/HCP even remember what was said to the patient?
- complex interactions and impact of inadvertent actions in shaping fear, hope and variable awareness of realities/prognosis

"A Good Death": Patient Preferences in End-of-Life Care

- being in control of care decisions
- being comfortable (freedom from pain)
- affirmation/value of self and life-lived
- trust in care providers and their decision
- minimize economic and emotional burden for family
- personal affairs in order

Approaching Death: Care at the End of Life

- patient preferences
  - intensity of intervention
  - preferred place of death
- death AND bereavement: impact on families

Palliative Care: The Importance of Advance Care Planning

- clinicians often unaware of patient preferences at end of life
- patients with no expressed preference for place of death more likely to die in hospital/ICU

"A Good Death": Patient Preferences in End-of-Life Care

- 'a good death'
- dignity
- death at home or hospice versus ICU and extended life support and intensive intervention
- fade away: state of unconsciousness induced by drugs

End-of-Life Cancer Care
(N.E. Morden et al. (2012) Health Affairs 31, 786)

- wide variation in clinical practice in different care settings
- poor national compliance with National Quality Forum metrics
  - lower rates of ICU use in last month of life
  - no new chemotherapy regimen in last 2 weeks of life
  - death at home or hospice versus hopsital/ICU

The Rise of Precision (Molecular) Medicine and Information-Based Medicine

Better Decisions

Better Outcomes

Better Allocation of Finite Resources

Better Cost-Effectiveness