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

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- cost (sustainability and value)
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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

localization of immune cells/soluble mediators and impact of $R_x$

balance of stimulatory and suppressive factors
The Path to Precision Oncology:

Superstitions

Symptoms

(Molecular) Signatures

Common sites and symptoms of Cancer metastasis:

- Brain
  - Headaches
  - Seizures
  - Vertigo

- Respiratory
  - Cough
  - Hemoptysis
  - Dyspnea

- Lymph nodes
  - Lymphadenopathy

- Liver
  - Hepatomegaly
  - Jaundice

- Skeletal
  - Pain
  - Fractures
  - Spinal cord compression
Precision Oncology:

- (Epi)Genomics
- Causal Relationships Between Disruption of Molecular Signaling Networks and Disease

- Big (Messy) Data
  - terabytes per individual
  - zettabyte – yottabyte

- Population databases

- Patient-Specific Signatures of Disease or Predisposition to Disease
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

- (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

Diagram showing network topology evolution over time from $T_1$ to $T_n$.
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
Understanding System State Shifts and Emergent Perturbations in Molecular Signaling Networks In the Health to Disease Continuum

T_1
health

T_2
subclinical disease

T_3
overt disease
Impact of Different Factors On The Risk of Premature Death

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?
The Future of Healthcare: Precision Medicine and Digital Medicine

new technology platforms
- multiplex profiling of molecular network topologies
- automation and advanced computing
- sensors, robotics

molecular classification of disease

the expanded care space
- wearables, sensors, telemedicine
- patient engagement
- social media and lifestyle metrics

remote monitoring of health status
The Future of Healthcare: Precision Medicine and Digital Medicine

- New technology platforms
- The expanded care space
- Big Data
- PHR/EHR
- Population health
- Precision medicine
- Digital medicine
- AI
- Analytics for improved decisions and clinical outcomes at lower cost (value)
- Remote monitoring of health status
- Wearables, sensors, telemedicine
- Social media and lifestyle metrics
- Patient engagement
- Multiplex profiling of molecular network topologies
- Sensors, robotics
- Automation and advanced computing
- Molecular classification of disease
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

- 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 hotline, 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*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opdivo</td>
<td>$13,100</td>
</tr>
<tr>
<td>Keytruda</td>
<td>$13,000</td>
</tr>
<tr>
<td>Bavencio **</td>
<td>$13,000</td>
</tr>
<tr>
<td>Tecentriq</td>
<td>$12,500</td>
</tr>
</tbody>
</table>

* 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

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

- public health and national security
- research community and public funding agencies
- translational science and development (public and private sectors)
- clinical trials and regulators
- consumers: patients
- physicians and other healthcare professionals
- payers
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

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 anticancer 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

\(b = H.\) 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
“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 Rx use
- No incentives to select less expensive Rx or palliative care
- Physician/payer refuge in slow pace of change in SOC guidelines to incorporate obligate molecular diagnostic profiling for Rx selection
- Unacceptable levels of use of new Rx regimen(s) in last two weeks of life
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

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

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

The Need for Rethinking Therapeutic Strategies to Combat Cancer
A Very Expensive DTC Campaign

First FDA Approved Immunotherapy
for previously treated advanced stage lung cancer

Most Prescribed Immunotherapy
For Previously Treated Advanced NSCLC

In a clinical trial of non-squamous patients, half of those on OPDIVO were alive at 12.2 months versus 9.4 months for chemotherapy (docetaxel).
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 ($\text{MD}_x$) and Therapeutics ($\text{R}_x$) in Oncology

- **$\text{MD}_x$ and PanOmics Profiling**
- **SOC $\text{R}_x$ guidelines**

- Disease Subtyping and ID of Rx-Responsive Cohorts
- High Cost Rx Without Subset Profiling

- Precision Diagnosis and Rational Treatment Selection
- 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
“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 Communications 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

- 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; 377:2192-2193
November 30, 2017
DOI: 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
MOST CHARACTERISTIC WORDS FOR DYING IN 2015 OBITUARIES, BY STATE

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
Physician-Assisted Death

- use of life-ending medications under physician’s supervision
- Oregon’s Death with Dignity statute 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
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- culture (expectations, motivations, incentives)
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