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

Dr. George Poste
Chief Scientist, Complex Adaptive Systems Initiative and Del E. Webb Chair in Health Innovation
Arizona State University
(e-mail: george.poste@asu.edu; Tel. 480-727-8662)
www.casi.asu.edu
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

Health Status

20% of the Population Generate 80% Cost

- multiple co-morbidities
- end-of-life care
- chronic disease progression
- chronic disease early stage
- acute disease

Value

Cost

- Healthy/ Low Risk
- At-Risk
- High Risk

- Value
- Cost

- $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

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

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
Improving Clinical Outcomes

Health (Wellness) vs. Illness
Confronting Cancer: Changing Outcomes to Reduce the Massive Clinical, Economic and Personal Impact of a Devastating Disease
Hope, Hype and Hubris

One goal: end cancer.

What if cancer were just a bad memory?

No radiation. No chemo. No cancer. Would you like to hear more?
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
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

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

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
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)

<table>
<thead>
<tr>
<th>Escape From Controls for Normal Tissue Architecture</th>
<th>Genome Instability and Emergence of Clonal Variants</th>
<th>Evasion of Detection/Destruction by Host Immune System</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.jpg" alt="Image 1" /></td>
<td><img src="image2.jpg" alt="Image 2" /></td>
<td><img src="image3.jpg" alt="Image 3" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Use of Host Systems by the Tumor to Promote Progression</th>
<th>Invasion and Metastasis</th>
<th>Emergence of Drug-Resistant Clones</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image4.jpg" alt="Image 4" /></td>
<td><img src="image5.jpg" alt="Image 5" /></td>
<td><img src="image6.jpg" alt="Image 6" /></td>
</tr>
</tbody>
</table>
The Foundation of Rational Healthcare: Better Decisions for Better Outcomes
Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly

Avastin: $3.059B
Rituxan: $2.466B
Herceptin: $1.526B
Revlimid: $1.373B
Gleevec: $1.285B
Taxotere: $1.042B
Alimta: $975M
Gemzar: $723M
Tarceva: $661M
Femara: $650M
Erbilux: $646M
Velcade: $598M
Xeloda: $508M
Arimidex: $494M
Leuplin: $483M

Responders
Non-responders

Medical Progress:
From Superstitions to Symptoms to Signatures
### Mapping The Molecular Signatures of Disease:
The Intellectual Foundation of Rational Diagnosis and Treatment Selection

<table>
<thead>
<tr>
<th>(Epi)Genomics</th>
<th>Proteomics</th>
<th>Molecular Pathways and Networks</th>
<th>Network Regulatory Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Genomics Image]</td>
<td>![Proteomics Image]</td>
<td>![Pathways Image]</td>
<td>![Networks Image]</td>
</tr>
</tbody>
</table>

- **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)

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

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerdelga</td>
<td>Gaucher’s disease</td>
<td>$310,250/year</td>
</tr>
<tr>
<td>Kalydeco</td>
<td>Cystic Fibrosis</td>
<td>$294,000/year</td>
</tr>
<tr>
<td>Solvadi</td>
<td>Hepatitis C</td>
<td>$84,000/12 weeks</td>
</tr>
</tbody>
</table>
Defining Value in Healthcare:
A Complex Technical, Economic and Social Calculus

- better performance at higher cost
- better performance at lower cost
- same (or worse) performance at higher cost
- same (or worse) performance at lower cost

higher cost  lower cost
Regulatory Criteria for Drug Approval

- safety
- efficacy

- 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”
## Cost Per Quality-Adjusted Life-Year (QALY)

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

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?

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

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

*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 disproportionately 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 hospital/ICU
The Rise of Precision (Molecular) Medicine and Information-Based Medicine

- Better Decisions
- Better Outcomes
- Better Allocation of Finite Resources
- Better Cost-Effectiveness