The Challenge of Comprehensive Cancer Control:
Complexity, Convergence, Cost, Communication, Computing and the Imperative for Radical Change

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Committee on National Strategy for Cancer Control in the United States
National Academies of Science, Engineering and Medicine
Washington, D.C. 6 June 2018
Confronting the Clinical, Economic and Human Toll of Cancer

New Diagnoses: 1.68 million (2017)

Deaths: 600,920 (2017)
The Pending “Tsunami” of Older U.S. Cancer Survivors

Number of survivors 65 and older – unprecedented increases
(Patients projected to survive at least 5 years to increase 37% in 10 years)

Cancer as a Complex Adaptive System

The Difference Between Complicated Systems and Complex Adaptive Systems
Complicated Systems: Human Design and Engineering

- behavior of the assembled system is predictable from the properties of the components
- proactive awareness of tolerance limits and most likely failure points
- system performance is fixed and not capable of autonomous evolution
- low degrees of design freedom
Complex Adaptive Systems: Fundamental and Ubiquitous Design Principals of Natural Systems

- System behavior not predictable from knowledge of the properties of individual subcomponents
- Dynamic behavior defined by constantly changing interactions between components in response to external inputs
- Robust, adaptive, evolvable
Complex Adaptive Systems in Biology: Robustness, Adaptation and Evolvability in the Architecture of Molecular (Informatics) Networks

- stable networks (health: physiology)
- perturbed networks (disease: pathophysiology)
- dynamic attractor landscapes of state spaces

- network structure robust to commonly encountered perturbations (homeostasis)
- fragile to novel perturbations that trigger major changes in system states (emergence)
The Challenge for Comprehensive Cancer Control

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

cumulative and combinatorial risks to individuals

tumor subtypes and different progression patterns and Rx responses

systems for care delivery and outcomes
biological complexity (the health to disease continuum)

implementation complexity (improved prevention, outcomes, detection and treatment)

policy complexity (infinite demand versus finite resources)

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

Superstitions

Symptoms

(Molecular) Signatures

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

- terabytes per individual
- zettabyte – yottabyte population databases

Patient-Specific Signatures of Predisposition to Disease or Overt Disease

Big (Messy) Data
Precision Medicine: “Computed Phenotypes” and ‘Digital Siblings’

Individual Data

Population Databanks

integration and analysis of large scale, diverse data categories

“matching” individuals to ‘best match’ cohorts using data on similarities of deep phenotyping profiles and treatment outcomes
5-YEAR SURVIVAL RATES FROM 2007 THROUGH 2013 FOR STAGE I OF THE MOST COMMON CANCERS

- Breast: 100%
- Lung & Bronchus: 55.1%
- Prostate: 100%
- Colon & Rectum: 88.1%
- Melanoma: 99.5%
Public Health Approaches to Cancer Prevention and Early Disease Detection

- historical focus on generic risk assessment tools and monitoring
  - sex or age categories
  - specific socio-cultural and environmental exposure risk cohorts
  - limited subpopulation analytics and variable screening intervals

- need for improved assimilation of new molecular insights in risk factor identification to increase precision and sensitivity of existing approaches
  - molecular exposures, including infectious agents
  - social media and behavioral/lifestyle factors
Estimated New Cancer Cases and Deaths – 2018

<table>
<thead>
<tr>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,735,350</td>
<td>609,640</td>
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### Male

<table>
<thead>
<tr>
<th>New Cases</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Prostate</td>
<td>19%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>6%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>4%</td>
</tr>
<tr>
<td>All sites</td>
<td>26%</td>
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</table>

<table>
<thead>
<tr>
<th>New Deaths</th>
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<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>26%</td>
</tr>
<tr>
<td>Breast</td>
<td>25%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
</tr>
<tr>
<td>Ovary</td>
<td>5%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
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<tr>
<td>All sites</td>
<td>100%</td>
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### Female

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<thead>
<tr>
<th>New Cases</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Breast</td>
<td>30%</td>
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<tr>
<td>Lung &amp; bronchus</td>
<td>13%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>7%</td>
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<tr>
<td>Urinary bladder</td>
<td>7%</td>
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<tr>
<td>Melanoma of the skin</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
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<tr>
<td>All sites</td>
<td>100%</td>
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The need for improved diagnosis, treatment, supportive care, and survivor care.
Large Scale Genome Sequencing as Flagship Projects for Precision Oncology: The Dangers of Reductionism and Ignoring Biological Complexity
Fraction of Tumor Samples with Alterations in 10 Curated Signaling Pathways

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

necessary but not sufficient

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

deep phenotyping: longitudinal integration of molecular, clinical, environmental and socio-cultural data
Most Events That Affect Our Health Occur Outside of the Healthcare System And Are Not Monitored
# Large Population Cohorts for Molecular Profiling

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

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

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

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

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

“People Analytics”
Social Activities and Behavior Become Quantifiable

- who knows why people do what they do?
  - the fact is that they do!

- these actions can now be traced and measured with unprecedented precision

- with sufficient data, the numbers reveal increasingly predictable behavior, individual risk patterns and health events

- the confessional of social media and the blurring of private and public spaces

- voluntary vs involuntary data capture

- complex ethical and legal issues
  - consent, privacy, security, surveillance
Major Investments in Digital Health by Major Corporations From Within and Outside of Traditional Healthcare Services
The Quest for Precision Oncology: A New Era of Massive Expansion of Molecular Profiling Data (Multi-Omics)

- (Epi)Genomics
- Transcriptomics
- Proteomics

Molecular Interactions and Pathway Analysis
Network Topology and Architecture
Network Perturbation(s) and Disease Subtypes
Biomarkers: The Core Technology Component of Precision Oncology

- disease predisposition markers
- molecular taxonomy of cancer subtypes
- new clinical trial designs
- companion Dx for target-centric Rx choice
- prediction of Rx response/resistance
Biomarkers: The Core Technology Platform in Making Precision Oncology a Reality

- profound mismatch between intellectual rationale and limited availability of validated biomarkers
- poor productivity and reproducibility of biomarker research (publish and vanish)
- insufficient R&D investment (public and private sectors)
- escalating cost of trials for multiplex biomarker validation and reimbursement barriers
- insufficient minimally invasive/imaging technologies for dynamic longitudinal monitoring of health to disease continuum profiling
  - static snapshots of dynamic disease progression
  - promise of liquid biopsy (ctDNA, CTC) not yet validated
Incidence of Biomarkers for Cancer Subtype Profiling for the Selection of Rx Biomarker-Driven Rx Selection (2017)

Source: FDA.gov and Drugs@FDA, Apr 2018; IQVIA, ARK R&D Intelligence, Apr 2018; IQVIA Institute, Apr 2018
Molecular Biomarkers Classification of Tumor Subtypes and New Clinical Trial Designs

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

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

Parallel Co-Development of Companion and Complementary Diagnostics
# Tissue-Agnostic Anti-Cancer Drugs in Clinical Trials


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

- Escape From Controls for Normal Tissue Architecture
- Genome Instability and Emergence of Clonal Variants
- Evasion of Detection/Destruction by Host Immune System
- Use of Host Systems to Promote Progression
- Invasion and Metastasis
- Emergence of Drug-Resistant Clones
Targeted Therapeutics and the Omnipresent Problem of $R_x$ Failure Due to Emergence of Drug Resistance Clones

Molecular Subtyping and $R_x$ Targets

Initial $R_x$ - Response to Targeted $R_x$

$R_x$ - Resistance via Redundant Molecular Pathways

B = 15 weeks $R_x$ (vemurafenib)

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

Cancer $R_x$: Ugly Realities

- In the majority of cancers, the efficacy of $R_x$ therapies (except immunotherapies) is either short-lived or completely ineffective.
- Mutations that confer $R_x$ resistance may pre-exist prior to treatment (intrinsic resistance) or arise during treatment (acquired resistance).
- Mutations are typically present in multiple pathways.
- Intrinsic and/or acquired mutations in non-targeted pathways can enable ‘by-pass’ signaling circuits that ensure tumor cell survival and ever-broadening resistance $R_x$ spectrum.
Performance Comparison for New Anti-Cancer Drugs Approved 2002-2014 for Top Ten Pharmaceutical Companies

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

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

\(^b\) = H. Kumar et al. (2016) JAMA Oncology 2, 1238
\(^c\) = J. C. Del Paggio et al. (2017) Ann. Oncol. 28, 157
Aspirations for Improved Cancer Treatment

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

Curing Cancer

Save Lives Now

Join the Battle Against Cancer Today

Newsweek

Solving Cancer

You Can't Cure What You Don't Understand

(x + y = -c) (x + y = -c) (x + y = -c) (x + y = -c)
Precision Oncology: Understanding the Disruption of Molecular Information Networks in Cancer

- encoded information and expression as cell-specific signaling networks
- patterns of information flow within signaling networks (network topology)
- stable networks and information fidelity (health)
- dysregulated networks and altered information patterns (disease)
Integrative Gene Expression Network Models and Classification of Functional Modules (Communities) That Span Multiple Chromosomes

Courtesy of Dr. J. Quackenbush, Dana Farber Cancer Center
Defining Short- and Long-Range Cis- and Trans- Regulation of Gene Networks

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

ChromEMT Mapping of Chromatin Ultrastructure and DNA Packing

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

From: International School of Advanced Studies (SISSA) [October 26, 2016]
From: H. D. Ou et al. (2017) Science eaaag.0025
Understanding System State Shifts (Phenomes) and Emergent Perturbations in Molecular Signaling Networks in the Health to Disease Continuum

$T_1(n)$
health

$T_2(n)$
subclinical disease

$T_3(n)$
overt disease
Multi–Attractor Landscapes and System State Space Occupancies in Biological CAS (After Haldane 1957)
Multi-Attractor Landscapes and State Space Occupancies in CAS

- state space
- environmental inputs (exposome)
- gene-regulatory networks
- functional pathways, modules and network subarchitectures
Multi-Attractor Landscapes, State Space Occupancies, and Adaptive, Evolutionary Pathways in CAS

- gene-regulatory networks
- functional pathways, modules and network subarchitectures
Multi-Attractor CAS Landscapes and State-Space Occupancies in the Health to Disease Continuum

- physiology (homeostasis)
- graded perturbations
- disease predisposition and/or subclinical disease
- clinical disease (pathology)
- disease subtypes and phenotypes
Dynamic Modeling of Signaling Pathways and Networks in Complex Systems

- what parts of the system and the subsystem networks are the most/least sensitive to perturbation?
- what part(s) of the network(s) are most/least influential on the rest of the network when perturbed?
- exploitation to identify new $R_x$ targets and prediction of most likely trajectories of $R_x$ resistance
A Disturbing Question:
Is Unifocal $R_x$ Modulation of Complex Network Dysregulation in Advanced Chronic Diseases Feasible or a Delusion?

• “too disrupted to restore”? (homeostatic reset) ?
• multi-node/multi-module/multi-subnetwork dysregulation
• low feasibility of multi-$R_x$ intervention against multiple dysregulated targets?
• even lower feasibility of design of promiscuous multi-target single $R_x$ ?
The Promise of Cancer Immunotherapy
Cancer Immuno-Oncology (I/O) Therapies in Clinical Trials (4/18)*

- over 300 investigational therapies and 1700 clinical trials
- late stage Phase II/III pipeline dominated by agents with 4 MOAs
  - anti-CTLA4, anti-PDI, anti-PD-L1, CD19 modulation (CAR-T cells)
- enthusiasm for indoleamine-pyrole-2, 3 dioxygenase (INDO/IDO) inhibitors dashed and recent corporate withdrawals (4/18)
- additional 52 immune-targets under investigation

*Source: Clarivate Analytics Coretllis; IQVIA Institute
Host Immune-Tumor Interactions and the Tumor-Immune Microenvironment (TIME)

Clone Wars

Relentless Emergence of New Tumor Cell Clones During Tumor Progression and Immune Evasion versus Activation of Host T Lymphocyte Clones to Kill (Neo)Antigen-Specific Tumor Clones
Therapeutic Strategies for Circumvention of Clonal Diversity in Malignant Tumors: Single Target Drugs (Rx) versus Immunotherapeutics (IrX)

targeted drugs

- Rx1
- Rx2
- Rx3
- Rx4
- Rx5

Cytotoxic T cells

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

- **tumor clones**
  - $Rx_1$
  - $Rx_2$
  - $Rx_3$
  - $Rx_4$
  - $Rx_5$

- **Rx-resistant clones/**
  - Rx refractory disease

- **tumor neoantigens**
  - $NA_1$
  - $NA_2$
  - $NA_3$
  - $NA_4$
  - $NA_5$

- **cytotoxic T cells**
  - $NA_{n1}$
  - $NA_{n2}$

- **adaptive evolution of immune response and expanded cytotoxic T cell responses**
Realizing The Promise of Cancer Immunotherapy

- wide variation in $R_x$ response rates
  - only 20 - 40% positive responses even in the most responsive tumors
- lack of diagnostic tests to reliably predict responder vs. non-responder patients
- improving response rates across all malignancies and all stages
- will I/O combinations increase response rates?
Tumor Mutational Burden and Objective Response Rate with Anti-PD-1 or Anti-PD-L1 in 27 Tumor Types

The Complexity of Cancer-Immune Phenotypes

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

Development of Multi-parameter ‘Immunoscore’ Assays to Predict Responsiveness to Immunotherapy

TIME in Four Consensus Molecular Subtypes (CMS) in Colorectal Cancer

The Promise of Immunotherapy: Is Widespread Adoption Economically Feasible?

- unit Rx cost ($100 - 400K)
- indirect care cost
- escalating cost of combination Rx regimens
- extravagant cost of cell-based therapies ($500K - $1.5 million)
- complex clinical management challenges and compatibility with community oncology services?
Understandable Enthusiasms But With Risk of Considerable Waste in Patient Resources and Cost

• proliferation of I/O combination trials absent biological rationale for dose selection, sequence, timing, number of cycles and duration
  - I/O : I/O
  - I/O : chemo
  - I/O : targeted Rx
  - I/O : oncolytic viruses

• patient expectations
  - informed consent vs informed risk

• market saturation and performance-based pricing?
Performance-Based Contracts and Pricing: The Inevitable Future Landscape for Cancer Therapy?

- Robust identification of responders and non-responders
- Companion diagnostics and labeling requirements
- Performance-based outcomes and premium pricing

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

Risk sharing
Hype Versus Hope- A Delicate Ethical Balance: Come and Be Cured by Us: (Go Elsewhere at Your Peril)!
H.R. 5427: “Right to Try” Legislation
Signed by President D. Trump 30 May 2018
Now Comes the Really Hard Part!

Building a Learning Healthcare System

Robust Data as the Core Element in Improved Cancer Control and Outcomes
Building a Learning Health Care System and a National Cancer Data Ecosystem
Making Precision Oncology a Reality

- deep phenotyping
- integration of molecular, clinical, social and environmental data
- longitudinal, dynamic data capture versus isolated static snapshots
- managing the data deluge
Precision Medicine and Computational Medicine: Evolving Inter-dependencies

molecular classification of disease and elucidation of disease mechanisms

large scale data aggregation, curation and analysis

RWE and learning healthcare systems

The Big Data Challenge

V6: volume, variety, velocity, veracity, virtualization, value
D3: distributed, dynamic, decision support
I3: infrastructure, investment, intelligent systems
Population Health Research and Precision Oncology: Blurring the Boundaries Between Daily Life and Interactions with the Healthcare System

- every encounter (clinical and non-clinical) is a data point
- every individual is a data node
- every individual is a research asset
- every individual is their own control
Welcome to
The World of
Biomedical Research
and
Healthcare Information Systems
The Democratization of Healthcare Information and Data

- m (mobile) health apps
- wearables/sensors/implanted devices and wireless technologies
- social media analytics
- geospatial sensors
- IoT
Integration of Molecular Profiling, Clinical and Social Datasets for Computable Disease Phenotypes

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

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

- NIH Big Data to Knowledge
- NIH ClinGen and ClinVar
Issues in Open Data Initiatives and Data Sharing

- HIPPA and protected health information (PHI)
- tracking data provenance in aggregated data/meta-analysis
- voluntary or imposed data deposition
- credits: researchers versus trialists versus informatician versus patient interests
- IP and regulatory policies for analytical algorithms for machine learning/artificial intelligence
- ownership, privacy, EU-GDPR
Early Entrants Into The Use of Blockchain for Secure Healthcare Data
Precision Medicine and Digital Health: Building a Learning Healthcare System

- qualitative, descriptive information of uncertain quality and provenance
- complex ecosystem of largely unconnected data sources

→

- quantitative data of known provenance and validated quality
- evolving, inter-connected networks of data sources for robust decisions and improved care
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
“I don’t think any physician today should be practicing without artificial intelligence assisting in their practice.

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

Bernard J. Tyson  
CEO, Kaiser Permanente  
Cited in Forbes: The Future of Work  
1 March 2017
Machine Learning and Big Data

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

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Prototypic algorithm: Generative adversarial networks
Convolutional neural networks
Random forests
Regression analysis
Human decision making
Just What the Data Ordered

Black Box Medicine:

Machine Intelligence and Algorithms for Clinical Diagnosis and Treatment Decisions
Machine Learning and Image Analysis in Clinical Medicine

- large scale training sets and classification parameters
- standardized, reproducible and scalable
- 260 million images/day for $1000 GPU
Critical Questions in the Application of ML/AI Platforms in Profiling Large Scale Biomedical Data

- overfitting and bias in datasets used in training
  - error propagation versus automated recognition and exclusion of questionable data

- scale and layered datasets
  - impact of accretion by incorporation of legacy systems of uncertain quality/provenance?

- “black box” effects versus “explainable AI”
  - algorithm evolution neither predicted nor understood by original coders?
  - generative adversarial networks (GANs)
Artificial Intelligence (AI) and Healthcare

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

- quantitative data
- large scale data mining
- clinical decision support systems

data mining

- descriptive qualitative data
- hypothesis-driven inquiry

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

1910-present
(science-centric)

2000 - present
healthcare as a learning system (data-centric)

2015 - ?
network topologies and dynamics in complex adaptive systems (network-centric):
major disruptions in education, R&D and care delivery
between investment in cancer prevention versus treatment

between aggressive non-I/O treatment regimens with curative intent but limited efficiency versus supportive care and palliation

between cost of therapeutics versus meaningful clinical outcomes and QOL (value)

between cancer control in HIC and MIC/LIC
between the intellectual rationale of precision oncology and translation into routine clinical practice

between limited availability, analysis and use of population-based of RWE versus comprehensive, data-driven analysis, and robust decision-support systems
The Evolution of Cancer Care: Precision Oncology and Digital Medicine

- new technology platforms
- the expanded care space
- Big Data
- automation and computing
- PHR/EHR
- Population Health
- Precision Medicine
- Digital Medicine
- AI
- sensors, robotics
- molecular classification of disease
- remote monitoring of health status
- patient engagement
- social media and life style metrics
- remote monitoring of health status
- analytics for improved decisions and clinical outcomes at lower cost (value)
- wearable sensors
- telemedicine
- multiplex profiling of network topologies
- social media and life style metrics
- analytics for improved decisions and clinical outcomes at lower cost (value)
Cancer As a Complex Adaptive System: Legacy of 32 Years of Prescient Perspectives Still Alarmingly Ignored

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

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

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

Ann Barker (2008)
NCI PSOP Meeting Summary

“Learning to manage cancer is learning to manage the evolutionary process.”

Dr. Richard L. Schilsky
CMO, ASCO
Oncology Times 25 June 2014
Slides Available @ http://casi.asu.edu/presentations