How to Transform Cancer Control

What Should We Be Doing Differently?

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Today’s Discussion – Thinking Differently About Cancer

What is “Cancer Control” ---- Yesterday and Tomorrow? Why do we need new thinking/ideas?

Status of Cancer Research – Cancer is a Complex Adaptive System

Data – Data – Data – Patients Become the Model System – Seismic Shift

The Future: Prospective Planning/Modeling for Cancer as Data Science (Perhaps Cancer Management)
Cancer Control is a Global Problem

Projected by 2030: 13 Million Deaths and 21.7 Million New Cases (2012 IACR Projection)

Worldwide cancer cases expected to soar by 70% over next 20 years (2018 WHO Projection)

Source: IACR, WHO
Cancer Control: Preparing for the Coming “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)

% Survival (Post Diagnosis) – Current U.S. Population of Cancer Survivors

- 67% will live at least 5 years
- 44% will live at least 10 years
- 17% will live at least 20 years

(Additional healthcare costs):
- Other types of cancer in many patients
- Delayed toxicities (e.g. immunotherapies)
- Co-morbidities (heart disease, pain, lack of mobility, etc.)
- Cognition issues
- Pain and neuropathy
- A long list of other issues including psychiatric problems

THE CANCER CONTROL CONTINUUM

Focus Areas

Etiology
- Environmental factors
- Genetic factors
- Gene-environment interactions
- Medication (or pharmaceutical exposure)
- Infectious agents
- Health behaviors

Prevention
- Tobacco control
- Diet
- Physical activity
- Sun protection
- HPV vaccine
- Limited alcohol use
- Chemoprevention

Detection
- Pap/HPV testing
- Mammography
- Fecal occult blood test
- Colonoscopy
- Lung cancer screening

Diagnosis
- Shared and informed decision making

Treatment
- Curative treatment
- Non-curative treatment
- Adherence
- Symptom management

Survivorship
- Coping
- Health promotion for survivors

CROSSCUTTING AREAS

Communications
Surveillance
Health Disparities
Decision Making
Dissemination of Evidence-based Interventions
Health Care Delivery
Epidemiology
Measurement

Adapted from David B. Abrams, Brown University School of Medicine

NCI, DCDPS
Cancer Control May Look More like a Gordian Knot
MAJOR FORCES IN CANCER, BIOMEDICAL AND INFORMATION RESEARCH THAT WILL RE-SHAPE CANCER CONTROL

REQUIRES NEW THINKING AND NEW MODELS
“OMICS”: The Focus of Cancer Research Today – Vision of Precision Medicine

Vision: understanding genomic (omics) changes will enable targeted intervention

- Since 2003: Sequencing costs fell from ~$1.0 million in 2001 to less than $500 - $1000 (an going down)
- Estimated that more than 500,000 genomes have been sequenced to date
- Patient sequencing could approach 1000 PB per year at maturity
Understanding Underlying Principles of Complexity (Cancer is Extremely Heterogeneous)
Example of Complexity: Genetic Heterogeneity in Triple Negative Breast Cancers

Triple Negative Cancers (about 16% of all breast cancers) express significant inter- and intra-tumor heterogeneity.
More Complexity: Developing the Molecular Profiles of Cancer Patients (OMES) was Step 1 – It’s About the Phenotype (Patient)

Individualized, Targeted Cancer Care

Single Patient Data × Populations = New Data Centric Complex Systems Models for Prevention, Diagnosis, Treatment and Survivorship
Ninety Percent of the Data in Biomedicine Created in the Past 2 Years Across All Fields – 1% Analyzed!!

“(Kryder’s law) Exponential growth of neuroimaging and genomics data, relative to increase of number of transistors per chip (Moore’s law)” (Image and Caption from Toga & Dinov, 2015).
The Data “Tsunami” in Cancer Clearly Requires New Models

Models that Capture the Complexity of the Cancer Patient
"A system in which large networks of components with no central control and simple rules of operation give rise to collective behavior, sophisticated information processing and adaptation via learning or evolution”

"A system that exhibits nontrivial emergent and self-organizing behaviors”

Melanie Mitchell
Complexity: A Guided Tour
Oxford Univ. Press 2009, p.13
Complex Adaptive Systems

- Composed of many elements (and connected subsystems)
  Elements/subsystems are interdependent
- Whole is more/different than the elements that comprise the system
- Self-organizing
- Co-evolve with the environment
- Robust (redundant)
- Demonstrates emergent properties (not predictable)
- System responds to feedback (negative and positive)
- Operate far from equilibrium (open systems)
- Operate with a number of "choices"
- System "learns" -over time – across scales – create new solutions
Biological Systems are Complex Adaptive Systems

Many Interacting Elements

Adaptable

Robust

Evolvable

Evolution: stochastic, unpredictable – incredibly diverse

Emergent Properties

- Redundancy
- Dynamic Evolution
- Heterogeneity
- Metastatic phenotype
- Innate resistance

CANCER IS INFORMATION: DATA FROM DIGITAL, WEARABLE TECHNOLOGIES, ETC.
Cancer is a Complex Evolving System (Composed of Multiple Subsystems)

Co-Evolution of Information-Driven Communication Between Cancer Cells/networks and their Environment (In Context) Across Scales
Genomic alterations drive the development of information that underlies the emergence of disease - emergent properties of the interactions of elements/subsystems across scales.
Cancer as a Complex System: Gene Regulatory Networks

Each network state is a point in N-dimensional state space.

State space (projected to a 2D plane) with epigenetic landscape:

- Cancer attractor (pre-existing or generated by mutation, normally unused)
- Epigenetic barrier (can be lowered by mutation)

"Potential" = elevation reflecting stability of a state

Each point is a network state:
- Un-stable = transient state
- Stable = mature cell type
- Stable = another mature cell type

Huang et al., Semin Cell Dev Biol, 2009
CANCER IS INFORMATION

And

Cancer Control will Be Driven by Information and Advanced Analytics in CAS Models to Build Learning Systems

ASU Complex Adaptive Systems Initiative
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Data are Not Information – and Information is Not Evidence

The Future: Using Artificial Intelligence Approaches to De-Convolute Complexity
Elon Musk Is Worried – Some Profound Questions

“WITH ARTIFICIAL INTELLIGENCE WE ARE SUMMONING THE DEMON.”
-ELON MUSK

- We will not know what questions that AI driven computers will be asking - what questions they are asking
- Human intuition will generally disappear from biomedical research – is that bad?
- Is AI the only hope to find real answers to our questions in the irreproducible complexity of biology?
- Will humans understand what AI may find – will it be the “black box” often predicted? Faith in the predictions – because it’s just too complex?
- Should we worry that E. Musk is Right? Man has never feared the future – is this different?
"I think you should be more explicit here in step two."
Embrace Cancer as a Complex System

- Cancer is a disease state attractor that develops and progresses as a result of interactions between the components of the system—individual cells (including cancer cells, normal cells, immune cells, etc.) and other factors in the microenvironment.
- These interactions have impacts across scales.
- Cancer cells are adaptive agents – this allows the system to evolve in response to changes in the microenvironment.
  - This results in non-linear outcomes and underlies the robust nature of difficult to treat tumors.
- Emergent properties.
  - Hallmarks of cancer are examples of specific emergent properties common to most cancers.
Evolution Drives Heterogeneity – and Resistance to Treatment – Future Must Engage Evolutionary Models

- Focus on understanding malignant tumors through characterization of targeted clones and fitness landscapes
- Identify what the selection pressures are – and where they have impact.
- If it makes sense – de-convolute the role of the numbers of types of mutations in different clones – and how they interact.
- Tumors are organ specific – and malignant clones find their way to specific organs – determine if the fitness programmed in the organ, the cancer cell, or both.
- Design cancer therapies to take into account selection pressures?
- Test combinations of agents that are designed to address evolution and associated changes in ecosystems.
- Develop biomarkers as predictive/prognostic/surrogate biomarkers to aid in addressing these issues.
We Must Learn How the Digital Information of the Genome Interacts with Its Ecology to EVOLVE

- Need to describe (measure) the information driving complexity—and inform rich mathematical models
- Cancer evolves in the context of its microenvironment, “niche”—information flows are not defined—need to engage scientists who measure “bits”, information flow and cellular decision making
- Critical need to define dynamics and information content of cellular communication (e.g., chemical gradients)–identify “fragile” communication nodes
- Need to define measurements that describe robustness”—redundancy
- Need to understand the myriad information that describes metastasis (Is it inherent, cellular decision and/or co-evolution?)
- Cancer is tissue/organ specific—need to better define/understand structure/spatial information and its value for diagnosis/treatment
Build New Learning Systems: Multi-Dimensional Information Across the Cancer Research-Delivery Continuum (Some Questions)

• Does the quality of the data matter – or will AI enable using “scruffy” health big data to learn what questions to ask? In other words when you are training algorithms if we let the data find patterns – if the data are biased will it affect the needed training?

• Do we need standards, must we achieve interoperability – or just take powerful algorithms and feed them data – and more data….

• AI/deep learning are layered networks – does this impact how we structure and interrogate data?

• Is there a form of AI that is more amenable to building a learning system than others?
Embrace Models: There will be too Much Data to Do Otherwise

Models offer hope to:

- Capture the important parameters of a system – or subsystem – build consensus
- Represent concepts and capture relationships - the architecture (structure and function) of a problem
- Bring focus to the “bottom line” vs. details
- Balance data (lower level of abstraction models) and information (higher level of abstraction – solution vs. problem)

However, the value of models is in the eye of the beholder – (for some structure – others function)
Success in Precision Medicine will Belong to Organizations that can De-convolute the Complexity of Diseases

Disease is more than the Digital Information we get from sequencing the Genome. Disease (e.g., Cancer) occurs in context – and we know little about how information flows and is interpreted in these complex systems (cells, organs and the patients). Collecting and analyzing big data to discover meaningful signals (biomarkers) will require new thinking and innovative approaches that integrate all of this information.
Building Predictive Disease Models

Citizens
- Self-reported Study Data
- Personal Observations
- Personalized Medicine
- Community Contributions

Open Access Health Data Exchange

Individual treatment records
- Complete health records
- Expert model guidance

Doctors

Natural History of Disease
- Aggregated Study Data

Study Designs
- Predictive Models of Disease

Researchers
Translate CAS Approaches to Patients Managing Cancer as a Complex Adaptive System

- Focus on the **emergent properties** of the “whole’

- **Optimize quality of patient information** – quantify at all scales (increase knowledge of genotype- phenotype measures)

- Insofar as possible **eliminate “noise”** focus on most meaningful data

- Create **algorithms that integrate multi-dimensional genotypic and phenotypic data**

- **Treat at multiple nodes and scales** (massively-parallelled combinations)

- **Best level of control** may not depend on detailed individual data – need meaningful patterns
Managing Cancer as an Emergent Complex Adaptive System

Environment, Diet

(High Information Content Interventions)

Inputs

Cancer Patient System

Internal States
(mostly hidden)

State evolution function (mostly unknown)

Outputs

Health Indicators (clinical measures)

(Molecular Data)

Patterns (Orthogonal Databases)

Adapted from Danny Hillis
Should Strategically Address:

- The significant increases in cancer associated with the aging of the U.S. population.
- The increasing number of cancer survivors who will develop additional cancers and co-morbidities.
- The economic impact of cancer.
- How the U.S. interfaces with the global cancer epidemic (and its geopolitical implications).
- Urgent need to integrate cancer research (discovery to delivery) with cancer control goals and approaches.

Should be built on:

- Advances in basic and clinical research that offers a unique opportunity to develop and support an inclusive cancer control learning system.
- Data - Information - and Knowledge Based Systems Focused Analytics.
- Patient centric models.
- New Innovative Clinical Trials.
- Innovation through New CAS Models.
- Public private partnerships.
Alexander the Great Cut the Gordian Knot – our Task is not that Simple
Actually Cancer Control May Looks a Lot More Like This