The Evolution of Precision Oncology:

George Poste, D.V.M., Ph.D, F.R.C.Path, F.R.S.
Chief Scientist, Complex Adaptive Systems Initiative
and Del E. Webb Chair in Health Innovation
Arizona State University
(george.poste@asu.edu; Tel. 480-727-8662)
www.casi.asu.edu

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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 Molecular Network Perturbations and Disease

Patient-Specific Signals and Signatures of Disease or Predisposition to Disease
Precision Oncology: Not If, But…

- when?
- what?
- how?
- value?
The Extravagant Landscape of Molecular Signaling Network Alterations in NSCLC

- “malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations and variable expression of Rx targets
- disturbing implications for therapeutic ‘cure’ and development of new Rx

Precision Oncology

- multi-platform (“panOmics”) molecular profiling and a new taxonomy of disease classification (subtypes)
- mapping the perturbations in molecular signaling networks in disease subtypes and individual patient variation
- intellectual foundation for improved diagnostic accuracy and rational therapy selection to improve clinical outcomes and cost-of-care
## Most Common Gene Mutations and CNV Alterations in Molecular Subtypes of Primary Breast Cancer

<table>
<thead>
<tr>
<th>Gene mutations</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2-positive</th>
<th>Triple negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA, GATA3, MAP3K1, TP53, CDH1, MLL3, MAP2K4, AKT1, FOXA1, CDH1, and RUNX1</td>
<td>PIK3CA, GATA3, and TP53</td>
<td>PIK3CA, and TP53</td>
<td>TP53 and PIK3CA</td>
<td></td>
</tr>
<tr>
<td>Gene gains, losses and amplifications</td>
<td>—</td>
<td>loss of ATM; amplification of CCND1, CDK4, CDK6, and MDM2</td>
<td>Amplification of multiple genes based on the HER2 amplicon size</td>
<td>loss of INPP4B, PTEN, and RB1; amplification of BRAF, CCNE1, EGFR, and KRAS</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Copy number alterations</th>
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<tbody>
<tr>
<td>Gains</td>
</tr>
<tr>
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<tr>
<td>Amplifications</td>
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Precision Oncology:
The Need for Multi-Dimensional, Systems-Based Integration
Across the Research to Clinical Care Continuum

- panOomics molecular profiling
- evidentiary standards and large scale data
- clinical utility
- regulation reimbursement
- care guidelines
The Overly-Simplistic, Reductionist Focus on Genome Sequencing
The Challenge of Genotype-Phenotype Predictions

Junk No More: Pervasive Transcription

- alternate transcription/translation/(co)splcicing
- SNPs, CNVs
- pseudogenes
- indels, SVs
- ncRNAs
- phasing
- epistasis
- imprinting
- silencing
- miRNAs/ceRNAs/circRNAs

recognition of genome organizational and regulatory complexity

Molecular Signaling Networks

Perturbed Signaling Networks and Disease
Molecular Profiling for Comprehensive Identification of Current Target: Drug Associations in NCCN Guidelines Requires a Technology Agnostic Approach

- **Sequencing** (Next-Gen, Sanger and Pyro; NGS = 46 hotspot and 592 gene w/ mutations, CNVs and fusions)
  - crizotinib
  - everolimus
  - lapatinib
  - T-DM1
  - trastuzumab

- **FISH** (3 makers)
  - trastuzumab
  - lapatinib
  - pertuzumab
  - T-DM1
  - everolimus

- **CISH** (5 makers)
  - trastuzumab
  - lapatinib
  - pertuzumab
  - T-DM1
  - everolimus

- **IHC** (25 markers)
  - everolimus
  - hormone therapy
  - lapatinib
  - pertuzumab
  - T-DM1
  - trastuzumab
  - pembrolizumab
  - crizotinib

**MAXIMIZING CLINICAL UTILITY WITH 60+ FDA-APPROVED THERAPY ASSOCIATIONS**
Molecular Profiling for Comprehensive Identification of Current Target: Drug Associations Requires a Technology Agnostic Approach

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- crizotinib

MAXIMIZING CLINICAL UTILITY WITH 60+ FDA-APPROVED THERAPY ASSOCIATIONS

Most Current Immunophenotyping Biomarkers are Non-Genomic
Demonstration of the Clinical Utility of Molecular Profiling in Precision Oncology

- assessment of treatment selection on clinical outcomes
- comparison of “matched” versus “unmatched” Rx regimens
  - Rx selection based on molecular profile (“matched”)
  - Rx selection by physician with inclusion of one or more Rx not recommended by the molecular profile (unmatched)
Molecular Profiling and Concordant (Matched) Rx Selection Improves Overall Survival for Ovarian Cancer Patients


**KEY FINDINGS:**
- Patients in the Matched cohort (n=121) had a **significantly higher median OS by 9 months** compared to those in the Unmatched cohort (n=103) (median OS 36 vs. 27 months, HR=0.62, p < 0.03).
- Matched cohort received **1.2 fewer lines of therapy** than the Unmatched cohort highlighting the benefit of avoiding potentially harmful therapies (median of 3.88 lines of therapy for Matched vs. 5.02 lines of therapy for Unmatched).

Precision Medicine Clinical Trials to Evaluate ‘Match’ of Rx Selection With Molecular Profiling on Clinical Outcomes

- NCI-MATCH and Pediatric-MATCH (Molecular Analysis for Therapy Choice)
- ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial)
- Lung-Map (Lung Cancer Master Protocol)
- NCI-IMPACT (Molecular Profiling-Based Assessment of Cancer Therapy)
- ASCO-TAPUR (Targeted Agent and Profiling Utilization Registry)
- NCI-Exceptional Responders Study
- Leukemia and Lymphoma Society: Beat AML Master Trial
- GBM AGILE (Adaptive Global Innovative Learning Environment)
Cancer as a Complex Adaptive System: The Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones During Progression and Treatment
Precision Oncology

- understanding the evolutionary dynamics of clonal diversification (heterogeneity)
- mapping the molecular pathways underlying the emergence of treatment-resistant (sub)clones
- design of new therapeutic strategies to circumvent (sub)clonal heterogeneity and treatment-resistant phenotypes
Wagner Parsimony Profiling of Intratumoral Clonal Heterogeneity in 11 Lung Adenocarcinomas and Different Trunk (Blue), Branch (Green) and Private (Red) Branches

Longitudinal Tumor Profiling and Adjustment of Treatment Selection to Reflect Dynamic Changes in (Sub)Clonal Composition

- initial diagnosis (‘static snapshot’)

- longitudinal profiling during treatment for earlier detection of emergence of drug-resistant clones

- more agile shifts in Rx regimen to reflect changing clonal dynamics driven by Rx selection pressure(s)
Detection of Tumor-Associated Biomarkers in Blood: ‘The Liquid Biopsy’

- cell-free tumor nucleic acids
  - DNA, miRNAs
- circulating tumor cells (CTC)
- exosomes
Liquid Biopsy (LB) Profiling in Monitoring of Disease Progression and Predictive Treatment Selection

- minimal invasiveness
  - cost, clinical-patient convenience
- analytical standardization
- sensitivity and detection thresholds
- reproducibility in larger N cohorts
- concordance between LB and tissue biopsy profiles?
  - intra- and inter-lesional heterogeneity
- relationship of LB positivity to tumor burden
- variation in systemic release of CTC/ctDNA from metastases in different organs?
The Urgent Need to Improve the Effectiveness of Current Therapy and the Design of New Treatment Strategies

The Clinical and Economic Imperative to Reliably Identify Rx Responder (R) and Non-Responder (NR) Patients
Targeted Therapeutics and the Omnipresent Problem of Rx Failure Due to Emergence of Drug Resistance Clone

Molecular Subtyping and RX Targets

Initial Rx-Response to Targeted Rx

Rx-Resistance via Redundant Molecular Pathways

B = 15 weeks Rx (vemurafenib)
C = 23 weeks Rx and emergence of MEK1$^{C121S}$ mutant

Understanding Emergent State Shifts in Molecular Signaling Networks and Identification of Triggers of Rx-Resistance (R)

- **Dynamic Molecular Signaling**
- **Network Topologies**

- **New Network Topologies**
  - To bypass Rx-vulnerable pathways

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**Emergence (E)**

- **Intrinsic Resistance** (pre-exist prior to Rx)
- **Acquired Resistance** (Rx as selection pressure)

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**R^1, R^2, ….. R^n**
An Ugly But Unavoidable Question

• Is the level of network dysregulation in metastatic disease so extravagant that ‘homeostatic reset’ for curative therapy by current categories of chemotherapy and/or targeted agents is unlikely?
  – clinical/QOL/cost challenges of ever larger Rx combinations
  – high likelihood of molecular signaling network redundancy and selection of Rx-resistant clones
  – clinical decision points for continued multi-line intervention(s) versus palliative care
The Promise of Immunotherapy
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

Host Immune-Tumor Interactions
Recognition of Tumor Neoantigens (NA) by Cytotoxic (Killer) T Cells

- NA-1
- NA-2
- NA-3
- NA-4
- \( N_A^n \)
Immunotherapeutic Strategies to Enhance Immune Responses to Patient-Specific Tumor Neoantigens

- **Immune Checkpoint Modulation**
  - Induce tumor cell destruction
  - Provide checkpoint blockade

- **Cancer Neoantigen Vaccines**
  - Identify potential neoantigens
  - Create synthetic vaccine (RNA, DNA, peptide)
  - Provide in combination with adjuvant and checkpoint blockade

- **Adoptive Cell Therapy TILs, TCRs, CARs**
  - Identify potential neoantigens
  - Induce or expand neoantigen specific T cells
  - Provide in combination checkpoint blockade

Cancer Immunotherapy

### FDA Approved Indications for PD-1, PD-L1 Immune Modulators (Nov. 2016)

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Atezolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSCLC</strong></td>
<td>✅</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>melanoma</td>
<td>✅</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>RCC</td>
<td>✅</td>
<td></td>
<td></td>
</tr>
<tr>
<td>head and neck</td>
<td>✅</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>✅</td>
<td></td>
<td></td>
</tr>
<tr>
<td>urothelial carcinoma</td>
<td></td>
<td></td>
<td>✅ metastatic</td>
</tr>
</tbody>
</table>
Ongoing Clinical Trials with PD-1, PD-L1 and PD-L2 Modulators (Nov. 2016)

- 803 registered trials
- 20 investigational agents
  - single agents
  - combinations with other immunotherapies, biologics, chemotherapy and vaccines
- need to recruit 166,736 patients
“I have never seen this before, where you have so much development activity in the same class of drugs.

Should these resources, I’m not only talking about financial resources but also patient resources, be better off spent into looking at more novel drugs.”

Dr. R. Pazdur,
Acting Director, FDA Oncology Center of Excellence
Cited in Cancer Letter 7 October 2016, p.4
The Evolution of Cancer Immunotherapeutics (I/O)

- likely to become SOC in increasing number of indications
- need for more informed rationale for combination regimens
- new tumor cell markers for acquired immune resistance
- will new panels of immune response biomarkers be needed for each new category of I/O agents?
Why Are Some Cancer Types More Responsive to Immunotherapy?

More Responsive

- melanoma
- NSCLC
- bladder
- renal
- head and neck

Less Responsive

- pancreatic
- colorectal
- ovarian
The Tumor Mutational Landscape and Responses to Immunotherapy Agents

• hypothesis that high(er) non-synonymous mutation burden generates neoantigens recognized by the immune system
• patients with higher neoantigen burden exhibit higher durable clinical benefit
• ‘mutanome’ profiling
  – ID mutant nonamer peptides with <500nM binding affinity for patient-specific class I HLA alleles
• combination with targeted anti-cancer agents
  – increase neoantigen release?
## Characterization of Tumor Classes Responsive to Immune Checkpoint Blockade

<table>
<thead>
<tr>
<th>Mutational Burden</th>
<th>Tumors</th>
<th>Mechanism?</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1000 mutations/genome</td>
<td><strong>MSI-H tumors</strong>&lt;br&gt;<strong>CRC, endometrial</strong></td>
<td><strong>germline DNA</strong>&lt;br&gt;<strong>MMR defects</strong></td>
</tr>
<tr>
<td>10-1000 mutations/genome</td>
<td><strong>NSCLC</strong>&lt;br&gt;<strong>melanoma</strong></td>
<td><strong>DNA damage</strong>&lt;br&gt;- smoking&lt;br&gt;- UV</td>
</tr>
<tr>
<td>&lt;100 mutations/genome</td>
<td><strong>renal cell carcinoma</strong>&lt;br&gt;<strong>lymphomas</strong>&lt;br&gt;<strong>head and neck cancers</strong></td>
<td><strong>viral neoantigens?</strong>&lt;br&gt;<strong>recurrent highly immunogenic and addicted neoantigens</strong></td>
</tr>
</tbody>
</table>

Recurrent Mutations in SERPINB3 and -B4 in Melanoma Patients Responsive to anti-CTLA4 Immunotherapy

- SERPINB3 significantly mutated in melanoma (TCGA)
- mutations in SERPINB3/4 cause protein misfolding and autophagy
  - potential role of aggregates/plaques in stimulating autoimmunity (SLE, psoriasis)?
  - potential role of autophagy in enhancing autoantigen expression?

Tumor Immunophenotypes Associated With Responsiveness to Immune Checkpoint Modulators

- high tumor mutation burden
- high tumor-infiltrating CD3+ CD8+ cytotoxic lymphocytes (TIL)
- CD45RO+ memory T cells
- high activated Th1 helper cells density
- high expression of Th1 stimulating cytokines
  - CCL5, CXC29, CXC10
- higher expression of TIL checkpoint receptors
  - PD-1, PD-L1, CTA-4, LAG3
Tumor Phenotypes Associated With Low Responsiveness to Immune Checkpoint Modulators

- low mutation frequency
- high regulatory T (Treg) lymphocyte population
- high myeloid-derived suppressor cell (MDSC) population
- lower expression of TIL checkpoint receptor
  - PD-1, PD-L1, CTLA-4, LAG3
- mutations in class I/II MHC and impaired neoantigen processing
- IFN-γ receptor and intracellular signaling pathway modulation and CTL-resistance
Landscape of IFN-Gamma Pathway Copy Number Alterations in Ipilimumab Responder and Non–Responder Patients (N=16)

Cancer Immunophenotyping: Creation of an “Immunoscore or Immunogram”

- High CD8+ Cytotoxic T Cell Infiltration
- Low Tumor Content of Inhibitory Treg and MDSC
- Low Soluble Inhibitory Mediators - IL-6, CRP
- Absence of Checkpoint Modulators - PD-1, PD-L1, PD-L2
- Absence of Inhibitory Tumor Metabolism - LDH, glucose utilization
- Tumor Sensitivity to Immune Effectors - MHC expression, IFN-gamma sensitivity
- Mutational Load

Immunophenotyping: Critical Questions

- how will reagents, assays and cut-off thresholds be standardized and validated?
- if pre-I/O-Rx (baseline) tissue biopsy is not a robust prediction for R or NR status when and how should post-I/O-Rx profiling be done?
- can immunophenotyping in blood accurately mirror intratumoral events in disseminated metastases with heterogeneous neoantigen expression burdens?
- is there an ‘over-arching’ immunophenotype characteristic for ‘R’ patients that will be valid for new I/O-Rx classes with different MOAs?
Activated Cell Therapy (ACT)

“Living Drugs”
Engineering Killer T Cells for Cancer Therapy

- cytotoxic anti-tumor T cells harvested from cancer patients
- harvested cells genetically engineered and expanded ex vivo to express T cell receptor(s) (TCRs) or chimeric antigen receptors (CARs) that recognize tumor antigen(s)
High remission rates and durable responses in acute lymphoblastic leukemia

Encouraging responses in NHL and chronic lymphocytic leukemia

Evolution of next-generation CAR designs to incorporate costimulatory molecules to drive/sustain in vivo expansion of CAR-T cells

Challenge of creating TCR/CARs for diverse neoantigens (hematopoietic vs. solid malignancies)

Cost and complexity of ‘individualized’ therapy
Engineering T Cells with Synthetic Notch (SynNotch) Circuits for Customizing Responsiveness to TME Signals and/or Drug Delivery

Precision Oncology: Managing the Big Data Challenge

Infrastructure Planning for Exabyte-Zettabyte Scale
The Quest for Democratization of Large Scale Shared Open Datasets in Precision Oncology
Obvious But Complex Issues in Data Sharing, Curation and Analysis

- scale
  - terabyte per patient and petabyte/exabyte dbases
- standards for data entry and dbase design
- depth and stringency of case documentation
  - clinical phenotyping, pathology-lab data, Rx use and outcomes
  - variation in case reporting formats
- different EMR vendors and interoperability barriers
- privacy, security and de-identification
- consent
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Data Ownership
The Future of Cancer Care

• demographics of an aging society
• new technologies and treatments
• standards and quality of care
• cost of care
• complex clinical, economic, ethical and legal landscape
The Future of Cancer Care

• demographics of an aging society
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• cost of care
• complex clinical, economic, ethical and legal landscape

We Can No Longer Afford (Economically and Ethically) to Avoid Asking Tough Questions About The Adequacy of Current Approaches to Cancer Treatment and Care
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

Is Widespread Adoption of Immunotherapy Economically Feasible?

- direct Rx cost
- 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
The Evolving Trajectory for Payer Policy for Cancer Therapeutics

- performance – based pricing
- indication – based pricing
- reference – based pricing
The Evolving Trajectory for Payer Policy for Cancer Therapeutics

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- indication-based pricing
- reference-based pricing

Robust ID of Responder and Non-Responder Patients
Key Issues in the Evolution of Precision Oncology: New Economic, Ethical and Legal Complexities

- ‘value-based’: ‘pay-for-performance’
  - ID of responder cohorts and restricted Rx use
  - indication-based pricing (industry risk)
  - clinical payment schedule linked to outcomes and Rx decisions (provider risk)
- ‘pricing life’
  - NICE comes to the USA
  - OALYs and other value-assessment metrics
- “when is enough, enough?”
  - decision criteria for balancing probability of intervention benefit versus palliative care/QOL
- ‘keeping current’
  - the data deluge and professional competency
  - new malpractice liabilities
Summary and Key Conclusions
Key Issues in the Evolution of Precision Oncology: Integration of Molecular Guidance Into Routine Care

• technology agnostic panOmics profiling
• integration of panOmics data into EMRs
• evidentiary standards for clinical utility of molecular profiling (matched vs. unmatched Rx)
• new analytical methods for monitoring tumor clonal dynamics in progression (liquid biopsy)
Key Issues in the Evolution of Precision Oncology: Integration of Molecular Guidance Into Routine Care

- anticipated rapid uptake of immunotherapy and new classes of I/O agents
- clinical and economic incentives for new immunophenotyping assays to identify responder and non-responder patients
- elucidation of mechanisms of acquired resistance to I/O agents
Key Issues in the Evolution of Precision Oncology: Integration of Molecular Guidance Into Routine Care

- patient profiling into ever smaller cohorts and new clinical trial designs
- agile regulatory and reimbursement policies and updating SOC guidelines to accommodate rapid changes in molecular phenotyping and therapeutic implications
- new value-based pricing and risk sharing models for pay-for-performance (outcomes)
Precision Oncology: Multi-Dimensional, Systems-based Integration Across the Research to Clinical Care Continuum

- panOmics profiling
- exposome/epigenetics
- ID of Dx, Rx targets

- cost-effectiveness
- responder-non-responder ID

molecular classification of disease

validation of clinical utility

regulation and reimbursement

new clinical trial designs

clinical care

- adaptive trials
- MDx stratified cohorts
- observational meta-data

- fit for purpose
- improved clinical outcomes
- risk reduction

- diagnosis
- Rx guidance
- disease monitoring
- EMR integration
- decision support
- continuing education
Precision Oncology: a Data-Intensive Discipline

- panOmics profiling
- exposome/epigenetics
- ID of Dx, Rx targets

Data Scale – the V5 Challenge:
- volume, variety, velocity, veracity, value
- molecular classification
- validation
- clinical utility
- clinical care
- diagnosis
- Rx guidance
- risk reduction
- continuing education

Data Integration:
- interoperability, infrastructure standards
- data science, machine learning, decision support systems
- MDx stratified cohorts
- observational meta-data
- prescriptive trials

Data Analytics:
- fit for purpose
- improved clinical outcomes
- EMR integration
- decision support
- regulation and reimbursement