Genomics-Driven Clinical Trials in Oncology: Principles and Practice

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Genomics-Driven Cancer Medicine: Guiding Principles

**Principle #1:** Molecular pathways involved in tumor survival and progression are often activated by genetic alterations.
In several major tumor types, ~40-60% harbor at least one genomic alteration affecting an “actionable” proliferation or survival mechanism.
Genomics-Driven Cancer Medicine: Guiding Principles

Principle #1: Molecular pathways involved in tumor survival and progression are often activated by genetic alterations.

Principle #2: Anticancer agents targeting many oncogenic pathways have entered clinical trials.
Spectrum of Targeted Anticancer Agents in Clinical Development
Genomics-Driven Cancer Medicine: Guiding Principles

Principle #1: Molecular pathways involved in tumor survival and progression are often activated by genetic alterations.

Principle #2: Anticancer agents targeting many oncogenic pathways have entered clinical trials.

Principle #3: Genomics technologies enable robust tumor genomic profiling in the clinical arena.
Molecular Profiling Today: Single Genes with Specific Alterations

- **BCR-ABL**
  - Imatinib
  - Dasatinib
  - Nilotinib

- **ERBB2 (Her2)**
  - Trastuzumab
  - Lapatinib
  - Pertuzumab
  - T-DM1

- **EGFR**
  - Erlotinib

- **ALK**
  - Crizotinib

- **KRAS**
  - Cetuximab
  - Panitumumab

- **BRAF**
  - Vemurafenib
Massively Parallel Sequencing in Cancer

**Illumina Hi-Seq:**
- 2 x 101 bp reads
- >300 Gb per 8-day run
- ~40 Gb per day

(the human genome is 3 Gb)
The Engine of Precision Cancer Medicine

- Does genetic/molecular stratification identify patient subgroups that benefit from novel agents?
- Does the drug inhibit the relevant oncogenic pathway?
- What are the mechanisms of resistance to existing or emerging agents?
- What combinations hold promise to achieve more durable control?
Patient → Tissue → Profiling → Interpretation → Communication → Decision-Making → Outcome
- Identification of patient
- **Consent** (genetics/data sharing)
- Genetic counseling
- Biopsies / Tissue Collection
- Quantity / Quality
- Sample tracking / LIMS
- Paired normal tissue / blood

_Institutional Infrastructure_
Tissue Processing
Profiling
Basic Analysis

- Multiplexed genotyping
- Targeted sequencing
- Whole exome sequencing
- RNA-seq
- Whole genome sequencing
- Methylome studies

- Build internal capabilities or outsource?
CanSeq: Prospective Whole Exome Sequencing

Prospective whole-exome sequencing on patients at DFCI/BWH with return of clinically actionable results to clinical care team

CanSeq

- Metastatic Lung Adenocarcinoma
  - Prior to 1\textsuperscript{st} line systemic therapy
  - 200 Patients

- Metastatic Colorectal Adenocarcinoma
  - Prior to 2\textsuperscript{nd} line systemic therapy
  - 200 Patients

- Metastatic Castrate-Resistant Prostate Cancer
  - At progression on hormonal therapy
  - 150 Patients

- Metastatic Her2+ or ER+ Breast Adenocarcinoma
  - Progression on trastuzumab/endocrine Rx
  - 100 Patients

Target of ~200 patients in year 1
CanSeq: Sequencing Production Overview

Neal Lindeman (BWH Path.)

DFCI/BWH

Cancer Genome Evaluation Committee (CGEC), DFCI (Judy Garber)

Final report to treating oncologist

Identification of somatic and germline alterations (Aim 1)

List of potentially “actionable” and “consequential” variants (Aim 2)

Prioritized events for oncology evaluation (Aim 3)

DNA quality control

OncoMap (top-tier “actionable” events, CLIA lab)

Sample transfer for WES

Whole exome sequencing and analysis

Library construction and hybrid selection
How can you interpret the profiling data for use by a clinician and patient?
Big Data in Oncology

Data points per patient

WES, WGS Transcriptome
Moore's Law

History and Physical Labs, Imaging Pathology...
SNaPShot OncoMap

Source: NHGRI
Precision Heuristics for Interpreting the Alteration Landscape (PHIAL)

Mutations: ACC, TAG

Insertion/Deletions: TCG, AACC

Copy Number Alterations: 

Rearrangements: 

PHIAL

Investigate Clinical Actionability
Investigate Biological Relevance
Cancer Genes
Cancer Pathways
COSMIC
Synonymous Variants

Eli Van Allen
## Evidence Levels for Somatic Alterations

<table>
<thead>
<tr>
<th>Tier 1 (FDA-Approved / Standard Therapies)</th>
<th>Tier 2 (Clinical Trials / Experimental Therapies)</th>
<th>Prognostic / Diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Clinically Validated</td>
<td>Eligibility Criteria for Trial</td>
<td>Clinically Validated</td>
</tr>
<tr>
<td>B Limited Evidence</td>
<td>Limited Evidence</td>
<td>Limited Evidence</td>
</tr>
<tr>
<td>C Evidence in another tumor type <em>only</em></td>
<td>Evidence in another tumor type <em>only</em></td>
<td></td>
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<tr>
<td>D Pre-clinical Evidence</td>
<td>Pre-clinical Evidence</td>
<td></td>
</tr>
<tr>
<td>E Theoretical</td>
<td>Theoretical</td>
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</tr>
</tbody>
</table>

Wagle, Berger *et al.*, *Cancer Discovery*, November 2011
Evaluating Actionable Alterations

CGEC Cancer Genome Report

- Patient Information
- Sequencing Metrics
- Actionable Alterations
- Somatic Mutations and Indels
- Somatic Copy Number Alterations
- Germline Analysis
- Analysis and References
Evaluating Actionable Alterations

Table 4. Actionable findings with details, sorted by actionability score

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Variant</th>
<th>Coverage</th>
<th>Allelic_fraction</th>
<th>Actionable:</th>
<th>Tier</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>p.A146V</td>
<td>Missense_Mutation</td>
<td>248</td>
<td>0.61</td>
<td>Tier 2-A,  Plausibly Actionable, Tier 1-B(R), Prognostic/Diagnostic-B</td>
<td>Click here</td>
<td></td>
</tr>
<tr>
<td>STK11</td>
<td>p.G279fs</td>
<td>Frame_Shift_Del</td>
<td>23</td>
<td>0.48</td>
<td>Plausibly Actionable: Tier 1-C, 1-D, and 2-B</td>
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<tr>
<td>ATM</td>
<td>p.K208fs</td>
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<td>39</td>
<td>0.36</td>
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</tr>
<tr>
<td>BCL6</td>
<td>p.E419V</td>
<td>Missense_Mutation</td>
<td>112</td>
<td>0.53</td>
<td>Theoretically Actionable: Tier 2-B</td>
<td>Click here</td>
<td></td>
</tr>
</tbody>
</table>

**KRAS p.A146V:** Activating mutations in KRAS are among the most common genetic alterations in human tumors. KRAS mutations play a central role in tumor progression in multiple cancer types, and have been implicated in poor prognosis and resistance to therapy. KRAS alterations are common across numerous malignancies. Activating KRAS mutations are found in 15 to 30% of all patients with non-small cell lung cancer (NSCLC).

This alteration has rarely been found in other cancer types. This alteration has only been reported in 15 colorectal cancer cases in the COSMIC database. An additional 68 cases of A146T have been reported in colorectal cancer in the COSMIC database. However, one systematic study of exon 4 mutations in colorectal cancer demonstrated the presence of A146 mutations in 5% of colon cancers.

This alteration is a known activating mutation, though may be less potent than the more common codon 12 and 13 mutations. Activating mutations in KRAS predict poor survival in patients with NSCLC, though these studies have generally only included codon 12 and 13 mutations. Activating mutations in KRAS may predict sensitivity to inhibitors of the RAS/RAF/MEK/ERK pathway. Preclinical studies have shown that MEK inhibitors, in particular, may be effective for KRAS mutant tumors, and these agents are in clinical trials for patients with KRAS mutant cancers. Activating KRAS mutations may also predict resistance to anti-EGFR therapies.

**STK11 p.G279fs:** STK11 is a well-known tumor suppressor (also known as LKB1) that is commonly inactivated in several cancers. Germline mutations in STK11 cause Peutz-Jeghers Syndrome (PJS).

This gene has been implicated in NSCLC. In addition, it is commonly seen in conjunction with KRAS mutations. This specific alteration has not been reported in the COSMIC database for NSCLC, though inactivating mutations in STK11 are common in this tumor type, occurring at a rate of 5-15% of NSCLC. They commonly co-occur with KRAS mutations. This alteration is likely inactivating, since it is a frameshift mutation that occurs at codon 279 out of 434.

Loss of STK11 activates the MTOR pathway and therefore may predict sensitivity to inhibitors of this pathway. Preclinical evidence suggests that MTOR
Cancer Genome Evaluation Committee (CGEC)

- Judy Garber, *Co-chair*
- Pasi Janne, *Co-chair*
- George Demetri
- Matthew Freedman
- Charles Fuchs
- Levi Garraway
- Gad Getz
- Monica Giovanni
- Stacy Gray
- Elaine Hiller
- Franklin Huang
- Katherine Janeway
- Steven Joffe
- Ian Krop
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- Mark Pomerantz
- Irene Rainville
- Huma Rana
- Scott Rodig
- Barrett Rollins
- Geoffrey Shapiro
- Sapna Syngal
- Eliezer Van Allen
- Nikhil Wagle
- Brian Wolpin
- Matthew Yurgelun
Patient Tissue Profiling Interpretation Communication Decision-Making Outcome

- Heuristic Tools
- Curation / Annotation Teams
- Genomics Tumor Boards
- Knowledgebase

- VUS investigative team
- Patient-derived cancer cell lines

- Outcomes database
- Genomics registry

- Integrative analyses
- Machine learning
Once the data has undergone clinical interpretation, how do you effectively communicate the information to the clinical team & patient in a usable way?
Reporting Results to Clinicians

CanSeq Cancer Genome Report

Patient ID: xxxxxxx
DOB: xxxx
Diagnosis: Lung Adenocarcinoma

### ACTIONABLE SOMATIC ALTERATIONS

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Action / Agent</th>
<th>FDA Approved?</th>
<th>Level of Evidence</th>
<th>Validated by</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS A146V</td>
<td>MEK inhibitors</td>
<td></td>
<td>Eligibility Criteria</td>
<td>Ion Torrent Seq</td>
</tr>
<tr>
<td></td>
<td>Resistance to EGFR Inhibitors</td>
<td></td>
<td>Limited Clinical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor prognosis</td>
<td></td>
<td>Theoretical</td>
<td></td>
</tr>
<tr>
<td>STK11 G279fs</td>
<td>Everolimus</td>
<td>Yes</td>
<td>Other tumor type</td>
<td>Ion Torrent Seq</td>
</tr>
<tr>
<td></td>
<td>Temsirolimus</td>
<td>Yes</td>
<td>Other tumor type</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mTOR inhibitors</td>
<td></td>
<td>Pre-clinical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td>Yes</td>
<td>Pre-clinical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FAK inhibitors</td>
<td></td>
<td>Pre-clinical</td>
<td></td>
</tr>
<tr>
<td>ATM K208fs</td>
<td>PARP inhibitors</td>
<td></td>
<td>Pre-clinical</td>
<td></td>
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**KRAS A146V**

- Activating mutations in KRAS are among the most common genetic alterations in human tumors. KRAS mutations play a central role in tumor progression in multiple cancer types, and have been implicated in poor prognosis and resistance to therapy.
- KRAS alterations are common across numerous malignancies. Activating KRAS mutations are found in 15–30% of all patients with non-small cell lung cancer (NSCLC).
- **This alteration is a known activating mutation**, though may be less potent than the more common codon 12 and 13 mutations (PMID: 20570890).
- **This alteration has not been reported in the COSMIC database for NSCLC.** Furthermore, A146 mutations in KRAS were not found in 2 studies comprised 449 cases of NSCLC in which KRAS was sequenced in its entirety (PMID: 18948947, 18632620).
- **This alteration has rarely been found in other cancer types.** This alteration has only been reported in 15 colorectal cancer cases in the COSMIC database. An additional 68 cases of A146T have been reported in colorectal cancer in the COSMIC database. However, one systematic study of exon 4 mutations in colorectal cancer demonstrated the presence of A146 mutations in 5% of colon cancers (PMID: 20570890).
- Activating mutations in KRAS predict poor survival in patients with NSCLC, though these studies have generally only included codon 12 and 13 mutations.
- **Activating mutations in KRAS may predict sensitivity to inhibitors of the RAS/RAF/MEK/ERK pathway.** Preclinical studies have shown that MEK inhibitors, in particular, may be effective for KRAS mutant tumors, and these agents are in clinical trials for patients with KRAS mutant cancers.
- Activating KRAS mutations may also predict resistance to anti-EGFR therapies.
Does the information provided impact clinical decision-making?
CanSeq: Patient with Lung Adenocarcinoma

• 61 year old man with a history of breast cancer who then developed lung adenocarcinoma
• Initially surgically resected but rapidly recurred as metastatic disease
• Progressed rapidly through standard chemotherapy
• Tested negative for *EGFR, KRAS, ALK, ROS* alterations
## Example: Patient with Lung Adenocarcinoma

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Action / Agent</th>
<th>Category</th>
<th>Tier</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS A146V</td>
<td>MEK Inhibitors</td>
<td>Predictive</td>
<td>II</td>
<td>Eligibility Criteria</td>
</tr>
<tr>
<td></td>
<td>CDK4/6 Inhibitors</td>
<td>Predictive</td>
<td>II</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>STK11 G279fs</td>
<td>Everolimus</td>
<td>Predictive</td>
<td>IIb</td>
<td>Other tumor type</td>
</tr>
<tr>
<td></td>
<td>Temsirolimus</td>
<td>Predictive</td>
<td>IIb</td>
<td>Other tumor type</td>
</tr>
<tr>
<td></td>
<td>mTOR Inhibitors</td>
<td>Predictive</td>
<td>II</td>
<td>Pre-clinical</td>
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*Enrolled on a clinical trial based on his activating KRAS mutation*
Does genomic profiling improve care and outcomes for patients with cancer?
Categories of Genomics-Driven Clinical Studies in Cancer

- 1. “G-to-P”
- 2. “P-to-G” (e.g., exceptional cases)
- 3. Decision impact (switch rate)
- 4. Platform/algorithm comparisons
Mutation-based Clinical Trials: “Drug-Centered” or “Basket” Approach

Cancer Patient Genomic Profile

- Mutation A
  - Drug A
- Mutation B
  - Drug A
- Mutation C [...]
- No mutation

**Test cohort:** 100% with mutant A or C

**Control cohort:** at-large randomization (?)

**Endpoints:** Drug A survival, response rates in test versus control cohort
“Genomics Driven” Clinical Trials: “BATTLE-like” Approach

Cancer Patient Genomic Profile

Mutation A → Drug A
Mutation B → Drug B
Mutation C → Drug C
No/other mutation

Patient Group #1: “Targeted group”
Mutation A + Drug A
Mutation B + Drug B
Mutation C + Drug C

Patient Group #2: “Empiric group”
Randomized agnostic to mutation status but controlled for tumor type

Endpoints: tumor response rate, survival in targeted versus empiric groups

Design integrated phase I/II trials to test “genomics-driven” hypotheses
Incorporation of correlative science (pharmacodynamics, imaging, additional omics)
Plan deep characterization of relapsing tumors
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- John Orechia
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- Yotam Drier
- CGA
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- Todd Golub
- Eric Lander

The Patients