Precision cancer medicine in the era of genomics
Disclosures

None

Equity holder in Microsoft
Five shares for my bar-mitzvah in 1993
Thanks to the Gros family!
Definitions

**Clinical computational biology:** the development and application of computational algorithms to analyze and interpret ‘omic data from patient samples

**Precision cancer medicine:** The use of “pan-omic” technology to inform patient care and translational studies
Precision oncology: A paradigm shift

Past → Present

Cancer → Non-specific chemotherapy

Present → Future

Cancer → Test for tumor-specific genetic targets that can be “drugged” → Targeted therapy

EGFR → erlotinib
BCR-ABL → imatinib
ALK → crizotinib
HER2 → trastuzumab
...

15th Annual Microsoft Research Faculty Summit 2014
Precision oncology: A paradigm shift

Past
Dacarbazine 5% response rate

Present
BRAF^{V600E}
Vemurafenib

Wagle, Emery, et al. JCO 2011
Big question: Can prospective knowledge of all alterations in a tumor genome impact patient care?
Clinical interpretation needs

Clinical Sequencing Pipeline Development

Clinical Genomics Data Interpretation

Data Representation for Clinicians

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“Big (genomic) data” in oncology

Data points per patient

Source: NHGRI
Clinical interpretation needs

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PHIAL

**Precision Heuristics for Interpreting the Alteration Landscape**

“May it be a light to you in dark places, when all other lights go out.”

---

1Galadriel, in Tolkien, The Fellowship of the Ring
PHIAL

Subclassifications per level

- Missense mutations
- Copy number directionality
  - Gain or loss

Linked pathways

- Actionable
- Unlinked
- Linked
- Wild-type

 KRAS A146V
• Rare activating alteration
• Not detected with deployed profiling technologies (at that time)

Impact on clinical decision-making
Metastatic advanced prostate cancer patient

Tumor-only variants

Inherited (“germline”) variant

PI3K inhibitor
AKT inhibitor
mTOR inhibitor

Responds to cisplatin!

PARP inhibitor
Platinum chemotherapy

BRCA2 K3326* nonsense

Five potential therapies for a patient who exhausted standard-of-care options!

PHIAL applied to diverse cancer types
Clinical interpretation needs

Clinical Sequencing Pipeline Development

Clinical Genomics Data Interpretation

Data Representation for Clinicians

The challenge of representation

Microsoft phone interview (~2002):
“Describe how you might make a mouse from scratch?

Eli: “I would start with a white-ish color, shaped around the palm of my hands...”

Did not get call back for second interview
The challenge of representation

True stories from oncology clinic (12/9/2013):

Patient’s genomic testing reveals $PIK3CA^{E545K}$ mutation
Specific inhibitors of this gene and pathway (“PI3K inhibitors”) are in clinical trials

“Why might you suggest PI3K inhibitor?” - Doc
“There is an activating PIK3CA mutation.” - Eli
“Oh, is PIK3CA part of the PI3K pathway?” – Doc
The state of clinical informatics
Digital genomics report
Digital genomics report

**Somatic Analysis**

This section investigates somatic mutations, insertion/deletions, and copy number alterations across...

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Variant</th>
<th>Coverage</th>
<th>Allelic_fraction</th>
<th>UniProt_Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>p.G12D</td>
<td>Mutation</td>
<td>84</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>STK11</td>
<td>p.S695fs</td>
<td>Frame_Shift_In</td>
<td>58</td>
<td>0.63</td>
<td>Protein kinase</td>
</tr>
<tr>
<td>EZH2</td>
<td>p.S277I</td>
<td>Mutation</td>
<td>288</td>
<td>0.17</td>
<td>Interaction with DNMT1, DNMT3A and DNMT3B</td>
</tr>
</tbody>
</table>

**Table: Somatic Curation Team results for selected alterations**

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Gene</th>
<th>Alteration</th>
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</tr>
</thead>
</table>

**Curated data**

- Good coverage at KRAS and allelic fraction of 44%
- Allelic fraction is 63% suggestive of LOH

**Links to focused ClinicalTrials.gov results**

- Reveals IGV screenshot
- Links to MutationAssessor
- Curated data
- OMIM
- Reference table used
- dbSNP
Big question: Can prospective knowledge of all alterations in a tumor genome impact patient care?

With the right computational approaches, we can study this on growing numbers of patients.
What are we missing?

A lot.

“Clinical” computational oncology is in its infancy

Much room for improvement

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American Cancer Society

CONQUER CANCER FOUNDATION of the American Society of Clinical Oncology
Save the planet and return your name badge before you leave (on Tuesday)