Clinical interpretation of the cancer genome for precision oncology

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Disclosures

• Consulting/Advisory
  – Syapse
  – Roche Ventana
  – Third Rock Ventures

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

For children of patients who have/had cancer
Sampling patients directly

Clinical

Computational

Analysis + interpretation algorithms

Oncology

Cancer (‘omic) biology
Precision medicine

The use of:

genomic technology
and
large-scale data
to guide:
1) individualized patient care
2) new discoveries
Precision cancer medicine: A paradigm shift

Past Dacarbazine

Present

$BRAF^{V600E}$

Vemurafenib

5% response rate

Wagle, Emery, et. al JCO 2011
Precision cancer medicine: A paradigm shift

Advanced Cancer

Test for tumor-specific genetic targets that can be “drugged”

EGFR  ➔  erlotinib
BCR-ABL  ➔  imatinib
ALK  ➔  crizotinib
HER2  ➔  trastuzumab
BRAF  ➔  vemurafenib
MEK1/2  ➔  trametinib
...

Targeted therapy

If one gene is good...
Clinical data explosion

Data points per patient

Whole exomes, genomes, and transcriptome

History and Physical Labs, Imaging Pathology...

Hotspot genotyping

Source: NHGRI
Can large-scale genomics guide individualized patient care in oncology?
Clinical interpretation (ca. 2012)

In Treatment for Leukemia, Glimpses of the Future

Second Chance: Lukas Wartman, a leukemia doctor and researcher, developed the disease himself. As he faced death, his colleagues sequenced his cancer genome. The result was a totally unexpected treatment.
Clinical interpretation (ca. 2012)

Why not throw everything we have at seeing if we can find a rogue gene spurring Dr. Wartman’s cancer, adult acute lymphoblastic leukemia, he asked? “It’s now or never,” he recalled telling them. “We will only get one shot.”

Dr. Ley’s team tried a type of analysis that they had never done before. They fully sequenced the genes of both his cancer cells and healthy cells for comparison, and at the same time analyzed his RNA, a close chemical cousin to DNA, for clues to what his genes were doing.

The researchers on the project put other work aside for weeks, running one of the university’s 26 sequencing machines and supercomputer around the clock. And they found a culprit — a normal gene that was in overdrive, churning out huge amounts of a protein that appeared to be spurring the cancer’s growth.

Even better, there was a promising new drug that might shut down the malfunctioning gene — a drug that had been tested and approved only for advanced kidney cancer. Dr. Wartman became the first person ever to take it for leukemia.

And now, against all odds, his cancer is in remission and has been since last fall.
The deranged cancer genome

Mutations
...ACC...
...TAG...

Insertion/deletions
...TCG...
...AACC...

Copy number alterations

Rearrangements

Per patient
10s–1000s
1s–1000s
10s–1000s
1s–1000s

Manual interpretation \(\rightarrow\) not scalable
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
  - Action

Investigate clinical relevance

- Mutations
- Insertion/deletions
- Copy number alterations
- Rearrangements

Investigate biological relevance

Synonymous variants

Linked pathways

- Actionable
- Unlinked
- Linked
- Wild-type

Alteration

Linked pathway

Impact on clinical decision-making

**KRAS A146V**
- Rare activating alteration
- Not detected with deployed profiling technologies

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**A Synthetic Lethal Interaction between K-Ras Oncogenes and Cdk4 Unveils a Therapeutic Strategy for Non-small Cell Lung Carcinoma**

(Cancer Cell Article)

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David Barbie
Leena Ghandi
Inherited genomics and interpretation

Tumor genome - Inherited genome = Tumor-only mutations

20,000-50,000 inherited variants per patient

Focus
- General and Context-specific Variant Filtering

Prioritize
- Population Frequency and Database Cross-Reference

Review
- Ranked Variants For Committee Review

Cancer-Specific
Cancer-Pharm
Other Pharm
Non-cancer
Therapy

Van Allen et al AACR 2013
Role for inherited genomics in treatment decision-making

Metastatic prostate cancer patient

Tumor-only variants

Inherited variant

**PHIAL**

**BRCA2 K3326**

nonsense

PI3K inhibitor
AKT inhibitor
mTOR inhibitor

Exceptional responses in genomically-enriched cases!

PARP inhibitor
Platinum chemotherapy

Remember the consumer
Usability testing genomic reports

• “What do all those colors mean?”
• “Look at this actionable Tier 4 mutation!”
• “Which copy number events are important?”
• …
State of the art in clinical informatics

van allen lab @vanallenlab • apr 17

hour 15/20 mandatory new #ehr training:
"click on the tiny triangle next to the house, expand window, find other triangle and scroll." sigh.
Standard or web-based/interactive reporting

Or

Web-based report
(revealed in survey)

Stacy Gray, Jordan Bryan
OncoSkins survey study

Clinical providers*

Traditional report

Web-based report

Genomic interpretation questions

*Medical, radiation, surgical, and pediatric oncology

We cannot improve the system without your contribution.
There are incentives for completing the report!

Coming soon (Protocol #16-101)
Expanding whole exome clinical sequencing

CanSeq

- Metastatic Lung Adenocarcinoma
  - Prior to 1st line systemic therapy
  - 100 Patients

- Metastatic Colorectal Adenocarcinoma
  - Prior to 2nd line systemic therapy
  - 100 Patients

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

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

**Levi Garraway, Nikhil Wagle, Stacy Gray, Judy Garber, Pasi Janne, Nelly Oliver, Philip Kantoff, Mary-Ellen Taplin, many others**
PHIAL in a CLIA lab!

CLINICAL RESEARCH SEQUENCING PLATFORM
BROAD INSTITUTE OF HARVARD & MIT

DNA
FFPE
Whole Blood
Cells
Tissue

Whole Exome LC & Sequencing

Picard Alignment

Germline calling of Normal

GATK Variant Calling

MuTect & Indelocator

Somatic calling

PHIAL Report
Question #2

Can genomics explain clinical resistance to cancer therapies?

= one patient
Targeted therapies and resistance

BRAF V600E $\rightarrow$ vemurafenib

Six months later…

Wagle et al. JCO 2011
Studying clinical resistance

Germline DNA
Pre-Treatment Biopsy

RAF Inhibitor

Whole Exome Sequencing

Post-Relapse Biopsy

Time

Whittaker et al, *Cancer Discovery* 2013
Van Allen, Wagle et al, *Cancer Discovery* 2014
Linking clinical data to genomics

Harder to obtain from the electronic health record than genomic data
New mechanisms of clinical resistance

MITF
Resistance heterogeneity

A

Chr1:115,256,509-115,256,558

Post-resistance
Q61R (T>C)
Reference: 681
Variant: 27

Post-resistance
T58I (G>A)
Reference: 449
Variant: 261

Pre-treatment
Reference: 560
Variant: 0

Pre-treatment
Reference: 593
Variant: 0

+ 

Chr15:66,727,463

Post-resistance
V60E (T>A)
Reference: 320
Variant: 24

Pre-treatment
Reference: 639
Variant: 0

NRAS

MEK1
Genomics and exceptional response/resistance

Everolimus (mTOR inhibitor) → 18 months later

Anaplastic thyroid cancer

Wagle et al. NEJM 2014
Genomics and exceptional response/resistance

In pre-treatment tumor only

In resistant tumor only

HEALTH

Finding Clues in Genes of ‘Exceptional Responders’

By GINA KOLATA OCT. 8, 2014

Grace Silva of Dartmouth, Mass., has a form of thyroid cancer that is considered untreatable, but she responded well to a drug. Kayana Szymczak for The New York Times

Scott Carter
Ali Amin-Mansour
Amaro Taylor-Weiner

= one patient
Can computational oncology enable discovery of genomic mechanisms of response to cancer therapies?
The rise of immunotherapies

Ott et al Clin Cancer Res 2013
Combining immunotherapies

Do genomic features drive selective response?

Larkin et al NEJM 2015
Mutations and “neo”-antigens

Wild-type
Patient₁ Gene₁ → Protein₁
...YLFSSYSAS...

Mutant
Patient₁ Gene₁* → Protein₁*
...YLFSSYSSS...

Can be a passenger or a driver...

Mutation causes “neo”-antigens
May appear foreign to immune cells
Drive response even if altered protein itself has no function?

Pieces of protein presented to immune cells = antigens
Searching for melanoma neoantigens

Diana Miao

Clinical cohort consolidation

Cohort development

Whole exome sequencing
tumor and germline
(n = 150)

Transcriptome sequencing
(n = 62)

Quality control

DNA sequencing
(n = 110)

RNA sequencing
(n = 42)

Somatic mutation calling (MuTect)
HLA-typing (Polysolver)

Mutational load
Neoantigen load
Gene-specific enrichment
n-mer signature

Integrated molecular analysis
(n = 40)

Microenvironmental signature

Enhanced neoepitope selection

Van Allen, Miao, Schilling et al, Science 2015
Neoantigen load and clinical benefit
Immunotherapy exceptional responders

Figure 1

Clinical computational oncology
Question #1 (Interpretation): Next Steps

- Improve integrative analyses
- Expanding tumor types
- Expanding clinical scenarios
- ...

Prospective clinical interpretation
Question #1 (Interpretation): Next Steps

Current best practices:
“First order” clinical interpretation

Multiple actionable targets?
No actionable targets?
Functional readout?

Clinical interpretation methodology for precision cancer medicine

Tumor Cellular State

Prioritize actionable targets
Identify new lesions
Match with preclinical models

Clinical-Preclinical Matchmaker

Machine learning methodologies

R21 ITCR Grant!
Question #1 (Interpretation): Transcriptional state finder

Towards “second order” interpretation

Patient data

DNA $[g_1v_1...g_nv_n, f_1...f_m]_{DNA}$

RNA $[g_1v_1...g_nv_n, f_1...f_m]_{RNA}$

TCGA Histology-matched $[g_1v_1...g_nv_n, f_1...f_m]_{RNA}$

Lasso-based feature compression

Bayesian mixture model

Prioritize patient-specific actionable cellular states

$g =$ gene
$v =$ variant
$f =$ feature

*Denotes cellular state including patient
Question #1 (Interpretation): Clinical-preclinical matchmaker
Question #2 (Resistance): Next steps

- More biopsies
- More cohorts
- More therapies
- More!
Question #3 (Response): Next steps

- Studying response to all therapy types (targeted, chemo, immuno)
- Integration into trials
- Algorithm enhancement
Let’s work together!

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Many others…

The Patients

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NIH
Kure it
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