Conflict of Interest

Gaurav Singal, MD is an employee of Foundation Medicine, Inc.

He receives salary from and has an equity interest in Foundation Medicine, Inc.
Agenda

1. Overview of Precision Medicine in Oncology
2. Novel Diagnostics including Genomic Sequencing
3. Evolution in Cancer Therapeutics
4. Role of Information Science and Decision Support
5. Real World Examples and Solutions
6. Conclusions
7. Q&A
Learning Objectives

1. Compare category 1, 2 and 3 molecular tests to understand the molecular information provided by each test

2. Use a database to access comprehensive genomic profiles of cancers to make informed therapeutic decisions

3. Recognize the potential shift in cancer care that could result from digital physician interaction focused on genomic information
STEPS Framework

The work described here will focus on the “Treatment and Clinical” benefits of Health IT, specifically in the context of precision medicine in Oncology
Introduction

• Trained as a computer scientist and a physician
  – AI, Machine Learning, and Computational Neuroscience at Columbia University
  – Medical school at Harvard and Internal Medicine residency at Massachusetts General Hospital
• Spent last decade+ at the intersection of health and technology
  – Research in computational vision & eye tracking
  – Life Sciences Venture Capital at Third Rock Ventures
  – Natural Language Processing Product Development @ MGH / QPID Health
• Currently practice medicine as an Attending at Massachusetts General Hospital and serve as the Director of the Innovations Unit at Foundation Medicine, a cancer genomics and molecular information company
Precision Medicine: The Vision

“I want the country that eliminated polio and mapped the human genome to lead a new era of medicine — one that delivers ... the right treatments at the right time, every time, to the right person.”

— President Barack Obama
State of The Union, January 2015
Clinical trials study populations
Physicians treat individuals
**Diagnostics**

More precisely define individuals within a population.

What characterizes their specific disease?

Who are the patients with whom they should be compared?

---

**Therapeutics**

Develop novel therapies to create a broader armamentarium.

Specifically, design therapies targeting specific subpopulations (and based on their disease characteristics).

---

**Information Science**

Understand impact of improved stratification on optimal management.

Match therapeutics to appropriate subpopulations.
Diagnostics

More precisely define individuals within a population

What characterizes their specific disease?

Who are the patients with whom they should be compared?

Therapeutics

Develop novel therapies to create a broader armamentarium

Specifically, design therapies targeting specific subpopulations (and based on their disease characteristics)

Information Science

Understand impact of improved stratification on optimal management

Match therapeutics to appropriate subpopulations

Precision Medicine: Diagnostics
Cancer: Anatomic + Histologic Definition

- Lung Cancer
- Breast Cancer
- Colon Cancer
Cancer: Anatomic + Histologic Definition

- Breast Cancer
  - Breast Invasive Ductal Carcinoma
  - Breast Inflammatory Carcinoma
  - Breast Carcinoma NOS
  - Breast Papillary Carcinoma
- Lung Cancer
- Colon Cancer
BREAST CANCER

BREAST INVASIVE DUCTAL CARCINOMA
Cancer Is A Disease Of The Genome

- Carcinogens
- Virus and infection
- Radiation
- Mistakes in DNA copying
Types of Genomic Alterations

- **Base Substitutions**
  - BRAF V600E
  - Vemurafenib

- **Insertions and Deletions**
  - EGFR Exon 19 Deletion
  - Erlotinib

- **Copy Number Alterations**
  - HER2 amplification
  - Trastuzumab

- **Rearrangements**
  - ALK Fusion
  - Crizotinib
## Identifying Genomic Alterations

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Detects</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Single Gene Testing</strong></td>
<td>• Single gene findings, class depends on the test</td>
<td>• Can only identify findings in single genes.</td>
</tr>
<tr>
<td>(eg IHC, FISH, PCR)</td>
<td></td>
<td>• Misses any finding the test was not specifically designed to identify a priori</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Higher risk of false positives (eg especially with IHC)</td>
</tr>
<tr>
<td><strong>Category 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hot Spot Panels</strong></td>
<td>• Multiple findings with specific a prior sequences</td>
<td>• Limited to a smaller set of genes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Misses any finding the test was not specifically designed to identify a priori</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cannot identify copy number alterations or Rearrangements</td>
</tr>
<tr>
<td><strong>Category 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comprehensive Genomic Profiling</strong></td>
<td>• All mutations in all 4 classes (Base Substitutions, Insertions and Deletions, Copy Number Alterations, and Rearrangements)</td>
<td>• May miss RNA-level events (including over-expression and alternative isoforms)</td>
</tr>
<tr>
<td></td>
<td>• Can detect findings not known about a priori</td>
<td></td>
</tr>
</tbody>
</table>
A Genomic View of Cancer

HER2
EGFR
ALK

PIK3CA MYC MCL1 CCND1 FGF19 FGF4 FGFR1 PTEN MYST3 CDH1 ESR1 CDKN2A
A Genomic View of Cancer

HER2

EGFR

ALK

ACTIVATING EXON 19 DELETION

L858R ALTERATION

T790M ALTERATION

ACTIVATING EGFR FUSIONS
BREAST CANCER
EGFR
HER2
BREAST INVASIVE DUCTAL CARCINOMA
L858R ALTERATION
AMPL
Precision Medicine: Therapeutics

**Diagnostics**
More precisely define individuals within a population
What characterizes their specific disease?
Who are the patients with whom they should be compared?

**Therapeutics**
Develop novel therapies to create a broader armamentarium
Specifically, design therapies targeting specific subpopulations (and based on their disease characteristics)

**Information Science**
Understand impact of improved stratification on optimal management
Match therapeutics to appropriate subpopulations
Targeted Therapies in Lung Adenocarcinoma

As per NCCN guidelines version 4.2015 NSCLC


Crizotinib

Vemurafenib, Dabrafenib
Trastuzumab, Afatinib
Crizotinib, Ceritinib
Erlotinib, Afatinib, Gefitinib
Cabozantinib
Crizotinib

[CATEGORY NAME]

HER2
ALK Fusions
EGFR
KRAS
PIK3CA
AKT1
MAP2K1
Unknown

ROS1 Fusions
NRAS
MET Amp

MET splice site
Personalized Approaches Improve Outcomes

Genomics-matched targeted therapy = BEST OUTCOME
Targeted therapy w/o mutation matching = Worst outcome

(Ref: Schwaederle et al., JCO 2015)
Number Of Targeted Therapeutics is Rising

Target Markers
- ROS1
- FBXW7
- VEGF/VEGFR
- STK11
- DDR2
- ERBB3
- GNAQ
- RET
- AURKA
- CCND1
- ERBB3
- CDK4
- DNMT3A
- GNAQ
- BRCA1
- BRAF
- CDK6
- TSC1/2
- MET
- PIK3CA
- TSC2
- IGF1R
- GATA3
- IGF/IGFR
- KDR
- NOTCH1
- HER2
- FGFR1
- FLT3
- CDKN2A
- AKT1
- RAF1
- MAP2K1
- NF1
- ALK
- TNF
- IDH1/2

Number Of Targeted Therapeutics is Rising
Precision Medicine: Information Science

Diagnostics
More precisely define individuals within a population
What characterizes their specific disease?
Who are the patients with whom they should be compared?

Therapeutics
Develop novel therapies to create a broader armamentarium
Specifically, design therapies targeting specific subpopulations (and based on their disease characteristics)

Information Science
Understand impact of improved stratification on optimal management
Match therapeutics to appropriate subpopulations
THE PERMUTATIONS ARE OVERWHELMING

- 200+ Tests
- 55 FDA Approved Targeted Therapies
- 3,208 Active Clinical Trials
- 500+ BioPharmas Developing Targeted Therapies
- 850+ Targeted Compounds in Development
- ?? Unique Patients
- 1 Brain per Human (even per Oncologist and Pathologist)
Enabling Precision Medicine with Information Science

- The Right Data Sets
- Exchangeable across institutional and geographic boundaries
- Usable by physicians in clinical care
BREAST CANCER

EGFR

L858R ALTERATION

HER2

BREAST INVASIVE DUCTAL CARCINOMA

AMPL
Putting it all together: Real World Examples

- **FGFR3**: Amplification
- **UROTHELIAL CARCINOMA**: Bladder Cancer
- **AMPLIFICATION**: Lung Cancer
- **EGFR**: Activating Fusion
- **NSCLC**: Non-Small Cell Lung Cancer
Real World Geographies
Making Real World Data Real

How do we enable physicians to exchange information about rare genomic findings and their treatment outcomes, across institutions & across geographies?
Physician Interface Concept

ASCO
CANCER® LINQ®
Learning Intelligence Network for Quality

Explore
Measure
MD Connect
Patients
Alerts

Welcome Dr. Demo
Facility: General Hospital
Sign Out

CancerLinQ Overview

ASCO
CANCER® LINQ®
Learning Intelligence Network for Quality

SYMPTOMS/TORTICITY MANAGEMENT

NHL Measure

NSCLC Measure

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HIMSS 2016
AACR Project GENIE is an international, multiphase, multiyear project that will provide the “critical mass” of genomic and clinical data necessary to improve clinical decision making and catalyze new clinical and translational research.

GENIE will aggregate existing and ongoing genotyping efforts from the seven phase 1 project participants into a single registry and link these data to select clinical outcomes, ultimately making these data publicly available.

The GENIE registry is a tool that can be used in many ways:

- The Center for Personalized Cancer Treatment, The Netherlands
- Dana-Farber Cancer Institute
- Institut Gustave Roussy, France
- Johns Hopkins University’s Sidney Kimmel Comprehensive Cancer Center
- Memorial Sloan Kettering Cancer Center
- Princess Margaret Cancer Centre, Canada
- Vanderbilt-Ingram Cancer Center
Real World Geographies

55,000+ Cases
Real World Data

- 61% No matches in ordering institution
- 91% Have been seen before
- 67% >15 patients
Making Real World Data Real: A third approach

What if, instead of centralizing data in a common repository, we could extend the age-old practice of the “curbside consult,” but adapt it for a modern, technological, molecular era?

Foundation Medicine has built a tool, PatientMatch*, to match patients and providers across this network based on their genomic signatures, allowing providers to exchange information about these rare cases with each other.

*Note: PatientMatch is a complementary service designed to enhance the utility of comprehensive genomic profiling and enable precision medicine
Dr. Cole receives a FoundationOne report for her patient with breast cancer with EGFR L858R.

Dr. Miller receives Dr. Cole’s request by email, and agrees to help her.

Dr. Miller is taken to FoundationICE where he is asked to answer 4 questions about his experience treating his matching patient.

PatientMatch reaches out to those physicians on Dr. Cole’s behalf, one of whom is Dr. Miller.

PatientMatch learns from Dr. Miller’s response, for Dr. Cole and for other physicians with similar questions.

After 72 hours, Dr. Cole receives an email informing her responses to her inquiry are available.

*note: this is a fictional case, and names do not refer to real patients or providers
Find out how other practitioners treated similar patients
(and request outcomes when available)

What is PatientMatch?

Contact practitioners who have seen similar patients with:

- **EGFR | L858R**
  - 7 practitioners with similar patients

- **ERBB2 | amplification**
  - 10 practitioners with similar patients

- **PI3KCA | H1047R**
  - 4 practitioners with similar patients

Have a general question? Contact Foundation Medicine's Medical Affairs by email or phone (617) 455-5246.
Send request to practitioners with matching patients

Good morning. Your practitioners with similar patients are participating in PatientMatch.

This email below will be sent to the following practitioners and their responses will be returned to you in 72 hours.

Who will receive this email?
- Physician at Memorial Sloan Kettering
- Nurse Practitioner at Tennessee Oncology
- Physician at Dana Farber Cancer Institute
- Physician at Iowa Oncology

I have a patient with breast cancer who has an EGFR L858R alteration identified by FoundationOne. I am considering targeting this alteration for the next step in treatment of my patient. Foundation Medicine has identified that you may have seen a similar patient in your practice.

Would you take a moment to answer a few simple questions that will help me and other physicians benefit from your experience and expertise?

Thank you,

Dennis Cole, MD
Oncologist, Massachusetts General Hospital
Boston, Massachusetts
Dear Vince,

I have a patient with breast cancer who had an EGFR L858R alteration identified by FoundationOne. I am considering targeting this alteration for the next step in treatment of my patient. Foundation Medicine has identified that you may have seen a similar patient in your practice.

Would you take a moment to answer a few simple questions that will help me and other physicians benefit from your expertise and experience?

Thank you,
Denise Cole, MD

[Yes I will share my experience button]

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Why did I receive this email?
This email was sent through Foundation Medicine’s PatientReach network at the request of Denise Cole. PatientReach is a feature of Foundation Medicine’s Interactive Cancer Explorer (ICE) which helps physicians ask questions, and share those questions with other physicians who have seen similar patterns. Your response will be shared with Denise to help him with his treatment decision and may be shared with other physicians who have similar questions in the future.
All communication through PatientReach is secure and your response will only be shared in a

#HIMSS16
Thank you for your time and response!

- Dr. Cole can contact me for more information
- I would like to add additional comments

Emma Potter
Patient details

Breast invasive ductal carcinoma

Physician: Dr. Jonathan Smith  
Location: PGH Cancer Center  
Report Date: Feb 15, 2014

Genomic Alterations

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERBB2 amplification</td>
<td>2</td>
</tr>
<tr>
<td>PIK3CA H1047R</td>
<td>2</td>
</tr>
<tr>
<td>EGFR L858R</td>
<td>2</td>
</tr>
<tr>
<td>TP53 K112N</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3 variants of unknown significance</td>
</tr>
</tbody>
</table>
Hi Denise Cole,

We have collected responses from six practitioners in the PatientMatch network responding to your request for information about patients with breast cancer and alterations in EGFR.

Four practitioners used a therapy targeting EGFR.

One practitioner started their patient on a clinical trial related to EGFR.

One practitioner did not use a therapy targeting EGFR.
Six practitioners responded to your question about targeting EGFR in breast cancer.

Four of these practitioners reported they used a therapy targeting EGFR:

<table>
<thead>
<tr>
<th>Respondent</th>
<th>Patient Demog.</th>
<th>Tumor Type</th>
<th>Genomic Profile</th>
<th>Therapy</th>
<th>Duration</th>
<th>Best Response</th>
<th>Last Updated</th>
<th>Contact</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nancy P, MD DFCI</td>
<td>45yo F</td>
<td>Lobular Breast Carcinoma</td>
<td>EGFR: L858R ERBB2: xxx ALK: xxx</td>
<td>Erlotinib</td>
<td>5 mo (ongoing)</td>
<td>Stable Disease</td>
<td>Jun 13, 2014</td>
<td>--</td>
<td>She's done really well on erlotinib</td>
</tr>
<tr>
<td>Greg S, DO UPenn</td>
<td>58yo F</td>
<td>Lobular Ductal Carcinoma</td>
<td>EGFR: xxx PIK3CA: xxx</td>
<td>Erlotinib</td>
<td>5 mo (stopped)</td>
<td>Some Response</td>
<td>Jan 14, 2014</td>
<td>@<a href="mailto:regis@upenn.edu">regis@upenn.edu</a></td>
<td>Please feel free to email me with questions</td>
</tr>
<tr>
<td>John A, MD BIDMC</td>
<td>45yo F</td>
<td>Lobular Breast Carcinoma</td>
<td>EGFR: xxx ERBB2: xxx ALK: xxx</td>
<td>Gefitinib</td>
<td>8 mo (ongoing)</td>
<td>Some Response</td>
<td>Oct 24, 2013</td>
<td>318-442-3423</td>
<td>It took a while to get insurance coverage but she's doing great</td>
</tr>
</tbody>
</table>
Information Science: Next Steps

The Right Data Sets

- Represented here is a limited set of high-value outcomes data, derived individually from providers
- Need ways of extracting and integrating more robust data elements (imaging, NLP, side effects, etc.) – ideally automatically

Exchangeable across institutional and geographic boundaries

- Need data to be usable outside of individual silos
- Several opportunities here: health information exchanges, large public registries and data exchanges (e.g., CancerLinQ, AACR Project GENIE)

Usable by physicians in clinical care

- Once data sets become more complex and nuanced, will need additional statistical approaches and automated CDS solutions
- Ideally will need these integrated into existing workflows (e.g., EMRs)
Conclusion

• The era of precision medicine has arrived – certainly in oncology – with major advances in diagnostics and therapeutics

• Patient’s tumors are now characterized not only anatomically and histologically, but also by the genomic drivers of their disease

• This paradigm shift has made evidence gathering and treatment decision making much more complicated

• We need new ways of collecting and assimilating data, as well as new clinical decision support tools to enable the practice of precision medicine in the clinic
The work described here explains how to use Health IT to enable “real world data” from a network of providers to improve treatment of oncology patients from the lens of personalized medicine.
Questions?

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