Big Data & Precision Medicine

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FLATIRON HEALTH

WWW.FLATIRON.COM
Big Data?
4% vs. 96%
Electronic health record adoption in the U.S. has surged since 2001.

This enables us to capture data from the 96% of patients not on a clinical trial.
Frustrations faced:

1. Clinical data is really messy and unreliable
2. Instrumentation data (including genomics) is really “big”
3. It’s incredibly hard to follow a patient’s complete journey
4. There is a lack of “real-world” evidence, which makes it difficult to talk with patients about expected outcomes
How can we leverage data in a meaningful way to enhance patient care and learn from their experiences?
Processing the Electronic Health Record
Structured Data Processing

- All terms are mapped to a common vocabulary, standard across all centers
- Matching algorithms can predict matches for ~90% of terms
- Data processing engine transcodes terms in real-time
- Any unmatched term is flagged for clinical review by Flatiron MD/RN

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Unit</th>
</tr>
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<tbody>
<tr>
<td>2220</td>
<td>Blood Serum Albumin</td>
<td>g/dL</td>
</tr>
<tr>
<td>QD25001600</td>
<td>ALBUMIN/GLOBULIN RATIO QD (calc)</td>
<td></td>
</tr>
<tr>
<td>QD25001400</td>
<td>ALBUMIN QD</td>
<td>g/dL</td>
</tr>
<tr>
<td>QD50058600</td>
<td>ALBUMIN</td>
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<tr>
<td>QD50055700</td>
<td>ALBUMIN</td>
<td>g/dL</td>
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<td>CL3215104</td>
<td>Albumin % (EPR)</td>
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<td>LC001081</td>
<td>ALBUMIN, SERUM (001081)</td>
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<td>LC133751</td>
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<tr>
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<td>Albumin%, Urine</td>
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<td>3234</td>
<td>ALBUMIN SS</td>
<td>g/dL</td>
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<tr>
<td>LC133686</td>
<td>Albumin, U</td>
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<tr>
<td>QD50060710</td>
<td>MICROALBUMIN</td>
<td>mg/dL</td>
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</table>
| QD50061100 | MICROALBUMIN/CREATININE RATIO, RANDOM URINE      | mcg/mg | creat
| QD85991610 | ALBUMIN                                          | relative % |
| 50058600   | ALBUMIN UPEP RAND                                | g/dL   |
| CL3210074  | ALBUMIN LEVEL                                    | g/dL   |
| QD86008211 | ALBUMIN/GLOBULIN RATIO (calc)                    |        |
| LC149520   | Albumin                                          | g/dL   |
| QD45069600 | PREALBUMIN                                       | mg/dL  |
| QD900415245| ALBUMIN, SERUM                                   | mg/dL  |
| QD900429745| ALBUMIN                                          | g/dL   |
| CL3215124  | Albumin Electrophoresis                          | g/dL   |
| LC16931    | Prealbumin                                       | mg/dL  |
| QD50060900 | MICROALBUMIN, 24 HOUR UR                         | mcg/min |
| QD85994821 | ALBUMIN, SERUM                                   | g/dL   |
| CL3213320  | PREALBUMIN                                       | mg/dL  |
| QD85995225 | PROTEIN ELECTROPHORESIS                          | g/dL   |
**Capturing Key Data From Unstructured Notes**

Leverage unstructured data processing to drive accuracy and completeness of data elements.

- KRAS testing status
- KRAS test result
- Date sample was collected
- Date sample was received in lab
- Date result was provided to physician
Technology leverages people & capabilities
A dataset is an amalgamation of many patient stories

- Diagnosed with Stage II NSCLC
- Undergoes surgery for early-stage disease
- Develops metastatic disease
- Tested for EGFR and ALK
- Starts 1L therapy
- Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR
- Starts 2L therapy, deteriorates and is hospitalized
- Death
Diagnosed with Stage II NSCLC

Develops metastatic disease

Tested for EGFR and ALK

Undergoes surgery for early-stage disease

Starts 1L therapy

Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR

Starts 2L therapy, deteriorates and is hospitalized

Death

Organize datasets around patient stories
Diagnosed with Stage II NSCLC

Undergoes surgery for early-stage disease

Develops metastatic disease

Tested for EGFR and ALK

Starts 1L therapy

Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR

Starts 2L therapy, deteriorates and is hospitalized

Death

- Patient age
- Gender
- Race
- Insurance
- Stage

- Regimen name
- Duration of therapy
- Dosage
- Concomitant meds

- Date of death

Structured EMR data
Diagnosed with Stage II NSCLC
- Patient age
- Gender
- Race
- Insurance
- Stage
- TNM staging

Undergoes surgery for early-stage disease
- Date of surgery

Develops metastatic disease
- Sites of metastases

Tested for EGFR and ALK
- Biopsy date
- Type of test conducted
- Turnaround time for test
- Number of unsuccessful tests
- Test result, if successful
- Type of EGFR mutation

Starts 1L therapy
- Regimen name
- Duration of therapy
- Dosage
- Concomitant meds
- Response

Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR
- Biopsy date
- Lab name
- Test result
- T790M mutation

Starts 2L therapy, deteriorates and is hospitalized
- Date of hospitalization
- Cost of care

Date of death

Date of death

Organize datasets around patient stories

Structured EMR data
- Unstructured EMR data
- External datasets
Organize datasets around patient stories

- Diagnosed with Stage II NSCLC
- Undergoes surgery for early-stage disease
- Develops metastatic disease
- Tested for EGFR and ALK
- Starts 1L therapy
- Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR
- Undergoes surgery for early-stage disease
- Starts 2L therapy, deteriorates and is hospitalized
- Death

- Patient age
- Gender
- Race
- Insurance
- Stage
- TNM staging

- Sites of metastases
- Time to recurrence
- Biopsy date
- Type of test conducted
- Turnaround time for test
- Number of unsuccessful tests
- Test result, if successful
- Type of EGFR mutation
- Regimen name
- Duration of therapy
- Dosage
- Concomitant meds
- Response
- Line of therapy
- Biopsy date
- Lab name
- Test result
- T790M mutation
- Date of death
- Date of death
- Consensus date of death
- Date of hospitalization
- Cost of care
- Line of therapy

Structured EMR data
Unstructured EMR data
External datasets
Algorithms
Diagnosed with Stage II NSCLC

Undergoes surgery for early-stage disease

Develops metastatic disease

Tested for EGFR and ALK

Starts 1L therapy

Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR

Starts 2L therapy, deteriorates and is hospitalized

Death

<table>
<thead>
<tr>
<th>Patient</th>
<th>Demographics</th>
<th>Stage</th>
<th>Diagnosis Date</th>
<th>Biomarkers</th>
<th>Treatment</th>
<th>Response</th>
<th>Hospital admissions</th>
<th>Mortality</th>
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<tr>
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</tbody>
</table>
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Develops metastatic disease.
Tested for EGFR and ALK.
Undergoes surgery for early-stage disease.
Starts 1L therapy.
Progresses on 1L, tested for PD-L1 and/or re-tested for EGFR.
Starts 2L therapy, deteriorates and is hospitalized.
Death.

Curating the complete picture

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<th>Diagnosis Date</th>
<th>Biomarkers</th>
<th>Treatment</th>
<th>Response</th>
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<th>Mortality</th>
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<tbody>
<tr>
<td>A</td>
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</table>
Data quality must be a focus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Structured data only</th>
<th>Flatiron data completeness</th>
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</thead>
<tbody>
<tr>
<td>Smoking status</td>
<td>0%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>94%</td>
</tr>
<tr>
<td>Histology</td>
<td>37%</td>
<td>99%&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage</td>
<td>61%</td>
<td>95%</td>
</tr>
<tr>
<td>ALK results (of those tested)</td>
<td>9%</td>
<td>100%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>EGFR results (of those tested)</td>
<td>11%</td>
<td>99%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of Met</th>
<th>Inter-abstractor Agreement</th>
<th>Kappa</th>
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</thead>
<tbody>
<tr>
<td>Bone</td>
<td>97%</td>
<td>0.93</td>
</tr>
<tr>
<td>Brain</td>
<td>96%</td>
<td>0.91</td>
</tr>
<tr>
<td>Liver</td>
<td>92%</td>
<td>0.83</td>
</tr>
<tr>
<td>Lung</td>
<td>94%</td>
<td>0.87</td>
</tr>
</tbody>
</table>
Data for a single organization
Nationally representative cohorts
Identified or de-identified
Processed EHR Data

- Mortality data
- Genomic data
- Progression data
- Claims data
- Derived variables
- Patient reported data
Distribution of Most Commonly Altered Genes

TP53 > KRAS > CDKN2A > EGFR > CDKN2B > STK11 > MYC > LRP1B > NX2-1 > PIK3CA > RB1 > ARID1A > KEAP1 > SMARCA4 > RBM10 > PTEN > NF1 > SPTA1 > MDM2 > BRAF > RICTOR > MLL2 > ERBB2 > ALK > MET > MCL1 > ATM > APC > CCND1 > DMDT3A > CDK4 > SOX2 > FAT1 > FGF10 > SETD2 > CTNNB1 > FGF19 > FGF3 > FGFR4 > ARID2 > TERC > FGFR1 > MYST3 > TET2 > SMAD4 > GNAS
Processed EHR data is now:

Organized
Readily Analyzable
High quality
Linked
So....what’s next?
<table>
<thead>
<tr>
<th>The Evolving Landscape in Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>How can we leverage data to better understand our patient population, monitor changes and document outcomes?</td>
</tr>
</tbody>
</table>
Current NSCLC Cohort
Total Patients: 22,762 (Community: 21,222, Academic: 1,540)
Number of Clinics Represented: 171

1/31/16
**Cohort Demographics**
(Number of Patients in Cohort: 21,222)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Histology</th>
<th>Smoking Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male 52.5% 11,133</td>
<td>Not otherwise specified (NOS) 6,5% 1,371</td>
<td>Unknown/Not documented 3.2% 682</td>
</tr>
<tr>
<td>Female 47.5% 10,086</td>
<td>Squamous cell carcinoma 24.8% 5,261</td>
<td>No history of smoking 12.3% 2,615</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at Advanced Diagnosis</th>
<th>Line of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age: 69</td>
<td>69.7% 9,511</td>
</tr>
</tbody>
</table>

- 25% of patients are male
- 12% have a history of smoking
- 70% of patients are 65+ years old
- 70% of patients received 3 or more lines of therapy after their advanced diagnosis
PDL1 Biomarker Test Overview

PDL1 Test Rate Among Active Patients

<table>
<thead>
<tr>
<th>Month</th>
<th># Active Patients PDL1 Tested</th>
<th>Total # of Active Patients</th>
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<tbody>
<tr>
<td>Aug-15</td>
<td>233</td>
<td>5,635</td>
</tr>
<tr>
<td>Sep-15</td>
<td>251</td>
<td>5,543</td>
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<tr>
<td>Oct-15</td>
<td>265</td>
<td>5,309</td>
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<tr>
<td>Nov-15</td>
<td>275</td>
<td>5,168</td>
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<tr>
<td>Dec-15</td>
<td>277</td>
<td>4,877</td>
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<tr>
<td>Jan-16</td>
<td>257</td>
<td>4,205</td>
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</tbody>
</table>

% of Patients

- Aug-15: 4.1%
- Sep-15: 4.5%
- Oct-15: 4.9%
- Nov-15: 5.3%
- Dec-15: 5.7%
- Jan-16: 6.1%

PDL1 Test Results of First Successful Test

- PD-L1 negative / Not detected: 54.7% (180 patients)
- PD-L1 positive: 45.0% (148 patients)
- Unknown: 0.6% (2 patients)

# of Patients with a Successful Test: 330
### Patient Share by Therapy Class

#### Patient Share

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<td>100%</td>
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<td>60%</td>
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### Number of Treated Patients

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<td>Platinum-based chemo combos</td>
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<td>776</td>
<td>806</td>
<td>808</td>
<td>810</td>
<td>821</td>
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<td>838</td>
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<td>830</td>
<td>805</td>
<td>804</td>
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<td>782</td>
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<td>697</td>
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<td>687</td>
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<td>627</td>
<td>610</td>
<td>578</td>
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<tr>
<td>Anti-VEGF-based therapies</td>
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<td>Other therapies</td>
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<td># of patients</td>
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<td>2,933</td>
<td>2,910</td>
<td>2,807</td>
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</table>

**Highlighted Values:**
- **1.4%**
- **24.5%**
- **687/2807**
Kaplan-Meier Survival Analysis

Time from advanced NSCLC diagnosis to death

Advanced dx date
1/1/2013 - 6/1/2015

Follow-up time (days)
0 - 1608

First Line Therapy
(All)

Histology
- Non-squamous cell carcinoma
- NSCLC histology NOS
- Squamous cell carcinoma

Smoking status
(All)

By EGFR status
(All)

By ALK status
(All)

All Patients
How likely are patients to receive KRAS testing?

Metastatic colorectal cancer: KRAS testing rate by year of metastatic diagnosis (evaluated in June 2015)

* Line of treatment is determined at Flatiron through a series of disease-specific business rules based on review of real-world data by oncologists.
How likely are patients to receive KRAS testing?

Metastatic colorectal cancer: KRAS testing rate by year of metastatic diagnosis (evaluated in June 2015)

* Line of treatment is determined at Flatiron through a series of disease-specific business rules based on review of real-world data by oncologists
Later lines of therapy are associated with a higher probability of KRAS testing.
Use our understanding of patient journeys...

mCRC diagnosed in 2012

- Tested IL
- Tested 2L
- Tested 3L+
- Not tested - appropriate
- Not tested inappropriate

2015: 71%
mCRC diagnosed in 2014

- Tested 1L
- Tested 2L
- Tested 3L
- Not tested - appropriate
- Not tested inappropriate

2015

57%
KRAS is among the most commonly altered gene in our lung cancer cohort, yet the implications of KRAS mutations are not yet understood.
Journey of a Patient on Targeted Therapy After NGS

Based on NGS testing, patient underwent treatment with **trametinib** in 2L

### ABOUT THE TEST:
FoundationOne® is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

### PATIENT RESULTS
- **3 genomic alterations**
- **3 therapies associated with potential clinical benefit**
- **0 therapies associated with lack of response**
- **15 clinical trials**

### TUMOR TYPE: LUNG ADENOCARCINOMA

#### Genomic Alterations Identified
- **KRAS**
  - **Q61H**
- **PTEN**
  - **loss**
- **CDKN2A/B**
  - **loss**

#### Additional Disease-relevant Genes with No Reportable Alterations Identified
- **RET**
- **ALK**
- **BRAF**
- **ERBB2**
- **MET**
- **EGFR**

---

### THERAPEUTIC IMPLICATIONS

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (in patient’s tumor type)</th>
<th>FDA Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS Q61H</strong></td>
<td>None</td>
<td><strong>Trametinib</strong></td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td><strong>PTEN loss</strong></td>
<td>None</td>
<td><strong>Everolimus</strong></td>
<td>Yes, see clinical trials section</td>
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<tr>
<td><strong>CDKN2A/B loss</strong></td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
</tr>
</tbody>
</table>

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient’s tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient’s tumor type.
Journey of a Patient on Targeted Therapy After NGS

Diagnosed with Stage II NSCLC

Undergoes surgery for early-stage disease

Develops metastatic disease

Tested for EGFR and ALK

Starts 1L therapy

Starts 2L trametinib (targeted therapy) for KRAS+

Progresses on 1L, undergoes NGS testing via Foundation

FLATIRON

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Journey of a Patient on Targeted Therapy After NGS

Diagnosed with Stage II NSCLC

Undergoes surgery for early-stage disease

Develops metastatic disease

Tested for EGFR and ALK

Starts 1L therapy

Starts 2L trametinib (targeted therapy) for KRAS+

Progresses on 1L, undergoes NGS testing via Foundation

• Biopsy date
• Site of biopsy
• Alterations found
• List of VUS
• Mutational load
• Microsatellite instability
• Variant annotation

• Patient age
• Gender
• Race
• Insurance
• TNM staging

• Sites of metastases

• Biopsy date
• Type of test conducted
• Turnaround time for test
• Number of unsuccessful tests
• Test result, if successful
• Type of EGFR mutation

• Regimen name
• Duration of therapy
• Dosage
• Concomitant meds
• Response

Structured EMR data
Unstructured EMR data
FMI Genetic Data
What About Outcomes For Other KRAS+ Patients?

PFS for NGS-Tested Patients

Design your cohort.  

Clinical Endpoint
- OS
- PFS

Start Date For PFS
- Initial Diagnosis Date
- Advanced Diagnosis Date
- 1st Line of Therapy Start Date

Add/Remove a second cohort

Filter Cohort 1 by:
- Gender
- Gene Alteration

Gene Name: KRAS  
Alteration Status: Altered

Filter Cohort 2 by:
- Gender
- Gene Alteration

Gene Name: KRAS  
Alteration Status: WT

PRELIMINARY ANALYSIS: DATA UNDER REVIEW