Research at scale—exploring what is possible with high-quality real-world data.

Examples from Flatiron Health

Amy Abernethy, MD, PhD
Chief Medical Officer/Chief Scientific Officer & SVP Oncology
Flatiron Health
Cohort Demographics

As of May 2018

Patients in cohort: 48,457 (Community: 44,422 | Academic: 4,035)

**Histology**

- Squamous cell carcinoma: 25.20%
- Non-squamous cell carcinoma: 69.10%
- Not otherwise specified: 12.10%

**Smoking Status**

- History of smoking: 86.20%
- No history of smoking: 12.10%
- Unknown / not documented: 1.80%
PDL1 Biomarker Testing and FDA Approvals of Immune Checkpoint inhibitors in NSCLC

PDL1 Status Among Tested Patients
- Positive: 16.6%
- Negative: 35.9%
- Unknown: 47.3%

PDL1 Testing Rate Among Actively Treated Patients

- Opdivo for recurrent squamous cell [Mar 2015]
- Keytruda for recurrent PDL1+ NSCLC [Oct 2015]
- Opdivo for recurrent NSCLC [Oct 2015]
- Keytruda for first line PDL1+ NSCLC [Oct 2016]
- Keytruda for first line NSCLC, regardless of PDL1 [May 2017]
- Keytruda plus chemo for first line NSCLC, regardless of PDL1 [May 2017]
- Keytruda for any MSI-High tumor [May 2017]
Patient Share by Therapy Class — PD1/PDL1

2nd or 3rd Line+

1% Q3 2014

50% Q2 2018
Cancer Drug Keytruda Keeps Some Patients Alive For 3 Years

by MAGGIE FOX

The drugs must be infused and they are pricey. Keytruda costs about $12,500 a month, or $150,000 a year.
Characteristics of Real-World Metastatic Non-Small Cell Lung Cancer Patients Treated with Nivolumab and Pembrozilizumab During the Year Following Approval

1344 patients treated with PD1 inhibitors in the first year after approval

1 year follow up
### Table 1. Characteristics of a cohort of 1,344 metastatic NSCLC patients who received nivolumab or pembrolizumab in the metastatic setting in U.S. community practices

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at PD-1 initiation, years, median (IQR)(^a)</td>
<td>69.0</td>
<td>(61.0–75.0)</td>
</tr>
<tr>
<td>Age categories at PD-1 initiation(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;49 years</td>
<td>45</td>
<td>(3.4)</td>
</tr>
<tr>
<td>50–64 years</td>
<td>435</td>
<td>(32.4)</td>
</tr>
<tr>
<td>65–74 years</td>
<td>500</td>
<td>(37.2)</td>
</tr>
<tr>
<td>75+ years</td>
<td>364</td>
<td>(27.1)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>597</td>
<td>(44.4)</td>
</tr>
<tr>
<td>Men</td>
<td>747</td>
<td>(55.6)</td>
</tr>
</tbody>
</table>

**Median age in clinical trials = 62; <8% were 75 or over**
No difference in overall survival by age group or line of therapy.
PDL1 expression predicts survival

**Findings:** Patients who were PD-1 positive had a significantly longer median survival time (by ~5 months) and higher 1-year survival probability than those who were PD-1 negative.
What does this story really tell us?
Exploding R&D Pipelines | Combination therapies

Segmenting patients & personalization

Rising cost & complexity of care

Value-based care | Better pricing models | Competition
The opportunity for Regulatory Grade RWE

21st Century Cures Act

“SEC. 505F. UTILIZING REAL WORLD EVIDENCE.

(a) In General.—The Secretary shall establish a program to evaluate the potential use of real world evidence—

(1) to help to support the approval of a new indication for a drug approved under section 505(c); and

(2) to help to support or satisfy post-approval study requirements.”
Current drug development paradigm

<table>
<thead>
<tr>
<th>Time</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV / Observational</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Regulatory Approval</td>
</tr>
<tr>
<td>Total Patients Exposed</td>
<td></td>
<td></td>
<td></td>
<td>General uptake in the market</td>
</tr>
</tbody>
</table>
21st Century Cures - Shift towards earlier approvals

Use of RWE to Monitor

Regulatory Approval

Earlier

Total Patients Exposed vs Time

I

II
How are we addressing this evolving landscape at Flatiron?
The Flatiron Network

2M
Active Patients

2,500
Clinicians

265
Cancer Clinics

800
Unique Sites of Care
Millions of electronic health records in a single common dataset.
Standardize EHR Data to a Common Data Model

Harmonization and normalization of structured data

- Certain structured data elements may be coded and collected in multiple ways in the EHR across practices (**example: albumin**)
- Combine and map datasets across sites to a single dataset
- Map all data elements to a single set of definitions (data model)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Unit</th>
</tr>
</thead>
<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>
<td>%</td>
</tr>
<tr>
<td>QD50055700</td>
<td>ALBUMIN</td>
<td>g/dL</td>
</tr>
<tr>
<td>CL3215104</td>
<td>Albumin % (EPR)</td>
<td>%</td>
</tr>
<tr>
<td>LC001081</td>
<td>ALBUMIN, SERUM (001081)</td>
<td>g/dL</td>
</tr>
<tr>
<td>LC003718</td>
<td>Albumin, U</td>
<td>%</td>
</tr>
<tr>
<td>LC001488</td>
<td>Albumin</td>
<td>g/dL</td>
</tr>
<tr>
<td>LC133751</td>
<td>Albumin, U</td>
<td>%</td>
</tr>
<tr>
<td>CL3215162</td>
<td>Albumin%, Urine</td>
<td>%</td>
</tr>
<tr>
<td>CL3215160</td>
<td>Albumin, Urine</td>
<td>mg/24hr</td>
</tr>
<tr>
<td>3234</td>
<td>ALBUMIN SS</td>
<td>g/dL</td>
</tr>
<tr>
<td>LC133666</td>
<td>Albumin, U</td>
<td>%</td>
</tr>
<tr>
<td>QD50060710</td>
<td>MICROALBUMIN</td>
<td>mg/dL</td>
</tr>
<tr>
<td>QD50061100</td>
<td>MICROALBUMIN/CREATININE RATIO, RANDOM</td>
<td>mcg/mg creat URINE</td>
</tr>
<tr>
<td>QD85991610</td>
<td>ALBUMIN</td>
<td>relative %</td>
</tr>
<tr>
<td>S0058600</td>
<td>ALBUMIN UPEP RAND</td>
<td>%</td>
</tr>
<tr>
<td>CL3210074</td>
<td>ALBUMIN LEVEL</td>
<td>g/dL</td>
</tr>
<tr>
<td>QD86008211</td>
<td>ALBUMIN/GLOBULIN RATIO  (calc)</td>
<td></td>
</tr>
<tr>
<td>LC149520</td>
<td>Albumin</td>
<td>g/dL</td>
</tr>
<tr>
<td>QD45069600</td>
<td>PREALBUMIN</td>
<td>mg/dL</td>
</tr>
</tbody>
</table>
Standardize EHR Data to a Common Data Model

Curate unstructured data from the chart

For every PD-1/PD-L1 test a patient receives, Flatiron biomarker Data Model captures:

- Test status
- Test result
- Date biopsy collected
- Date biopsy received by laboratory
- Date result received by provider
- Lab name
- Sample type
- Tissue collection site
- Type of test (e.g., FISH)
- Assay / kit (e.g., Dako 22C3)
- Percent staining & staining intensity

<table>
<thead>
<tr>
<th>Lab Name</th>
<th>Section of PD-L1 Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Collection Site</td>
<td>For every PD-1/PD-L1 test a patient receives, Flatiron biomarker Data Model captures:</td>
</tr>
<tr>
<td>Tissue Collection Site</td>
<td>For every PD-1/PD-L1 test a patient receives, Flatiron biomarker Data Model captures:</td>
</tr>
</tbody>
</table>

![Image of PD-L1 Report]

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Technology Enabled Abstraction

Expert abstractors

A network of abstractors comprised of oncology nurses, certified tumor registrars, and oncology clinical research professionals.

Flatiron Patient Manager

Software helps trained human abstractors efficiently organize and review unstructured documents to capture key data elements in predetermined forms.
Expanded with linked datasets.

<table>
<thead>
<tr>
<th>Flatiron</th>
<th>External</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Genomic</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Claims</td>
</tr>
<tr>
<td>Visits</td>
<td>Patient reported</td>
</tr>
<tr>
<td>Therapies</td>
<td>Mortality</td>
</tr>
<tr>
<td>Physicians Notes</td>
<td>Sensors</td>
</tr>
<tr>
<td>Discharge Notes</td>
<td></td>
</tr>
<tr>
<td>Pathology Reports</td>
<td></td>
</tr>
<tr>
<td>Radiology Reports</td>
<td></td>
</tr>
<tr>
<td>Mortality*</td>
<td></td>
</tr>
</tbody>
</table>

© Flatiron Health 2017
Resulting clinical data quality and completeness

<table>
<thead>
<tr>
<th>Variable</th>
<th>Structured data only</th>
<th>Flatiron data completeness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic diagnosis</td>
<td>26%</td>
<td>100%</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0%(^1)</td>
<td>94%</td>
</tr>
<tr>
<td>Histology</td>
<td>37%</td>
<td>99%(^2)</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%(^3)</td>
</tr>
<tr>
<td>EGFR results (of those tested)</td>
<td>11%</td>
<td>99%(^3)</td>
</tr>
</tbody>
</table>

\(^1\) 58% are free text in dedicated field in EHR (requiring hand abstraction)

\(^2\) Including 8% of patients with results pending or unsuccessful test

\(^3\) Including 6% of patients with results pending or unsuccessful test

### Completeness of technology-enabled abstraction

*Example: Advanced NSCLC*

<table>
<thead>
<tr>
<th>Site of met</th>
<th>Inter-abstractor agreement</th>
<th>Kappa</th>
</tr>
</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>

### Accuracy of technology-enabled abstraction

*Example: Sites of metastases*
Diagnosed with Stage II NSCLC

Undergoes surgery for early-stage disease

Develops metastatic disease

Tested for EGFR and ALK

Starts 1L therapy

Starts 2L therapy, deteriorates and is hospitalized

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

Death

Documentation of source, quality and provenance.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Stage at Dx</th>
<th>Biomarkers</th>
<th>2L Treatment</th>
<th>Progression</th>
<th>Date of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jane Doe</td>
<td>II</td>
<td>EGFR-, ALK-, PD-L1-</td>
<td>nivolumab</td>
<td>2017-03-08</td>
<td>2017-04-12</td>
</tr>
</tbody>
</table>

- **Diagnosed with Stage II NSCLC**
- **Undergoes surgery for early-stage disease**
- **Tested for EGFR and ALK**
- **Starts 1L therapy**
- **Starts 2L therapy, deteriorates and is hospitalized**
- **Progresses on 1L, tested for PD-L1 and re-tested for EGFR**
- **Death**
**Patient:** Jane Doe  
**Stage at Dx:** II  
**Biomarkers:** EGFR-, ALK-, PD-L1-  
**2L Treatment:** nivolumab  
**Progression:**  
-  
**Date of Death:** 2017-04-12

---

### Abstraction Details

- Abstracted by Sue Smith on 4/30/17 at 10:10am
- Physician notes and scan interpretation reviewed
- Medical record from West Florida Cancer Clinic

#### Quality of Progression abstraction

- Completeness: 99%
- Sue Smith is 96% accurate at last testing
- Inter-abstractor agreement: 97%
- Kappa: 0.93

- Audit trail for any changes
- Dataset freeze and storage

---

### Diagram Notes

- Undergoes surgery for early-stage disease
- Tested for EGFR and ALK
- Develops metastatic disease
- Diagnosed with Stage II NSCLC
- Progresses on 1L, tested for PD-L1 and re-tested for EGFR
- Starts 1L therapy
- Starts 2L therapy, deteriorates and is hospitalized
- Starts 1L therapy
- > Abstracted by Sue Smith on 4/30/17 at 10:10am
- > Physician notes and scan interpretation reviewed
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- Kappa: 0.93

- Audit trail for any changes
- Dataset freeze and storage

---
Diagnosed with GBM
Undergoes surgery
Receives adjuvant therapy
Progresses on adjuvant therapy
Starts 1L therapy
Starts on 2L
Progresses on 1L
Patient deteriorates leading to hospitalization / death

**Structured EMR data**
- Date of surgery
- Patient age
- Gender
- Race
- Insurance
- Group Staging
- Smoking Status
- Site of Disease
- Comorbidities
- Medical admins / orders
- Dosage
- Concomitant meds
- Regimen name
- Duration of therapy
- Adverse events
- Response
- Reason for discontinuation

**Unstructured EMR data**
- Date of met Dx (time to recurrence)
- Sites of metastases
- Date of progression (with scan or lab result to confirm)

**External mortality data**
- Date of death
- Date of death
- Date of death
- Consensus date of death

**Combined / derived data**
- Date of death
- Date of death
- Date of death

*Relative timing not exact*
Longitudinal cancer-specific registries with 30d recency & flexible data models

- Ovarian Cancer
- Advanced Head and Neck Cancer
- Small Cell Lung Cancer
- Advanced Urothelial Carcinoma
- Metastatic Prostate Cancer
- Advanced Gastric / Esophageal / GEJ Cancer
- Chronic Lymphocytic Leukemia
- Multiple Myeloma
- Metastatic Renal Cell Carcinoma
- Metastatic Colorectal Cancer
- Metastatic Breast Cancer
- Advanced Non-Small Cell Lung Cancer
- Advanced Melanoma
On the path to Regulatory Grade RWE

Data quality & validation is critical
RWE QUALITY

RWE is generated from high-quality data that are 1) retrieved from relevant RWD sources, 2) cleaned, harmonized, and normalized to fill in gaps, and 3) include endpoints. Quality assurance needs to encompass the entire process to generate RWE, from initial input sources and processing to defining appropriate use cases (Figure 1).

Figure 1. Open in figure viewer | Download Powerpoint slide

The journey from data to evidence. Real-world data (RWD) are data that are routinely collected in the form of electronic health records (EHRs), patient disease registries, wearables, genomic datasets, medical claims registries, and others. These data can be aggregated, linked, and processed to produce key conclusions in the form of real-world evidence (RWE). The proposed checklist can be used to assess if the quality of the RWD is regulatory-grade.

Abstract

The role of real-world evidence (RWE) in regulatory, drug development, and healthcare decision-making is rapidly expanding. Recent advances have increased the complexity of cancer care and widened the gap between randomized clinical trial (RCT) results and the evidence needed for real-world clinical decisions. Instead of remaining invisible, data from the >95% of cancer patients treated outside of clinical trials can help fill this void.

DEFINING RWE
Meta-characteristics of RWD and RWE
Regulatory grade RWE, a potential checklist

- **Clinical Depth**
  Data granularity to enable appropriate interpretation and contextualization of patient information.

- **Completeness**
  Inclusion of both structured and unstructured information supports a thorough understanding of patient clinical experience.

- **Longitudinal Follow-up**
  Ability to review treatment history and track patient journey going forward over time.

- **Quality Monitoring**
  Systematic processes implemented to ensure data accuracy and quality.

- **Timeliness / Recency**
  Timely monitoring of treatment patterns and trends in the market to derive relevant insights.

- **Scalability**
  Efficient processing of information with data model that evolves with standard of care.

- **Generalizability**
  Representativeness of the data cohorts to the broader patient population.

- **Complete Provenance**
  Robust traceability throughout the chain of evidence.
Data quality & analytic guidance provided with data deliverables

- Deliver comprehensive analytic guide including:
  - Study Overview
  - Research Questions
  - Inclusion/Exclusion Criteria
  - Data Elements
  - Baseline Characteristics
  - Data Quality and Provenance
  - Data Freeze and Retention Process
  - Overview of Abstracted Variables Data Quality
  - Measure Inter-Rater Reliability
  - Interpreting Agreement
  - De-identification of Flatiron Data
  - Analytic Notes
Non-small Cell Lung Cancer 1st line of therapy

NCCN Recommendation

- Molecular testing
  - Consider EGFR mutation and ALK testing in never smokers or small biopsy specimens, or mixed histology
  - Consider ROS1 testing
  - Testing should be conducted as part of broad molecular profiling
- PD-L1 testing

Testing

**ALK Gene Rearrangement**
- Positive
- Negative
- Not tested
- Unknown

**EGFR Mutation Status**
- Positive
- Negative
- Not tested
- Unknown

**ROS1 Rearrangement**
- Positive
- Negative
- Not tested
- Unknown
Effect of first line therapy on cost of care: NSCLC
What does this story really tell us?

- Data + technology infrastructure
- Tech + science + clinical + business
- Software enabled but still requires people
- Details matter
- Regulations matter
- Focus on your core customers & stakeholders

- Modernizing evidence development
- Democratization of care
- Better payment models
What is possible today?

What does this tell us about tomorrow?
Regulatory-Grade Real World Evidence
Use of real-world data to simulate clinical trial control arms:
Moving from historical controls to contemporaneous rwCA

CASE STUDY 1
Using RWE as a control arm

OS results: Alectinib Phase II data vs Flatiron RW control arm

Survival Probability

Time (months)

Median OS: 15.6
(95% CI: 13.5-NR)

Median OS: 26.0
(95% CI: 21.2-NR)

Adapted from Davies J, Martinec M, Martina R, Delmar P, Coudert M, Bordogna W, Golding S, Crane G. Retrospective indirect comparison of alectinib phase II data vs ceritinib real-world data in ALK+ NSCLC after progression on crizotinib. European Lung Cancer Conference (ELCC), May 5-8, 2017; Geneva Switzerland
Using RWE as a control arm (OS)

OS results: Alectinib Phase II data vs Flatiron RW control arm

Adapted from Davies J, Martinec M, Martina R, Delmar P, Coudert M, Bordogna W, Golding S, Crane G. Retrospective indirect comparison of alectinib phase II data vs ceritinib real-world data in ALK+ NSCLC after progression on crizotinib. European Lung Cancer Conference (ELCC), May 5-8, 2017; Geneva Switzerland
Using RWE as a control arm (RR/PFS)
<table>
<thead>
<tr>
<th></th>
<th>Flatiron (n = 107)</th>
<th>PALOMA-2 (n = 222)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unmatched analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PFS Median (95% CI)</strong></td>
<td>18.7 months (14.6 - 24.1)</td>
<td>14.5 months (12.9 - 17.1)</td>
</tr>
<tr>
<td><strong>ORR % (95% CI)</strong></td>
<td>40.2% (30.8 - 50.1)</td>
<td>38.3% (31.9 - 45.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Matched analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PFS Median (95% CI)</strong></td>
<td>18.5 months (13.7 - 24.1)</td>
<td>19.2 months (13.7 - Not Estimable)</td>
</tr>
<tr>
<td><strong>ORR % (95% CI)</strong></td>
<td>39.2% (28.4 - 50.9)</td>
<td>36.7% (26.1 - 48.3)</td>
</tr>
</tbody>
</table>
Figure 2: Progression-Free Survival in Patients Receiving First-Line Letrozole Therapy For HR+/HER2– Metastatic Breast Cancer

A. Unmatched Data

B. Propensity Score—Matched Data

Number of patients at risk

Flatiron RW
PALOMA-2 RCT

Time, months

Progression-free Survival, %

Flatiron RW cohort, median 18.2 (95% CI, 14.6–24.3) months
PALOMA-2 RCT cohort, median 14.3 (95% CI, 12.8–17.1) months

Flatiron RW cohort, median 18.5 (95% CI, 13.7–24.1) months
PALOMA-2 RCT cohort, median 19.2 (95% CI, 13.7–NE) months

CI=confidence interval; HR2=human epidermal growth factor receptor 2; negative; HR+=hormone receptor–positive; NE=not estimable; PFS=progression-free survival; RCT=randomized controlled trial, REW=rewind world

* Intent-to-treat population.

* Caliper width = 0.10.
Assessing safety in patients excluded from clinical trials:
Using real world evidence to fulfill a health authority request

CASE STUDY 2
Trastuzumab emtansine usage in low LVEF patients

Data Need

- EMA Pharmacovigilance Risk Assessment Committee (PRAC) requested data on safety outcomes for patients at risk for cardiotoxicity. These patients were excluded from a clinical trial due to safety concerns
- Roche was only able to find 3 patients who met the profile of interest across multiple prospective registries

Methods / Analysis

- Flatiron and Roche developed a retrospective study of safety outcomes in metastatic breast cancer patients in the Flatiron network who received trastuzumab emtansine and who were in the subpopulation of interest (LVEF≤50% at treatment initiation)
- rwEndpoints: cardiac outcomes

Impact

- Flatiron was able to identify over 50 patients who received trastuzumab emtansine who also met the profile of interest, and delivered a dataset on those patients (with annual upcoming refreshes planned)
- Flatiron data submitted to PRAC to inform risk/benefit assessment in this patient population, and study design has been accepted to fulfill post-marketing commitment
Defining the cohort of interest

- Patients with ICD9/10 diagnosis of breast cancer, two visits on or after 1/1/2011, structured medication order for trastuzumab emtansine
- Pathology consistent with breast cancer
- Evidence of stage IV or recurrent metastatic breast cancer (at any date)
- Treatment with trastuzumab emtansine as identified by a structured medication order or administration and confirmed through unstructured data
- LVEF ≤ 50% at time of trastuzumab emtansine initiation, as defined by the most recent measurement prior to trastuzumab emtansine initiation
- The most recent LVEF value between 40-50% up to 60 days prior to trastuzumab emtansine initiation
Data quality control

Assessing data quality of cardiac information

- Complex information in chart
- Duplicate abstraction
- Clinical adjudication

**Indication:** Cardiomyopathy. assess L.V function.

**Left Ventricle Ejection Fraction:** 46.9%

**Final Conclusions:**
1. Sinus rhythm.
2. This was a technically adequate study.
3. This was a limited exam for LV function assessment.
4. The left ventricular size is normal.
5. Left ventricular wall thickness is normal.
6. Overall left ventricular systolic function is mildly impaired with an EF between 45-50%. Stable from 2019. Okay for Kadyla.
7. Compared to prior study of , no change.

**INTERPRETATION SUMMARY**
The global left ventricular systolic function is low normal. LV EF is estimated at 50%
There is no evidence for regional wall motion abnormality.
RWE Case Study: Patient Journey

[Graph showing patient journey with lines of therapy, biomarkers, and outcomes]
RWE Case Study: Patient Journey

LVEF 45%

Kadcyla
RWE Case Study: Patient Journey

Monitor LVEF over time

Hospitalizations: Discern if cardiac or cancer related
Linking datasets in support of discovery:
Creating a continuously aggregating clinico-genomics database

CASE STUDY 3
Linked Clincogenomic Data Support Discovery

Comparison to TCGA

Figure 1 | Somatic mutations in lung adenocarcinoma. a, Co-mutation plot from whole exome sequencing of 230 lung adenocarcinomas. Data from TCGA samples were combined with previously published data\textsuperscript{12} for statistical analysis. Co-mutation plot for all samples used in the statistical analysis (n = 412) can be found in Supplementary Fig. 2. Significant genes with a corrected P value less than 0.025 were identified using the MutSig2CV algorithm and are ranked in order of decreasing prevalence. b, c, The
DATA FROM FH-FMI NSCLC CG Database

Reproduces and extends findings of the The Cancer Genome Atlas project

*NOTE: Data shown below reflects initial Q1 2016 link (n=770). Dataset is now n=2139, nearly 10x that of TCGA*
Supporting clinical trials

CASE STUDY 4
Reimagining the Clinical Trials Process

STARTUP & RECRUITMENT

- DESIGN
- FEASIBILITY
- SITE SELECTION
- ACTIVATION
- ENROLLMENT
- DATA CAPTURE
- MONITORING
- FOLLOW-UP

EXECUTION

DESIGN
Review patient records on an ongoing basis, identifying potentially eligible patients at the right time.

- Diagnosed with Stage II NSCLC
- Undergoes surgery for early-stage disease
- Develops Stage IV NSCLC
- Starts 1L therapy
- EGFR & ALK mutation -
- WATCH AND WAIT
- Progresses on 1L
- EGFR & ALK mutation - / PD-L1 +
- WINDOW OF ELIGIBILITY
- Starts 2L therapy
Study data is captured from the EHR - any EHR

Clinical data entered into the EHR does not need to be re-entered into an EDC
Remaining study data is captured through trial-specific notes and documents in the EHR

Example: Domains in an oncology study with EHR data source

- Demographics (DM)
- Subject Visits (SV)
- Con Meds (CM)
- Exposure (EX)

- Adverse Events (AE)
  - Disposition (DS)
  - Med History (MH)
  - Protocol Deviations (DV)
  - I/E Criteria (IE)
  - Lab Test Results (LB)
  - Physical Exam (PE)
  - Vital Signs (VS)
  - Tumor ID (TU)
  - Response (RS)
  - Procedures (PR)
  - Subject Elements (SE)
  - Death (DD)
  - Reproductive (RP)
  - Healthcare Encounters (HO)

Example: Flatiron Note for Adverse Events
Monitor the trial centrally, using direct access to source data in the Electronic Health Record
Prospective real world evidence is on a continuum with traditional clinical trials.
What is possible today?

What does this tell us about tomorrow?
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- Evolving role of data & technology
- Speed
- Artificial intelligence accelerates
- Rapidly changing standard of care
- Blurring of retrospective & prospective research
- Merging of care & research
- Tools for clinicians & patients
- Cost is just a variable in the model
- Stakeholders are involved differently
What does this tell us about tomorrow?

Learning Healthcare
Clinical Evidence Development
Personalized Medicine
Patient-centered Care
Value Based Care
Outcomes Based Pricing
Competition
Thank you

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