Precompetitive Data Sharing and Collaboration to Develop PD-1/PD-L1 Combinations

National Cancer Policy Forum

17 July 2018

FOUNDATION MEDICINE®

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Disclosures

I am a salaried employee and shareholder of Foundation Medicine

Topics

1. Background & Context: Biomarkers & Real World Data (RWD)
2. A case study in bridging data silos to unlock the potential of RWD
3. Potential impact of RWD on immunotherapy research and development

BACKGROUND

Biomarkers & Real World Data (RWD)

Biomarkers in Cancer Immunotherapy

Increasing importance
Growing complexity
Emerging challenges

1

Complexity

No single biomarker today completely predicts who will or won't respond to immunotherapy

2

Heterogeneity

Each study looks at a single therapy or regimen, specific endpoints, select biomarkers and thresholds

3

Generalizability

Clinical trials study selected populations – how do these results apply to the range of patients treated in the "real world"

Real World Data is emerging as a key enabler

Numerous efforts are actively underway to bridge **data silos** (genomic + clinical data) and **institutional silos** (across institutions and across practice settings) to begin to **apply real world data to important problems in oncology**

ACADEMIC MEDICAL CENTERS

VANDERBILT-INGRAM CANCER CENTER

Memorial Sloan Kettering Cancer Center

DANA-FARBER CANCER INSTITUTE

UCSF

Wake Forest® Baptist Medical Center
Comprehensive Cancer Center

Yale CANCER CENTER

CONSORTIA

AACR American Association for Cancer Research
FINDING CURES TOGETHER™

PROJECTGENIE
Genomics Evidence Neoplasia Information Exchange

ASCO CANCER LINQ LLC
Learning Intelligence Network for Quality

STAND UP TO CANCER

PMEC

INDUSTRY COLLABORATIONS

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Use of Real World Evidence

Beginning to understand opportunities to use real world endpoints derived from the EHR

FRIENDS of CANCER RESEARCH

Establishing a Framework to Evaluate Real-World Endpoints

July 10, 2018
Washington, DC

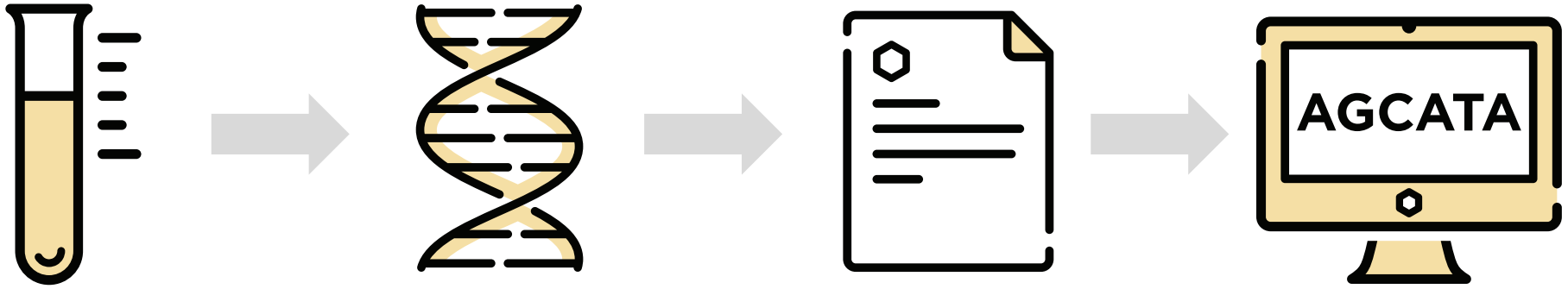
A CASE STUDY

The Clinicogenomic Database (CGDB)

A collaboration between a genomics lab (Foundation Medicine) and an EMR/data company (Flatiron Health) to bridge real world data silos

FoundationCORE™

Building a World-Class Genomic Database



2000+ samples
sent *each week* to Foundation Medicine for analysis from 100s of centers across the country

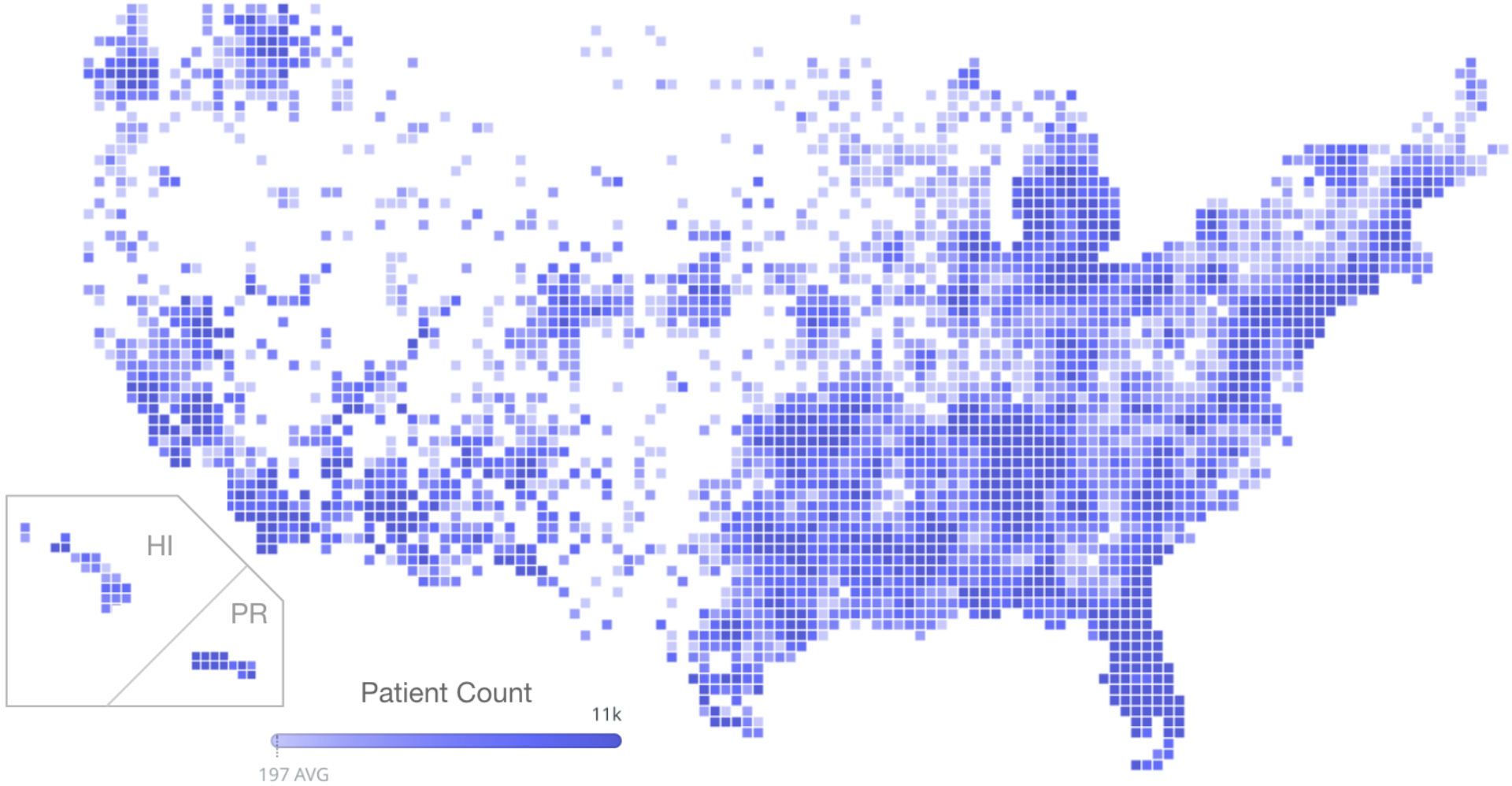
Sequencing
is performed on a highly validated[1] platform, identifying all classes of mutations in >300 genes

Reports
are sent to ordering doctors with genomic findings and therapies and trials to consider

FoundationCORE™
contains >200,000 de-identified results, including genomic alterations, tumor mutational burden, microsatellite instability (MSI), and, for many patients, PD-L1 results

[1] *Frampton et al., Nature Biotech 2013*

Flatiron: EHR data integrated at the source



2M
Active Patients

2,500
Clinicians

265
Cancer Clinics

800
Unique Sites of Care

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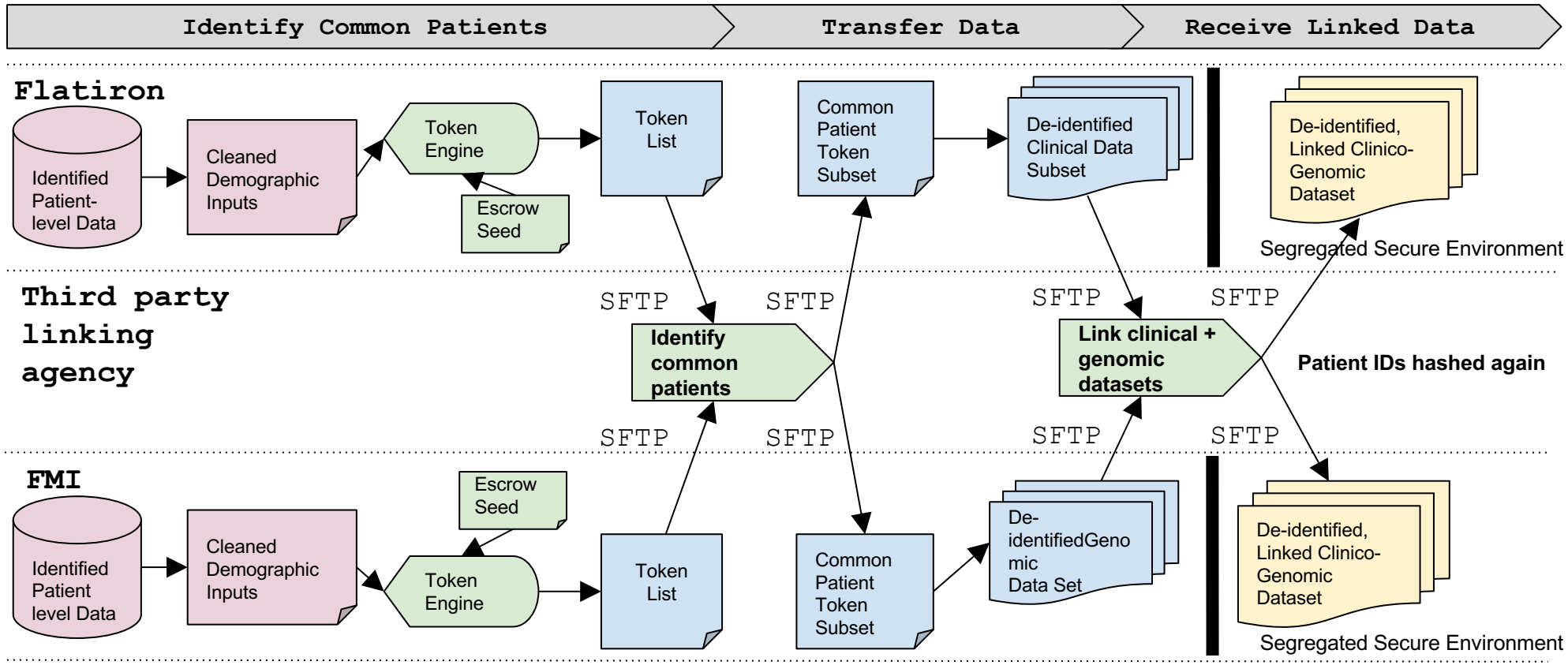
Linking genomic and clinical datasets



Red - Identified Data
Blue - De-identified Data
Yellow - De-identified Linked Data
Green - Third party linking agency's technology

This entire process is repeated quarterly at FH-FMI for longitudinal refresh of the data (e.g., new chart abstraction)

Final linked clinico-genomic dataset cannot be re-identified or linked to other FH or FMI datasets (unique patient ID)

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Development and Validation of a Real-World Clinico-Genomic Database

Gaurav Singal[1], Peter Grant Miller[1], Vineeta Agarwala[2], Jie He[1], Anala Gossai[2], Gerald Li[1], Shannon Frank[2], David Bourque[1], Bryan Bowser[2], Thomas Caron[2], Ezra Baydur[2], Kathi Seidl-Rathkopf[2], Ivan Ivanov[2], Alex Parker[1], Ameet Guria[1], Garrett Michael Frampton[1], Ann Jaskiw[2], Dana Feuchtbaum[2], Nathan Coleman Nussbaum[2], Amy Pickar Abernethy[2], Vincent A. Miller[1]

[1]Foundation Medicine, Inc., Cambridge, MA, and [2]Flatiron Health, New York, NY

BACKGROUND

- Genomic findings have diagnostic, prognostic, and predictive utility in clinical oncology.
- Population studies have been limited by reliance on trials, registries, or institutional chart review, which are costly and represent narrow populations.
- Integrating electronic health record (EHR) and genomic data collected as part of routine clinical practice may overcome these hurdles.

METHODOLOGY

- Oncology patients from community practices were identified for whom Flatiron EHR abstraction and Foundation Medicine next generation sequencing (NGS) was performed
- The information was linked in a HIPAA-compliant fashion through a third party to create the clinico-genomic database (CGDB) which is updated quarterly
- Currently there are 2139 non-small cell lung cancer (NSCLC) cases, which were used as a validation set for the database

Figure 1. Schematic of generation of CGDB (left) and cohort selection (right).

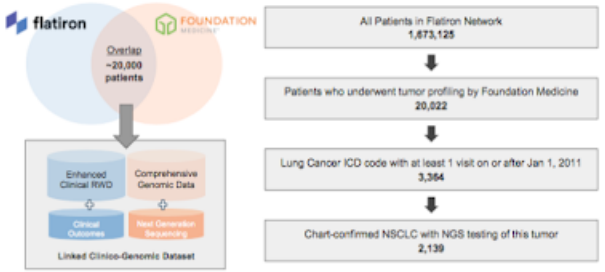
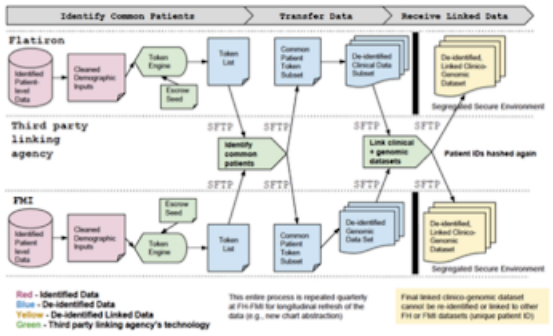


Figure 2. The linking of patient data between Flatiron and Foundation databases is performed by generation of a token list and subsequent linking of the tokens using a third party in an IRB-approved, HIPAA-compliant fashion.



RESULTS

CLINICAL CHARACTERISTICS

Table 1. Clinical characteristics of patients in the clinico-genomic database. The distribution of features such as median age, smoking history, and histology are consistent with prior studies.

Total Patient Count	2139	**Stage of Disease**	
		Stage I	207 (9.68%)
Age at advanced diagnosis (median, [IQR])	66.0 (58.0-73.0)	Stage II	161 (7.53%)
Gender		Stage III	403 (18.8%)
Female	1146 (53.6%)	Stage IV	1243 (58.1%)
Male	993 (46.4%)	Not reported	124 (5.80%)
Smoking Status		**Histologic Subtype**	
History of Smoking	1600 (74.8%)	Non-squamous cell carcinoma	1706 (79.8%)
No History	489 (22.9%)	NSCLC NOS	118 (5.52%)
Unknown / Not documented	50 (2.34%)	Squamous cell carcinoma	315 (14.7%)
Race		**Number of LOT Received**	
Asian	80 (3.74%)	0	722 (33.8%)
Black or African American	108 (5.05%)	1	633 (29.6%)
White	1407 (65.8%)	2	405 (18.95)
Other / Unknown	544 (25.4%)	3+	379 (17.7%)

GENOMIC CHARACTERISTICS

Figure 3. Genomic characteristics of the NSCLC tumors in the clinico-genomic database are largely consistent with prior studies in large populations, including the TCGA. As expected, the presence of a driver mutation (EGFR, ALK, ROS1, MET, BRAF, RET, or ERBB2) was associated with younger age, female gender, and non-smoking status.

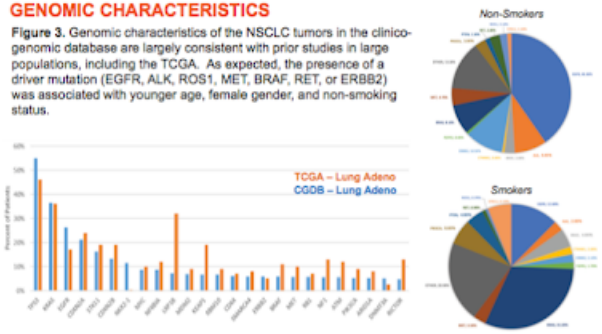
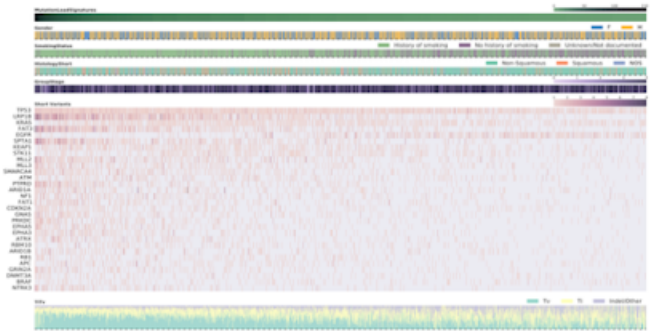


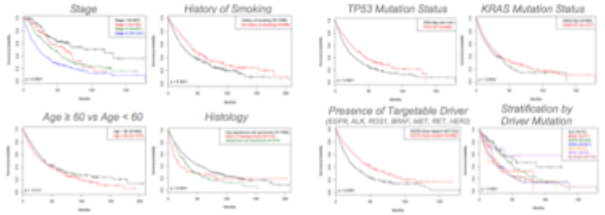
Figure 4. Representation of integrating clinical and genomic features from the database.



RESULTS

CLINICAL AND GENOMIC PROGNOSTIC IMPLICATIONS

Figure 5. Kaplan-Meier overall survival analysis from initial diagnosis recapitulates known relationships with clinical and genomic features in NSCLC. Advanced stage, older age, a history of smoking, and squamous histology were all associated with a worse overall survival (left). TP53 and KRAS mutations were associated with worse OS. The presence of a targetable driver was associated with a higher OS, with variation among the specific driver subtypes (right).



TESTING AND THERAPEUTIC RESPONSE PREDICTION

Figure 6. Using the CGDB to understand and predict response to therapy. The presence of an EGFR mutation was predictive of response (defined as both survival and maximal response to therapy), use of NCCN-recommended therapy when appropriate was associated with increased OS, and higher TMB was associated with increased duration on the PD-1 blocking agent, Nivolumab.

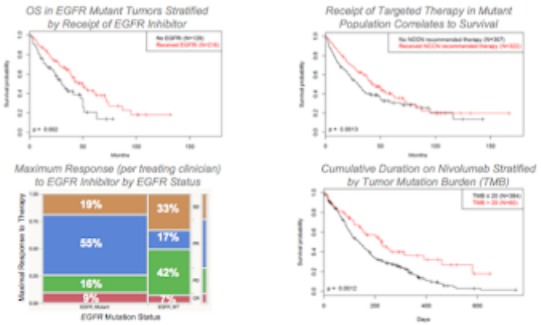


Table 2. EGFR and ALK results documented in the EHR ("Outside") and from Foundation Medicine ("FMI") testing. Outside testing was considered "mutant" if any test was reported as positive. Of the 14 patients (bold, asterisk) documented as ALK WT by outside testing and mutant by FMI, 11 received an ALK inhibitor, with a mean duration on treatment of 219 days. Of the 5 discordant patients with a documented maximal response in the EHR, 4 had a partial response and 1 had stable disease.

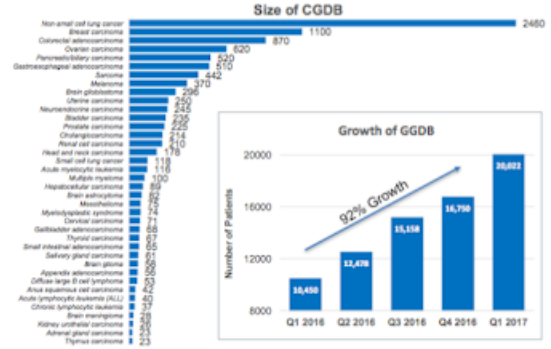
EGFR		Outside Testing: WT (n=675)	Mutant (n=187)	Discrepancy	Unknown/Not Performed (n=1270)
FMI Testing	WT (n=1747)	621	21	3.3%	1105
	Mutant (n=385)	54	166	24.5%	165

ALK		Outside Testing: WT (n=716)	Mutant (n=43)	Discrepancy	Unknown/Not Performed (n=1373)
FMI Testing	WT (n=2047)	702	8	1.1%	1337
	Mutant (n=85)	**14***	35	28.6%	36

FUTURE DIRECTIONS

GROWTH OF THE CLINICO-GENOMIC DATABASE

Figure 7. Patient counts and growth of the clinico-genomic database, by disease (June 2017). The CGDB covers 38 tumor types and continues to grow and receive updates on a quarterly basis.



FUTURE APPLICATIONS

- **Unmet Needs**
  - Populations for whom current treatments do not exist
  - Therapies for whom an appropriate population needs to be better defined
- **Trial Design**
  - Characterizing the natural history of a biomarker-defined population for trial design
  - Integration of NGS testing into trials to further biomarker and drug discovery
- **Targeted Therapy**
  - Prioritizing genomic lesions for drug development
  - Better understanding of mechanisms of resistance to current therapies
- **Immuno-Oncology**
  - Integrating tumor mutation burden into our predictive and prognostic algorithms
  - Defining genomic subpopulations with differential sensitivity to checkpoint blockade
  - Rational approaches to combining targeted therapy with checkpoint blockade

CONCLUSIONS

- We have built a de-identified, HIPAA compliant, real-world clinico-genomic database by linking longitudinal clinical data with high resolution genomic information. The dataset consists of 2139 NSCLC cases, more than 20,000 total cases, and is both growing and updated on a quarterly basis.
- The clinico-genomic database shares similar genomic and clinical characteristics as NGS-tested population estimates, and recapitulates a broad array of expected findings regarding (a) genomic prognostic factors, (b) clinical prognostic factors, and (c) genomic implications for therapeutic response.
- Future uses include novel biomarker discovery, better clinical trial design, comparative effectiveness of therapeutics, and better characterizing natural history of genomic subpopulations (e.g., to serve as in silico control arms)

APPLICATIONS

Potential Impact of RWD

RWD may help address some of the existing challenges with cancer immunotherapy biomarker research

Opportunity 1: Generalizability

Clinical trial results, especially for genomic populations, may benefit from RWD for generalizability

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FIRST OPINION

We need more answers about immunotherapy for the elderly

By ANKUR PARIKH / JUNE 22, 2018

Half of cancer patients are over the age of 65, while only 17% of patients in clinical trials are

https://www.statnews.com/2018/06/22/immunotherapy-elderly-cancer-treatment/

Pembrolizumab Response Rate by Tumor Type.*

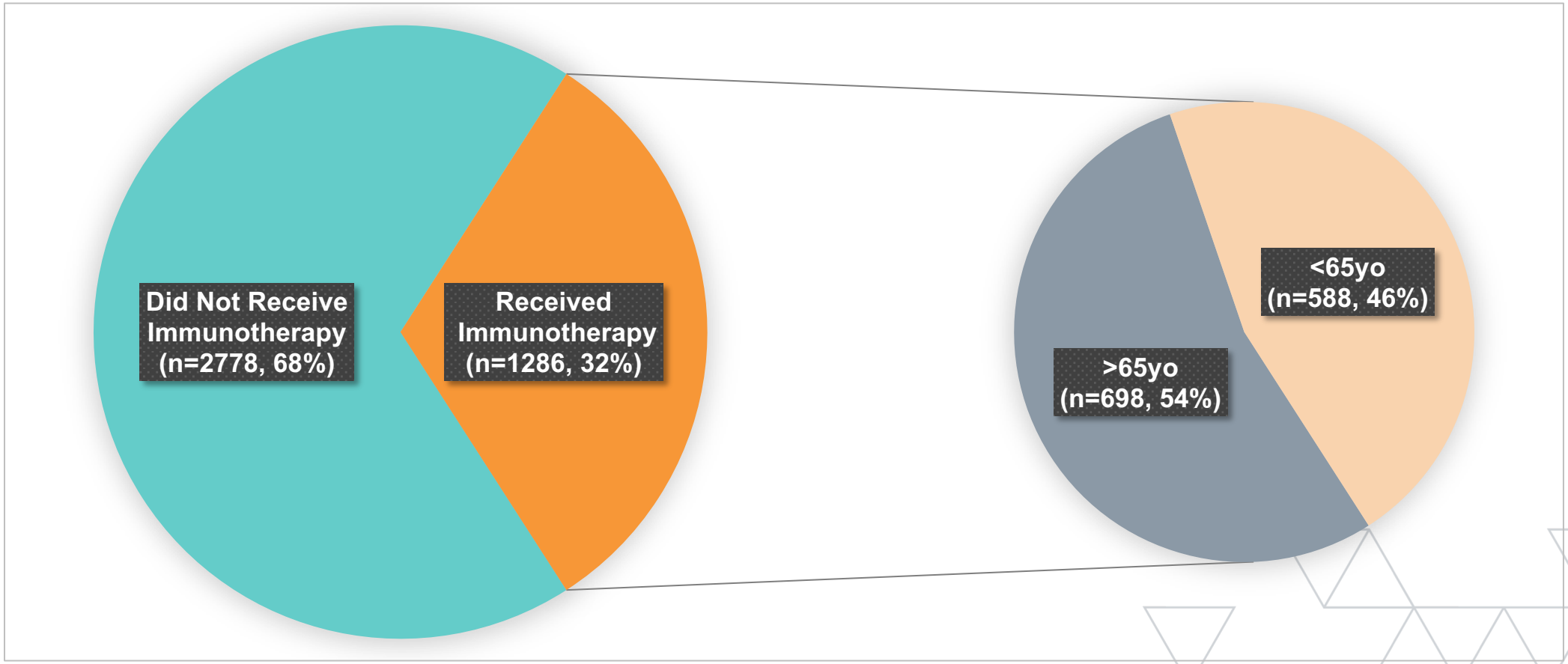
Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

Studies of rare biomarkers, especially when histology agnostic, often include few (or no) patients in some histologies

Challenge 1: Generalizability

Real world data can help us evaluate non-clinical trial populations

In the Flatiron-Foundation Medicine Clinicogenomic Database of ~4000 patients with non-small cell lung cancer:



Use of Cancer Immunotherapies in the Real-World in the Setting of Microsatellite Instability

Vineeta Agarwala MD PhD[1,3], Anala Gossai PhD[1], Gaurav Singal MD[2], Claire O'Connell[1], Gerald Li PhD[2], Ken Kao[1], David Bourque[2], Dana Feuchtbaum[1], Garrett Alpha Cobb PhD[2], Allen Nunnally[2], Sarah Kramarz[1], Sally Trabucco PhD[2], Garrett Frampton PhD[2], Siraj Ali MD PhD[2], Amy Abernethy MD PhD[1]

[1] Flatiron Health, New York, NY
[2] Foundation Medicine, Cambridge, MA
[3] Stanford University School of Medicine, Stanford, CA

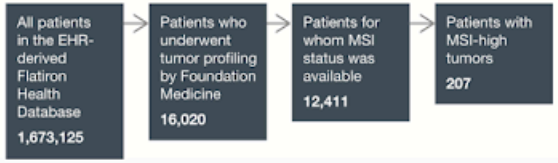
Background

- In May 2017, the FDA issued its first tissue/site agnostic drug approval.[1]
- Pembrolizumab was approved for unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors.
- Real-world data on the frequency of MSI/dMMR across tumor types and the impact on treatment selection are scant, especially outside of colorectal cancer.[2,3,4]

Methods

- This retrospective study utilized the EHR-derived Flatiron-Foundation Medicine linked Clinico-Genomic Database. The study cohort included all patients diagnosed in the Flatiron Health network (>265 community and academic oncology practices, representing ~800 distinct sites of care across the U.S.) between January 2011 and May 2017, who also underwent FoundationOne next generation tumor sequencing as part of routine clinical care.
- Clinical and genomic data were linked at the patient level via a third party linking agency in a HIPAA-compliant process. The resulting database was strictly de-identified.
- Clinical data were curated from electronic health records, through normalization and standardization of structured data elements (e.g. demographics, medication administration).
- Tumor type was determined by pathologist review of specimens submitted to Foundation Medicine.
- Genomic data were obtained from Foundation Medicine next-generation tumor sequencing across the coding regions of >300 cancer-related genes. Data included alteration-level detail, as well as specimen-level MSI status and tumor mutation burden (# mutations / Mb). To assess MSI status, optimized homopolymer repeat loci on the FoundationOne sequencing panel were analyzed for length variability and compiled into an overall MSI score via principal components analysis. Each microsatellite locus had repeat length of 7-39 bp. The next-generation sequencing based "MSI score" was translated into categorical MSI-High (MSI-H), MSI ambiguous, or microsatellite stable (MSS) by unsupervised clustering of specimens for which MSI status was previously assessed via gold standard methods (e.g., IHC).[4]

Figure 1: Cohort Selection



Results

Rate of MSI-high and high TMB in the real-world

- As of May 2017, the linked Clinico-Genomic Database included 16,020 patients, among whom MSI status could be assessed in 12,411 patients (**Figure 1**).
- The overall rate of MSI-high was 1.7% (207/12,411) across all tumor types combined.
- Tumor-specific rates of MSI-high varied significantly, from 4.9% in colorectal adenocarcinoma to 0.3% in breast and non small cell lung cancer (**Table 1, Figure 2**). The rate of MSI-high was relatively high (2.4%) among patients with an unknown primary based on pathology review (**Figure 2**).
- Likewise, the frequency of high tumor mutational burden (TMB>20) varied across tumor types, ranging from 12.6% in non-small cell lung cancer to 2.3% in breast cancer (**Table 1**).

Rate of treatment with checkpoint inhibitors

- A total of 1,534 patients in the database received common checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab). Among those checkpoint-inhibitor treated patients with known MSI status (n=1,363), 21 (1.5%) had MSI-high tumors, and colorectal cancer was the most common tumor type among these patients (n=8).
- Among all 207 patients in the database with MSI-high tumors, 21 (10.1%) received therapy with checkpoint inhibitors.
- When comparing MSI-high patients in the data set as of May 2017 vs. a longitudinally refreshed dataset including n=18,931 total patients (n=14,944 with MSI status available) treated through September 2017, the overall rate of MSI-high remained similar (251/14,944 = 1.7%). However, the rate at which MSI-high patients were treated with checkpoint inhibitors increased from 10.1% (21/207) in May 2017 to 15.1% (38/251) in September 2017 (**Figure 3**).

Table 1:
Real-World Rates of Microsatellite Instability and High Tumor Mutation Burden in Patients with Common Tumor Types

	Breast Carcinoma N=1703	Colorectal Adeno-carcinoma N=1911	Non-Small Cell Lung Cancer N=3050	Other tumor types combined N=8315	Unknown Primary N=1041
# MSI High (%)	4 (0.23%)	73 (3.82%)	8 (0.26%)	103 (1.24%)	19 (1.83%)
# MSI Stable (%)	1249 (73.3%)	1408 (73.7%)	2353 (77.1%)	6299 (75.8%)	774 (74.4%)
# MSI Ambiguous (%)	10 (0.59%)	22 (1.15%)	28 (0.92%)	56 (0.67%)	6 (0.58%)
# MSI unknown (%)	440 (25.8%)	408 (21.4%)	662 (21.7%)	1857 (22.3%)	242 (23.2%)
% patients MSI High, excluding unknown	0.32%	4.86%	0.34%	1.59%	2.38%
Mean TMB (mut/Mb) [IQR]	3.60 [1.80;5.41]	3.78 [2.70;6.31]	7.21 [2.70;13.5]	2.70 [1.67;5.41]	3.78 [1.80;9.01]
% patients TMB High (TMB>20)	39 (2.29%)	100 (5.23%)	384 (12.6%)	464 (5.58%)	111 (10.7%)

Figure 2:
Real-World Rates of Microsatellite Instability in Different Common Tumor Types

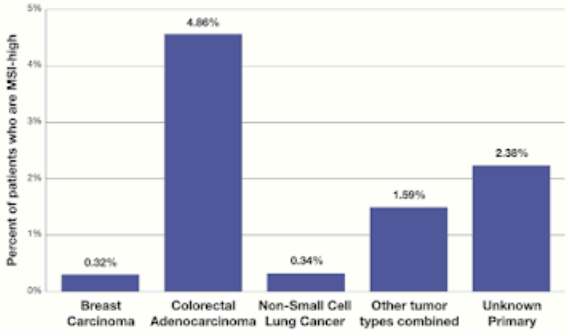
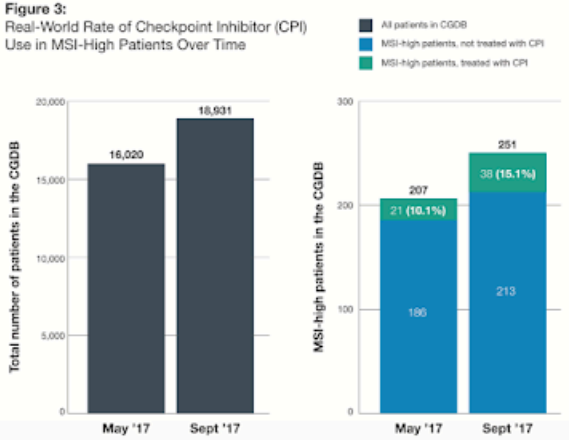


Figure 3:
Real-World Rate of Checkpoint Inhibitor (CPI) Use in MSI-High Patients Over Time



Conclusions

- MSI-high is rare in real world cancer care settings among patients who undergo next generation sequencing (<2%), with significant variability in frequency among disease sites.
- The rate of MSI-high in cancers of unknown primary is higher than many other cancer types. MSI/MMR assessment (including by NGS) may be particularly important in this clinical setting in order to guide treatment choice.
- Early data suggests that the rate at which MSI-high patients are being treated with checkpoint inhibitors is increasing over time. Further evaluation of the real-world effectiveness of immune checkpoint inhibitors in the MSI-high population is still needed.
- Because deficient mismatch repair is an uncommon event, most patients receiving checkpoint inhibitors do not have MSI-high tumors. As such, exploration of additional biomarkers for immunotherapy response is critical. Tumor mutational burden, which may be associated with neoantigen expression, is one example of a biomarker that is being explored as a putative predictor of clinical benefit from immune checkpoint inhibitors.

Limitations

- Before September 2017, MSI status was calculated retrospectively from tumor sequencing data, and was not, in most cases, reported to treating physicians in order to guide treatment decisions.
- In some cases (e.g., in colorectal cancer patients), physicians may have separately ordered MSI testing (from another diagnostic laboratory) in order to learn the MSI status for their patients.
- As with any retrospective real-world data set, this convenience cohort may not be a representative sample of all cancer patients.

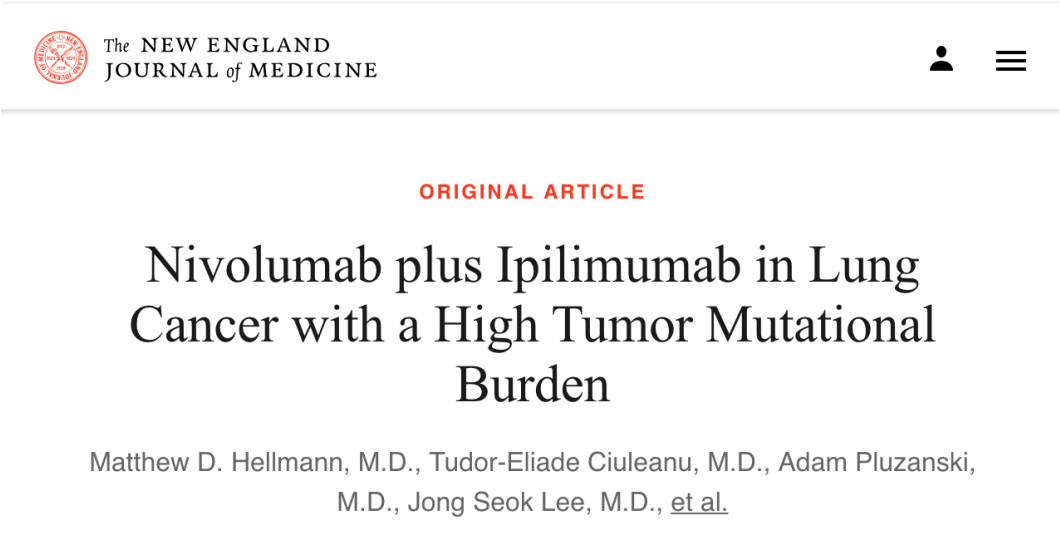
References

1. The U.S. food and Drug Administration. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm>. May 30, 2017.
2. Campbell, B. B. et al. Comprehensive Analysis of Hypermutation in Human Cancer. Cell 171, 1042-1056 e1010, doi:10.1016/j.cell.2017.09.048 (2017).
3. Hause, R. J., Pritchard, C. C., Shendure, J. & Salipante, S. J. Classification and characterization of microsatellite instability across 18 cancer types. Nat Med 22, 1342-1350, doi:10.1038/nm.4191 (2016).
4. Chalmers, Z. R. et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 9, 34, doi:10.1186/s13073-017-0424-2 (2017).

This poster was presented at the 2018 ASCO-SITC Clinical Immuno-Oncology Symposium; Jan 24-25, 2018. For additional information, contact Vineeta Agarwala at vineeta@flatiron.com.

Opportunity 2: Heterogeneity

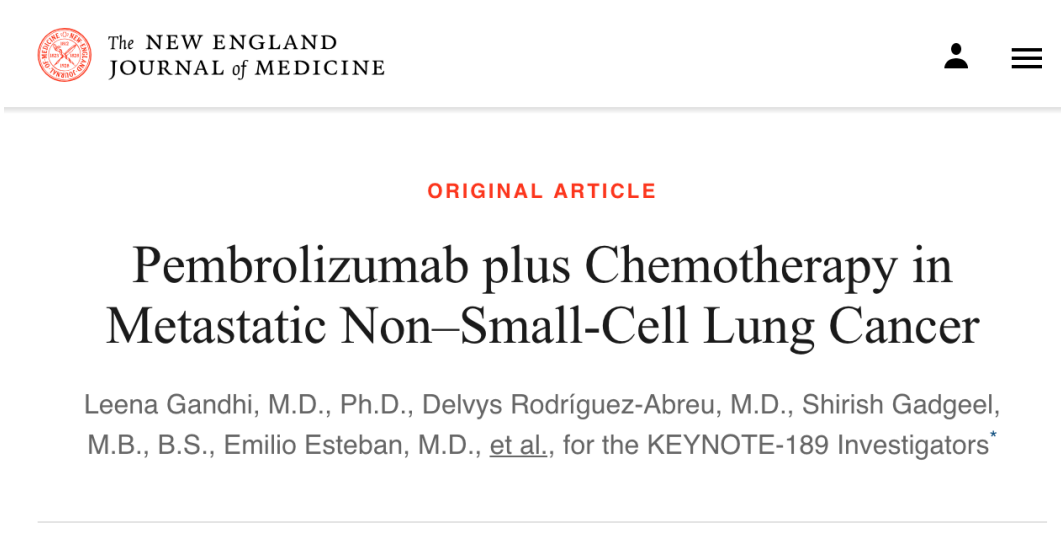
Each study studies individual patient populations, therapies, and biomarkers



CHECKMATE-226[1]

Therapies: Nivolumab + Ipilimumab

Biomarkers: PD-L1 (multiple thresholds), Tumor Mutational Burden (10 mut/Mb)



KEYNOTE-189[2]

Therapies: Pembrolizumab + Chemotherapy

Biomarker: PD-L1 (multiple thresholds)

[1]Hellmann MD et al. N Engl J Med 2018;378:2093-2104
[2]Socinski MA et al. N Engl J Med 2018;378:2288-2301

Opportunity 3: Complexity

RWD can help tackle the complexity of immunotherapy response and resistance

ORIGINAL ARTICLE

Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma

Jesse M. Zaretsky, B.S., Angel Garcia-Diaz, Ph.D., Daniel S. Shin, M.D., Helena Escuin-Ordinas, Ph.D., et al.

Observations from 4 patients who developed resistance to immunotherapy in melanoma at a single academic medical center, who ultimately underwent advanced sequencing

Zaretsky JM et al. N Engl J Med 2016;375:819-829

CANCER DISCOVERY

Research Articles

STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma

Combining RWD from multiple academic medical centers led to the discovery of a new resistance mechanism for immunotherapy

Skoulidis F et al. Cancer Discovery 2018

Concluding thoughts & Open Questions

Concluding Thoughts

- Multiple **real world data sets are emerging:** across academic medical centers, consortia, and industry-driven initiatives.
- These **datasets can complement and extend data generated through clinical trials** – helping generalize findings, evaluate multiple therapies with common biomarkers, and explore the complexity of evolving disease.
- Additional applications could include better trial design and assessment of post-approval efficacy, especially of histology agnostic therapies

Open Questions

- Can real world data be used to **accelerate development of therapies for niche patient populations** by serving as a real world control arm?
- Can real world data be used to **facilitate discovery of new targets and combinations**, perhaps by engaging patients in research?
- How will complex biomarkers ultimately be **translated into clinical care and decision making**, and what role will real world data and technology play?

Thank you