Identification of resistance mechanisms to EGFR treatment in the real world using a clinicogenomic database

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INTRODUCTION

- Use of targeted therapies often results in resistance mediated by genomic evolution. However, discovery of resistance mechanisms has historically been opportunistic.
- A more scalable approach may be to uncover resistance mechanisms from real world patient experience. Use of a clinico-genomic database (CGDB) that integrates electronic health record (EHR) and genomic data collected as part of routine clinical practice may overcome these hurdles.

METHODOLOGY

GENERATION OF THE CLINICOGENOMIC DATABASE

- We developed a real-world clinicogenomic database (CGDB) of patients with non-small cell lung cancer (NSCLC). NGS testing and EHR data were linked through a HIPAA de-identification linking process (Singal et al, ASCO 2017).
- Patients (1) underwent profiling with Foundation Medicine's FoundationOne next generation sequencing (NGS) assay as part of routine care, and (2) have electronic health record (EHR) data in the Flatiron Health database.
- A cohort of patients diagnosed with NSCLC having received a 1st or 2nd-generation EGFRi were subset for analysis.
- As demonstration of the ability to identify resistance mechanisms from real world data, we examined differences in alterations within EGFRi-treated NSCLC patients pre- and post-EGFRi treatment in a 'hypothesis-agnostic' manner, without interrogation of known resistance mechanisms *a priori.*
- Analyses presented here are performed on the January 2017 version of the NSCLC-CGDB, derived from 20K patients. For all analyses (Fig. 4-8), Fisher's exact test was applied to genes (Fig. 4-7) or alterations (Fig. 8) with >1% prevalence. Top 25 genes/alterations by prevalence shown.

Figure 1. Schematic of generation of CGDB (left; January 2017 version) and NSCLC cohort selection (right).

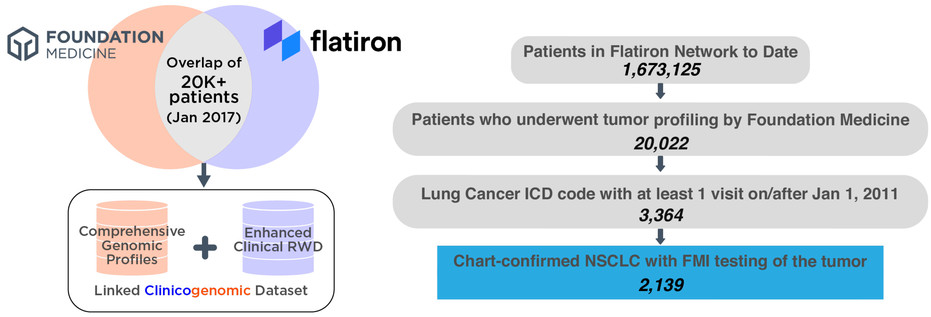
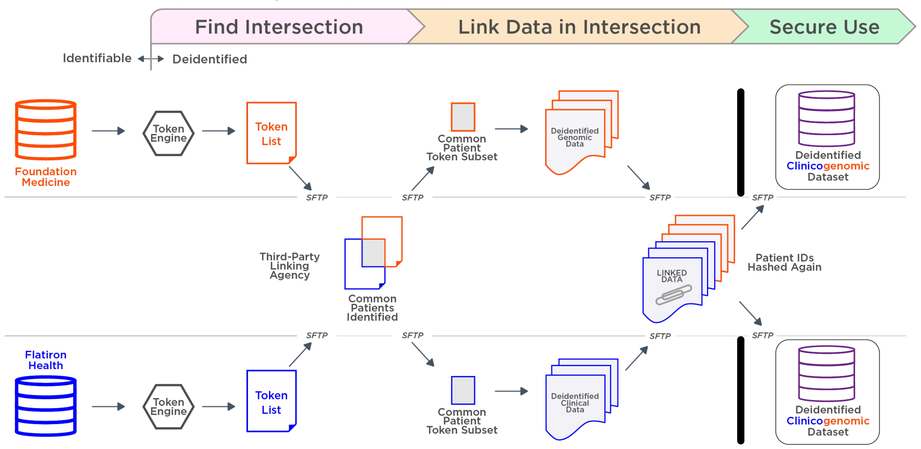


Figure 2. Linking of patient data between Flatiron and Foundation databases is performed via tokenized PHI by a third party in an IRB-approved, HIPAA-compliant fashion. The dataset contains both enhanced clinical Real World Data (RWD) and comprehensive genomic profiles, IHC, and annotations.



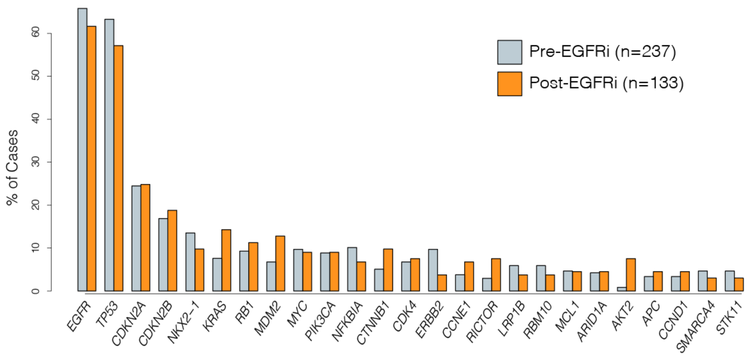
EGFRi COHORT SELECTION

Figure 3. Patients who received first and second generation EGFR inhibitors **(EGFRi; afatinib, cetuximab, erlotinib, gefitinib, lapatinib, panitumumab)** were segmented into those undergoing NGS testing before treatment ("pre-treatment cohort") and those biopsied at least 3 months after treatment start ("post-treatment cohort").

RESULTS

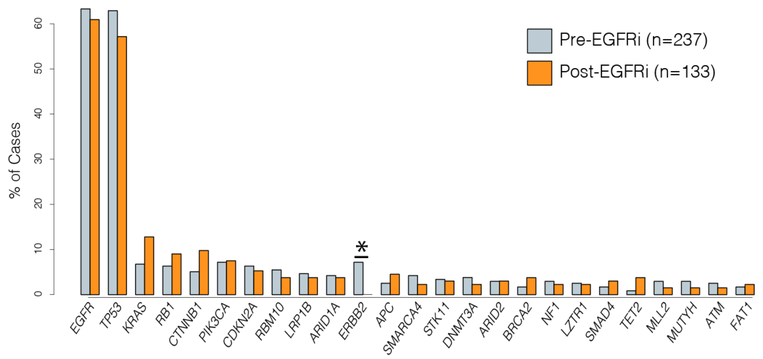
GENOMIC LANDSCAPE OF EGFRi-TREATED PATIENTS

Figure 4. Long-tail plot of genes having short variants (SNVs and indels), copy number alterations, and/or complex arrangements (e.g. fusions). Comparison is done between patients sequenced pre- and post-treatment with an EGFRi.



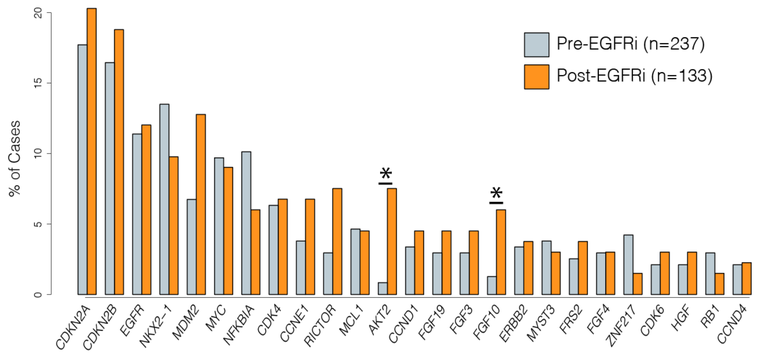
SHORT VARIANTS

Figure 5. Long-tail plot of genes with short variants (SNVs and indels). Segmented by patients sequenced pre- and post-treatment with an EGFRi. The frequency of ERBB2 short variants was significantly lower in the post-treatment cohort (7.2% vs 0%, p=0.0005). Note: <65% of EGFRi-treated patients were found to have an EGFR SV.



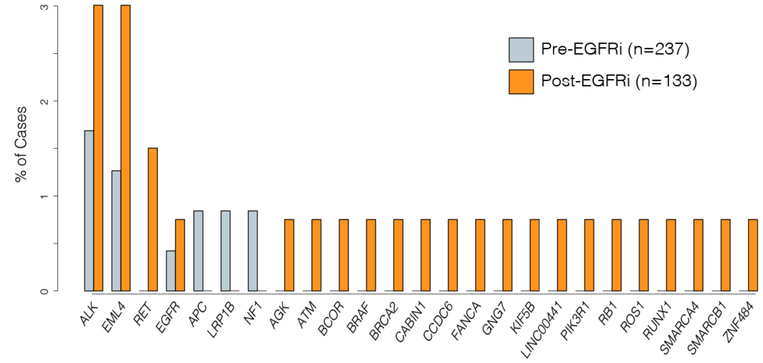
COPY NUMBER ALTERATIONS

Figure 6. Analysis of copy number variations demonstrated significant post-treatment enrichment of amplifications in AKT2 (0.84% vs 7.5%, p<0.001) and FGF10 (1.3% vs 6.0%, p=0.02). RB1 loss, a previously-observed resistance mechanism, was observed but did not reach significance.



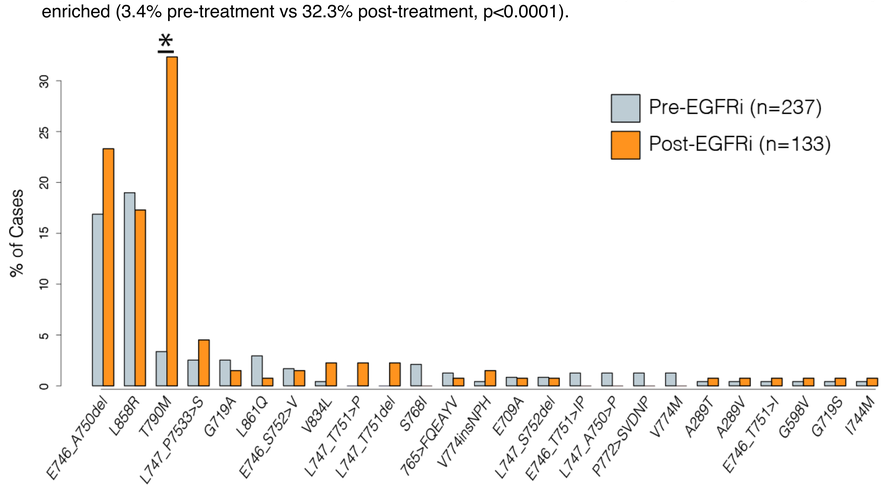
REARRANGEMENTS

Figure 7. Long-tail plot of genes with complex rearrangements. Rearrangements were determined to be less frequent than both short variants and copy number alterations.



EGFR SHORT VARIANTS

Figure 8. 51 distinct EGFR short variants were identified (top 25 shown). Only T790M was significantly enriched (3.4% pre-treatment vs 32.3% post-treatment, p<0.0001).



CONCLUSIONS

- Population-based analyses of a scalable, real-world clinicogenomic database, derived from data generated as part of routine patient care, can recapitulate and generate hypotheses for novel mechanisms of resistance to EGFR inhibitors.
- 'Hypothesis-agnostic' examination of differences in alterations in an NSCLC cohort pre- and post-EGFRi treatment led to re-identification of a subset of known EGFRi resistance mechanisms. Re-identification of T790M[1] as a resistance mechanism and determination of copy number variations (e.g. ERBB2 loss[2]) in post-EGFRi patients were demonstrated.
- Known mechanisms of acquired resistance[3] (e.g. c-MET amplifications[4], HER2 aberrations[5]) not recapitulated in our analysis may be due to the size of the dataset at the time of the analysis and study design.
- These findings were made from the January 2017 version of the NSCLC-CGDB. **A recent update of the CGDB (Jan 2018) exceeds 33,000+ patients overall and 4,000+ patients diagnosed with NSCLC**.
- 600+ EGFRi-treated patients are in the most recent dataset (January 2018) – nearly double the number of data points powering this analysis. Extension of the database and longitudinal follow-up over time may further elucidate novel mechanisms of resistance to a broad array of cancer therapies.

References:

1. Zhou W, Ercan D, Chen L, et al. Nature 2009;462:1070–4.
2. Oxnard GR, Thress K, Paweletz C, et al. J Thorac Oncol 2015;10(Suppl 2):ORAL17.07.
3. Morgillo F, Della Corte CM, Fasano M, et al. ESMO Open 2016;1: e000060.
4. Fan W, Tang Z, Yin L, et al. Cancer Res 2011;71:4494–505.
5. Takezawa K, Pirazzoli V, Arcila ME, et al. Cancer Discov 2012;2:922–33.