EPCO-10: Systems biology-based therapeutic predictions with gbmSYGNAL and clinical correlates in the real-world longitudinal outcomes registry XCELSIOR

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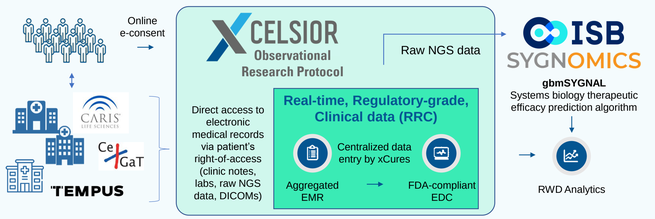
Abstract



Glioblastoma is an aggressive disease with multiple disrupted signaling networks in the same tumor, demanding the development of personalized combination regimens. Using SYstems Genetics Network AnaLysis we analyzed TCGA multiomics datasets for 422 glioblastoma patients to generate a predictive disease network model (gbmSYGNAL). This model seeks to uncover how subsets of mutations causally modulate regulators (transcription factors, miRNAs, etc.) that mechanistically regulate gene modules ("regulons") associated with disease progression. Using the real-world registry XCELSIOR (NCT03793088), we identified 55 anti-cancer therapies utilized in glioblastoma treatment (N = 354 patients) and associated them with positive or negative regulon activity within individual patients across the TCGA cohort. A median of 12 regulons were targeted by each drug. Interestingly, nilotinib targeted only 5 regulons but they were found to be active in 38% of patients and regulons overactive in >35% of patients were targeted by repurposed anti-cancer drugs including celecoxib, hydroxychloroquine, and tocilizumab. Standard-of-care treatments lomustine and bevacizumab were predicted to be active in only 28% and 23% of patients, respectively. Using gbmSYGNAL, we then prioritized drugs for 12 additional patients from the XCELSIOR registry. Median overactive regulons per patient was 110 (range 55-254) represented by a median 28 molecular targets (range 17-37). Surprisingly, regulons targeted by metformin were predicted to be overactive in all patients. Certain regulons displayed a binary pattern (high "on" activity or completely "off" per patient) including those targeted by pemetrexed, pembrolizumab, and valproic acid while others showed a gradient of activity across patients including selinexor, panobinostat, palbociclib, and alpelisib. Systems biology analysis of commercially available NGS data combined with the XCELSIOR direct patient engagement platform yielded therapeutically actionable insights for glioblastoma patients in real time. Correlation with clinical outcomes is ongoing for ~50 additional patients and will be presented at the meeting.

Demographics and Dataset

72 Glioblastoma patients analyzed

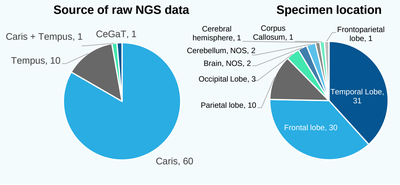
1.0 years (IQR = [0.73, 1.39]) median follow up from diagnosis

57 years (range = [14 - 81]) median age at diagnosis

1.48 years median OS

70 primary GBM, **2** secondary GBM

81 total specimens analyzed (**9** patients with two independent specimens sequenced)



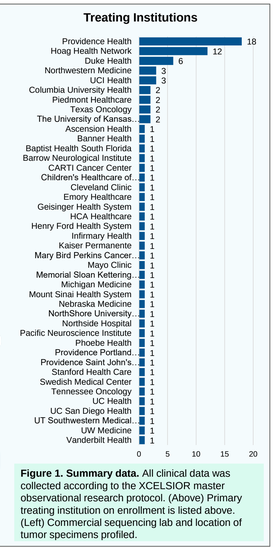


Figure 1. Summary data. All clinical data was collected according to the XCELSIOR master observational research protocol. (Above) Primary treating institution on enrollment is listed above. (Left) Commercial sequencing lab and location of tumor specimens profiled.

Results

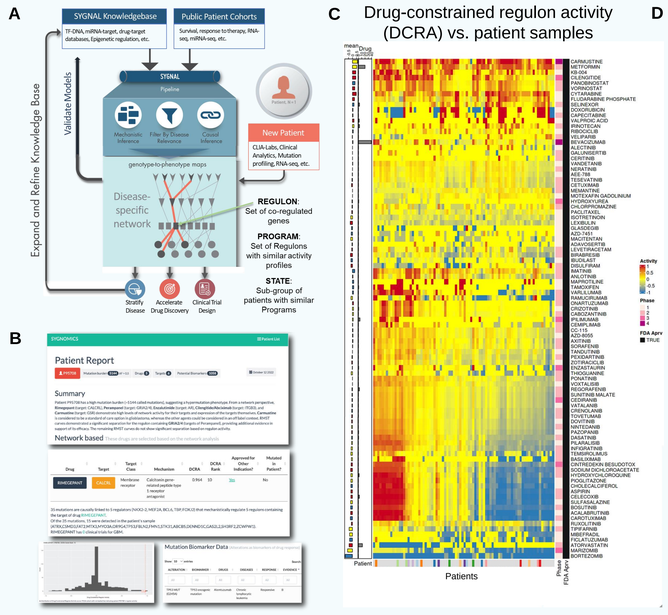


Figure 2. gbmSYGNAL profiling on raw NGS data from XCELSIOR patients. (A) Diagram of SYGNAL workflow to provide therapeutic activity predictions based on systems biology analysis of exome, transcriptome, and other 'omics datasets. (B) Sample patient report dashboard providing predictions from gbmSYGNAL. (C) Heatmap of Drug-Constrained Regulon Activity (DCRA) for FDA-approved therapies vs. XCELSIOR profiled patient samples. Phase refers to clinical development phase in glioblastoma. (D) Example bar plots showing distribution patterns of DCRA for therapies across the patient samples.

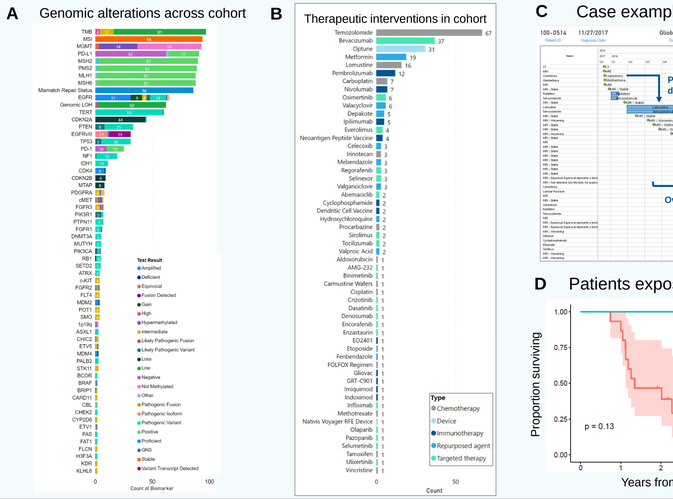


Figure 3. Cohort details and example clinical correlations. (A) Genomic findings in patient samples from Caris, Tempus, and CeGaT sequencing platforms, combined with pathology when available. (B) Counts of patients within the dataset treated with the indicated anti-cancer therapeutic interventions. (C) Treatment journey of one patient with positive DCRA for lomustine who gained long term benefit from combination TMZ/lomustine. Later lines of treatment were not predicted to show activity. (D) Overall survival plot showing single patient with predicted lomustine activity

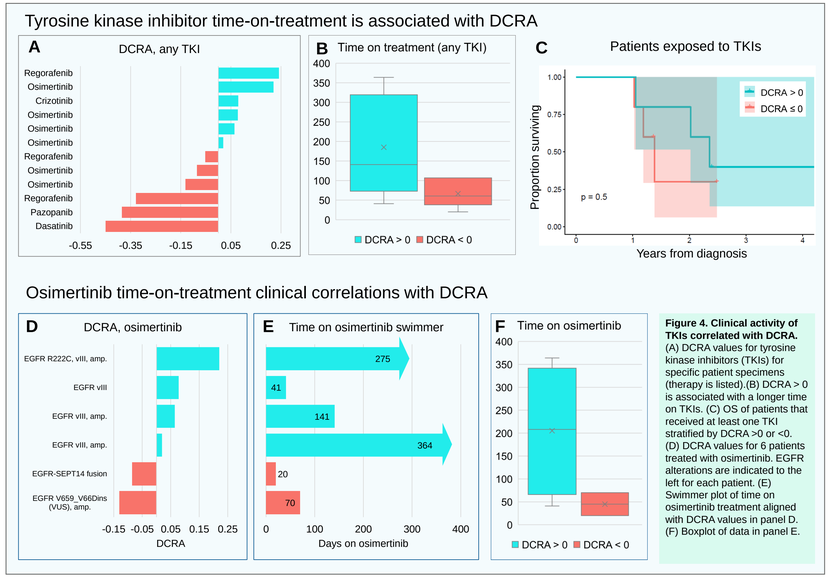


Figure 4. Clinical activity of TKIs correlated with DCRA. (A) DCRA values for tyrosine kinase inhibitors (TKIs) for specific patient specimens (therapy is listed).(B) DCRA > 0 is associated with a longer time on TKIs. (C) OS of patients that received at least one TKI stratified by DCRA >0 or <0. (D) DCRA values for 6 patients treated with osimertinib. EGFR alterations are indicated to the left for each patient. (E) Swimmer plot of time on osimertinib treatment aligned with DCRA values in panel D. (F) Boxplot of data in panel E.

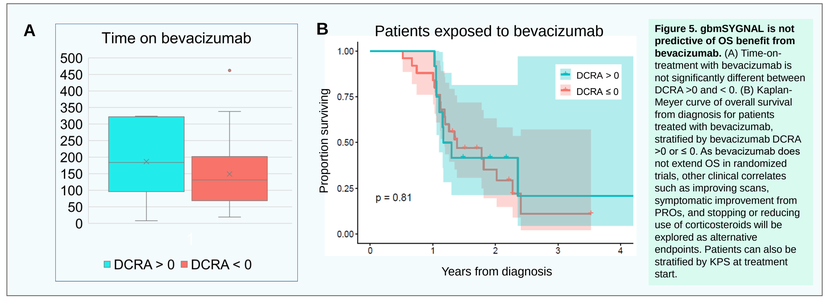


Figure 5. gbmSYGNAL is not predictive of OS benefit from bevacizumab. (A) Time-on-treatment with bevacizumab is not significantly different between DCRA >0 and < 0. (B) Kaplan-Meyer curve of overall survival from diagnosis for patients treated with bevacizumab, stratified by bevacizumab DCRA >0 or ≤ 0. As bevacizumab does not extend OS in randomized trials, other clinical correlates such as improving scans, symptomatic improvement from PROs, and stopping or reducing use of corticosteroids will be explored as alternative endpoints. Patients can also be stratified by KPS at treatment start.

Conclusions

Decentralized approach

- The XCELSIOR master observational research protocol and xCures decentralized clinical research platform have permitted rapid translation of the gbmSYGNAL algorithm to real world patient samples
- Patient right-of-access permits efficient collection of EMR from all sites of care and raw NGS data to generate **Real-time, Regulatory-grade, Clinical data (RRC)**

gbmSYGNAL clinical correlations

- Clinical activity of tyrosine kinase inhibitors was the therapeutic class best predicted by the gbmSYGNAL algorithm
- Bevacizumab DCRA did not correlate with time on treatment or OS, so future analyses will utilize other clinical outcomes (time to improving MRI scan; ORR; symptom resolution and clinical improvement from PROs)

Next Steps

- Continue gbmSYGNAL profiling of patients enrolled in XCELSIOR
- Develop a prospective clinical study to test rational combination regimens
- **To participate in this research effort, scan the QR code!**