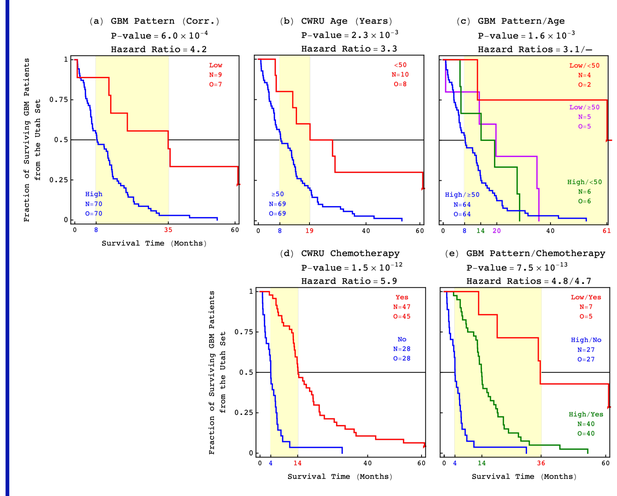
Prospective Validation from a Retrospective Trial That Validated an AI/ML-Derived Whole-Genome Biomarker as the Most Accurate and Precise Predictor of Survival and Response to Treatment in Glioblastoma

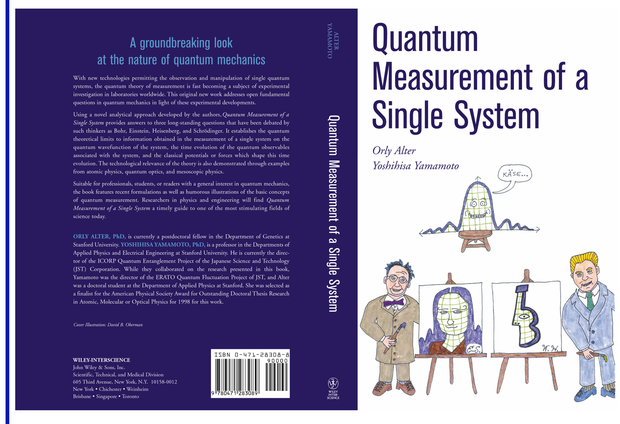
Orly Alter,[1]* Sri Priya Ponnapalli,[1] Jessica W. Tsai,[2] Penelope Miron,[3] Kristy L. S. Miskimen,[3] Kristin A. Waite,[4] Nadiya Sosonkina,[5] Sara E. Coppens,[6] Anthony C. Bryan,[6] Estevan P. Kiernan,[7] Huanming Yang,[8] Jay Bowen,[6] Ghunwa A. Nakouzi,[5] Jill S. Barnholtz-Sloan,[4] Andrew E. Sloan[9,3] and Tiffany R. Hodges[3]

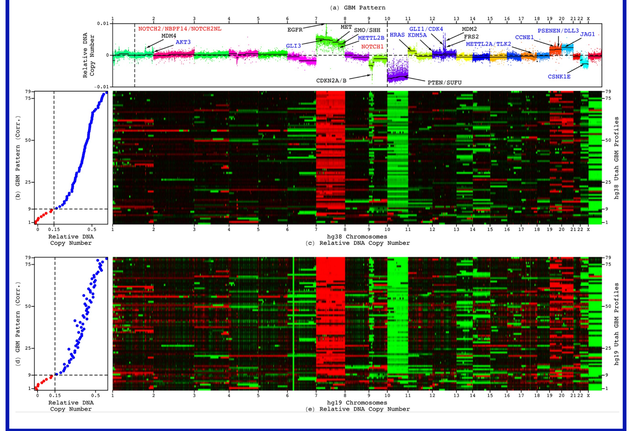
[1]University of Utah, Salt Lake City, UT, [2]Children's Hospital of Los Angeles and University of Southern California, Los Angeles, CA, [3]Case Western Reserve University School of Medicine, Cleveland, OH, [4]National Cancer Institute, Bethesda, MD, [5]HudsonAlpha Clinical Services Lab LLC, Huntsville, AL, [6]The Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH, [7]Illumina, Inc., San Diego, CA, [8]Beijing Genomics Institute (BGI) -Shenzhen, Shenzhen, Guangdong, China and [9]Piedmont Healthcare, Atlanta, GA; ***orly@sci.utah.edu**

Background: For 70 years, the best indicator of glioblastoma (GBM) survival has remained age at diagnosis. Factors across the entire genome affect every aspect of the disease. But typical artificial intelligence and machine learning (AI/ML) would require 3B-patient training sets to generate predictive models from the whole 3B-nucleotide genome. As a result, all other attempts to associate a tumor's DNA copy-number alterations (CNAs) with the patient's outcome failed.



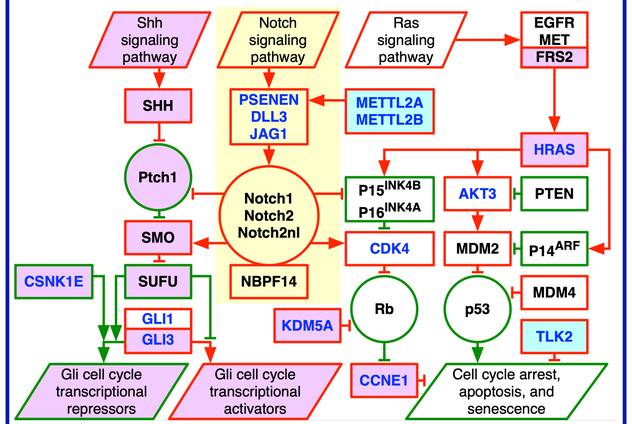
Methods: A genome-wide pattern of DNA CNAs in primary GBM tumors was recently validated in a retrospective clinical trial as the most accurate and precise predictor of survival and response to treatment [Ponnapalli, et int., Alter, *APL Bioeng* 2020]. Applicable to the general population, this biomarker, the first to encompass the whole genome, and biomarkers in lung, nerve, ovarian, and uterine cancers, were repeatedly identified in open-source datasets from as few as 50–100 patients by using our data-agnostic unsupervised AI/ML, which extends the mathematics of quantum mechanics to overcome the limitations of typical AI/ML [Bradley, et int., Alter, *APL Bioeng* 2019; Alter et al., *PNAS* 2003].

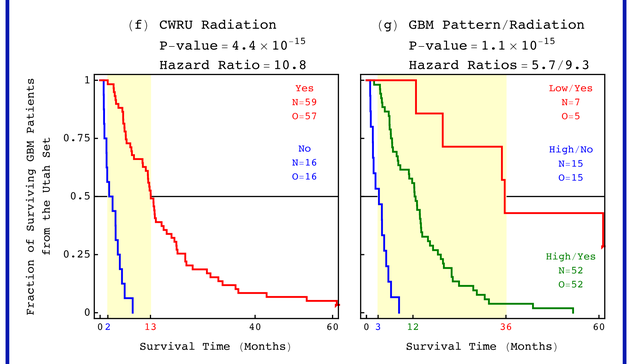




Results: At 75–95% concordance, our biomarker is more accurate than and independent of age and all other indicators, including the one-gene tests for *MGMT*, *IDH1*, and *TERT*. Platform- and reference genome-agnostic, the biomarker's >99% precision is greater than the community consensus of <70% reproducibility. It describes disease mechanisms and identifies drug targets and combinations of targets to sensitize tumors to treatment.

Now, in follow-up results from the trial we, first, show correct prospective prediction of the outcome of the five of the 79 patients who were alive four years earlier, at the time of first results (log-rank *P*-value $=3.9 \times 10^{-2}$). Two patients, who were predicted to have shorter survival, lived less than five years from diagnosis, whereas of the three patients predicted to have longer survival, one lived more than five, and the remaining two are alive >11.5, years from diagnosis. Second, we demonstrate 100%-precise clinical prediction for the 59/79 patients with remaining tumor DNA, by using whole-genome sequencing in a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP) laboratory. Third, we establish that the risk that a tumor's whole genome confers upon outcome, as is reflected by the biomarker's univariate Cox hazard ratio of 4.2 and Kaplan-Meier median survival difference of 2.25 years (log-rank *P*-value $=6.0 \times 10^{-4}$), is greater than that conferred by the patient's Karnofsky performance score and access to chemotherapy, and the tumor's percent resection, and is surpassed only by the patient's access to radiotherapy.





Conclusions: This is a proof of principle that our AI/ML is uniquely suited for personalized medicine.

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Ethics: The Institutional Review Board (IRB) at the University Hospitals of Cleveland (CASE 1307-CC296, Ohio Brain Tumor Study) approved the use of de-identified clinical data and biospecimens in this study.

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