

A Potential Multigene Biomarker for Predicting Benefit of Chemotherapy Gastric Cancer

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DESCRIPTION

Here we discuss our recently published research on the development of a clinically applicable 53-gene prognostic assay that predicts chemotherapy benefit in Gastric Cancer (GC)[1]. This is a reliable high-throughput mRNA hybridization-based assay, providing a solution to better measure the 53-gene expression in FFPE tissues from patients. Its predictive power in GC was successfully validated in three hospital cohorts and patients with good prognostic scores exhibited a significantly better 5-year Overall Survival (OS) rate from adjuvant FOLFOX (leucovorin, fluorouracil, and oxaliplatin) chemotherapy after surgery than from other chemotherapies. Future work should focus on prospective trials to fully deploy this system into clinical utility.

The 5-year OS rate of GC in advanced stage remains poor (below 30%) [2]. Currently, the curative surgery in combination with adjuvant chemotherapy is the most common treatment for stage II-III patients. GC is a polygenic and heterogenic disorder with four molecular subtypes [3]. Also several gene expression signatures have been reported to predict patient outcomes [4-9]. However, effective translation of these findings depends on both their clinical implications and assay development for clinical laboratory utility. Extended validation of bioinformatics findings is still rare with prognostic and/or predictive biomarker signatures in GC, and no multigene biomarker(s) has yet been recommended for tailoring individual treatment plans.

Over the years, we developed and employed a multi-step bioinformatics strategy (Figure 1) to mine publicly available omics and clinical data, e.g., TCGA and NCBI-GEO, to identify robust multigene expression prognostic signatures and to build related scoring systems, including a 53-gene panel for GC, a 27-gene panel for lung adenocarcinoma, a 11-gene panel for ovarian cancer and a 15-gene panel for colorectal cancer [1,4,10-12]. More importantly, we successfully demonstrated that these signatures were superior in predictive power of prognosis in comparison to other already reported multigene signatures,

clearly indicating that our strategy has its own advantage. In the study discussed here, we used a TCGA gastric adenocarcinoma cohort (TCGA-STAD) to compare the performance of our 53-gene signature with three recently published multigene signatures and discovered that the 53-gene score significantly performs better than other signatures in discriminatively determining OS of patients with GC [1].

In the next steps, we normally perform univariate and multivariate COX regression analysis on all available clinical parameters to examine whether the prognostic impact of a multigene signature is independent of any potential confounding factors that may affect the prognostic capability. We also rule out any significant correlation of our signature with molecular subtypes of a cancer type, if any. For instance, in GC, we explored whether the prognostic impact of the 53-gene signature would be enriched in certain molecular subtype(s), as such subtypes are associated with different survival outcomes and treatment benefits [13]. We confirmed that this signature is independent of the four molecular subtypes [1].

We pay special attention to the clinical validation of these signatures, which can be done in two ways: (1) using transcriptome data from publicly available independent datasets and (2) collecting patient samples to measure gene expression for validation, ideally a multicenter study. In the paper discussed in this commentary, following our previously established 53-gene prognostic signature for OS of GC patients, we carried out a retrospective multi-center study and successfully validated the prognostic power of the assay in 540 patients from three independent hospitals [1].

One key discovery of this work was that this prognostic signature is also predictive of drug response in GC patients, i.e., our score system is able to predict adjuvant chemotherapy benefit in gastric cancer, when the effect of FOLFOX and other first-line chemotherapies were compared for patient survival in different prognostic score groups [1]. We found that patients with good score had a significantly better 5-year OS rate from FOLFOX

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than from other treatments. The 5-year OS rate reached 82% for patients underwent FOLFOX in the good prognostic score group, which is significantly higher than that (61%) in the patients with other chemotherapies ($P=0.028$). There was no significant difference in intermediate and poor score groups between the two treatment groups. These data suggest that patients with a good score may experience much better benefit from adjuvant FOLFOX chemotherapy after gastrectomy as compared with other chemotherapies. Therefore, the 53-gene prognostic signature could be a promising predictive biomarker for FOLFOX, the most commonly used chemotherapy for GC after surgery in the patients enrolled in our study. Future prospective studies with large patient sizes are warranted to fully deploy this multigene signature and its score system into clinical use.

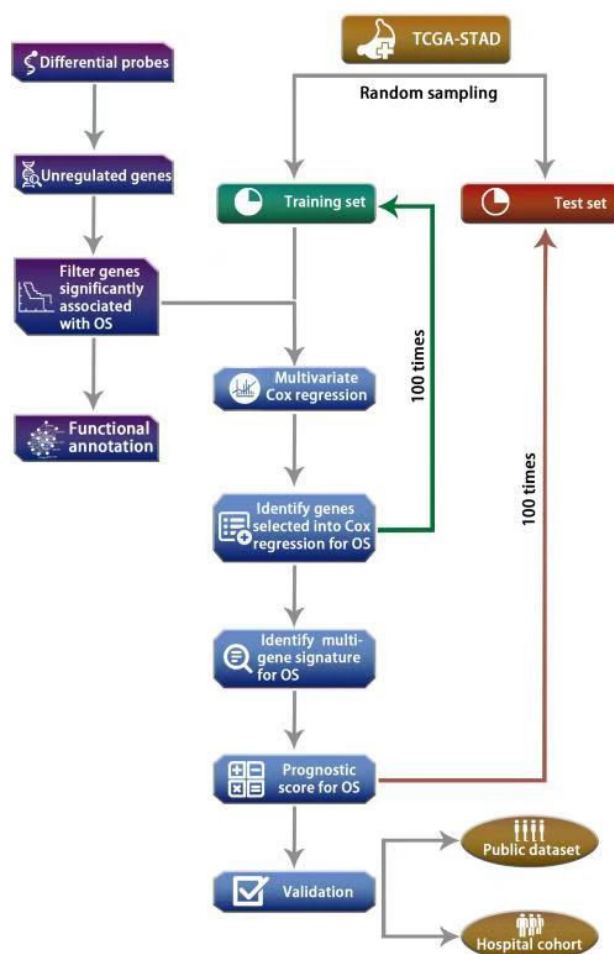


Figure 1: A schematic diagram for the identification and development of a prognostic multigene panel. This shows a working flowchart to screen consistently unregulated genes in cancer tissue using meta-analysis and identify OS-associated genes with Kaplan–Meier analysis using log-rank testing (left panel); and to develop a gene expression-based prognostic signature and score system using TCGA dataset (e.g., STAD)(right panel).

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