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PROSPECTIVE HISTOLOGY AND MUTATION AGNOSTIC ASSESSMENT OF SYSTEMIC TUMOR BURDEN WITH PLASMA CELL-FREE DNA CONCENTRATION IN 1000 CANCER PATIENTS

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Conflicts of Interest:
A.H.Z. serves in a consultant/advisory role for Previse, Delfi Diagnostics, Prognomiq, BilliontoOne, and Gilead. He has received research funding from Eli Lilly, Prognomiq, Delfi Diagnostics, BilliontoOne, Genece Health, Exai Bio, Myriad Genetics, and Tempus. A.H.Z. has equity interest in Previse, TG Therapeutics, and Gritstone Bio.

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Background: Circulating tumor DNA assays have shown promise for monitoring tumor burden in cancer patients. However, many such assays have cost and performance limitations due to reliance on somatic mutational analysis. Here we assess the utility of cell-free DNA (cfDNA) concentration, a histology and mutation agnostic assay, for approximating systemic tumor burden in a large prospective cohort of cancer patients.
Methods: One thousand cancer patients were prospectively enrolled in a registry/repository study which included peripheral blood draws. cfDNA was isolated from whole blood using a benchmarked, standardized, and reproducible protocol. Patient clinicodemographics, tumor burden metrics and survival outcomes were assessed for associations with cfDNA concentration (ng/mL) with nonparametric univariate methods, multivariable linear regression, and time-to-event tests as appropriate.
Results: cfDNA concentration was associated with several tumor burden metrics by univariate analysis, including stage (P=1.21E-8), metastatic disease (P=1.88E-9), number of tumors (P=1.11E-14), and size of largest tumor (cm; P=2.33E-12)(Fig.1). These remained significant when controlling for age, sex and histology in multivariable analysis. cfDNA concentration was higher in patients with malignant effusions, malignant ascites, carcinomatosis, or metastases to various specific organ sites (Fig.1). Patients had higher cfDNA concentration in palliative versus curative, adjuvant, or surveillance phases of care (P=4.45E-9)(Fig.1). Those with higher cfDNA concentration had reduced overall survival (HR=2.56, P=8.63E-15), progression-free survival (HR=1.97, P=1.86E-12), and disease-specific survival (HR=2.59, P=4.75E-14).
Conclusion: Plasma cfDNA concentration, a histology and mutation agnostic assay, approximated systemic tumor burden in a prospective cohort of 1000 cancer patients. Prospective validation is ongoing along with assessment of performance evaluating tumor burden during cancer treatments.

Fig.1: Plasma cfDNA concentration is a histology and mutation agnostic assessment of systemic tumor burden. Scatter plots and box and whisker plots (Tukey's method) depicting continuous and categorical variable associations with cfDNA concentration (ng/mL). Statistical comparisons were performed using Spearman's rank correlation with overlaid simple linear regression to illustrate linearity, Wilcoxon rank-sum test, or Kruskal-Wallis test by ranks as appropriate.