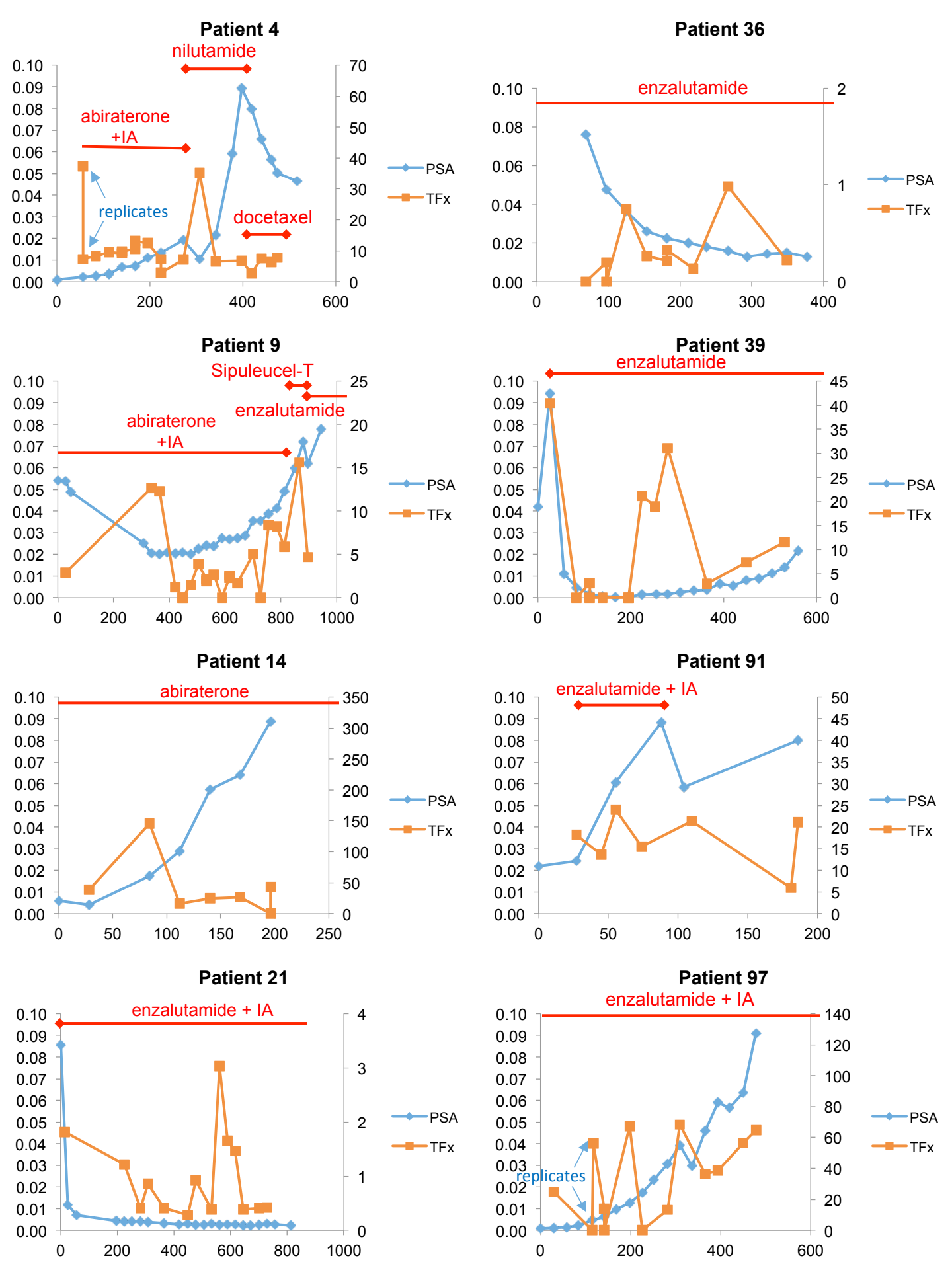
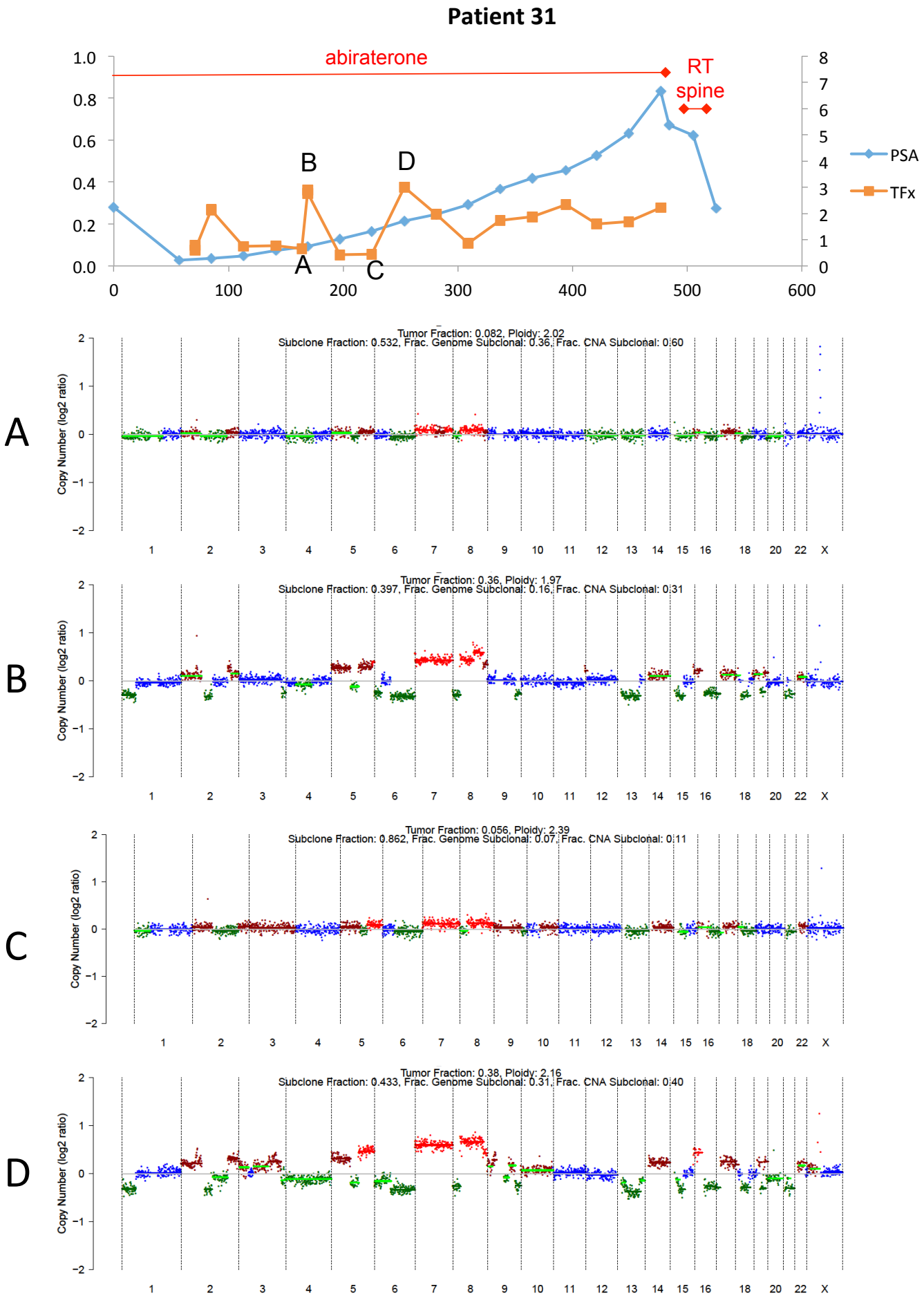
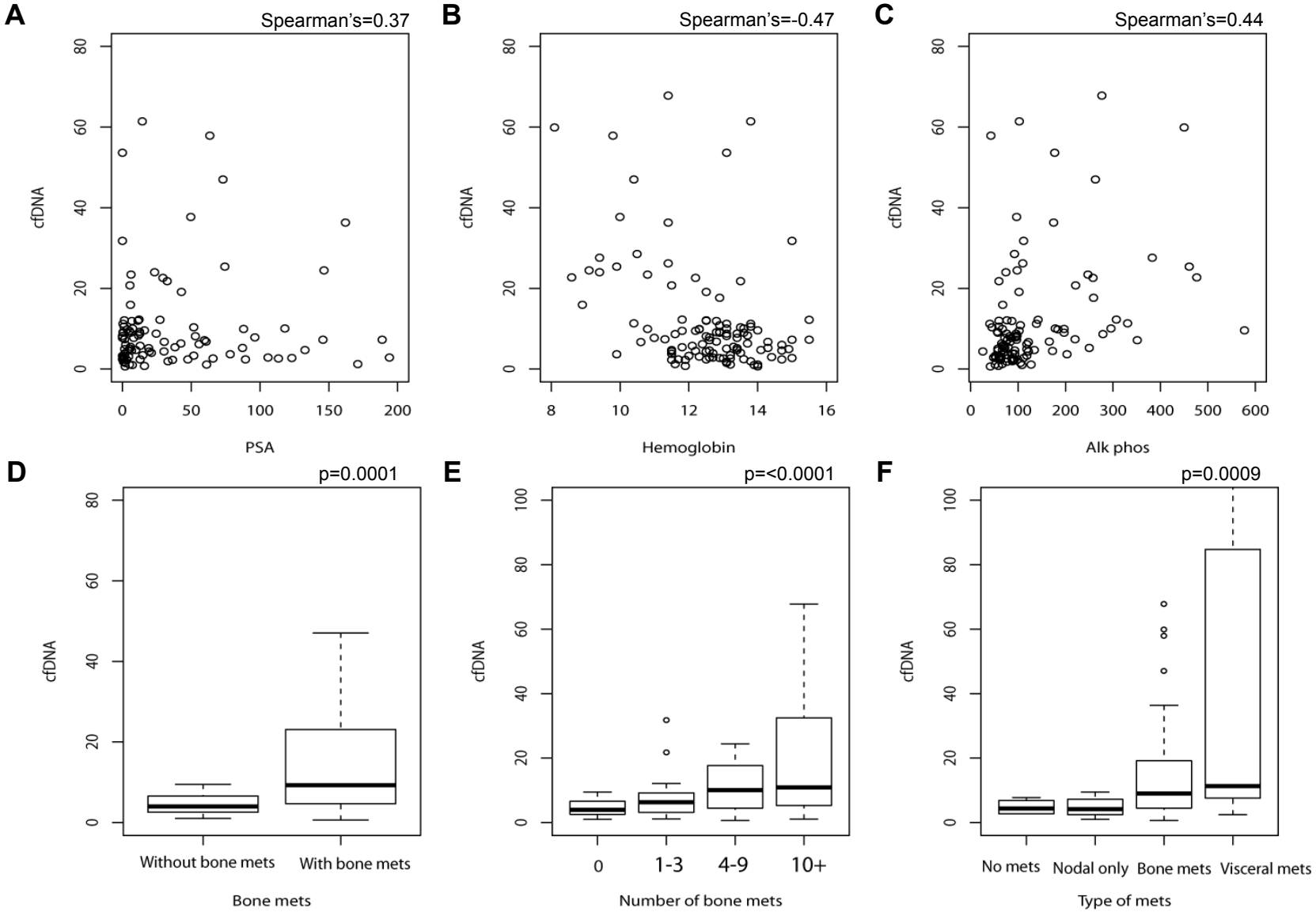



**Supplemental Figure 1.** Depiction of TFx and PSA over time for eight patients in the cohort with fluctuating TFx readings from 0 to ~0.05 - 0.07 not explained by PSA changes or treatment switches. Note the scale for TFx here is 0 - 0.10 (rather than 0 - 1.0 in the main Figures) to depict the underlying variability, or noise, at low TFx values. Two markers from the same time point for Patients 4 and 97 denote replicates from the same blood draw but with independent cfDNA isolation, library construction and sequencing steps.




**Supplemental Figure 2.** Top: TFx over time for patient 31. Samples from four time points with variable TFx unrelated to a treatment switch or PSA change are marked as A, B, C, D. Bottom: Genome-wide plots from ULP-WGS of plasma samples depicted in the top panel. Copy number changes are concordant in all four samples, demonstrating that these specimens are from the same patient and do not represent mislabeling or other mix up; plots demonstrate very little noise, suggesting high quality sequencing results.




**Supplemental Figure 3. A-C**. Scatter plots depicting the relationship between total cfDNA yield at the time point during longitudinal monitoring when the highest TFx value was seen with **A.** PSA **B.** Hemoglobin and **C.** Alkaline Phosphatase at that time point. Each dot represents an individual patient. Spearman correlation coefficients are noted in the corner of each plot. **D-F**. Box plots depicting the relationship between TFx at the time point during longitudinal monitoring when the highest TFx value was calculated with **D.** presence or absence of bony metastases by skeletal scintigraphy **E.** number of bony metastases detected by skeletal scintigraphy and **F.** site(s) of metastasis detected by bone scintigraphy and/or computed tomography (CT) imaging at that time point. "Nodal only" denotes macrometastatic disease involving lymph nodes but not distant bony or visceral sites, "Bone only" denotes metastatic disease involving bone (+/- lymph nodes) but not distant visceral sites, and "Visceral mets" denotes involvement of distant visceral sites (liver, lung, brain, adrenal gland) and does not include extension of local disease (i.e. to bladder/ureter or rectum.)