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Adaptive Dynamic Artificial Poly-ligand Targeting (ADAPT): aptamer-based profiling of liquid biopsies to improve the accuracy of breast cancer diagnoses in women with dense breast tissue

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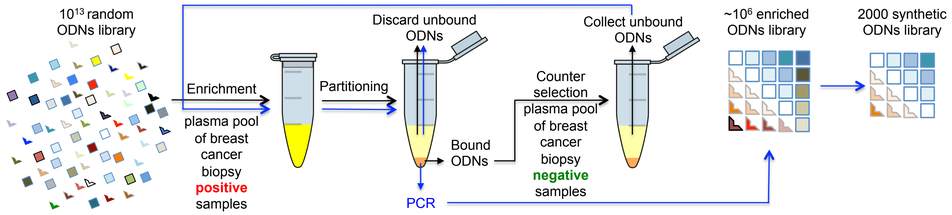
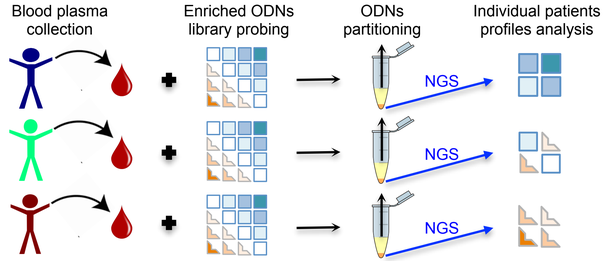
Introduction: Breast cancer screening relies upon mammography, which is often uninformative for women with dense breast tissue. Routine screening identifies suspicious breast lesions in some women, but the pain and risk associated with follow-up biopsies along with the poor accuracy of traditional histopathology urgently call for improved approaches to breast cancer screening. This is especially important for those high-risk patients for whom mammography is of limited value. We describe a non-invasive liquid biopsy method of profiling plasma exosome preps designed to improve the accuracy and safety of breast cancer screening for women with dense breast tissue.

Enrichment of aptamer library for ADAPT



ADAPT workflow



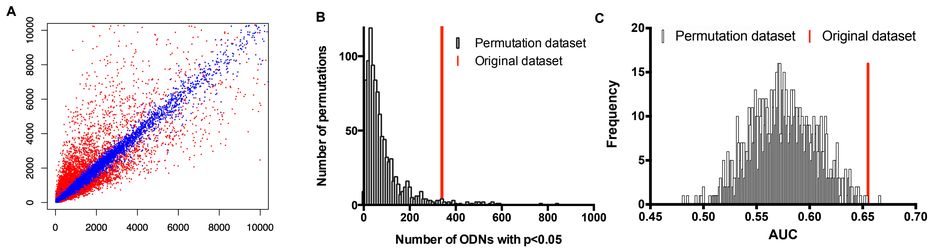
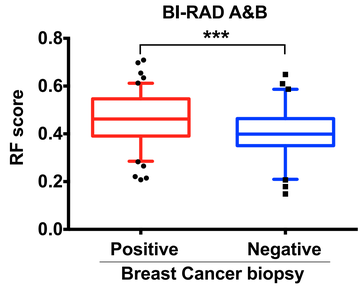


Figure 1. ADAPT principle, characterization and evaluation on 500 clinical samples: (A) Distribution of normalized counts of aptamers recovered from ADAPT on technical replicates from the same sample (blue dots, r>0.99) compared to average counts from 3 replicates of two non-related samples (red dots, r=0.77). (B) F-test on original and permutation datasets based on ADAPT of 500 patients with an enriched library of 2000 ODNs (L_{2000}). (C) Random-Forest (RF) Out-of-Bag (OOB) ROC AUC from 500 clinical samples and permutation analysis of its reliability; the ROC AUC in the original dataset is 0.66, which is significantly higher compared to the majority of 1000 permutations (p=0.002).



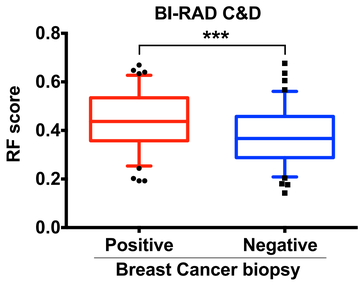
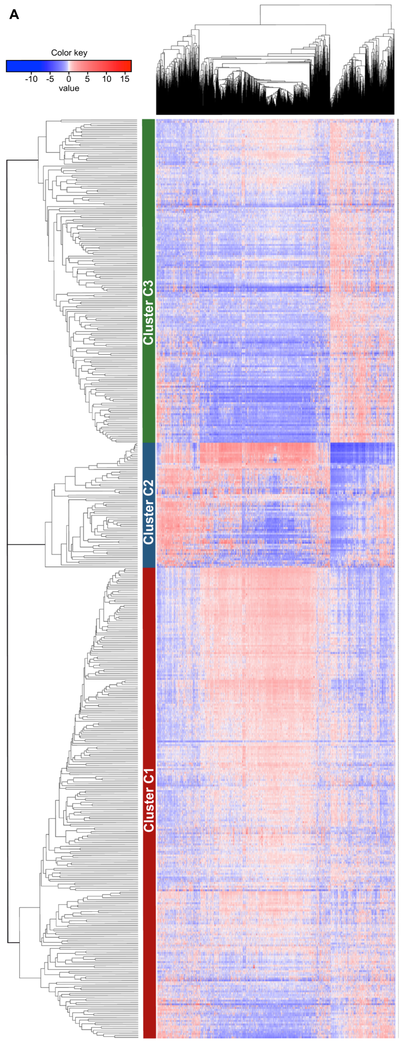
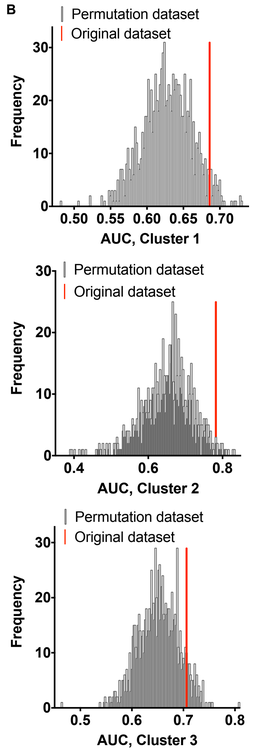


Figure 2. RF based probability of a cancer incident in both biopsy positive and negative sample types and corresponding radiographic Bi-RAD C&D scores suggesting that ADAPT reliably differentiates cancer from control groups even when using samples from women with dense breast tissue (BI-RAD A&B and C&D Cancer/Control p<0.001).





C

	AUC	p-value
All 500	0.66	0.002
Cluster 1	0.69	0.046
Cluster 2	0.78	0.018
Cluster 3	0.71	0.09

D

	Cluster		
	1	2	3
Cancer Dx+	115	28	63
Cancer Dx-	89	20	68
Normal	52	20	45
Total	256	68	176

Figure 3. ADAPT profiling reveals 3 disease-independent intrinsic clusters in a population of women with or without diagnosed breast cancer. (A) Heat map of ADAPT profiles from 500 plasma specimens using the library L_{2000}. The heat map reveals the existence of 3 clusters independent of health status. (**B, C**) Performance of ADAPT within 3 disease-independent intrinsic biological clusters. RF OOB AUC/ROC within each cluster and permutation analyses of their reliability. (**D**) Sample type representation in each cluster in (**A**).

Summary:

- ✓ We profiled blood plasma from women with and without breast cancer (n=500) using the library L_{2000}; RF-based statistical modeling yielded AUC of 0.66.
- ✓ The performance of the model was not affected by BI-RAD scores, indicating that ADAPT may aid in breast cancer screening of women with dense breast tissue.
- ✓ ADAPT profiling revealed three disease-independent clusters; AUC showed improved ability to distinguish cancer from non-cancer in two clusters, compared to entire set of 500 samples.
- ✓ ADAPT–derived, liquid biopsy breast cancer test could serve as a minimally invasive adjunct diagnostic for facile integration into clinical practice.