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Blood-based genome-wide copy number analysis of 500 cancer patients

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INTRODUCTION

Copy number variation (CNV) is an important feature of the cancer genome. Blood-based low-pass whole genome sequencing (LP-WGS) has been increasingly used to identify CNVs of large genomic regions in cancer. In this study, we report the development of a proprietary NGS platform to identify segment-based CNVs and CNV abnormality in plasma samples from 500 cancer patients, including breast, prostate, pancreatic and lung cancers. With low volume of plasma sample input, our study demonstrates cancer type-specific pattern of CNV across chromosome arms. The chromosome instability (CIN) score is capable to distinguish cancer patients from healthy individuals and monitor disease progression for longitudinal patient samples.

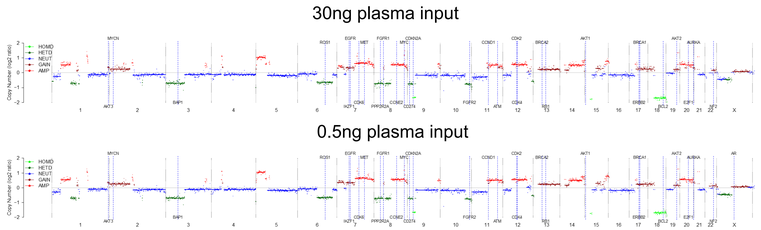
METHODS

A.

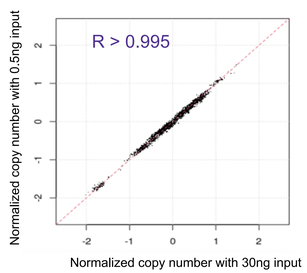
B.

Titration (%)	Sample num	TP num	FP num	FN num	PPV (%)	PPA (%)
15	55	53	0	2	100	96
20	55	55	0	0	100	100
25	55	55	0	0	100	100

C.



D.



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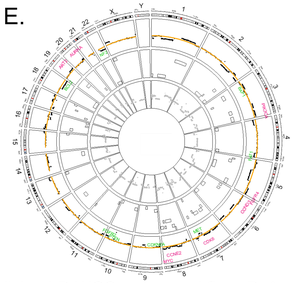
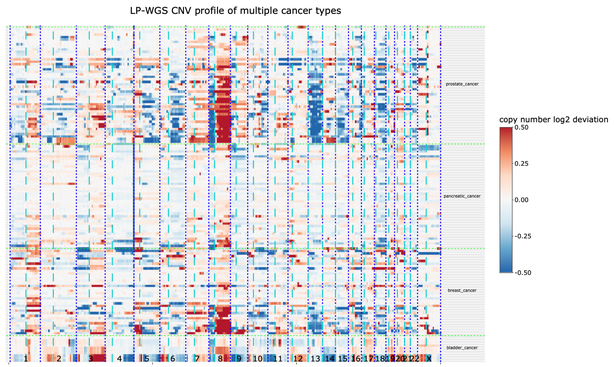


Fig. 1 Liquid biopsy based LP-WGS analysis. A. Predicine LP-WGS assay workflow. **B.** Assay performance of LP-WGS CNV detection. **C**. LP-WGS CNV profile of 30ng and 0.5ng input plasma. **D**. LP-WGS copy numbers are highly consistent between 30ng and 0.5ng cfDNA input. **E**. LP-WGS CNV circos plot, in which the outer track represents chromosome cytobands, 2nd outer track represents genome-wide LP-WGS CNV profile, highlighting signature CNA and CNL genes, 3rd outer track represents the CNA and CNL segments, and most inner track represents genome coverage of LP-WGS data.

RESULTS

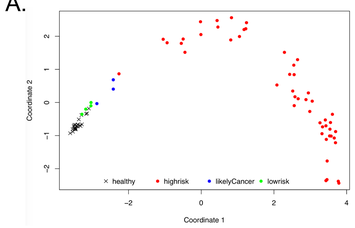
Fig. 2: LP-WGS revealed distinct CNV patterns across different cancer indications



LP-WGS CNV profiles of different types of cancer patients. Chr8q gain and chr13q loss have higher recurrence in prostate cancer than the other cancers.

Fig. 3: CIN can distinguish cancer patients from healthy individuals.

A.



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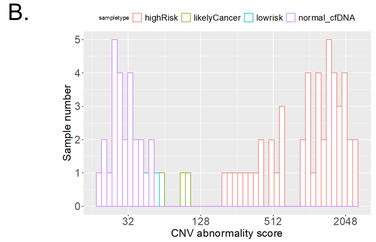

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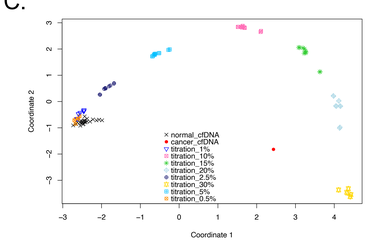

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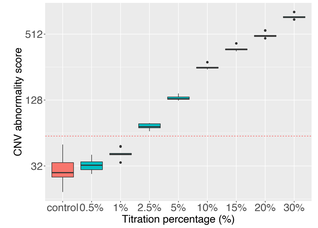
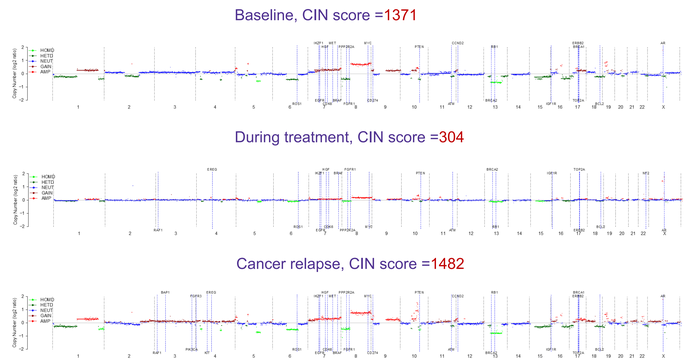


LP-WGS CNI score has high sensitivity to distinguish cancer patients from healthy individuals. A. Multidimensional scaling to distinguish prostate cancer patients from healthy persons, where cancer patients can be further categorized as low-risk, likely cancer, and high-risk groups. **B**. CIN score distribution of prostate cancer patients and normal samples. **C**. Multidimensional scaling to separate normal samples and cancer samples with various tumor fractions. **D.** Correlation between cancer titration and CIN score.

Fig. 4: Clinical application of Predicine LP-WGS and CIN score for disease monitoring.

A.



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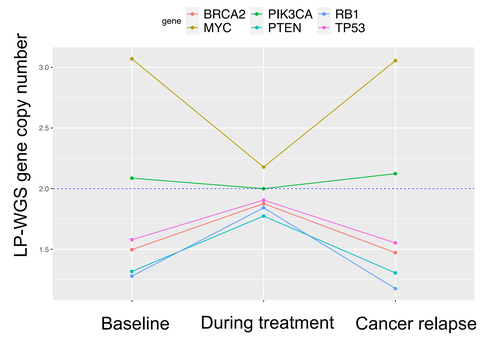

LP-WGS CIN score to monitor disease progression. A. LP-WGS CNV profile of longitudinal prostate cancer patient samples at baseline, during treatment, and disease relapse. **B**. LP-WGS gene copy number of key prostate cancer genes at baseline, during treatment and disease relapse.

CONCLUSIONS

We have developed a proprietary Predicine LP-WGS assay platform. The assay's CNV detection LOD is 15% tumor fraction with as low as 0.5ml plasma volume or **0.5ng cf**DNA input. The CNV abnormality LOD is 2.5% tumor fraction. Clinical application of the Predicine LP-WGS assay demonstrates high sensitivity to distinguish cancer patients from normal individuals and and the CIN score exhibits ability to monitor disease progression and early cancer detection.