Optimizing ctDNA limits of detection for DLBCL during first line therapy

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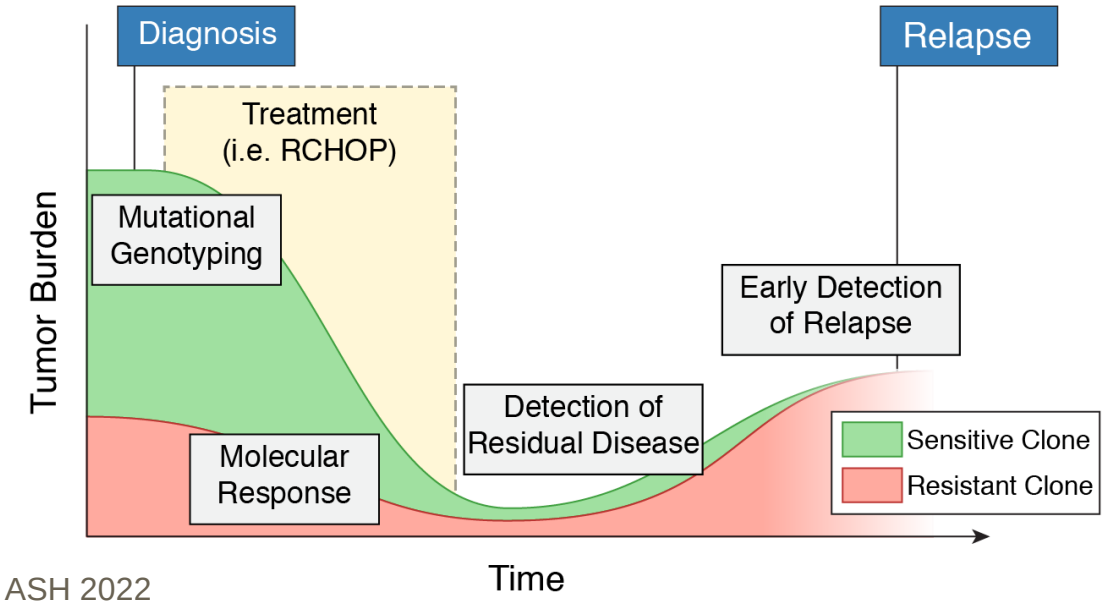
Background

- DLBCL 1L treatment consists of anthracycline-based chemoimmunotherapy

- Response criteria rely on PET/CTs, which lack sensitivity/specificity
  - Do not measure disease at molecular level

- Quantification and detection of ctDNA has been shown to be a prognostic biomarker before, during and after treatment



Kurtz et al., JCO 2018; Roschewski et al., ASH 2022

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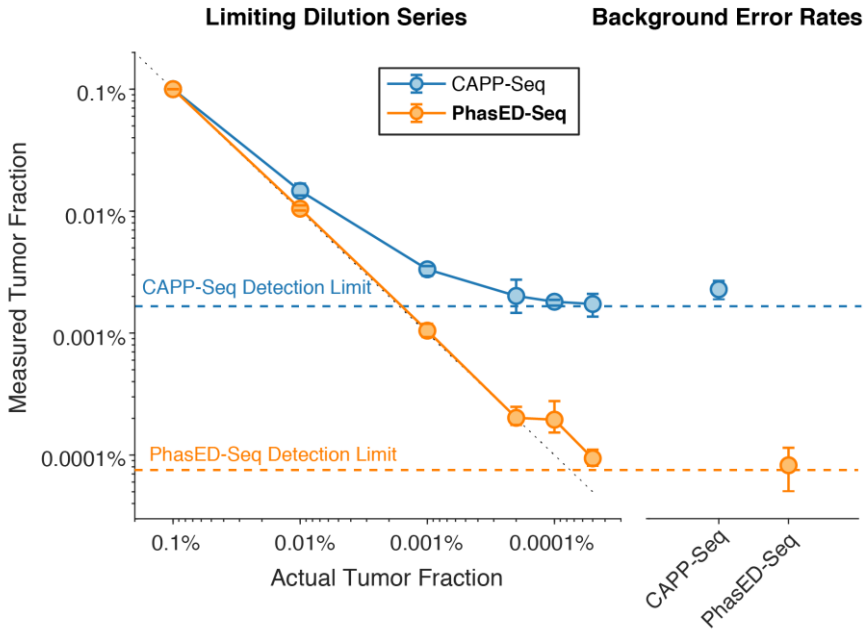
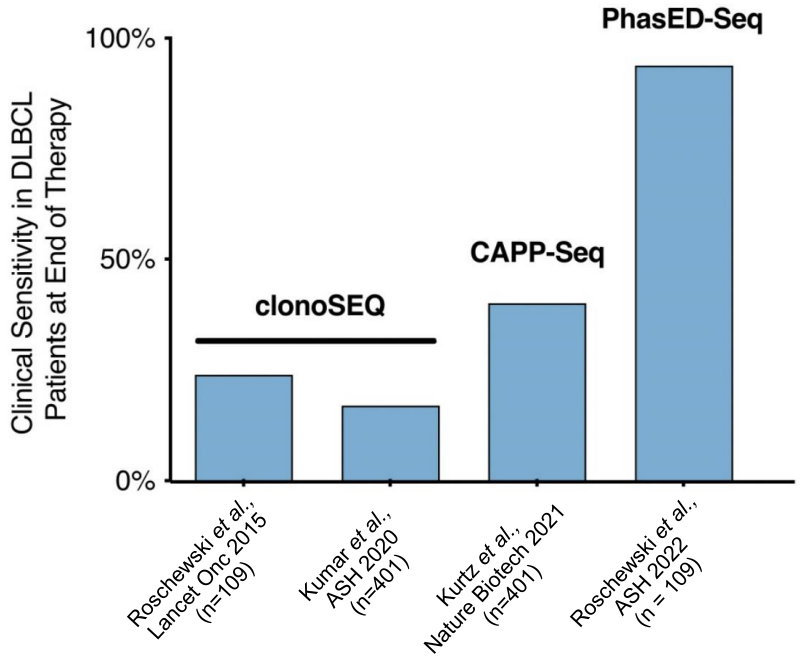
ctDNA assays have different limits of detection

- Several ctDNA assays have been studied in DLBCL with differing performance
  - ClonoSEQ (Adaptive)
  - CAPP-seq (Avenio)
  - PhasED-seq (Foresight)





Kurtz et al., Nat Biotechnol 2021; Roschewski et al., ASH 2022

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Understanding limit of detection (LOD) in ctDNA

- Variable definitions used in literature
- Proposed definition: Lowest concentration of ctDNA that will be detected with 95% probability (LOD95)
  - Analytical sensitivity
  - Typically expressed as Variant Allele Fraction (VAF) or Tumor Fraction

↓ Limit of Detection requires:

- ↑ Number of mutations being detected
- ↓ Background error rate of the assay
- ↑ Amount of cfDNA in the blood sample

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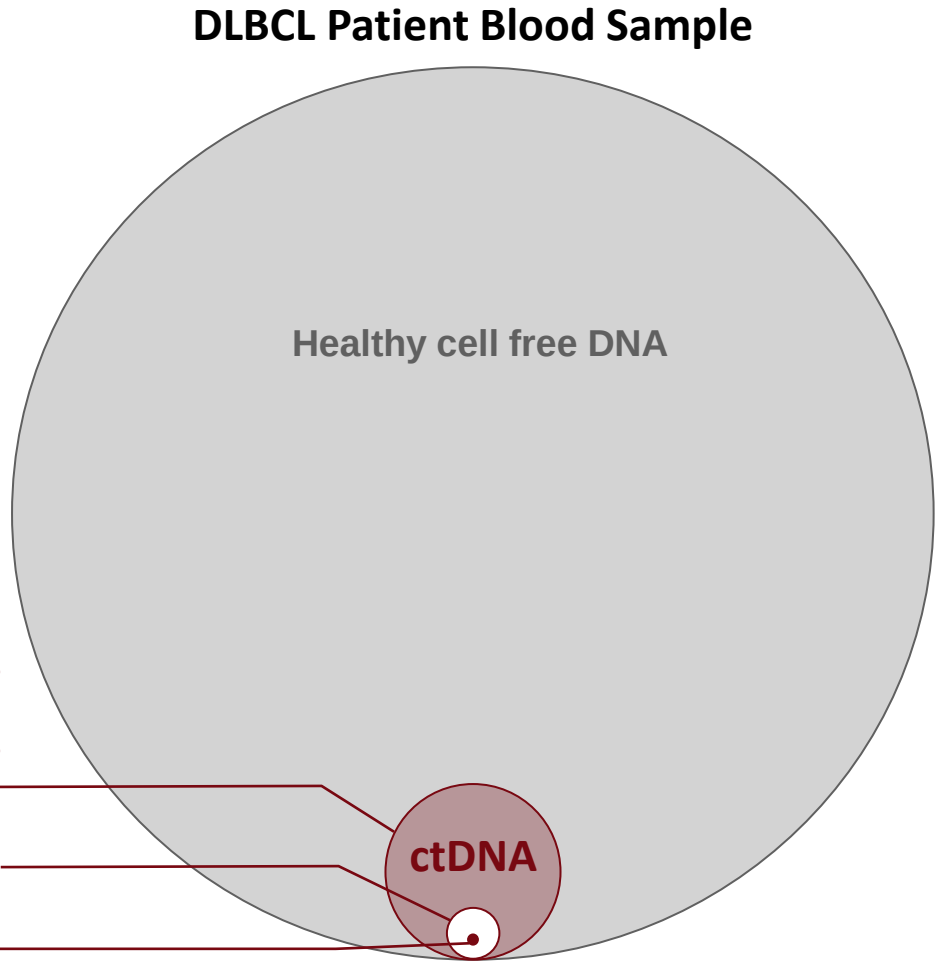
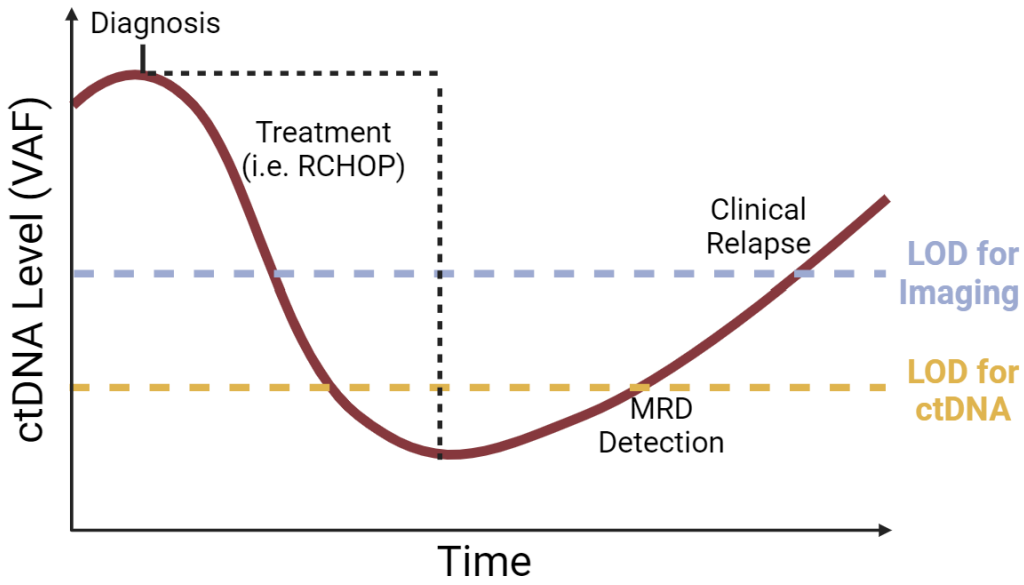
Lower LOD improves ability to detect disease

Tumor VAF	LOD
1%	10^{-2}
0.01%	10^{-4}
0.0001%	10^{-6}





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Aim

- Understand how analytical LOD impacts ctDNA MRD prognostic performance during 1L treatment
  - Do ultrasensitive assays improve prognostic performance?
  - Important to understand for trial design and clinical adoption

- We hypothesized that lower LOD can improve clinical sensitivity and predictive ability for PFS during and after treatment

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Methods

- Used a pooled cohort with prospectively collected samples from 5 different cohorts
  - ctDNA assays were all performed using PhasED-seq
  - Cases were selected based on having:
    - High quality pre-treatment genotyping
    - Availability of surveillance samples at pre-treatment, C2, C3, C4, or EOT timepoints

- Assessed predictive ability for PFS of ctDNA MRD at various LOD for 1L timepoints
  - Simulated LOD to classify MRD +/- based on ctDNA VAFs
    - LODs ranged from 10^{-2} through 10^{-6}

- Assessed incorporation of MRD into novel endpoint, modified PFS (mPFS)

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Cohort Details

Pooled cohort with prospectively collected samples from 5 different cohorts

Cohort	Trial	Anthracycline-based Regimen	Trial Therapy	Patients
NCI	NCT04002947	R-CHOP or DA-EPOCH-R	Acalabrutinib	30
UW	NCT04231877	DA-EPCH-R	Polatuzumab	17
MDACC	NCT02529852	CHOP	Lenalidomide Obinutuzumab	26
Samsung	Observational	R-CHOP-like	N/A	81
Kurtz et al, Nature Biotech 2021	NCT00398177 Observational	R-CHOP or DA-EPOCH-R	N/A	87

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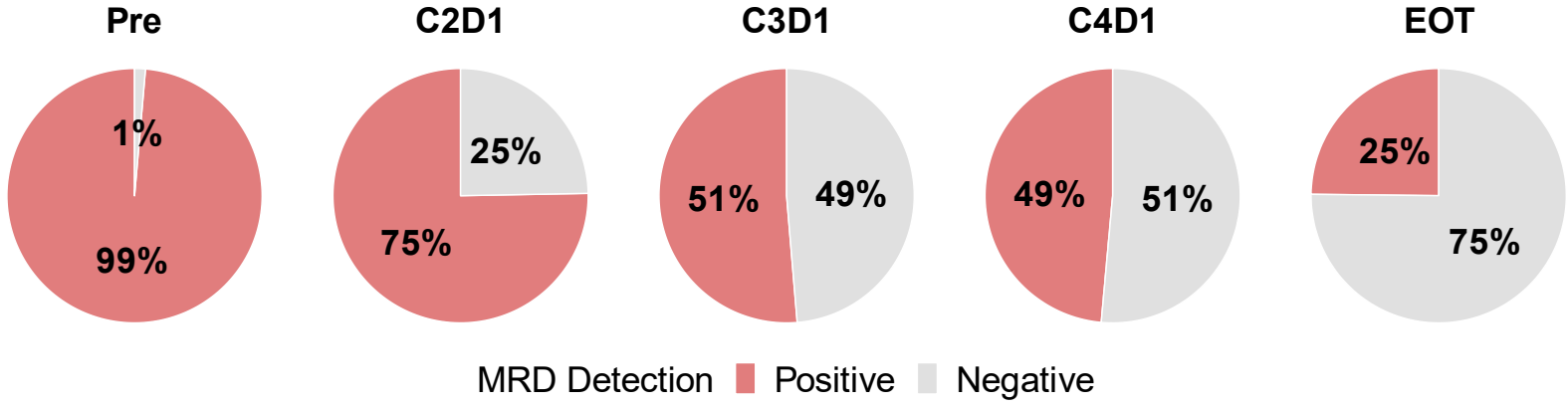
Dataset

230 patients included
588 ctDNA plasma samples profiled

	Pre-tx	C2D1	C3D1	C4D1	EOT
Positive	216	64	58	34	36
Negative	3	21	55	36	109
Total	**219**	**85**	**113**	**70**	**145**



Median follow-up = 22 months (IQR 10 – 29 months)

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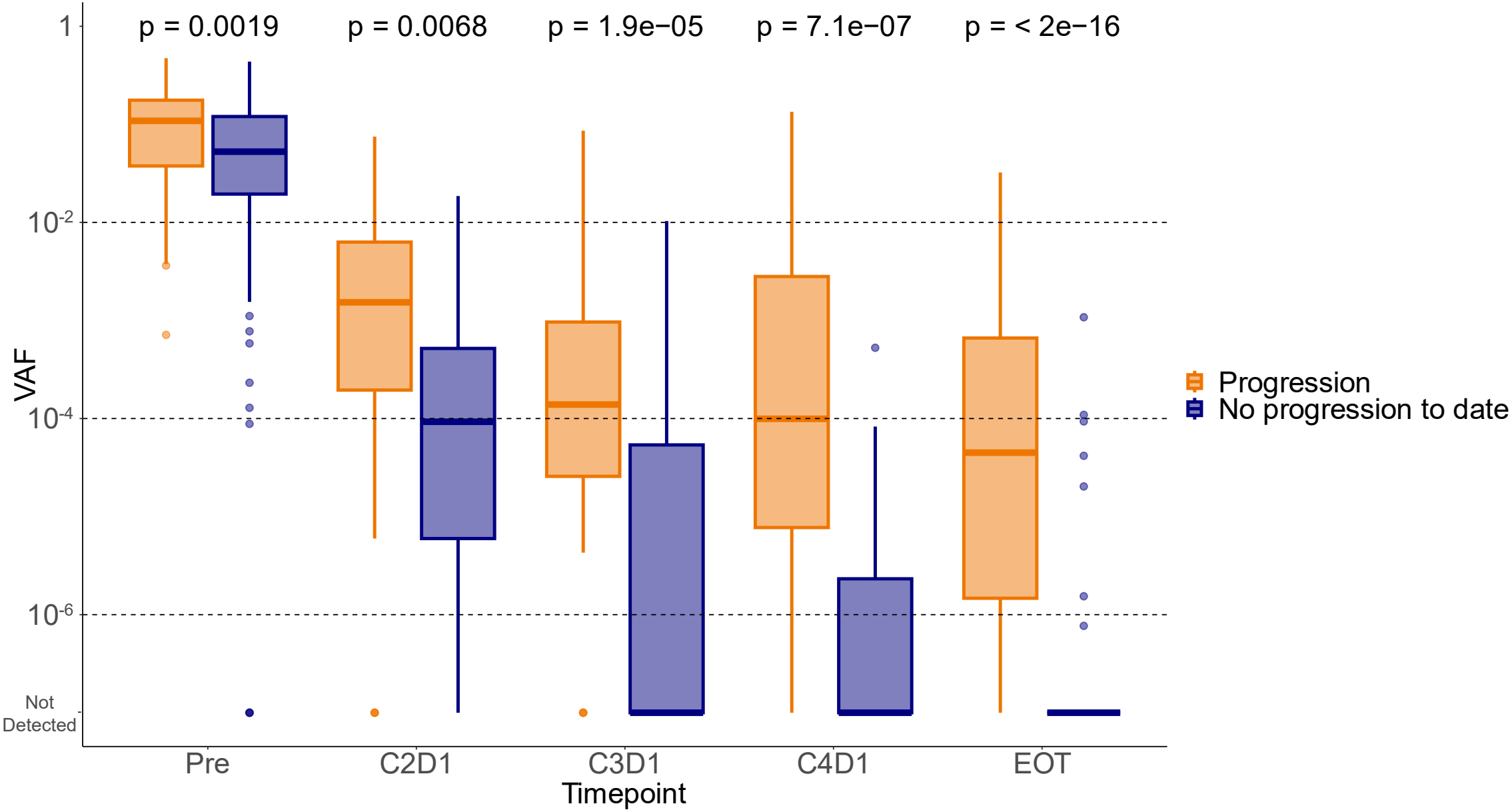
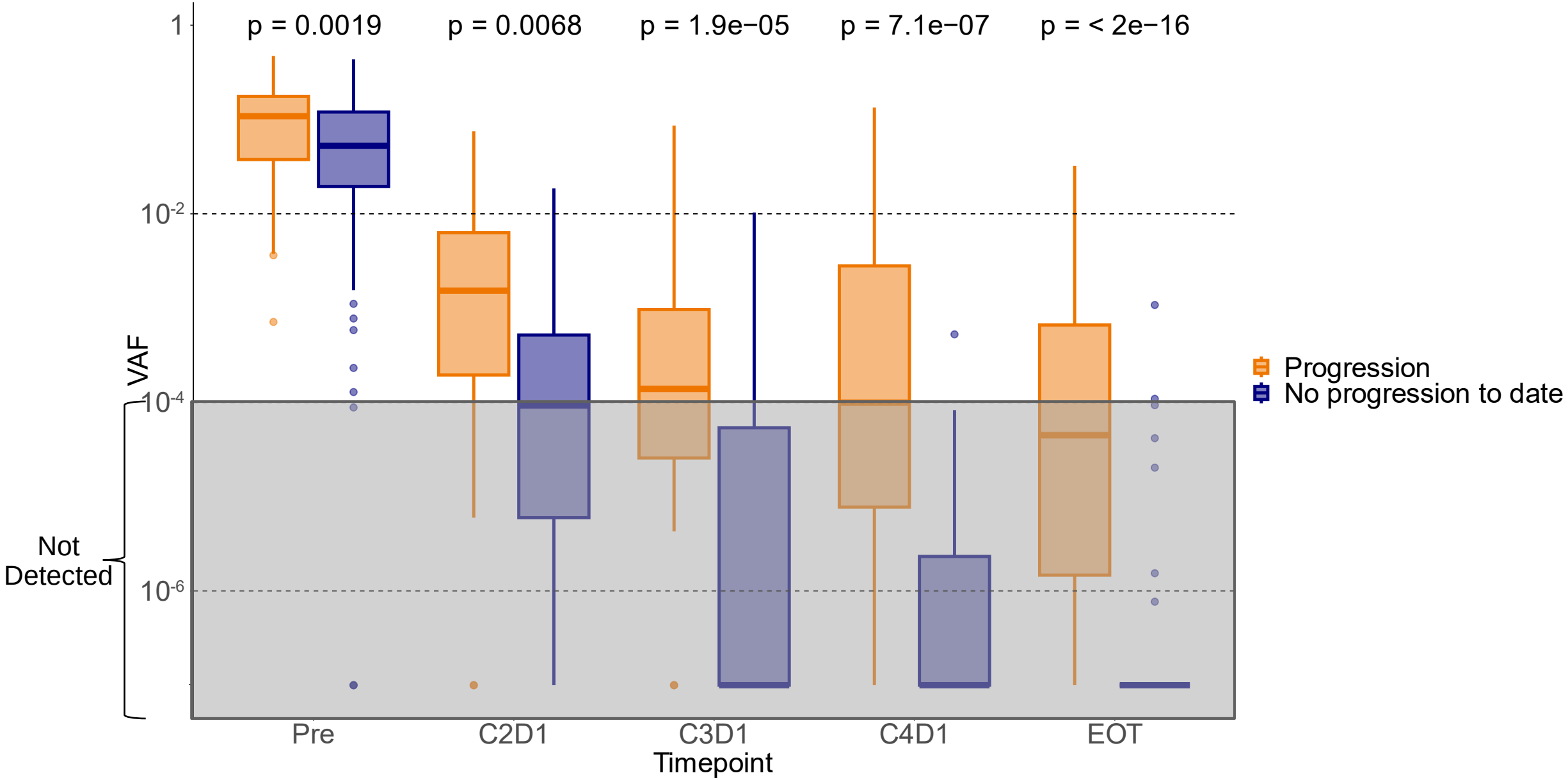
ctDNA VAF distributions during therapy



ctDNA VAF distributions during therapy

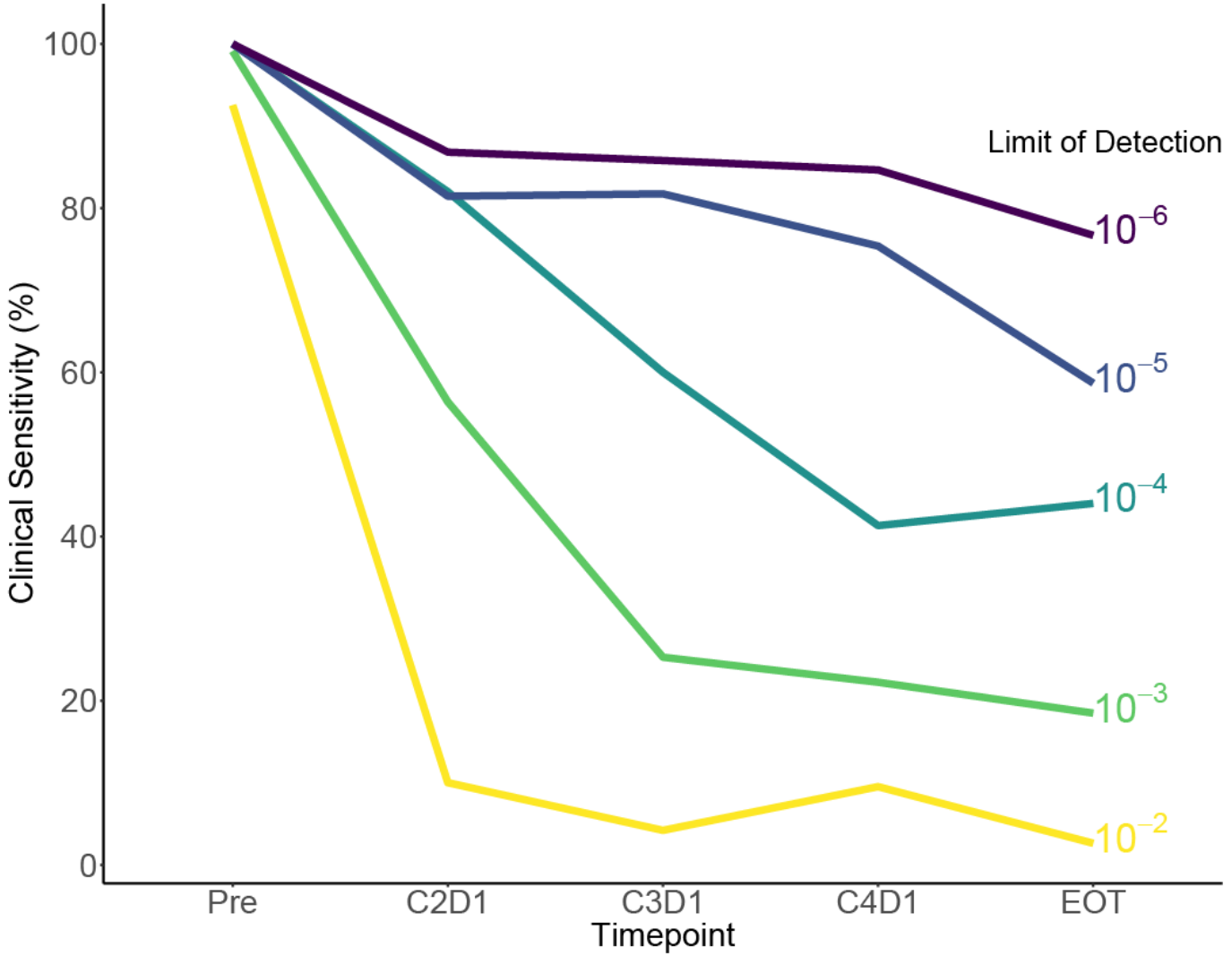


Improved analytical sensitivity leads to higher clinical sensitivity

Clinical Sensitivity

% of patients that progress within 24 months who have detectable ctDNA at a given LOD

- Generated time-dependent ROC curves for predicting PFS at 24 months



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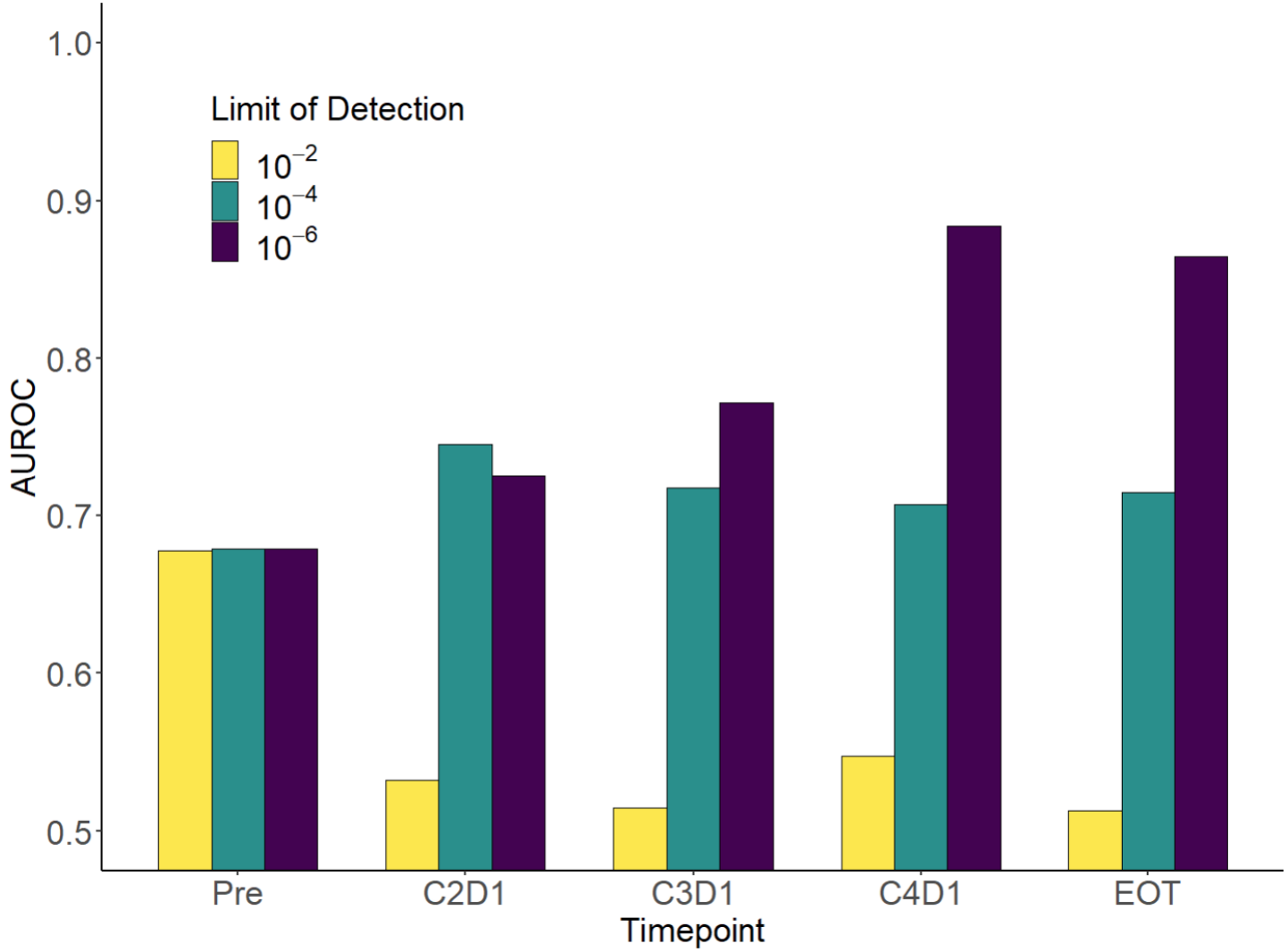
Lower LOD improves PFS prediction later in 1L therapy

AUROC

Predictive ability for PFS by MRD at a given LOD



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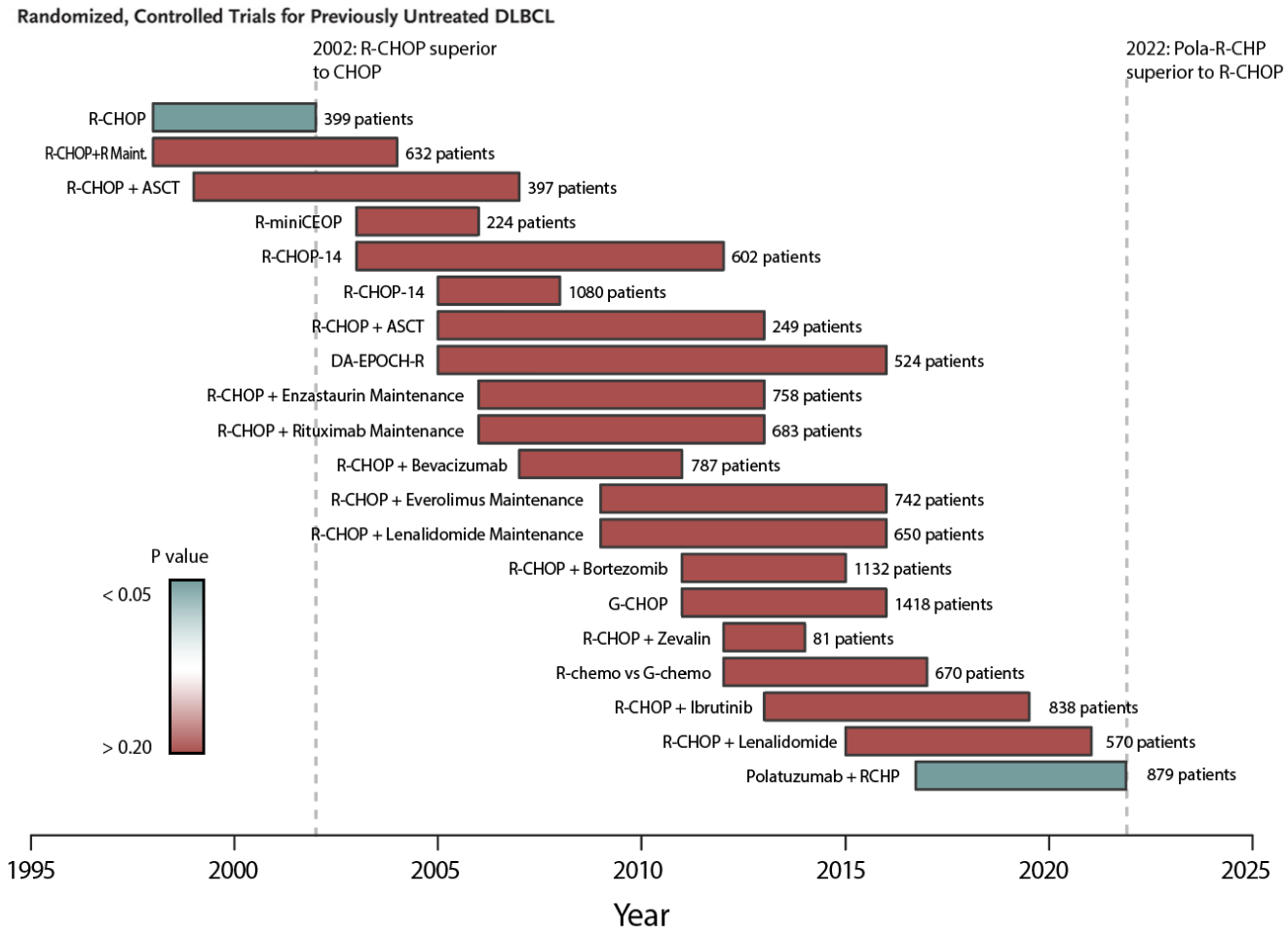
Can ctDNA MRD accelerate clinical development in 1L DLBCL?

- Long timeline between trials improving 1L DLBCL outcomes
- Can time to trial readout be improved with novel surrogate endpoints?



Palmer et al., NEJM 2023

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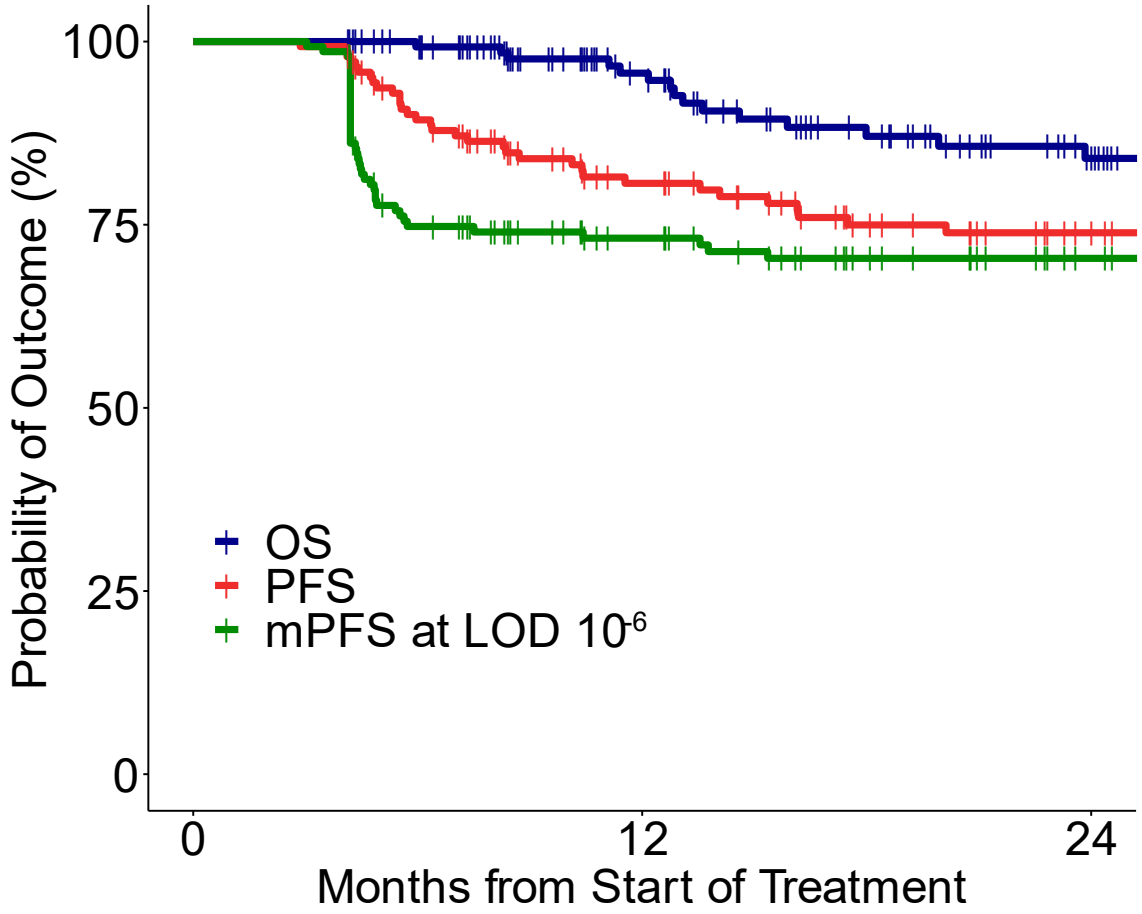
Incorporating MRD into a proposed modified PFS (mPFS)

- Definition:
  - Relapse or progression of DLBCL at any time after treatment initiation
  - Death from any cause
  - **Detectable residual ctDNA after completion of therapy**
    - Requires assays with high sensitivity and specificity

PFS



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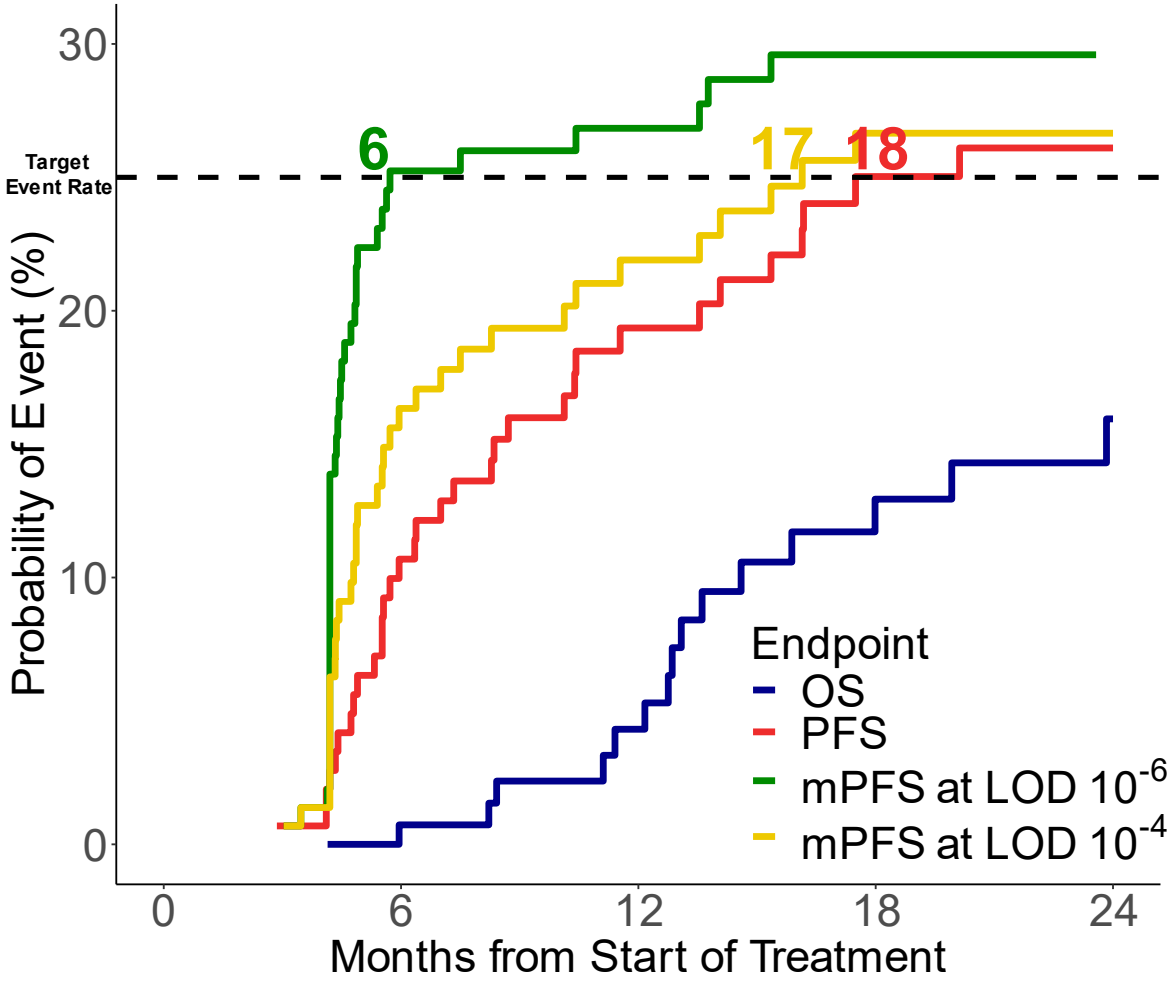
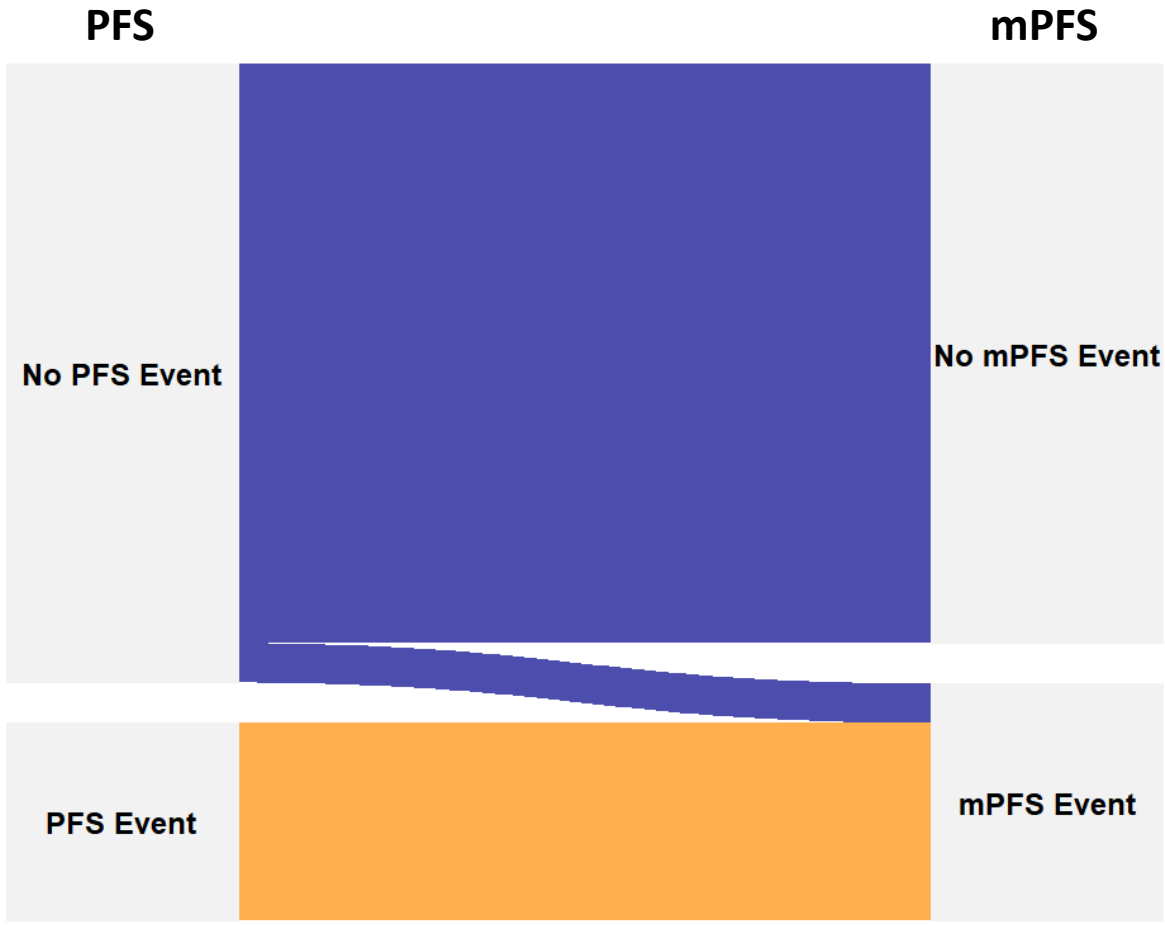
mPFS shortens time to event while maintaining event classification



mPFS can shorten time to 25% target event rate
by 12 months



mPFS with LOD 10^{-6} and PFS events highly concordant

- 138/145 cases (95%)

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Conclusion

- Ultrasensitive MRD assays better predict PFS, particularly at later timepoints
  - Improved disease detection and outcome prediction

- Use of assays with lower LOD can maximize the efficacy of MRD risk-adapted therapeutic strategies

- Ultrasensitive MRD detection can be incorporated into surrogate endpoints, such as mPFS, to expedite drug development

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Acknowledgements

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