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# Mutant KRAS in Circulating Tumor DNA as a Biomarker in Pancreatic Cancer in Patients Treated with Neoadjuvant Chemotherapy

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the third leading cause of cancer-related death in the United States. Currently, carbohydrate antigen 19-9 (CA 19-9) is the only validated biomarker in use for PDAC. Given the need for deeper understanding in tumor biology, the limitations of CA 19-9, and ongoing investigations in other solid malignancies, circulating tumor DNA, (ctDNA) has emerged as a PDAC biomarker candidate. Digital droplet PCR (ddPCR) is distinct from NGS in detection of ctDNA in that it is 1000 times more sensitive as well as less costly than NGS testing. Given our prior results, we sought to evaluate the detection and prognostic capability of mutant KRAS ctDNA in PDAC patients treated with neoadjuvant chemotherapy (NAC) as assessed by ddPCR.

## Objectives

1. To assess the detection ans prognostic capability of mutant *KRAS* ctDNA in PDAC patients treated with NAC
2. To understand ctDNA dynamics and evaluate the prognostic implication of ctDNA clearance

## Methods

Data source: Prospectively recruited cohort

### Inclusion Criteria
- Newly diagnosed PDAC
- Patients with resectable disease
- Patients planned to undergo NAC

### Exclusion Criteria
- Surgically unresectable
- Not a candidate for NAC
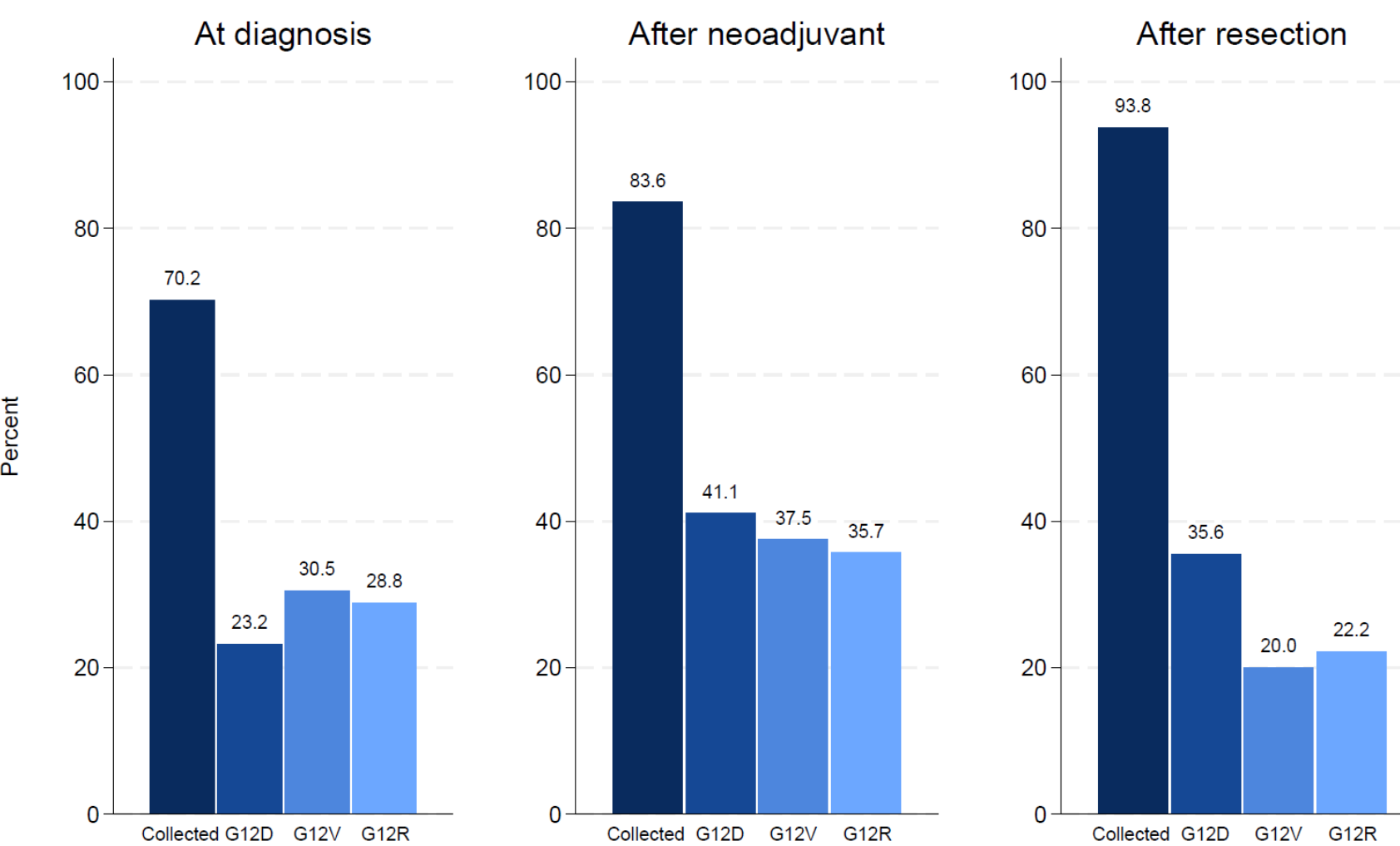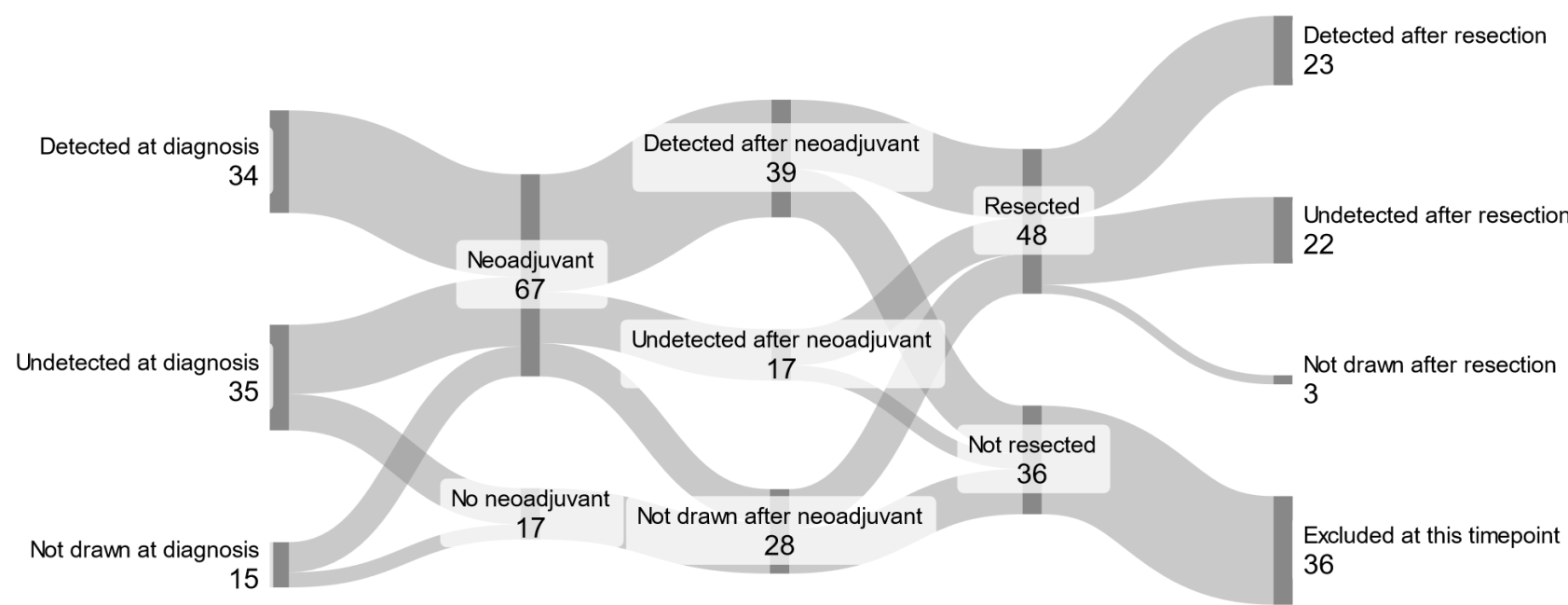- Not undergoing curative-intent treatment
- 1 or fewer samples collected

### Sample handling
- Peripheral blood samples collected at diagnosis, after NAC, and after resection
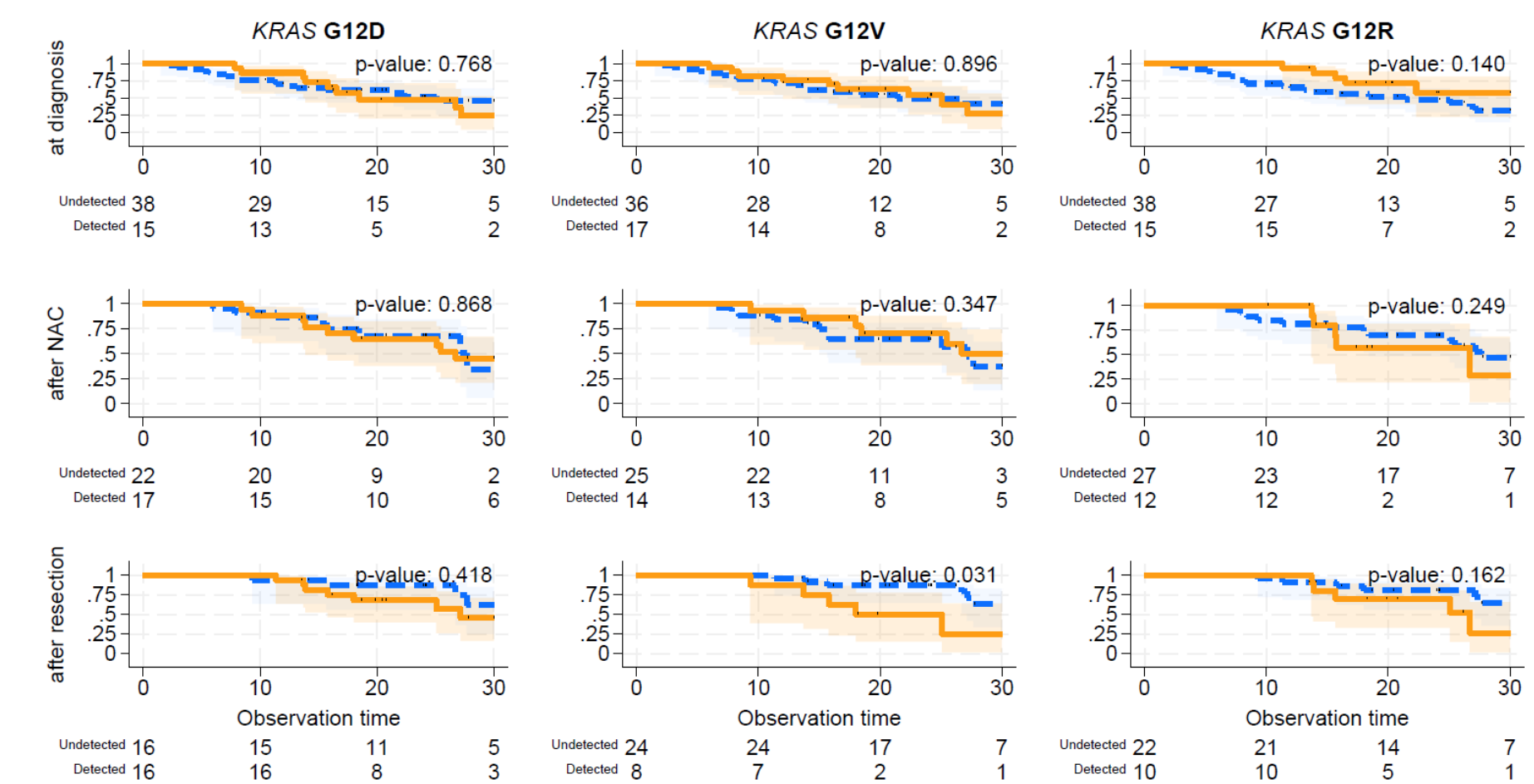- Samples analyzed by ddPCR for mutant *KRAS* G12D, G12V, and G12R

### Analysis
- Primary outcome was overall survival (OS)
- Kaplan-Meier with log-rank testing and multivariable Cox regression assessed survival differences

## Results – Descriptive Statistics and Regression



Sankey diagram: Detected at diagnosis 34; Undetected at diagnosis 35; Not drawn at diagnosis 15 → Neoadjuvant 67 / No neoadjuvant 17 → Detected after neoadjuvant 39; Undetected after neoadjuvant 17; Not drawn after neoadjuvant 28 → Resected 48 / Not resected 36 → Detected after resection 23; Undetected after resection 22; Not drawn after resection 3; Excluded at this timepoint 36



Bar charts — At diagnosis: Collected 70.2, G12D 23.2, G12V 30.5, G12R 28.8; After neoadjuvant: Collected 83.6, G12D 41.1, G12V 37.5, G12R 35.7; After resection: Collected 93.8, G12D 35.6, G12V 20.0, G12R 22.2

| . | HR | p-value | 95% CI | | | HR | p-value | 95% CI | |
|---|---|---|---|---|---|---|---|---|---|
| G12V | | | | | | | | | |
| Undetected | 1 | (ref) | | | | | | | |
| Detected | 36.75 | 0.01 | 2.93 | 461.38 | G12V copy number | 4.02 | 0 | 1.58 | 10.24 |
| Age | 1.03 | 0.42 | 0.96 | 1.11 | Age | 1.02 | 0.66 | 0.95 | 1.09 |
| Pathologic stage | | | | | Pathologic stage | | | | |
| Stage IA | 1 | (ref) | | | Stage IA | 1 | (ref) | | |
| Stage IB | 127.93 | 0.01 | 3.82 | 4285.71 | Stage IB | 98.85 | 0.01 | 3.78 | 2587.15 |
| Stage IIB | 2.27 | 0.57 | 0.13 | 39.04 | Stage IIB | 1.69 | 0.71 | 0.11 | 27.18 |
| Stage III | 7.19 | 0.13 | 0.55 | 93.61 | Stage III | 6.21 | 0.16 | 0.49 | 78.98 |
| CA 19-9 | 1 | 0.68 | 0.99 | 1.01 | CA 19-9 | 1 | 0.25 | 1 | 1.01 |

## Results – Kaplan-Meier Estimates



Kaplan-Meier curves for KRAS G12D, G12V, and G12R at diagnosis, after NAC, and after resection.

KRAS G12D: at diagnosis p-value 0.768; after NAC p-value 0.868; after resection p-value 0.418
KRAS G12V: at diagnosis p-value 0.896; after NAC p-value 0.347; after resection p-value 0.031
KRAS G12R: at diagnosis p-value 0.140; after NAC p-value 0.249; after resection p-value 0.162

## Conclusions

1. Genomic *KRAS* mutations are detectable in ctDNA samples obtained in peripheral blood samples in patients with PDAC by ddPCR
2. These mutations are detectable treatment with NAC
3. The presence and copy number concentration of mutant *KRAS* G12V after resection was independently predictive of prognosis
4. Clearance was also associated with improved survival

Further study by our group using ddPCR in the detection of mutant KRAS ctDNA will include examination of recurrence and the association of oncologic outcomes with the quantitative information provided by ddPCR.

## References

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