Prevalence of Oncogenic RAS Mutations in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) Derived From the Real-World Evidence Database FoundationCORE

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Introduction

- More than 60,000 patients are diagnosed with pancreatic cancer in the United States every year,[1] with most patients diagnosed at the metastatic stage.[2] Pancreatic ductal adenocarcinoma (PDAC) is the most common histological subtype, accounting for ~90% of all pancreatic cancers.[3]
- KRAS driver mutations are frequent in PDAC.[4] KRAS (along with NRAS and HRAS) belongs to the RAS family of small GTPases. Hotspot mutations (mutations occurring at amino acid positions G12, G13, or Q61) in RAS stabilize the GTP-bound, active, RAS(ON) state and promote oncogenic signaling.
- Novel inhibitors targeting one or more RAS mutants are under development for PDAC, but the mutational landscape in RAS mutant PDAC remains incompletely described. An improved understanding of the incidence of these RAS mutations is therefore an important step toward developing improved therapeutic strategies.
- To comprehensively characterize the incidence of RAS mutations in patients with PDAC, we employed FoundationCORE, an extensive database housing genomic profiles from advanced cancer patients in the US. From this dataset, we define the spectrum of RAS mutations in PDAC and shed insight on the co-mutational and biomarker landscape of RAS mutant PDAC.

Materials and Methods

Mutational frequencies:

- NGS-based comprehensive genomic profiling (CGP) data from 27,298 PDAC tissue samples were accessed from the FoundationCORE database (Data cutoff 07 May 2024). Only 'short variants' in RAS genes (KRAS, NRAS, and HRAS) occurring at amino acid positions G12, G13, or Q61 that had a mutational frequency of 0.1% or greater were included (hereafter referred to as RAS mutant). RAS wild-type (WT) population defined as PDAC samples lacking RAS mutations at any of these three positions. To estimate the number of new US cases of RAS-mutated PDAC, pancreatic cancer incidence estimates[1] were adjusted by the derived RAS mutation prevalence values. All incidence estimates were rounded to the nearest 100.

Actionable biomarker prevalence:

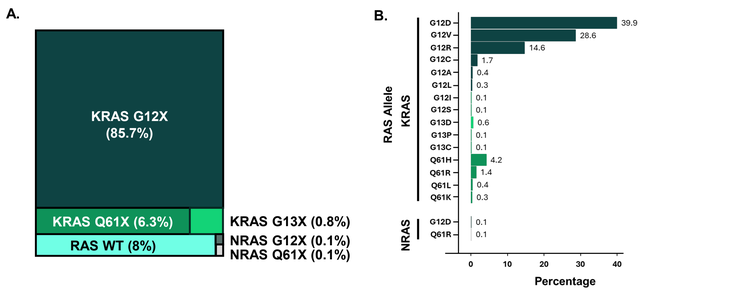
- Targeted therapies and immunotherapies approved for PDAC were identified from the Pancreatic Cancer Action Network.[5] This list was further refined to match those with biomarkers assayed for by CGP. TMB-H was defined as ≥10 mut/Mb. MSI-H samples were classified according to Foundation Medicine's internal definitions. dMMR is defined as samples with "Functional Status" of "known" or "likely" mutations in genes MLH1, MSH2, MSH6 or PMS2.

Co-mutation frequencies:

- For each RAS hotspot mutation position, the top ten most frequently co-mutated genes were identified, resulting in 16 genes for the cumulative list. Only variants with "Functional Status" of "known" or "likely" encompassing short variants, copy number alterations, and rearrangements were included.

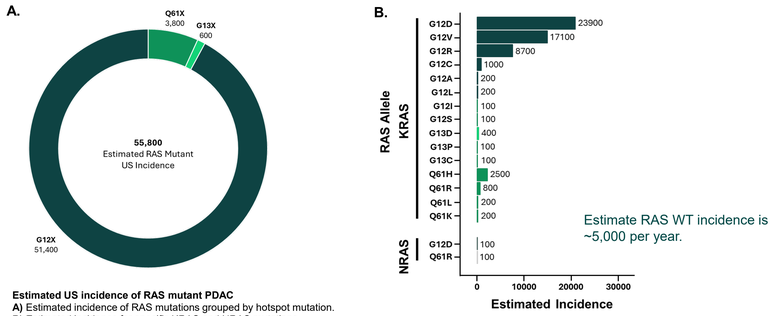
Key Results

92% of Patients with PDAC have a Hotspot RAS Mutation



Frequency of RAS mutant PDAC
A) Proportion of PDAC with KRAS, NRAS, or HRAS mutations at amino acid positions G12, G13, and Q61 or RAS WT. RAS WT population defined as PDAC samples lacking RAS mutations at any of these three positions. No HRAS mutations passed minimum frequency for inclusion (>=0.1%).
B) Mutational frequency of specific KRAS and NRAS alleles.

~56,000 New Cases of RAS Mutant PDAC are Diagnosed in the US Each Year



Estimate RAS WT incidence is ~5,000 per year.

Estimated US incidence of RAS mutant PDAC
A) Estimated incidence of RAS mutations grouped by hotspot mutation.
B) Estimated incidence for specific KRAS and NRAS mutations.

Actionable Biomarkers with Approved Therapies in RAS Mutant PDAC are Rare

A) Frequency of select tumor biomarkers for targeted therapies

Biomarker	Therapy	RAS Mutant	RAS WT
BRAF V600E	Dabrafenib + trametinib	N.D.	3.8%
RET Fusion	Selpercatinib	N.D.	1.2%
NTRK1/2/3 Fusion	Larotrectinib/ entrectinib	N.D.	0.5%

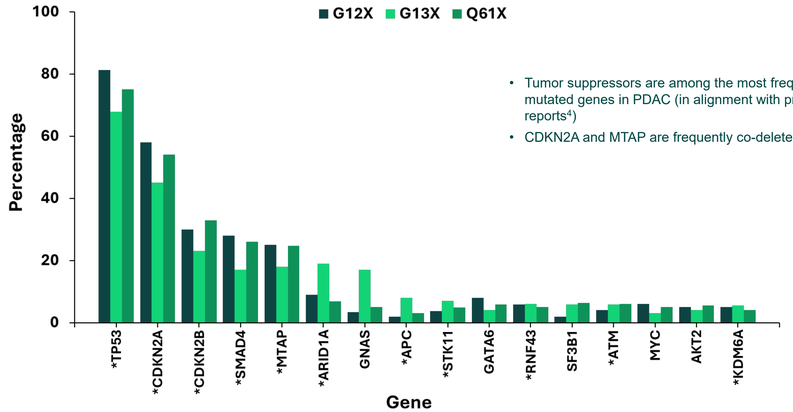
N.D. = Not Detected (below 0.1% mutational frequency).

B) Frequency of immunotherapy biomarkers

Biomarker	Therapy	RAS Mutant	RAS WT
TMB-H	Pembrolizumab	0.90%	6.0%
MSI-H	Pembrolizumab	0.35%	2.3%
dMMR	Pembrolizumab	1.5%*	4.0%*

*Does not account for samples with mutations in multiple MMR genes, therefore final percent may be an overestimate.

Most Co-Mutated Genes in RAS Mutant PDAC are Tumor Suppressors



- Tumor suppressors are among the most frequently mutated genes in PDAC (in alignment with previous reports[4])
- CDKN2A and MTAP are frequently co-deleted[6]

Percentage of co-mutated genes in RAS mutant PDAC
*Indicates tumor suppressor gene.

Conclusions

- In FoundationCORE's dataset of advanced PDAC, oncogenic RAS mutations are identified from tissue NGS testing in >90% of patients
- An estimated 56,000 new patients with RAS mutant PDAC are diagnosed each year in the U.S., with the vast majority being RAS G12X (>51,000)
- Actionable biomarkers with approved therapies are relatively rare in RAS mutant PDAC
- Most frequently co-mutated genes in RAS mutant PDAC are tumor suppressors
- Both the frequency and diversity of RAS mutations in PDAC in this dataset validate that PDAC is largely a RAS-addicted cancer and broadly targeting RAS may be useful in this disease

References
1. Siegel RL, et al. *CA Cancer J Clin*. 2024;74:12-49; 2. Park W, et al. *JAMA*. 2021;326:851-862; 3. Halbrook CJ, et al. *Cell*. 2023;186:1729-1754; 4. Cancer Genome Atlas Research Network. *Cancer Cell*. 2017;32:185-203.e13; 5. Pancreatic Cancer Action Network. Available at: https://pancan.org/facing-pancreatic-cancer/treatment/treatment-types/. Accessed December 10, 2024; 6. Ngoi N, et al. *J Clin Oncol*. 2022;40:604.

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Abbreviations
dMMR, DNA mismatch repair deficient; MSI-H, microsatellite instability high; N.D., not detected; PDAC, pancreatic ductal adenocarcinoma; TMB-H, tumor mutational burden high; WT, wild-type.

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