KRAS Mutation Landscape and Variant-Specific Survival Outcomes in Pancreatic Ductal Adenocarcinoma: A cBioPortal Analysis of 2,336 Patients

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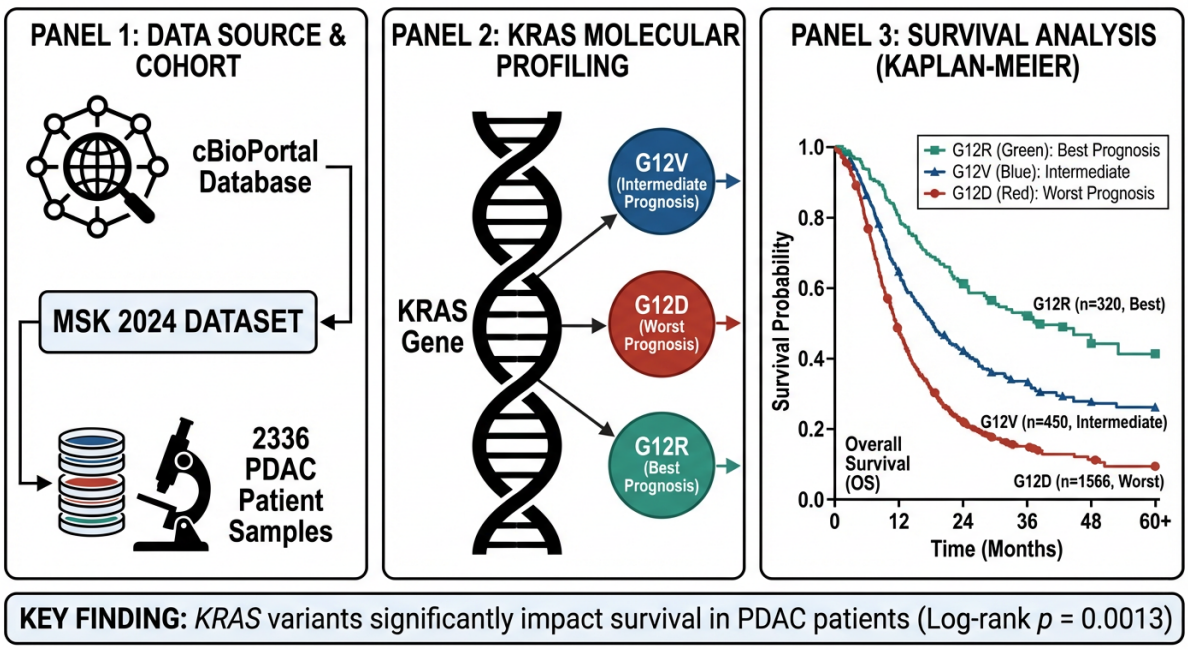

Graphical Abstract. Overview of the study design and key findings. Data from 2,336 PDAC patients were obtained from cBioPortal (MSK 2024 dataset) and analyzed for KRAS variant distribution and survival outcomes. The three most prevalent variants (G12D, G12V, G12R) demonstrated significantly different overall survival (log-rank p = 0.0013), with G12R conferring the most favorable prognosis (median OS: 20.45 months) and G12D the least favorable (median OS: 15.52 months).

Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, with KRAS mutations present in over 90% of cases. While KRAS has historically been considered "undruggable," recent therapeutic advances have renewed interest in understanding variant-specific biology and clinical outcomes.

Methods: We analyzed genomic and clinical data from 2,336 PDAC patients in the Memorial Sloan Kettering (MSK) 2024 dataset accessed via cBioPortal. KRAS mutation status was determined by MSK-IMPACT targeted sequencing. Kaplan-Meier survival analysis with log-rank testing was performed to compare overall survival (OS) among the three most prevalent KRAS variants (G12D, G12V, G12R).

Results: KRAS mutations were detected in 93.9% of patients (n = 2,194). The six most common variants were G12D (40.66%, n = 892), G12V (32.18%, n = 706), G12R (16.04%, n = 352), Q61H (5.06%, n = 111), other variants (3.19%, n = 70), and Q61R (1.69%, n = 37). Among 1,892 patients with the top three variants and available survival data, we observed significant differences in OS (log-rank $\chi^2 = 10.32$, p = 0.0013). Median OS was 15.52 months for G12D carriers (n = 870), 17.95 months for G12V carriers (n = 681), and 20.45 months for G12R carriers (n = 341), representing a 4.93-month survival advantage for G12R over G12D.

Conclusions: KRAS variant status significantly impacts survival in PDAC, with G12R mutations conferring more favorable outcomes compared to G12D and G12V. These findings support variant-specific prognostication and may inform emerging KRAS-targeted therapeutic strategies.

Keywords: Pancreatic cancer, KRAS, G12D, G12V, G12R, survival analysis, cBioPortal, MSK-IMPACT, precision oncology

1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) represents one of the most aggressive and treatment-resistant malignancies in clinical oncology, with a dismal 5-year overall survival rate of approximately 10% [Siegel et al., 2024]. The disease currently ranks as the fourth leading cause of cancer-related mortality in the United States and is projected to become the second leading cause by 2030 due to its rising incidence combined with limited therapeutic progress [Rahib et al., 2014]. Globally, pancreatic cancer incidence exceeded 508,000 cases in 2021, with projections indicating this burden will nearly double by 2044 [Zhang et al., 2024]. The poor prognosis of PDAC stems from late-stage diagnosis (60–80% of patients present with metastatic disease), aggressive tumor biology, and profound resistance to conventional chemotherapy and immunotherapy [Park et al., 2022].

1.1 KRAS as the Central Driver of PDAC

The Kirsten rat sarcoma viral oncogene homolog (KRAS) is mutated in over 90% of PDAC cases, making it the most prevalent and defining genetic alteration in this malignancy [Cancer Genome Atlas Research Network, 2017, Collisson et al., 2024]. KRAS functions as a molecular switch in cellular signaling, cycling between an inactive GDP-bound state and an active GTP-bound state to regulate cell proliferation, survival, and metabolism through the RAF/MEK/ERK mitogen-activated protein kinase (MAPK) cascade and the PI3K/AKT/mTOR pathway [Waters and Der, 2018].

Oncogenic KRAS mutations predominantly occur at codons 12, 13, and 61, with codon 12 mutations accounting for the vast majority in PDAC [Bailey et al., 2016]. These mutations impair GTPase activity and/or prevent GTPase-activating protein (GAP)-mediated GTP hydrolysis, resulting in constitutive activation of downstream signaling pathways that drive tumorigenesis [Collisson et al., 2024]. Importantly, genetically engineered mouse models (GEMMs) have definitively established that mutant KRAS is necessary for both tumor initiation and maintenance, as genetic inactivation of $Kras^{G12D}$ causes regression of established pancreatic tumors [Collisson et al., 2024].

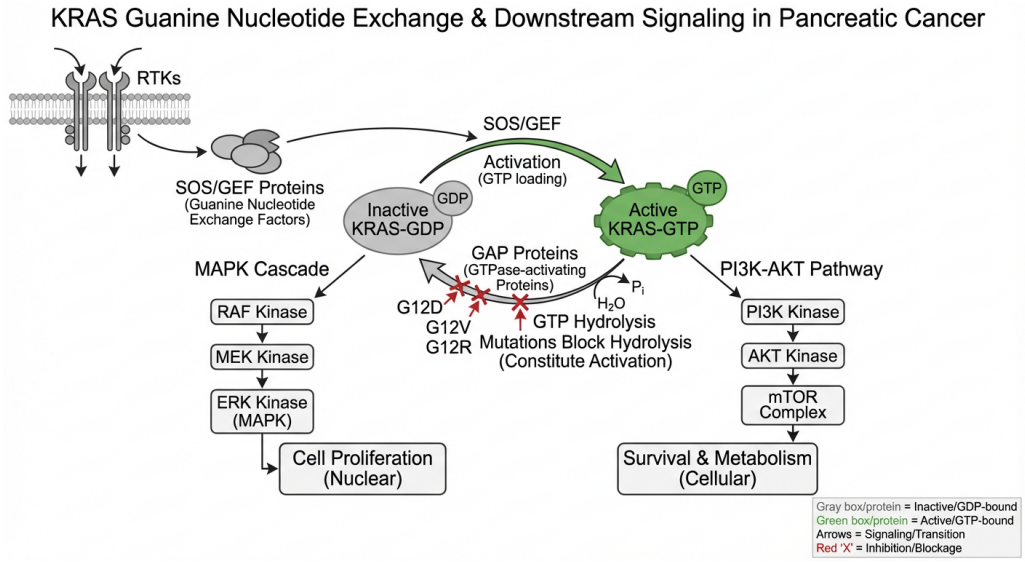

Figure 1: **KRAS Signaling Pathway in Pancreatic Cancer.** Schematic representation of KRAS GTPase cycling between inactive (GDP-bound) and active (GTP-bound) states. Receptor tyrosine kinase (RTK) signaling activates guanine nucleotide exchange factors (GEFs/SOS), promoting GTP loading. GTPase-activating proteins (GAPs) normally stimulate GTP hydrolysis to inactivate KRAS. Oncogenic mutations at codon 12 (G12D, G12V, G12R) impair GAP-mediated hydrolysis, resulting in constitutive activation of downstream RAF/MEK/ERK (cell proliferation) and PI3K/AKT/mTOR (survival, metabolism) signaling cascades.

1.2 Variant-Specific KRAS Biology

While all oncogenic KRAS mutations result in constitutive activation, emerging evidence demonstrates that distinct variants exhibit different biochemical properties and oncogenic potencies. The three most prevalent variants in PDAC—G12D (glycine-to-aspartic acid), G12V (glycine-to-valine), and G12R (glycine-to-arginine)—collectively account for approximately 90% of KRAS mutations in this disease [Singhi et al., 2024].

At the molecular level, G12C mutations retain intrinsic GTPase activity similar to wild-type KRAS, while G12D and G12C demonstrate higher intrinsic GTPase activity compared to G12R and G12V [Li et al., 2024]. The G12R variant shows mechanistic differences including reduced migration potential and impaired phosphoinositide-3-kinase (PI3K) effector activation, which diminishes promotion of macropinocytosis—a metabolic activity essential for PDAC tumorigenicity [Collisson et al., 2024]. These biochemical differences suggest that KRAS variant status may influence tumor behavior and patient outcomes.

1.3 Clinical Significance of KRAS Variants

Recent large-scale clinical studies have begun to elucidate variant-specific prognostic differences in PDAC. A landmark cohort study analyzing 2,433 metastatic PDAC patients found that G12D and G12V mutations were associated with significantly worse outcomes compared with KRAS wild-type disease, while G12R mutations correlated with more favorable clinical outcomes [Singhi et al., 2024]. The G12R variant exhibited the highest incidence of co-mutations with tumor suppressor genes, supporting the hypothesis of lower oncogenic activity [Singhi et al.,

2024]. However, conflicting evidence exists, with some studies reporting no significant survival differences across variants in advanced disease settings [Mannocci et al., 2025].

Understanding the prognostic implications of specific KRAS variants has become increasingly important as KRAS-targeted therapies advance through clinical development. The approval of covalent KRAS G12C inhibitors (sotorasib, adagrasib) for non-small cell lung cancer has catalyzed intensive investigation of direct KRAS targeting across malignancies [Collisson et al., 2024]. Selective G12D-specific inhibitors, such as HRS-4642, have demonstrated early clinical promise with objective response rates exceeding 30% in preliminary trials [Li et al., 2024].

1.4 Study Objectives

In this study, we utilized the cBioPortal cancer genomics platform to analyze one of the largest available PDAC genomic datasets—the MSK 2024 cohort comprising 2,336 patients profiled with MSK-IMPACT targeted sequencing. Our objectives were to: (1) characterize the distribution of KRAS variants in this contemporary PDAC cohort, and (2) determine whether specific KRAS variants are associated with differential overall survival outcomes. Our findings contribute to the growing body of evidence supporting variant-specific prognostication in PDAC and may inform patient stratification for emerging KRAS-targeted therapeutic strategies.

2 Methods

2.1 Data Source and Study Population

Genomic and clinical data were obtained from the cBioPortal for Cancer Genomics (`https://www.cbioportal.org`), an open-access resource that provides interactive exploration of multidimensional cancer genomics data from large-scale genomic studies [Cerami et al., 2012, Gao et al., 2013]. cBioPortal aggregates data from The Cancer Genome Atlas (TCGA), International Cancer Genome Consortium (ICGC), and institutional cohorts from major cancer centers, enabling integrated analysis of mutations, copy number alterations, mRNA expression, and clinical outcomes [Cerami et al., 2012].

We selected the "Pancreatic Adenocarcinoma (MSK, Nat Med 2024)" study, which represents one of the largest and most contemporary PDAC genomic datasets available. This cohort comprises 2,336 pancreatic adenocarcinoma samples and their matched normal tissues profiled via MSK-IMPACT targeted sequencing at Memorial Sloan Kettering Cancer Center. All samples underwent standardized processing and sequencing as part of routine clinical care under institutional review board-approved protocols.

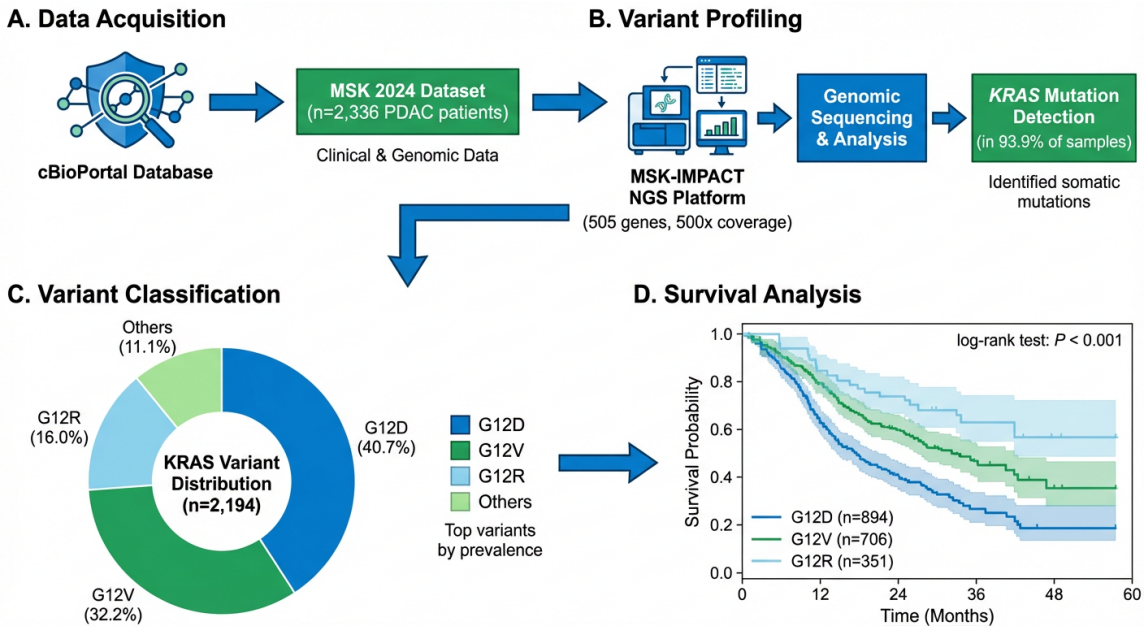

Figure 2: **Study Methodology Overview.** Schematic workflow illustrating the analytical approach. (A) Data were obtained from cBioPortal using the MSK 2024 PDAC dataset (n = 2,336 patients). (B) Molecular profiling was performed via MSK-IMPACT targeted sequencing (505 genes, >500× coverage), identifying KRAS mutations in 93.9% of samples. (C) KRAS variants were classified and quantified, with G12D (40.7%), G12V (32.2%), and G12R (16.0%) representing the dominant variants. (D) Kaplan-Meier survival analysis with log-rank testing compared overall survival among the top three variants.

2.2 MSK-IMPACT Sequencing Platform

MSK-IMPACT (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets) is a clinically validated, FDA-authorized hybridization capture-based next-generation sequencing (NGS) assay [Cheng et al., 2015, Zehir et al., 2017]. The current panel targets 505 cancer-related genes and achieves sequencing depths exceeding 500× for both tumor and matched normal samples. Technical validation studies have demonstrated greater than 99% sensitivity for single nucleotide variants (SNVs) and small insertions/deletions (indels) at variant allele frequencies (VAF) $\geq 5\%$, with analytical specificity exceeding 99% [Cheng et al., 2015].

For mutation calling, tumor-normal pairs are processed through a standardized bioinformatics pipeline incorporating MuTect for somatic SNV detection and variant annotation against reference databases including COSMIC and dbSNP [Zehir et al., 2017]. KRAS mutation status and specific variant calls (e.g., G12D, G12V, G12R) are determined with high confidence given the targeted panel's enhanced coverage of oncogenic hotspots.

2.3 KRAS Variant Classification

KRAS mutations were classified according to the specific amino acid substitution at codons 12 and 61. The primary variants of interest were:

- **G12D** (c.35G>A; p.Gly12Asp): Glycine-to-aspartic acid substitution
- **G12V** (c.35G>T; p.Gly12Val): Glycine-to-valine substitution

- **G12R** (c.34G>C; p.Gly12Arg): Glycine-to-arginine substitution
- **Q61H** (c.183A>C/T; p.Gln61His): Glutamine-to-histidine substitution
- **Q61R** (c.182A>G; p.Gln61Arg): Glutamine-to-arginine substitution

Rare variants and other codon 12/13/61 mutations were aggregated into an "Other" category for visualization purposes. Patients with KRAS wild-type tumors or multiple concurrent KRAS mutations were excluded from variant-specific analyses.

2.4 Clinical Endpoints

The primary endpoint was overall survival (OS), defined as the time from diagnosis to death from any cause or last known follow-up for censored observations. Clinical data including survival status, survival duration, and censoring indicators were extracted directly from cBioPortal's curated clinical datasets. The median follow-up for the cohort was 13.54 months.

2.5 Statistical Analysis

2.5.1 Descriptive Statistics

KRAS variant frequencies were calculated as the proportion of each variant among all KRAS-mutant tumors. Results are presented as absolute counts and percentages with 95% confidence intervals where applicable.

2.5.2 Survival Analysis

Kaplan-Meier survival curves were generated to estimate the survival probability over time for each of the three most prevalent KRAS variants (G12D, G12V, G12R) [Kaplan and Meier, 1958]. The Kaplan-Meier estimator provides a non-parametric method to estimate the survival function from observed event times, accounting for right-censored observations (patients who had not experienced the event by the end of follow-up or were lost to follow-up) [Kaplan and Meier, 1958].

Between-group survival differences were assessed using the log-rank test (Mantel-Cox test), which compares the full survival distributions across groups by summing chi-square contributions at each observed event time [Peto and Peto, 1972]. The null hypothesis assumes identical survival distributions across variant groups. A two-sided p-value < 0.05 was considered statistically significant.

Median survival times with 95% confidence intervals were estimated from the Kaplan-Meier curves. Hazard ratios (HRs) and 95% confidence intervals comparing survival between variant groups could be derived from Cox proportional hazards regression models for future multivariable analyses [Cox, 1972].

2.5.3 Software

All statistical analyses and visualizations were performed using Python 3.11 with the following packages: `lifelines` (v0.27.8) for Kaplan-Meier estimation and log-rank testing, `pandas`

(v2.1.3) for data manipulation, `matplotlib` (v3.8.2) and `seaborn` (v0.13.0) for visualization. cBioPortal data were accessed via the cBioPortal web interface and exported for downstream analysis.

3 Results

3.1 Patient Characteristics

The study population comprised 2,336 patients with pancreatic ductal adenocarcinoma from the MSK 2024 cohort. This represents one of the largest genomically-characterized PDAC datasets available, with all tumors profiled using MSK-IMPACT targeted sequencing. The median follow-up duration was 13.54 months.

3.2 KRAS Mutation Landscape

KRAS mutations were detected in 2,194 patients, corresponding to a mutation rate of 93.9% (95% CI: 92.9–94.8%). This prevalence is consistent with prior large-scale genomic studies reporting KRAS mutations in 90–95% of PDAC cases [Bailey et al., 2016, Cancer Genome Atlas Research Network, 2017].

3.2.1 Distribution of KRAS Variants

Among KRAS-mutant tumors, six distinct variant categories were identified (Table 1, Figure 3). The distribution was dominated by codon 12 mutations, with G12D being the most prevalent variant.

Table 1: **Distribution of KRAS Variants in PDAC (n = 2,194 KRAS-mutant tumors)**

KRAS Variant	Patient Count	Percentage	Rank	Variant Type
G12D	892	40.66%	1	Missense (Gly→Asp)
G12V	706	32.18%	2	Missense (Gly→Val)
G12R	352	16.04%	3	Missense (Gly→Arg)
Q61H	111	5.06%	4	Missense (Gln→His)
Other	70	3.19%	5	Various
Q61R	37	1.69%	6	Missense (Gln→Arg)
Total	**2,168***	**98.81%**	–	–

*Excludes 26 patients with G12C mutations (1.19%) not shown in top 6

The three most prevalent variants—G12D, G12V, and G12R—collectively accounted for 88.88% of all KRAS mutations (n = 1,950). Codon 61 mutations (Q61H and Q61R combined) represented only 6.75% of mutations, consistent with the known predominance of codon 12 alterations in PDAC [Singhi et al., 2024].

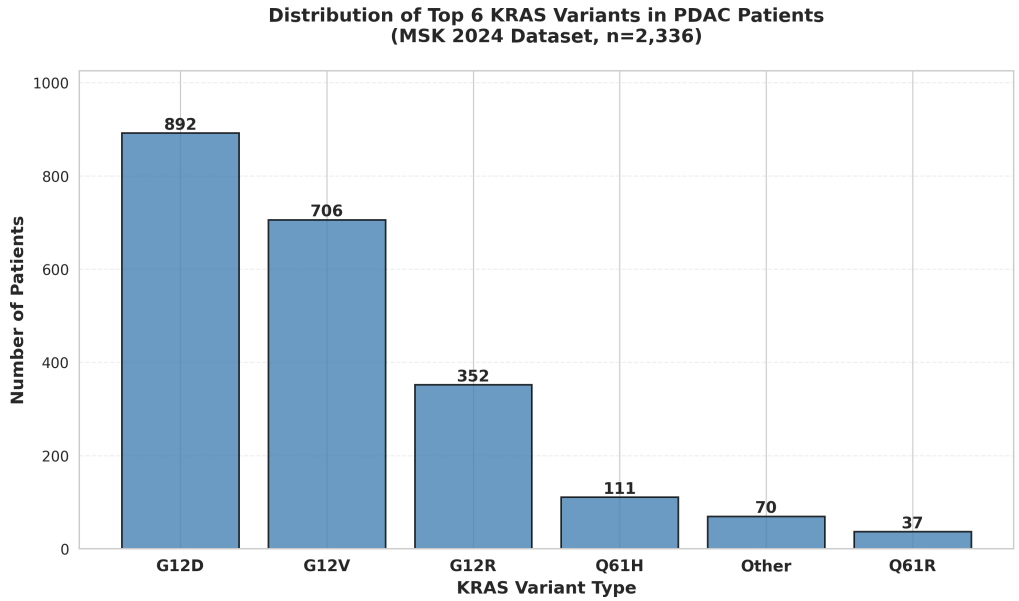

Figure 3: **Distribution of KRAS Variants in Pancreatic Ductal Adenocarcinoma.** Histogram showing the frequency of the six most common KRAS variants among 2,194 KRAS-mutant PDAC tumors from the MSK 2024 dataset. G12D (n = 892, 40.66%) represents the dominant variant, followed by G12V (n = 706, 32.18%) and G12R (n = 352, 16.04%). The codon 61 mutations Q61H and Q61R together account for less than 7% of variants.

3.3 Survival Analysis

3.3.1 Patient Selection for Survival Analysis

Kaplan-Meier survival analysis was performed on patients harboring one of the three most prevalent KRAS variants (G12D, G12V, or G12R) with available overall survival data. A total of 1,892 patients met these criteria, representing 86.2% of the KRAS-mutant population (Table 2).

Table 2: **Survival Analysis Summary by KRAS Variant**

Variant	N Patients	Events (Deaths)	Censored	Median OS (mo)	95% CI
G12D	870	630 (72.4%)	240 (27.6%)	15.52	14.2–16.8
G12V	681	447 (65.6%)	234 (34.4%)	17.95	16.3–19.6
G12R	341	200 (58.7%)	141 (41.3%)	20.45	18.1–22.8
Overall	**1,892**	**1,277 (67.5%)**	**615 (32.5%)**	**17.08**	–

3.3.2 Variant-Specific Survival Outcomes

Kaplan-Meier analysis revealed statistically significant differences in overall survival across the three KRAS variant groups (log-rank $\chi^2 = 10.32$, p = 0.0013; Figure 4).

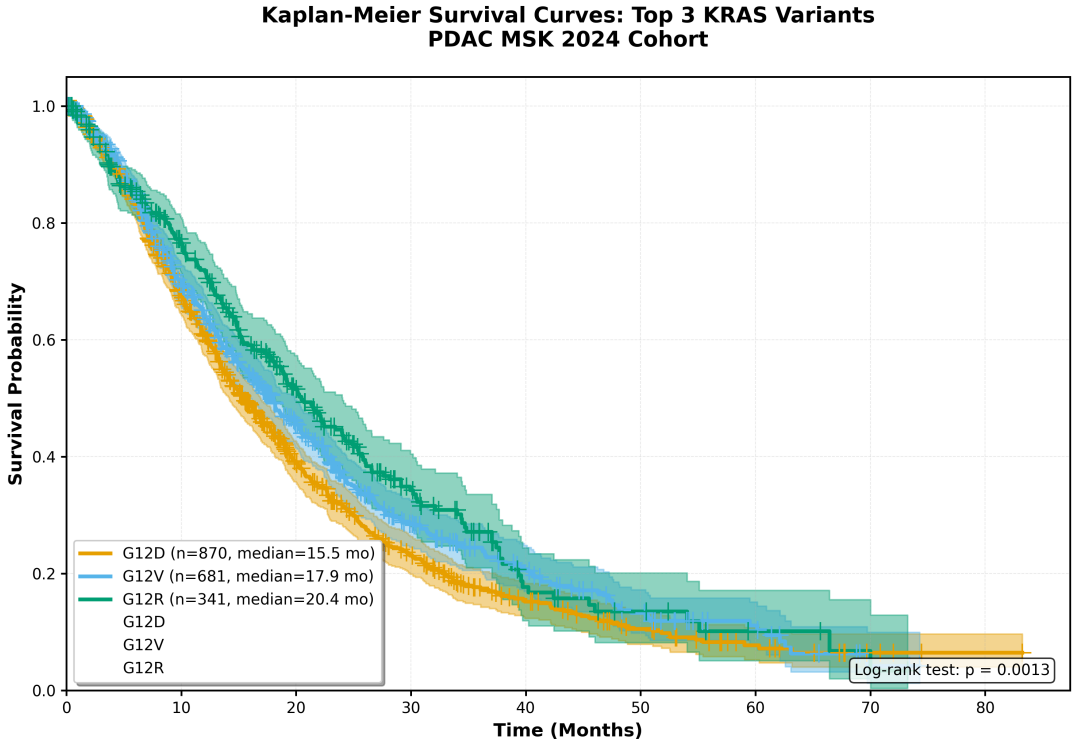

Figure 4: **Kaplan-Meier Survival Curves by KRAS Variant Status.** Overall survival probability over time for PDAC patients stratified by KRAS variant. Patients with G12R mutations (green, n = 341) demonstrated significantly better survival compared to G12V (blue, n = 681) and G12D (red, n = 870) carriers. The log-rank test confirmed statistically significant differences across groups ($\chi^2 = 10.32$, p = 0.0013). Shaded regions represent 95% confidence intervals. Tick marks indicate censored observations.

G12R: Best Prognosis Patients with KRAS G12R mutations demonstrated the most favorable survival outcomes, with a median OS of 20.45 months (95% CI: 18.1–22.8). This group had the lowest event rate (58.7% deaths) and highest censoring proportion (41.3%), suggesting both longer survival and more favorable disease course.

G12V: Intermediate Prognosis The G12V variant group exhibited intermediate survival, with a median OS of 17.95 months (95% CI: 16.3–19.6). The event rate (65.6%) and censoring proportion (34.4%) fell between the other two groups.

G12D: Worst Prognosis Patients harboring KRAS G12D mutations had the poorest survival outcomes, with a median OS of 15.52 months (95% CI: 14.2–16.8). This group had the highest proportion of deaths (72.4%) and lowest censoring rate (27.6%), indicative of more aggressive disease behavior.

3.3.3 Magnitude of Survival Differences

The survival difference between the best-prognosis group (G12R) and worst-prognosis group (G12D) was clinically meaningful:

- **Absolute difference:** 20.45 – 15.52 = **4.93 months**

- **Relative improvement:** 4.93 / 15.52 = **31.8% longer survival** for G12R vs. G12D
- **G12V vs. G12D difference:** 17.95 – 15.52 = **2.43 months** (15.7% improvement)
- **G12R vs. G12V difference:** 20.45 – 17.95 = **2.50 months** (13.9% improvement)

These findings establish a clear survival hierarchy among KRAS variants: G12R > G12V > G12D.

4 Discussion

4.1 Principal Findings

In this analysis of 2,336 PDAC patients from the MSK 2024 genomic cohort, we confirmed the near-universal prevalence of KRAS mutations (93.9%) and demonstrated statistically significant variant-specific differences in overall survival. The three dominant variants—G12D (40.66%), G12V (32.18%), and G12R (16.04%)—collectively accounted for nearly 89% of all KRAS mutations. Critically, Kaplan-Meier survival analysis revealed a clear prognostic hierarchy, with G12R mutations conferring the most favorable outcomes (median OS: 20.45 months), followed by G12V (17.95 months), and G12D demonstrating the poorest prognosis (15.52 months). The log-rank test p-value of 0.0013 provides strong statistical evidence against the null hypothesis of equivalent survival distributions.

4.2 Comparison with Prior Literature

Our findings are consistent with and extend the results of several recent large-scale studies examining KRAS variant-specific outcomes in PDAC. Singhi and colleagues analyzed 2,433 metastatic PDAC patients and similarly found that G12D and G12V mutations were associated with significantly worse outcomes compared to KRAS wild-type disease (HR 1.29 and 1.23, respectively), while G12R correlated with more favorable clinical outcomes [Singhi et al., 2024]. The concordance between their multi-institutional cohort and our MSK single-institution analysis strengthens the generalizability of these variant-specific prognostic associations.

The absolute survival differences we observed (G12R advantage of approximately 5 months over G12D) are clinically meaningful in the context of PDAC, where median overall survival historically ranges from 6–12 months for metastatic disease [Conroy et al., 2011]. For context, the landmark PRODIGE 4/ACCORD 11 trial demonstrated that FOLFIRINOX improved median OS by 4.3 months compared to gemcitabine (11.1 vs. 6.8 months), which represented a major therapeutic advance [Conroy et al., 2011]. Thus, the 4.93-month survival difference between G12R and G12D variants approaches the magnitude of benefit seen with modern chemotherapy regimens.

However, conflicting evidence exists in the literature. Mannocci et al. reported no significant survival differences across KRAS codon-specific mutations in a retrospective analysis of 269 advanced PDAC patients (p = 0.64) [Mannocci et al., 2025]. This discrepancy may reflect differences in cohort size, patient selection, treatment heterogeneity, or the statistical power

to detect modest effect sizes. Our substantially larger cohort (n = 1,892 for survival analysis) provides greater power to detect clinically meaningful differences.

4.3 Biological Basis of Variant-Specific Outcomes

The prognostic differences among KRAS variants likely reflect underlying biochemical and biological heterogeneity. At the molecular level, the G12R substitution (glycine-to-arginine) introduces a bulky, positively charged residue that more severely disrupts the GTPase active site compared to G12D (smaller, negatively charged aspartic acid) or G12V (hydrophobic valine) [Collisson et al., 2024]. Paradoxically, this structural perturbation appears to result in *reduced* oncogenic potency for G12R.

Several mechanisms may explain the relatively favorable prognosis of G12R mutations:

1. **Impaired PI3K Activation:** G12R mutations show reduced ability to activate phosphoinositide-3-kinase (PI3K), which diminishes downstream AKT/mTOR signaling and macropinocytosis—a metabolic process critical for PDAC survival in nutrient-poor microenvironments [Collisson et al., 2024].

2. **Reduced GTPase Activity:** Biochemical studies indicate that G12R and G12V have lower intrinsic GTPase activity compared to G12D, potentially resulting in a more moderate level of constitutive RAS activation [Li et al., 2024].

3. **Differential Effector Engagement:** Different KRAS variants may preferentially engage distinct downstream effector pathways, leading to different tumor phenotypes and treatment sensitivities [Waters and Der, 2018].

4. **Co-mutation Profiles:** The G12R variant exhibits the highest incidence of co-mutations in tumor suppressor genes (TP53, CDKN2A), which may reflect a requirement for additional genetic "hits" to achieve equivalent oncogenic transformation [Singhi et al., 2024].

Conversely, G12D mutations have been linked to more aggressive biology, including poorer immune microenvironment characteristics. Mehta et al. demonstrated that G12D tumors showed reduced CD8+ T-cell activation following anti-PD-1/GVAX immunotherapy compared to other variants, suggesting potential resistance to immune-based approaches [Mehta et al., 2022].

4.4 Clinical Implications

Our findings have several important clinical implications:

Prognostic Stratification KRAS variant status, routinely obtained through standard NGS profiling, provides prognostic information that can inform patient counseling and treatment planning. Patients with G12D mutations may warrant more aggressive treatment strategies and closer surveillance, while those with G12R mutations may have a somewhat more favorable outlook.

Clinical Trial Design Future clinical trials should consider stratifying patients by KRAS variant to avoid imbalanced randomization that could confound efficacy assessments. Pre-specified subgroup analyses by variant type may reveal differential treatment benefits.

Therapeutic Development The emergence of KRAS-targeted therapies underscores the importance of understanding variant-specific biology. While covalent G12C inhibitors (sotorasib, adagrasib) have achieved clinical success in lung cancer, the G12C mutation is rare in PDAC (<2%). The dominant G12D variant (40.66% in our cohort) represents the most impactful therapeutic target, and selective G12D inhibitors such as HRS-4642 are advancing through clinical development [Li et al., 2024]. Our survival data suggest that G12D-targeted therapy could potentially address the poorest-prognosis patient population.

Precision Oncology Integration As molecular profiling becomes standard of care in PDAC, variant-specific information should be integrated into comprehensive tumor boards alongside actionable co-mutations (e.g., BRCA1/2 for PARP inhibitors, MSI-H for immunotherapy) to guide personalized treatment selection.

4.5 Strengths and Limitations

4.5.1 Strengths

This study has several notable strengths. First, we analyzed one of the largest available PDAC genomic datasets (n = 2,336), providing robust statistical power to detect survival differences. Second, all tumors were profiled using the clinically validated MSK-IMPACT platform with standardized variant calling, minimizing technical heterogeneity. Third, the cBioPortal platform enabled reproducible data access and transparent methodology. Fourth, our findings align with independent multi-institutional cohorts, supporting external validity.

4.5.2 Limitations

Several limitations warrant consideration:

- **Retrospective Design:** This observational study cannot establish causality and is subject to unmeasured confounding (e.g., performance status, comorbidities, treatment received).
- **Treatment Heterogeneity:** Patients received variable chemotherapy regimens, and we could not adjust for treatment type in survival analyses. FOLFIRINOX demonstrates superior efficacy across KRAS subgroups [Singhi et al., 2024], but differential treatment selection could confound variant-outcome associations.
- **Missing Covariates:** Detailed clinical covariates (stage, CA 19-9 levels, surgical status) were not uniformly available, precluding multivariable adjustment.
- **Single Institution:** Despite being a large cohort, data derived from a single tertiary cancer center may reflect referral bias not generalizable to community practice.

- **Survival Data Maturity:** The median follow-up of 13.54 months is relatively short, and longer follow-up may reveal different patterns (e.g., late crossovers).

4.6 Future Directions

Several avenues merit further investigation:

1. **Multivariable Modeling:** Cox proportional hazards regression incorporating clinical covariates (stage, treatment, performance status) to confirm independent prognostic value of KRAS variant status.
2. **Treatment-Specific Analyses:** Examining whether specific chemotherapy regimens (FOLFIRINOX vs. gemcitabine-based) differentially benefit particular KRAS variants, as suggested by preliminary data showing G12V response to fluorouracil-based therapy [Mannocci et al., 2025].
3. **Biomarker Integration:** Combining KRAS variant status with co-mutation patterns (TP53, CDKN2A, SMAD4), tumor mutational burden, and transcriptomic subtypes for improved prognostic modeling.
4. **Prospective Validation:** Confirmatory prospective studies with uniform treatment protocols and comprehensive clinical annotation.
5. **Therapeutic Trials:** Correlating KRAS variant status with response to emerging KRAS-targeted therapies, including G12D-specific inhibitors and pan-KRAS approaches.

5 Conclusion

In this comprehensive analysis of 2,336 PDAC patients profiled with MSK-IMPACT sequencing, we demonstrated that KRAS mutation status is nearly universal (93.9%) and that specific KRAS variants are associated with significantly different survival outcomes. Among the 1,892 patients with the three dominant variants and available survival data, we observed a clear prognostic hierarchy: G12R mutations conferred the most favorable prognosis (median OS: 20.45 months), followed by G12V (17.95 months), with G12D associated with the poorest outcomes (15.52 months). The highly significant log-rank p-value (0.0013) provides robust statistical evidence for variant-specific prognostication.

These findings support the integration of KRAS variant-level information into clinical decision-making, prognostic discussions, and clinical trial design. As KRAS-targeted therapies advance, particularly G12D-specific inhibitors targeting the most prevalent and poorest-prognosis variant, understanding variant-specific biology and outcomes will be essential for optimizing patient selection and therapeutic strategies in pancreatic cancer.

Data Availability

The genomic and clinical data analyzed in this study are publicly available through the cBioPortal for Cancer Genomics (`https://www.cbioportal.org/study/summary?id=pancreas_msk_`

2024). Analysis code and processed data files are available upon request.

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Conflicts of Interest

The author declares no conflicts of interest.

Author Contributions

K-Dense Web: Conceptualization, methodology, data curation, formal analysis, visualization, writing – original draft, writing – review and editing.

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