An overview of KRAS and it's importance in pancreatic cancer

Cancer arises from genetic mutations or changes in the DNA that allows cells to grow unregulated. Healthy cells don't divide unless given signals from the environment to initiate proliferation, mutations that allow a cell to grow, divide, or survive indiscriminately will initiate cancer. The *RAS* family of genes is made up of *KRAS, NRAS,* and *HRAS* and these genes encode proteins involved in telling a cell to start to undergo replication and division. While *HRAS* and *NRAS* mutations are found in 2.4 and 5.5% of cancers, respectively, *KRAS* mutations are the most commonly occurring *RAS* mutations in cancer found in about 20% of all cancer patients. [1] *KRAS* is mutated in colorectal cancer, lung cancer, and most prominently in pancreatic cancer.

KRAS mutations are found in over 85% of pancreatic ductal adenocarcinomas (PDACs; the most common form of pancreatic cancer) and are the first mutation, known as the driver mutation, for PDAC kicking off transformation from healthy cell to cancer cell. [1,2,3] KRAS* protein generally exists in its inactive form. When KRAS becomes activated, it signals through multiple pathways that allow a cell to grow, divide, and survive. Mutations in the *KRAS* gene result in KRAS protein that is always active, disconnecting growth and division from the normal directions a healthy cell receives. This unchecked proliferation allows for the addition of more genetic mutations that are known to accumulate as a healthy cell turns into precancerous lesions (pancreatic intraepithelial neoplasms or PanINs) then pancreatic cancer during the progression of PDAC.

One reason that *KRAS* mutations are so prevalent in cancer is because there are multiple mutations that can lead to unregulated activation. Proteins are made up of amino acids put together by the code of the gene's DNA. Some genetic mutations swap out amino acids in a protein in a way that affects the function of the protein. In KRAS there are three amino acids that are seen mutated frequently, glycine 12 (G12), glycine 13 (G13), and glutamine 61 (Q61). [1,2,3] These amino acids can get replaced by a number of different amino acids that all result in an activated KRAS protein. G12 mutations are the most commonly seen in more than 90% of PDACs and the most common of these is G12D (glycine replaced with aspartic acid) seen in ~ 40% of PDAC tumors (Table 1).

Since *KRAS* mutations are the initiating event in PDAC and also found in other cancers, targeting *KRAS* for therapy is an area of active research. Researchers have looked for drugs that could block the activation of KRAS or the function of active KRAS but that has been difficult to date. The structure of KRAS protein doesn't have any obvious places where a drug could bind to and inhibit KRAS activity in this way. However, new advances have recently led to the discovery of inhibitors to specific KRAS mutations (Table 1) and these drugs are being tested in clinical trials alone and in combination with other types of therapy.

Inhibitors targeting G12C mutations were the first developed, have been tested in multiple clinical trials (Table 1) and have shown promising results for lung cancer. However, this specific mutation is only present in ~1% of PDACs. Many of these agents are also early in clinical trials and results have yet to be reported. Agents targeting the more prevalent *KRAS* G12D mutation in PDAC are starting to enter the clinic with promising preclinical data but are yet to report clinical results for PDAC patients. Additionally, other ways to target KRAS have been developed and include pan-RAS inhibitors (that target mutant and

wild-type* RAS), KRAS degraders (agents that destroy mutant KRAS proteins) and siRNA technology (instructs the cell not to produce mutant KRAS proteins). Like most targeted therapies, resistance is expected to develop underlining the need to test these KRAS targeted therapies in combination with other types of drugs for optimal responses.

Mutation	Frequency in PDAC	Therapies in development
G12D	~40%	MRTX1133, RMX-9805, HRS-4642
G12V	~30%	
G12R	~15%	
Q61H	5%	
G12C	1%	Multiple agents in the clinic for multiple indications: Sotorasib(AMG510), Adagrasib (MRTX849), Divarasib (GDC-6036), MK-1084, Garsorasib, JDQ443, IBI351, BEBT-607, BI-1823911, BPI-421286, D3S-001, GEC255, HBI-2438, Ly3537982, RMC-6291, HS-10370, Glecirasib, and YL-15293
G12S	<1%	
G12L	<1%	
Q61K	<1%	
Q61R	<1%	
A11T	<1%	
G13P	<1%	
G13D	<1%	
Q61H/G12D	<1%	

Table generated with data from [refs 1,2,3]

References
[1] Waters and Der. 2018. Cold Spring Harb Perspect Med
[2] Linehan, McDermott, and O'Kane. 2024. Front. Med.
[3] Luo J. 2021. Semin Oncol

*Genes are *italicized* and proteins are not, which is why KRAS is sometimes italicized but other times isn't, *KRAS* is the gene and KRAS is the protein.

*When a gene does not carry a genetic mutation it is referred to as "wild-type" and when a gene has changes in the DNA when compared to the wild type sequence it is referred to as "mutant"

Level up your giving with a Donor-Advised Fund (DAF)

The Hirshberg Foundation has partnered with DAF Day for a new way to make a difference. On October 10, 2024, we'll be joining a collaborative group of leading nonprofits, fundraising platforms, and providers of Donor-Advised Funds (DAFs) for a single day of unprecedented generosity. DAF Day is a new kind of giving day that reframes how Donor-Advised Funds are used and who uses them.

A Donor-Advised Fund is one of philanthropy's fastest-growing vehicles today.As the Hirshberg Foundation drives research forward and provides critical services for patients and families, we understand that you want your contributions to make a significant impact. By opening a Donor-Advised Fund (DAF), you can easily amplify the value of your annual donations and make a difference.

You might think that Donor-Advised Funds (DAFs) are only for the financially established, but that's a common misconception. By

opening a DAF (with no minimum amount required), you can start making contributions to let those funds grow tax-free until you're ready to donate! You can even give your DAF account a name that's meaningful to you and your loved ones.

Young donors are opening brokerage accounts and financial literacy is woven into pop-culture. The reality is that teenagers are investing more than ever as well. You're never too young or too old to set a goal to donate to your favorite charity every year.

Here's how a Donor-Advised Fund will change the way you give, create a new financial vehicle to grow your wealth, and allow you to make a greater impact in the fight against pancreatic cancer.

WHAT IS A DAF?

Donor-Advised Funds (DAF) began to grow in visibility and popularity in the 1990's, and today they are philanthropy's fastest-growing vehicles. A DAF is an easy, tax-smart investment option for charitable giving. To put it simply: a DAF is an account set up through a brokerage firm where you can contribute cash and non-cash assets, invest, allow funds to grow over time, and then make an even bigger tax-free donation!

WHAT ARE THE REQUIREMENTS?

If you're a U.S. permanent resident with a social security number, you've met the criteria. You likely already have a checking and savings account – to start a Donor-Advised Fund you'll simply open a brokerage account and fill out a form. Banks like Wells Fargo, Charles Schwab, Vanguard, and Fidelity offer DAF accounts as well as online apps like Daffy and Charityvest. You may already have an account used to invest in stocks, save for retirement, or set aside money for your child's college fund. Sign in to your account and visit the charitable giving section.

WHAT ARE THE STEPS TO MAKE A DAF GIFT?
There are three simple steps to get the ball rolling:

1. Open an account and contribute cash, assets, or investments
2. Invest by selecting from some optional investment pools
3. Grant funds to a public charity such as the Hirshberg Foundation

HOW TO PERSONALIZE YOUR DAF…
When you create your Donor-Advised Fund, there will be a moment when it's clear just how meaningful this financial step is for you personally. It's the moment when you name your DAF. This is an opportunity to name it after your family or a loved one. You'll often find DAFs named "the Johnson Family Fund" or named after a loved one, such as "the Sharon Smith Fund."

Questions about Donor-Advised Fund giving? Contact Sarah Banks, Development Director sbanks@pancreatic.org or (310) 473-5121.

Early Detection Initiative for High-Risk Individuals

For those at high risk of pancreatic cancer, navigating the uncertainties of the disease can be a challenge. Whether due to a family history, genetic predispositions, or other risk factors, proactive measures and early detection are critical. The Pancreatic Cancer Early Detection (PRECEDE) Consortium offers a vision of collaborative excellence to transform how we approach these challenges and provide new hope to those at increased risk.

The PRECEDE project, spearheaded by Dr. Diane Simeone, represents a significant leap forward in early detection and patient support. This international consortium unites top experts and institutions with a shared goal: to elevate the 5-year survival rate for pancreatic cancer from 13% to 50% over the next decade. This ambitious target underscores a commitment to improving outcomes through advanced research and personalized care.

How PRECEDE Supports High-Risk Individuals

For individuals with a family history of pancreatic cancer, pathogenic gene mutations, or other high-risk factors, PRECEDE offers a valuable resource:

1. Personalized Monitoring: Through the PRECEDE study, participants receive tailored monitoring based on their specific risk factors. This includes regular blood tests every 6 to 12 months and additional imaging for those in particularly high-risk groups. This individualized approach aims to catch potential issues early, before symptoms arise.

2. Innovative Screening Techniques: The consortium is developing and refining advanced screening methods to enhance early detection. These efforts are focused on identifying pancreatic cancer at its most treatable stages, thereby improving the likelihood of successful interventions.

3. Comprehensive Risk Management: By studying individuals with known risk factors—such as chronic pancreatitis, pancreatic cysts, or genetic mutations—PRECEDE aims to deepen our understanding of the disease. This research is critical for developing effective early detection tests and comprehensive prevention strategies.

4. Longitudinal Follow-Up: Under the guidance of experts like

UCLA's Dr. Donahue, the PRECEDE study will follow participants over time, providing ongoing support and monitoring. Dr. Donahue emphasizes the importance of early detection, stating, "Early detection would drastically change the trajectory of the disease and ultimately save thousands of lives."

If you or someone you know is at high risk for pancreatic cancer, consider enrolling in the PRECEDE study. Your participation can contribute to groundbreaking research and potentially save lives by advancing early detection and prevention methods.

For more information on how you can be part of this transformative study, visit PRECEDE Study.

To hear more from Dr. Diane Simeone about the PRECEDE project, watch her Symposium Speaker Spotlight.

By working together, we can advance towards a future where early detection and proactive prevention truly transform outcomes for those facing pancreatic cancer.

Family Genetics in Pancreatic Cancer and High-Risk Individuals

Pancreatic cancer remains one of the most challenging cancers to detect and treat, with significant disparities affecting certain populations. The Hirshberg Foundation is dedicated to improving outcomes through research, awareness, and support, particularly

focusing on family genetics, early detection and high-risk communities.

While most pancreatic cancers develop due to acquired gene mutations influenced by factors like smoking, obesity, age, and chronic pancreatitis, genetic predispositions can play a significant role. Approximately 10% of pancreatic cancer cases are hereditary, linked to inherited gene mutations known as Familial Pancreatic Cancer (FPC). FPC refers to families with at least two immediate family members with pancreatic cancer but no known hereditary cancer syndrome.

If you have a first-degree relative diagnosed with pancreatic cancer, your risk of developing the disease may be increased. It is strongly advised that your family member undergo genetic testing for inherited mutations. If their test results are negative, you typically may not need genetic testing. However, if their results are positive or uncertain, or if multiple close relatives have cancer, it is recommended to consult with a genetic counselor to determine if you should undergo genetic testing for inherited cancer risks and consider monitoring options. The risk increases further if more family members are affected or if there is a history of certain familial cancers. About 10% of pancreatic cancer cases are due to inherited mutations.

Black Americans are disproportionately affected by pancreatic cancer, facing higher incidence rates and significant obstacles to early detection and treatment, exacerbated by socioeconomic disparities, racial discrimination in healthcare settings, and late-stage diagnoses. Additionally, Ashkenazi Jews also face a higher incidence, possibly due to mutations in the BRCA1 or BRCA2 genes, which are associated with hereditary cancer predisposition.

To help further understand these risk factors and monitor individuals with genetic risks, researchers have established pancreatic cancer tumor registries. These registries include:

- The Pancreatic Tumor Registry at Memorial Sloan Kettering Cancer Center (MSKCC)
- The National Familial Pancreatic Tumor Registry (NFPTR) at Johns Hopkins University
- The Cancer of the Pancreas Screening-5 (CAPS5) Study which is also a clinical trial currently conducted at 8 universities

These pancreatic cancer tumor registries collect valuable data that can lead to early detection and potentially life-saving interventions for high-risk individuals.

Addressing pancreatic cancer requires a multifaceted approach that includes understanding genetic risks, improving early detection, and ensuring equitable healthcare. The Hirshberg Foundation is committed to transforming outcomes for high-risk families and communities through research, education, and support.

Resources:

- Hirshberg Foundation – Paving the Way to Better Outcomes
- American Cancer Society – Health Disparities Research
- FDA – Racial and Ethnic Minorities in Clinical Trials
- National Institutes of Health – Clinical Trial List

Through research, education, and community support, we strive to make significant strides in the fight against pancreatic cancer, ensuring no one faces this disease alone.

Pancreatic Cancer Patient Support Groups

Living with pancreatic cancer can create an array of emotional and physical challenges. Fortunately, these new life difficulties can be greatly improved with the right support system in place. While family and friends can offer assistance there are many benefits to speaking with other pancreatic cancer patients and those with a shared experience. While not conventionally thought of as part of your medical team, support groups can provide a wealth of resources, tips and helpful information.

Participating in a support group online can make the difference between feeling alone and isolated versus feeling empowered and connected. Support groups can be beneficial for both the patient and the caregivers as it provides a safe space to connect with people going through comparable medical and psychological experiences. Not all support groups operate the same; some gather virtually while others are online forums where patients post questions, so take the time to find one that feels right for you.

Below are some of our partners and organizations that understand the importance of support groups for both pancreatic cancer patients and their loved ones.

- American Cancer Society provides free support services for anyone living with cancer and their loved ones. Search for support programs and services in your area.
- CancerCare provides free, professional support services for people living with cancer. They offer counseling with an oncology social worker to help cope with the emotional and practical challenges of pancreatic cancer. They also

provide free online support groups for both pancreatic cancer patient and caregivers.

- Cancer Support Community offers a toll-free helpline and live web chat where anyone affected by cancer can speak with licensed counselors. Through MyLifeLine, you can create a private support webpage to stay connected with friends and family.
- WeSPARK offers an array of free support groups, from a caregivers group to a singles support group as well as in-treatment and post-treatment groups. They also offer various supplemental programs such as acupuncture, reflexology and tai chi. They advise an intake session where they review your history to better recommend programs that may be a good fit.
- Pancreatic Cancer Connections is an online social community that provides a safe space for pancreatic cancer patients and their loved ones to share their experiences, get valuable coping resources, and support one another.
- If you're comfortable with social media, there's a Facebook group called the Whipple Surgery Survivor Group. With patients from around the world, this vast community can be the right resource for those looking to connect with other patients on Facebook. This group does require you to have a Facebook account and posts may not be private.
- The Smart Patients Pancreatic Cancer discussion forum is an online support group for patients and caregivers dealing with pancreatic cancer. Members share help, advice and information about treatments, symptoms and side effects.
- Cancer Support Community South Bay offers a free, virtual group for pancreatic cancer patients, survivors, caregivers, and family members to build and maintain a

support community from diagnosis through treatment and recovery. (Available for California residents only)
- If you're looking to connect with other patients and caregivers, ANCAN offers a virtual peer-to-peer support group with the mission to provide all pancreatic cancer patients with a better quality of life.
- Another virtual peer-to-peer group is led by long-term survivor Tom. Tom facilitates a space for patient and caregivers to share experiences, knowledge and support. Zoom calls are every Friday from 9:00am until 10:30am PST, contact Tom for more details.

If you are a patient or caregiver with questions, contact Patient & Family Support today.

Researchers receive $4 million to advance immunotherapy treatment for pancreatic cancer

We are proud to share that our collaborative efforts with the UCLA Health Jonsson Comprehensive Cancer Center have led to a transformative $4 million grant from the National Cancer Institute (NCI). This grant aims to advance immune-based therapies for pancreatic ductal adenocarcinoma (PDAC) to improve treatment and patient outcomes.

Immunotherapy employs drugs to boost the immune system's ability to identify and attack cancer cells. Under the guidance of Dr.

Timothy Donahue, Director of the Agi Hirshberg Center for Pancreatic Diseases, Dr. Zev Wainberg, co-director of the UCLA Health GI Oncology Program, and Dr. Caius Radu, professor of molecular and medical pharmacology, a multidisciplinary team is delving deep into the role of adenosine in the immune suppression associated with pancreatic cancer. Their work seeks to understand how adenosine, a molecule in the body, affects the tumor environment and interactions between immune and cancer cells.

The grant will also fund a follow-up clinical trial examining a small molecule inhibitor combined with the existing combination of PD-1, an immunotherapy drug, and chemotherapy before surgery. Building on promising initial results, this trial seeks to diminish adenosine production within tumors, potentially boosting the immune system's ability to fight cancer more effectively. Previous Hirshberg Foundation Seed Grant Awardees, Dr. Thuc Le and Dr. Evan Abt, have also been working to study adenosine.

"By introducing a small molecule inhibitor to the existing chemotherapy and PD-1 inhibition regimen, we hope to limit adenosine production in the tumor microenvironment, thereby enhancing the immune response against the cancer," said Donahue in the article published by UCLA Health. "We are hopeful this strategy will help the body's natural defenses fight the cancer more effectively, leading to better treatments for people with pancreatic cancer."

This substantial grant is a beacon of hope. We are optimistic that this research will uncover new therapeutic strategies that target adenosine, enhancing patient outcomes and leading to better treatments.