Making sense of the nonsensical when faced with pancreatic cancer

Wendy Hammers is a dear friend of the foundation and an inspirational pancreatic cancer survivor. She has shared her story and wisdom at our annual Symposium on the Patient & Caregiver Panel, through our Patient & Family Webinar Series – twice – and most recently, with UCLA Health. She is a joy and brings light to a difficult diagnosis. Her talks on "breaking up with cancer" are tangible tools that help patients and loved ones focus on the aspects they can control and encourage us all to laugh a little more.

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By Leo Smith

"Comedy is part of the reason I'm alive," says Wendy Hammers, who gives motivational talks about how she "broke up with cancer." (Photo by John McCoy/UCLA Health)

Click on her 2015 video clip and you'll see Wendy Hammers in a hospital room, an IV tube connecting her to a small, drab machine as she undergoes chemotherapy for pancreatic cancer. She is dancing and smiling during the infusion.

Hammers has approached her cancer journey – from the first excruciating pain to the diagnosis, and then through the treatment – with a positive attitude and a sense of humor.

“There were three prongs of treatment – chemotherapy, surgery and mindset. For me, mindset was the most important. It was the one that gave me the inner strength to deal with the other two,” Hammers said. “Comedy is part of the reason I’m alive. Humor is just another word for perspective – it helps makes sense of the nonsensical.”

Hammers has honed that attitude as a stand-up comic and actress who now travels the country giving motivational talks, loaded with laughs, on how she “broke up with cancer.”

A cancer with few clues

Pancreatic cancer is the No. 3 cause of cancer deaths in the U.S., behind lung and colon cancers. The five-year survival rate is just 13%, but improving by about 1% annually largely due to advances in treatment and therapies, said Timothy Donahue, MD, director of the UCLA Agi Hirshberg Center for Pancreatic Diseases.

Unlike other cancers – such as prostate cancer, which can be detected early through a prostate-specific antigen (PSA) blood test – there are no known early markers for pancreatic cancer.

“They’ve never found an accurate tumor marker that can be used for screening and earlier diagnosis among the broader population,” said Dr. Donahue, a member of the UCLA Health Jonsson Comprehensive Cancer Center and professor of surgery at the David Geffen School of Medicine at UCLA. “The main precursor lesion that turns into pancreatic cancer cannot be seen on any imaging tests.”

For Hammers, unexpected weight loss may have been the first clue that something was wrong. But it was a severe stabbing pain on her left side, near her hip, that caught her attention.

“I felt good, until I felt terrible,” she said. “I lived with that pain for about a week before I went to the doctor.”

Diagnosis and treatment

The pancreas, a gland located in the back of the abdomen, helps with digestion and blood sugar regulation. Most tumors arise in the head of the pancreas, on the right side, said Dr. Donahue. In those cases, the cancer is usually diagnosed earlier than other parts of the organ because the tumors obstruct the bile duct causing patients to develop jaundice, a yellowing of the skin and the whites of the eyes.

Diagnosis of pancreatic cancer is divided into three categories: a small tumor confined to the pancreas (stage 1); a tumor that has grown outside the pancreas and involves blood vessels (stage 2 or 3); and a cancer that has spread to other organs, in most cases the liver (stage 4), Dr. Donahue said.

“When Wendy was first diagnosed, her tumor was partially involving some of the essential blood vessels around the pancreas. She was probably in the stage 2-3 range, a relatively early stage where it hadn’t spread to other organs,” Dr. Donahue said.

”In cases like that, we try to shrink the tumor with chemotherapy before pancreatic surgery, so hopefully we won’t have to do any major vascular work and reconstruction. We only have to remove the part of the pancreas with the tumor,” he said. “Her treatment was some chemotherapy first, then surgery, then a little more chemo to complete her course of therapy.”

Humor and positivity

Hammers recalled that when she received her diagnosis, instead of asking “Why me?” she thought, “How am I going to manage this?”

Her optimistic approach remained constant as treatment progressed. During her six-day post-surgery hospital stay, friends decorated her room with cards and flowers, they played music. She had an essential oil diffuser filled with lavender to relax her and the staff and she inhaled orange oil to mask the medicinal smell of rubbing alcohol during chemotherapy sessions.

She had mood lighting brought in to help take the focus away from the medical machinery.

“There’s no question that a positive outlook and optimism – and our partnership with patients as they try to maintain hope and an outlook that they’re going to beat this thing – certainly helps their survival and helps them tolerate their treatments better,” said Dr. Donahue. “For those who are less fortunate than Wendy, who don’t wind up beating it, a positive outlook improves their quality of life, of the time they have left.”

Dr. Donahue said he encourages his patients to think positively, despite the challenging circumstances. Hammers said she benefited directly from his coaching.

He said, “You have cancer. You’re going to be fine. I’ll be with you the whole time,” she recalled.

Hammers’ advice to others with cancer is to build a similar network of supporters.

“Choose doctors that you feel are team members,” she said. “And express yourself – that will lead to less tension, better sleep

and elevation of the immune system.”

And if you can, incorporate some humor into the cancer treatment plan.

“It’s so absurd, with things hanging out of your body,” Hammers said. “You need a way to laugh at it.”

What is Pancreatitis?

Pancreatitis is an inflammatory condition of the pancreas, with both acute (short-lived) and chronic forms, and a known risk factor for developing pancreatic cancer, especially in cases of long-term chronic inflammation.

Inflammation is an important part of the body’s response to infection or physical injury; it’s the signal that brings in the immune cells to fight the infection or to start the healing process. Usually, when the infection or injury is resolved, inflammation stops, but sometimes, this does not happen. This is called chronic inflammation and can damage cells and tissues. While pancreatitis is rare, it is a risk factor for developing pancreatic cancer.

Acute vs Chronic Pancreatitis

- **Acute Pancreatitis**: This is a sudden inflammation often caused by gallstones that physically block the vessels of the pancreas or with heavy alcohol consumption. The main symptom is severe abdominal pain. While it usually affects just the pancreas, it can sometimes be more widespread and life-threatening.

- **Chronic Pancreatitis**: This type involves long-term inflammation that damages the pancreas tissue over time and can decrease the ability of the pancreas to function. A mixture of risk factors includes chronic alcohol use, tobacco use, and inherited genetic mutations. As the pancreas gets damaged, it can lead to issues like weight loss, malnutrition, and diabetes, and it raises the risk of pancreatic cancer.

Pancreatitis is generally considered acute (short-lived) or chronic, but there is a spectrum of disease between these two designations. Patients can have one acute case over the course of their lives or multiple episodes, and acute pancreatitis, when not treated, can lead to chronic pancreatitis.

Chronic Pancreatitis & Substance Abuse

Alcohol abuse can cause chronic pancreatitis and increase the risk of developing pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer. The risk is further increased in those patients who also smoke. As the body breaks down alcohol, it generates byproducts that can be toxic to cells. If there is a buildup of these toxic byproducts, an increase in digestive enzymes can occur. An overproduction of these enzymes, meant to break down protein in our foods, can disrupt the cells of the pancreas and lead to further health problems.

While genetics and inherited conditions are beyond our control, we can limit inflammation and reduce risk factors. Ongoing research aims to find better treatments and improve outcomes for pancreatitis patients. If you or a loved one has pancreatitis and needs help, please contact Patient Support.

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.