

# REGISTRAR PIP

Visit [SEER\\*Educate](#): A comprehensive training platform for registry professionals

## The RAS Initiative

### Introduction

When thinking about a potential topic for this post, I decided to check into what the current “front burner” research issues at the National Cancer Institute (NCI) were to see whether something applied to the work we do and was worth sharing with everyone. Long ago we decided it was important to make ourselves aware of and locally promote what the NCI was financially supporting internally to ensure the registry continually evolved to remain relevant to researchers and clinicians. Relevance helps with securing funding for operations.

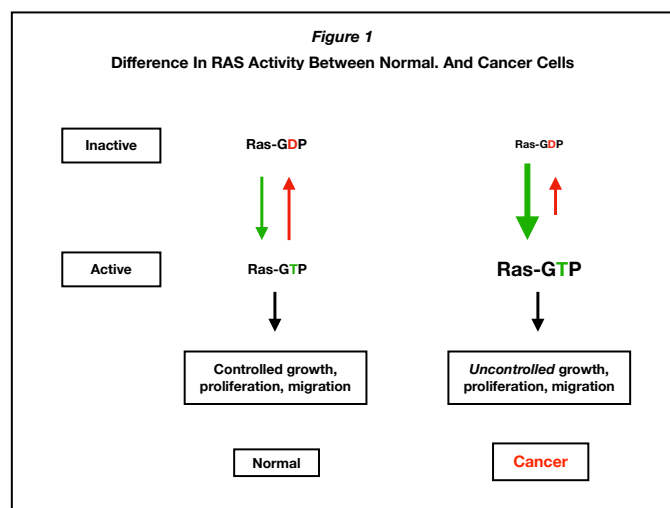
Given the years of registry data collection associated with the KRAS gene for colorectal cancers and the widespread interest in targeted therapy drugs, it’s probably not surprising that the NCI webpage associated with RAS gene mutations caught my eye. The RAS Initiative’s prominent web presence on the NCI site made me wonder what recent advances have been made in this area of research and whether we should anticipate data collection requirement changes in the future.

### KRAS Mutations and Cancer

Cancer incidence and severity are influenced by both the specific type of KRAS mutation and the tissue in which the mutation is located. The KRAS mutation is an error in a protein in normal cells. Normally KRAS serves as a sort of information hub for signals in the cell that lead to cell growth. When there is a mutation in KRAS, it signals too much and cells grow without being told to, which causes cancer.

The more technical explanation is that KRAS is a signal transducer protein playing a role in various cellular signaling events, including the regulation of cell proliferation. It cycles between active GTP (guanosine triphosphate)-bound and inactive GDP (guanosine diphosphate)-bound states. For example, in healthy cells KRAS acts as an on-off switch controlling cell growth. It does this by binding a **KRAS-activating molecule, GTP**, and then converts it to **GDP, which inactivates the protein**.

Unfortunately, in many cancers the mutated KRAS gene becomes stuck in the “on” position ignoring signals to the contrary and thus driving the cells to become cancerous. These cancer cells begin to grow uncontrollably avoiding death signals and they also activate the downstream pathways. This multiplication of cancer cells and tumor growth that can also cause metastases is illustrated in Figure 1, which is a graphic created by Jim Hartley of the NCI RAS Initiative.



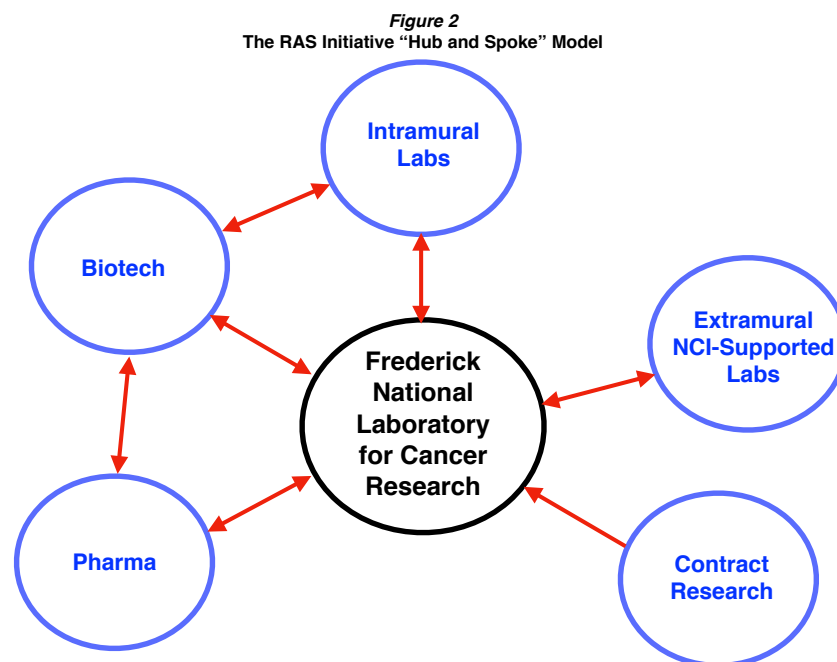
Process Improvement Pointers • Feedback/Questions to [Registrar-PIP@FredHutch.org](mailto:Registrar-PIP@FredHutch.org)

CSS is funded by the National Cancer Institute’s SEER Program, Contract Number HHSN2612018000041

### The RAS Initiative

A couple years prior to the development of the initiative, the importance of KRAS as a cancer driver in pancreatic cancer was well known. According to researchers at the Institute of Basic Medicine and Cancer in China, for decades “targeting KRAS mutations with drugs proved challenging because KRAS had been considered **undruggable** due to the lack of classic drug binding sites.” The need for effective therapies was clear given the lack of outcome improvement for patients diagnosed with pancreatic cancer. By 2012, researchers at Genentech and Vanderbilt, using nuclear magnetic resonance-based fragment screens, identified molecules that bind to KRAS directly. This opened the door to the potential to develop drugs to target KRAS.

Given the combination of clinical urgency and advances in technology, Dr. Harold Varmus, Director of the NCI at the time, believed there was an opportunity to use Frederick National Laboratory for Cancer Research (FNLCR), its research and development center, to address these challenges. Dr. Varmus challenged FNLCR to propose a plan to leverage existing funds and resources to form the RAS Initiative. Their proposal included an experimental and drug discovery core that would collaborate closely with the National Institutes of Health (NIH) intramural labs, extramural NCI-supported labs, contract research and the biopharmaceutical industry in a “hub-and-spoke” model to better coordinate research and drug development efforts. See Figure 2.



While KRAS is the best-known oncogene with the highest mutation rate among all cancers, the profile of KRAS mutations differs significantly among different types of cancer. The RAS Initiative, which NCI launched in 2013, investigates innovative approaches to attack the proteins encoded by mutant forms of RAS (e.g., KRAS, HRAS, and NRAS) genes in order to address the unmet clinical needs with effective therapy options for patients with KRAS-driven cancers.

Most of us are probably aware that 40%-45% of colorectal cancers are thought to result from mutations in the RAS family of genes; but did we all know that approximately 90% of pancreatic ductal adenocarcinoma and 25%-30% of all cancers are believed to be caused by these types of mutations? KRAS mutations are also common in

non-small cell lung cancer patients. This initiative was launched initially, in part, to address the lack of progress previously made in developing drugs against KRAS-driven cancers, especially pancreatic cancer, which was and continues to be highly fatal.

The current belief is there will be more drug targeted therapies in the future if researchers can more accurately describe RAS proteins' interaction with the plasma membrane and are able to activate effectors (a type of immune system cell that carries out a specific activity in response to stimulation). It's not surprising, a key initial and still relevant goal of the RAS Initiative involves an ongoing collaboration between academia and the biopharmaceutical industry to accelerate the development of drugs targeting KRAS cancers.

Granted, in the past researchers had greater difficulty developing targeted therapies because the small-sized KRAS protein has a smooth surface without deep pockets drugs could bind to. In addition, the KRAS protein binds very tightly to GTP in its activated state, which made **directly** blocking activated KRAS challenging. However, there are now some drugs that seem effective in blocking subsets of the KRAS mutations. At present there is also the potential to divide all the KRAS mutations into individual cancers, which opens the possibility of more targeted therapy options to treat each cancer type. Because KRAS also activates several downstream pathways, researchers are now also investigating the potential of **indirectly** blocking those pathways activated by KRAS.

### Conclusion

Gaining an understanding of the work being done in this area might give registrars an opportunity to learn **if**, **how** and **when** it might impact our data collection efforts in the future. It's probably not too much of a stretch to imagine more KRAS data collection one day as researchers are able to discover more about how the RAS proteins interact with the plasma membrane and their importance in initiating and sustaining tumor growth. While targeting KRAS mutations with drug therapy directly was once thought impossible, those involved in the RAS Initiative are committed to achieving a better understanding of KRAS mutations. This knowledge would promote the development of drugs targeting various mutations in order to improve the life and longevity of cancer patients.

How will we know when significant progress is being made on both the research and drug development fronts? A clue might prove to be that we will be asked to collect more KRAS data for many more primary sites given that the specific KRAS mutations seem to differ by primary site. When potentially asked to perform additional data collection, as registrars we will need to support the inclusion of this type of expansion, then actively look for and suggest methods to streamline its collection using electronic rather than manual methods.