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PANCREATIC CYSTS ARE COMMON AND USUALLY BENIGN—EXCEPT THOSE THAT TURN DEADLY

An NCI trial compares surveillance regimens. An argument can be made that only a government research agency like NCI has the capacity to answer questions about monitoring pancreatic cysts—and how some of them turn malignant.

→ PAGE 6

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In this issue

CLINICAL ROUNDUP

DRUGS & TARGETS

NCI TRIALS

PANCREATIC CYSTS ARE COMMON AND USUALLY BENIGN—EXCEPT THOSE THAT TURN DEADLY

AN NCI TRIAL COMPARES SURVEILLANCE REGIMENS

By Paul Goldberg

An argument can be made that only a government research agency like NCI has the capacity to answer questions about monitoring pancreatic cysts—and how some of them turn malignant.

Nobody knows exactly how prevalent pancreatic cysts are, just like no one knows exactly what to do once they appear on a scan.

The majority of these cysts are benign, but some signal the beginning of pancreatic cancer. There are two principal strategies for follow-up—one more intensive than the other. But since these regimens have never been compared in a randomized trial, no one knows which one is better.

And if you want to treat the disease surgically, options include pancreaticoduodenectomy, also known as the Whipple procedure. Alas, it's unknown whether the surgery leads to a decrease in mortality. Nor is there a way to predict which patients would benefit from surgery.

To sort through some of these unknowns, NCI is conducting a prevention trial—EA2185—that seeks to enroll 4,600 patients with newly identified pancreatic cysts measuring 1 cm or greater.

Stopping short of providing an answer on surgical intervention, the trial compares two commonly used regimens for monitoring pancreatic cysts, measuring impact on a composite of "unfavorable" outcomes, which include any pancreatic cancer without surgery and diagnosis of unresectable pancreatic cancer at surgery.

"I can tell you, because I do this for a living, the challenge is that the imaging studies are becoming so good that, inadvertently, we're finding pancreatic cysts are incredibly common, and we've got to get our arms around figuring out how to manage these," said Mitchell D. Schnall, a radiologist at the University of Pennsylvania and co-chair of ECOG-ACRIN Cancer Research Group. "Because every time somebody's getting a workup because of hematuria, we're looking at their kidneys. Every time somebody's getting a workup because of GI distress or because their biliary tract is being worked up, right, we're seeing the pancreas.

"And there's almost an epidemic of pancreatic cystic lesions, and frankly, this is emblematic. There's corollaries in other areas as well, where imaging is so good, there's a proliferation; of small renal cell carcinomas, for example. And it's not because there's suddenly a proliferation, it's because we're seeing stuff that we've never seen before and trying to figure out how we should be caring for these patients is absolutely crucial," Schnall said to *The Cancer Letter.*

A conversation with Schnall and Peter J. O'Dwyer, an oncologist at Penn and co-chair of ECOG-ACRIN appears on page 18.

The trial compares two guidelines for surveillance of these cysts. One set of guidelines in the trial is similar to the Fukuoka regimen and the lower-intensity guidelines similar to those promulgated by the American Gastroenterological Association.

"Guidelines get promulgated in all sorts of settings, by all sorts of groups and they're never compared, or they're rarely compared," David S. Weinberg, a gastroenterologist at Fox Chase Cancer Center and the principal investigator on the trial, said to *The Cancer Letter.*

"We thought that this trial was important, because it allowed not only the opportunity to address an important question, it goes to the heart of one of NCI's, and that should be anybody's, concerns about over-diagnosis versus under-diagnosis. As we've discussed.

"The stakes of missing the cancer are high and the stakes of overreacting to a CAT scan or an MRI are also high," Weinberg said. "So, getting a good answer makes sense. The ability to compare guidelines makes sense- and cost effectiveness is not a specific goal of this trial, but we would be foolish not to consider how much resources of all sorts are used here.

"When you think about it, if there are roughly 50 million people in the United States over the age of 60, and even a fraction of that, 2, 3%, has a cyst that in theory requires some form of serial cross-sectional imaging," Weinberg said. "The back of the envelope estimate is that we spend at least a billion dollars a year in the United States alone on radiology studies associated with pancreatic cysts. If I'm going to spend the billion dollars, I want to spend it well.

A conversation with Weinberg appears on page 10.

"The ECOG-ACRIN study is asking a critical question to help the field understand how to manage individuals with pancreatic cysts," Lynn Matrisian, chief science officer at the Pancreatic Cancer Action Network, said to *The Cancer Letter.* "Because of the dismal survival rates of pancreatic cancer, detection at the earliest indication of progression to malignancy can greatly increase the patient's likelihood of a good outcome."

Matrisian said that whenever people atdiagnosed with cysts call PanCAN's Patient Services, case manager encourage them to get involved with this study. Altogether, 85 individuals have been accrued to the study.

The trial complements an ongoing longitudinal cohort study supported by the NCI Early Detection Research Network, National Institute of Diabetes, Digestive and Kidney Diseases, and Pan Coast, designed to create a cohort of people who are newly diagnosed with diabetes in the hopes that this group, who are at increased risk of being diagnosed with pancreatic cancer, provide the clues in

their blood and tissues for investigations in pancreatic cancer.

The timing of the launch of the ECOG-ACRIN trial was unfortunate, Weinberg said.

"We started about a year ago. If you wanted to design the perfect study to be interrupted by COVID, this is it, because pancreatic cysts are not an emergency," he said. "So, if patients are less likely to be going to their doctor because of COVID-related concerns, particularly a year ago—as we all know, there were many fewer visits to doctors, many fewer visits to emergency rooms, and many fewer incidental identifications of cysts.

"Further, if a family member called me and said, hey, I had a CAT scan, I did not have a kidney stone, but they told me I had a pancreatic cyst, do I have to deal with that right away, the answer, except under rare circumstances, is no, you can wait.

"So, in our trial, of course, we've got a protocol. And the protocol is that the cyst needs to be identified within the last six months. So, if a patient doesn't get back to their doctor for six-and-a-half months after this CAT scan, because there's nothing emergent on it, then unfortunately the patient can't be a participant in our trial. COVID of course has also made it difficult to find research staff and keep research offices fully humming.

"That's slowly coming back as well."

Accruing patients to this study has been all the more difficult because institutions have to come up with ways to identify prospective patients and because physicians enrolling the patients aren't oncologists, and many of them are unfamiliar with the mechanics of NCI trials.

"The individuals who would put patients on this study are not medical oncologists, who are the drivers of most of the therapeutic studies, and they are often in specialties outside the traditional cancer research specialties, in this case, gastroenterology and surgical specialties, but also maybe less for this, but to a certain extent primary care," O'Dwyer said to *The Cancer Letter.*

> "And it's not because there's suddenly a proliferation [of pancreatic cysts], it's because we're seeing stuff that we've never seen before and trying to figure out how we should be caring for these patients is absolutely crucial."
>
> – *Mitchell Schnall*

"Could we streamline [the process] in such a way as to have something like a 'registration light' for individuals who are not going to be treating patients, who don't need to have their pharmacy information in there, for example, and other aspects that are required by our current registration procedures, so simplifying this, making it easier, ultimately for primary care," O'Dwyer said.

"Our focus should be on primary care physicians, because if large screening trials are going to ever be implemented, we're going to need the patients--they're not even patients--the subjects to be screened at the level of their local doctor. So, that's a big part of the way that we're thinking about how to engage more people in this process."

Physicians who put patients on these trials also have to figure out how their costs are reimbursed, essentially tapping into money coming from NCI.

Given the complexity of medical institutions, this is no simple task, Schnall said.

"And to us, as a group, it means that we've got to put a ton of resources into that primary care doc to educate them on what it is to be in the NCTN, to walk them through a bunch of paperwork, most of which are irrelevant to the trial they're going to go on that they've never seen before, heard before, and really are scared of, to work and try to create a relationship between them and the cancer center that would keep them whole for their costs and participating in the trial. It really creates challenges to getting these folks on these trials.

Recently, NCI Director Ned Sharpless asked an ad hoc group to review the institute's portfolio of prevention trials, which were impacted by the COVID pandemic. (*The Cancer Letter,* Sept. 4, Sept. 11, 2020).

The 13-member group focused primarily on the Tomosynthesis Mammographic Imaging Screening Trial.

In a report earlier this spring, the group recommended that while TMIST needs to be streamlined, it should continue (*The Cancer Letter,* March 19, 2021).

Q & A

Weinberg spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

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CONVERSATION WITH THE CANCER LETTER

David Weinberg: Only NCI has the capacity to answer public health question on managing pancreatic cysts

> Nobody, patients or doctors, want to operate on people who aren't going to benefit. By the same token, they don't want to withhold surgery from patients who will.

David S. Weinberg, MD, MSc
Chair, Department of Medicine,
Chief, Section of Gastroenterology,
Audrey Weg Schaus and Geoffrey Alan Weg Chair in Medical Science,
Fox Chase Cancer Center

Prevention and early detection trials have been especially vulnerable to being disrupted by the COVID-19 lockdown, and a comparison of two regimens for monitoring pancreatic cysts—EA2185—was more vulnerable than most.

"If you wanted to design the perfect study to be interrupted by COVID, this is it, because pancreatic cysts are not an emergency," David S. Weinberg, a gastroenterologist at Fox Chase Cancer Center and the principal investigator on the study, said to *The Cancer Letter.*

"So, if patients are less likely to be going to their doctor because of COVID-related concerns, particularly a year ago—as we all know, there was many fewer visits to doctors, many fewer visits to emergency rooms, and many fewer incidental identifications of cysts," Weinberg said.

"Further, if a family member called me and said, 'Hey, I had a CAT scan, I did not have a kidney stone,' but they told me, 'I had a pancreatic cyst, do I have to deal with that right away?' the answer, except under rare circumstances, is 'No, you can wait,'" Weinberg said.

"So, in our trial, of course, we've got a protocol. And the protocol is that the cyst needs to be identified within the last six months. So, if a patient doesn't get back to their doctor for six-and-a-half months after this CAT scan, because there's nothing emergent on it, then, unfortunately, the patient can't be a participant in our trial. COVID, of course, has also made it difficult to find research staff and keep research offices fully humming."

A video of the conversation is available here.

Weinberg spoke with Paul Goldberg, editor and publisher of *The Cancer Letter.*

Paul Goldberg: Dr. Weinberg, thank you for agreeing to talk with me about this. Why don't we focus on the whole series of scientific questions arising from your trial, which is EA2185. What is the main question that you're trying to answer?

David S. Weinberg: The main question is how to optimally take care of a very large group of patients, who I think are, for the most part, under-appreciated.

Pancreatic cysts are extraordinarily common, particularly in older people. The overwhelming majority will never cause any of them a problem.

However, there's a small fraction of cysts that over time will turn into pancreatic cancer, and pancreatic cancer, obviously, is a terrible disease for which we have, at this point anyway, no way to reliably prevent or, some might even argue, diagnose early. So, there's a small percentage of the population, patients with cysts, maybe patients with Type 2 diabetes, whom you could target as a group who are at higher risk to develop cancer.

So, there are a variety of recommended surveillance strategies for pancreatic cysts, and our trial is comparing the two major strategies. One is based on the so-called Fukuoka guidelines. And the other is based upon the guidelines promulgated by the American Gastroenterological Association. In some ways, the recommendations for surveillance are the same in that both focus on the available tools we have today for surveillance, and that is mostly cross-sectional imaging supplemented by endoscopic ultrasound in selected patients.

The difference between the two surveillance strategies rests upon the intensity of surveillance: How often are MRIs or CAT scans of the abdomen recommended, what characteristics of the cyst need to be present to recommend endoscopic ultrasound? In our study, in part to avoid confusing anyone by saying we are rigorously and completely following the Fukuoka guidelines or rigorously and completely following the AGA guidelines, each of which has strong adherents, I might add, we've instead called one arm of the trial high intensity surveillance, similar to Fukuoka, and the other low intensity, similar to the AGA.

Bottom line is, if you're in the high intensity surveillance arm, you're more likely to get cross-sectional imaging more frequently, you're more likely to get an endoscopic ultrasound. What we purposely are not doing for this trial is comparing indications to proceed with surgery. That's a completely different issue from surveillance, and we've adopted the standard changes either on CAT/MRI scans or endoscopic ultrasound that would prompt surgery and held them equivalent for both arms.

I see, but to establish kind of the stakes of this thing, the surgery is the Whipple?

DSW: Right. So, the reason this matters, once you get past the practical aspects of surveillance, is that, frankly, neither of these surveillance strategies is great. And that's really the problem, because what you're of course trying to do is identify patients at high enough risk for cancer to justify operating on them.

The problem is that you don't want to operate on people who aren't going to benefit, namely patients who don't have cancer, or, unfortunately, patients

whose life expectancy will not be meaningfully changed by surgery.

You don't want to operate on more people than you need to. On the other hand, as we were talking about a few minutes ago, there are very few ways to prevent pancreatic cancer. So, if you happen to find that group of patients who will in fact benefit from surgery, patients with presumably either early-stage cancer, that not only is resectable, but is resectable in a way that five-year survival after surgery is meaningful.

Unfortunately, that's still a small group even of resectable patients. We're also considering, for our trial, a success when a patient at surgery has high-grade dysplasia in their pancreatic cyst. Nobody knows with confidence what's the transformation rate from high-grade [dysplasia] to cancer.

But if this part of the GI tract is similar to other parts of the GI tract, high-grade dysplasia is certainly a major stepping-stone to development of malignancy. And if you can operate on patients and prevent them from getting pancreatic cancer that will kill them, at least in 2021, that's the best that we can hope for.

Can I interrupt for a second? Maybe I could ask you to summarize in a nutshell what the benefit would be from having conducted this trial. What will you know then that you don't know now?

DSW: Right. So, the basic tension, the take-home messages. Nobody, patients or doctors, want to operate on people who aren't going to benefit. By the same token, they don't want to withhold surgery from patients who will.

Our ability to risk-stratify needs to improve because missing the chance to prevent cancer is a terrible thing. On the other hand, subjecting someone to a major operation with major complications, at least potentially, is also a terrible thing. So, how to balance those two poles through a surveillance strategy is the question.

We want to figure out which of the surveillance strategies works better, and better for this trial is defined clinically, meaning we have a series of outcomes, which we're defining as either good or bad, but there also are questions of resource utilization. So, if you get twice as many CAT scans and MRIs and your clinical outcomes are unchanged, then you spend a lot of money and resources without getting any benefit.

And that also doesn't make any sense.

Okay, but it's also, what is the prevalence of pancreatic cysts? Does anybody know?

DSW: The prevalence of pancreatic cysts, all comers, if you're not worried about the size of the cyst, depends on how you do the imaging, but MRI is the most sensitive. And in patients over 60, the studies range anywhere from 5% of the entire population over 60 to 50% of the population over 60.

Our trial focuses on one centimeter or greater pancreatic cysts, which are certainly less common and might be seen in two to 5% of the over-60 population.

And you also have that in kidney; right? Or not?

DSW: Well, I'm not as familiar with the kidney literature, but certainly, incidentaloma findings in various intra-abdominal organs are common, liver cysts, pancreatic cysts, kidney cysts. I suspect that for the patients and the doctors who care for those individuals, everybody wants a good way to know that this finding on the CAT scan is either important or it's not.

So, you're talking about risk stratification that may have implications for other organs? Or not?

DSW: No, in this trial we're focusing only on pancreas.

Yes, but in terms of methodology [and] approach.

DSW: I think the question of how to take available tools and do the best method of risk stratification, of course, it's a common theme across any organ system. Where pancreas, anyway, at this point, perhaps lags behind some other areas is that we don't have good biomarkers, and one of the goals of our trial through correlate studies is to identify new and better markers, whether they are blood-based, something you can pick up in the DNA if you do a buccal swab etc.

We also have a large component of radiomics in this trial, or taking the available images and analyzing them in more sophisticated ways, all looking for markers that either would add to our current surveillance strategy to come up with a better risk stratification tool, or if we really hit a home run, replace some of those existing studies.

What is, maybe we should just do the numbers here, how many patients are you trying to accrue? And what is the budget? How much would it cost to do this study?

DSW: Well, the number of patients we'd like to accrue is about 4,600 evenly divided in that patients will be randomized to either the high intensity or low

intensity surveillance strategy, and then regardless of arm, each group would be followed for five years.

This is an expensive trial. The actual budget is a little hard to calculate in that, like many cooperative group trials, it's being conducted at, hopefully, at least in terms of places that have signed up, more than 200 sites around the United States, and we've recently added Canada, and we're looking for a couple of other international sites.

There's obviously a tremendous amount of money that could be spent as the number of participants grows, because we're banking biosamples, we're banking radiomics data, and those are costs that in theory are budgeted for the trial, but won't be expended unless we have the samples.

So, what is the amount of money do you think it's going to cost? Does anyone know this at this point, is there an estimate or a range of estimates?

DSW: I think the NCI has money set aside, and it's certainly in the tens of millions of dollars for a trial this size.

Okay, so the numbers aren't really known, right? Or are they?

DSW: The numbers, an interesting feature of cooperative group trials is even if you are the overall chair of the trial, which would be me, the construction of the budget is a complicated dance between the cooperative groups, NCI and NIH, I suspect.

So, unlike when I submit an R01, where I control all aspects of the budget, there are parts of this one that I don't have any particular reason to need to know about, as long as I can be assured that every time a blood sample shows up at the centralized biobank for the trial, it's appropriately handled.

Oh, interesting. So, who is diagnosing these cysts, for the most part ,and what kind of docs will be putting patients on your trial? These are not oncologists?

DSW: Not generally. And that's one of the challenges of trying to do this trial through the cooperative groups. The cooperative groups are a wonderful entity that science in general and medicine in particular has benefited from for years.

But the way the cooperative groups are set up is, of course, they emphasize oncology treatment trials. So, prevention trials, or early detection trials like this, in terms of practical aspects, if you weren't in the trial, patients are generally seen by gastroenterologists or surgeons.

Their cysts are generally identified by radiologists, and in many ways, the providers most immediately responsible for the patient's care, or primary care doctors, because the most common scenario since these cysts are nearly always completely asymptomatic is that they're identified serendipitously.

Somebody has abdominal pain, their primary care doctor gets a CAT scan of their abdomen looking for a kidney stone, they might find a kidney stone, but lo and behold, the radiologist picks up a 1.1-centimeter cyst in the head of the pancreas.

That information typically then goes back to the primary care doctor who has to figure out what to do about that. Generally, the response, at least hopefully, is referral to someone who is more familiar with the longitudinal management of cysts, and that tends to be gastroenterologists or surgeons. And as you've already suggested, generally not medical oncologists, because these patients for the most part, thankfully, will never get pancreatic cancer and wouldn't need a medical oncologist to take care of them.

But NCTN, for example, does not really deal with primary care physicians very much, if ever, I don't know about gastroenterologists. I haven't heard of many being involved, and radiologists are another category, and they do trials, so how do you get them into this thing? And then the next question would be how do institutions set up the structures so the money follows the service?

DSW: Those are great questions that need better answers than the ones we have now.

Certainly, we have struggled in our trial, and I know in other large prevention trials that struggle with the basic premise of how to make sure that the physicians who direct the cancer trial programs, whether that's in the NCTN centers, or whether that's in the NCORP centers, as you suggested, generally those are medical oncologists as we've already discussed. These are not patients who typically would see medical oncologists.

I think that problem is increasingly recognized by NCI and by DCP, the Division of Cancer Prevention. My hope, and certainly all evidence suggests to date, that knowledge that this is a particular problem, at least for EA2185, hopefully will drive a variety of novel solutions. I don't think that without a change to some of these basic premises—NIH's shorthand for who can put patients on studies is basically called rostering—and the question is how to roster gastroenterologists and surgeons through NCTN or NCORP sites, so that they can be more active participants in these trials.

Certainly, above my pay grade is the question of how the money gets distributed from NIH to NCI to cancer centers, whether that's NCORP or NCTN, but in general, a problem that we've seen in this study is a concern by some sites that the money for the trial is controlled by the cancer center, but the physicians and other investigators participating in the trial might not even be members of the cancer center. How do you fix that problem so that you incorporate more of the providers who care for these patients to facilitate trials like this.

Well, you haven't mentioned primary care physicians. I can't even figure that one out, how does that work?

DSW: So, primary care physicians are a real challenge.

I think that radiologists are too. Remember the name of one of the cooperative groups is ECOG-ACRIN ,and ACRIN, of course, are radiologists.

So, how to probably use information systems more effectively than we use them now to identify patients is one of the solutions that, certainly for EA2185, we want to look at and want to look at very aggressively.

Electronic medical records, in theory, allow for relatively easy searchability, at least they should, or software can be put on top of them that allows for that searchability. It isn't difficult for me to imagine, but so far it's been difficult, understandably, to execute, to set up a data search system for a radiology department where once a week anyone who had a pancreatic cyst on a CAT scan or an MRI is culled from the radiology records. And, of course, with all the appropriate HIPAA protections, those patient names are forwarded to the research team.

How to then approach those patients, roping in, as you said, the involved docs. If I were a primary care physician and somebody started contacting my patients without me knowing about it, I would find that potentially problematic.

On the other hand, if it's clear that primary care doctors are eager participants in the trial, they don't have to work real hard to get their patients in, they just have to give approval that if there's a patient who might be eligible, it's okay to approach those patients, then that may solve a problem.

Some places have tried to do that. I work at a smaller cancer center, Fox Chase, and it's easier for us to search the radiology database, but to search the radiology database of a large academic medical center, that's a lot of moving pieces, where everybody has to agree that we're going to do it and what are we going to do with the information.

That said, that is certainly one way that we could find a lot of these patients more effectively than now, which is essentially opportunism. If a patient is referred to a doctor who's involved in the trial, the patient might hear about the study. And generally patients when they hear about the study are willing to participate.

When does the study begin? What's the status of it right now?

DSW: We started about a year ago. If you wanted to design the perfect study to be interrupted by COVID, this is it, because pancreatic cysts are not an emergency. So, if patients are less likely to be going to their doctor because of COVID-related concerns, particularly a year ago—as we all know, there were many fewer visits to doctors, many fewer visits to emergency rooms, and many fewer incidental identifications of cysts.

Further, if a family member called me and said, 'Hey, I had a CAT scan, I did not have a kidney stone,' but they told me, 'I had a pancreatic cyst, do I have to deal with that right away?' the answer, except under rare circumstances, is 'No, you can wait,' Weinberg said.

So, in our trial, of course, we've got a protocol. And the protocol is that the cyst needs to be identified within the last six months. So, if a patient doesn't get back to their doctor for six-and-a-half months after this CAT scan, because there's nothing emergent on it, then unfortunately the patient can't be a participant in our trial. COVID, of course, has also made it difficult to find research staff and keep research offices fully humming.

That's slowly coming back as well.

So, it's a long way to get to the answer to your question, which is we've been open for about a year, but our enrollment is far below what we had hoped for, a fraction of it, honestly. And I think COVID on a list of one to 10, is problem one through eight. So as COVID disappears, hopefully this will become easier.

But as we were talking about a few minutes ago, the challenges of getting patients enrolled, at least on a large scale, in cancer prevention trials through the cooperative groups remains. And I think there is great interest and effort on the part of NCI and DCP, working in concert with cooperative groups like ECOG-ACRIN to come up with solutions for how to fix that. It'll benefit all of us.

If not cooperative groups then who? Who the heck cares about this scientific problem, because there are no drugs involved, it's not an industry issue, it's a total publicly funded clinical trials question.

DSW: Right. And because the size of the trials and the budgets are way bigger than the budgets for any individual grant that most people could submit either to a federal agency or anywhere else. So, there are very few mechanisms except federal funding to mount trials of this size, to answer public health questions, which, as you put it, are not going to be ones that industry has a stake in.

The only potential exception to that, and it's not a trivial one, is there are plenty of people, both in the federal government and in private groups who are interested in the development of biomarkers that would allow for better diagnosis.

This trial, not to blow our own horn, could put together a prospectively acquired cohort of 4,500 people or so, where we have all of the clinical data, accrued prospectively: blood, and other biosamples, radiology data that could be analyzed, and all of that was available to link back with clinical outcomes...

At this point, we don't have a good enough biomarker or a good enough radiographic marker. Even if an industry partner came to us, there just isn't enough data to suggest that you take a finite resource like that, meaning all of the data and biosamples that we acquire, and indiscriminately, let people use it.

I absolutely want to let people use the data we've got, but pancreatic cyst fluid, something that we would collect as part of this trial, is measured in milliliters, and once you use up that resource, you can't get it back.

So, we need a mechanism, and we're certainly discussing what it should be, to be able to prioritize biomarkers described already or described over the next couple of years as the trial rolls on, that seem to have the highest likelihood of being a winner, because no one else will have the data we've got. Most trials in pancreatic cysts are done in patients retrospectively. They're almost always done in patients who go to surgery, which is a fraction of the patients with pancreatic cysts, and we don't know anything about the ones who don't.

So, we have, or we hope to have, a database which is really a great resource for all investigators interested in this area, we just need to get the patients in the trial.

Oh, fascinating. This really should have been my first question, but I'm saving it to closer to the end. How did you come across this issue as the PI? What is the genesis of your interest in this?

DSW: So for full disclosure, while I did not write the AGA's pancreatic cyst surveillance guideline, I was the chairman of the AGA's committee on guideline composition at the time. So, when the AGA's guideline was released, it created in the world that worries about pancreatic cysts, tremendous discussion, shall we say, because there are some very strongly held views about what to do with these patients, and it's entirely understandable why.

If I were taking care of someone and I had a surveillance strategy that I didn't think was rigorous enough and a patient slipped through my fingers and developed a cancer that couldn't be cured, I would feel like I had failed that patient.

As we talked about a while ago, the AGA guidelines, the low-intensity surveillance arm in our study, is less resource-intensive. Patients do generally go longer. The recommendation for how long to wait to repeat a CAT scan or an MRI is generally longer. And that makes a lot of people nervous, understandably. On the other hand, there is absolutely zero evidence that one strategy works better than another.

So, this is, in fact, an important question at a perfect time to study it, where any investigator who participates in this trial clearly can be at clinical equipoise. They don't know what to do. And if we don't know what to do, it makes sense to do a trial where you actively compare two guidelines, which incidentally is a very unusual thing in medicine.

> "The back of the envelope estimate is that we spend at least a billion dollars a year in the United States alone on radiology studies associated with pancreatic cysts. If I'm going to spend the billion dollars, I want to spend it well."

Guidelines get promulgated in all sorts of settings, by all sorts of groups and they're never compared, or they're rarely compared. So, we thought that this trial was important because it allowed not only the opportunity to address an important question, it goes to the heart of one of NCI's, and that should be any-

body's, concerns about over-diagnosis versus under-diagnosis. As we've discussed the stakes of missing the cancer are high and the stakes of overreacting to a CAT scan or an MRI are also high.

So, getting a good answer makes sense. The ability to compare guidelines makes sense- and cost effectiveness is not a specific goal of this trial, but we would be foolish not to consider how much resources of all sorts are used here. When you think about it, if there are roughly 50 million people in the United States over the age of 60, and even a fraction of that, 2%, 3%, has a cyst that in theory requires some form of serial cross-sectional imaging.

The back of the envelope estimate is that we spend at least a billion dollars a year in the United States alone on radiology studies associated with pancreatic cysts. If I'm going to spend the billion dollars, I want to spend it well.

Right, right. You were involved in the guideline development though, not directly, of course, so, what happens next? Do you come back to work and say, 'Hey, let's come up with a trial and compare the guidelines?' How did that work for you?

DSW: So I initially went to PCORI with the trial protocol, because as we've already discussed, there are not a lot of mechanisms to allow for such a large trial with a bigger budget than most individual grants would allow. PCORI has its own set of priorities, and they're good priorities, PCORI's.

I think this is a good priority too, but in their system of what they wanted to emphasize, at least when we went to them, this didn't rank high enough to be an area that they wanted to emphasize.

They had plenty of good areas. I then started talking with colleagues who were involved in cooperative groups because as a gastroenterologist, even when working at a cancer center, I don't have much to do with their cooperative groups.

So, it's been an interesting learning experience to work in this framework. It gives you the opportunity to do remarkable studies, but as we've talked about, not just for me, because I'm a gastroenterologist, but for anybody who's doing prevention trials, it's clearly an area of emphasis for NCI, there's no doubt about it, but the rules to get these trials done, meaning what do you have to do to get patients enrolled at an adequate rate, are probably different than the rules required when you compare chemotherapy A to chemotherapy B, and how to make sure that the substantial resources that are spent on prevention trials result, in a completed trial with valuable data.

I think everybody wants to figure out how to do that better, in that everybody starts from anyone at NIH and NCI down to investigators like me.

Oh, that's fascinating. Is there anything we forgot? Anything you'd want to mention?

DSW: I think we covered everything that was of top importance.

Well, thank you so much for talking with me.

Q & A

O'Dwyer and Schnall spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

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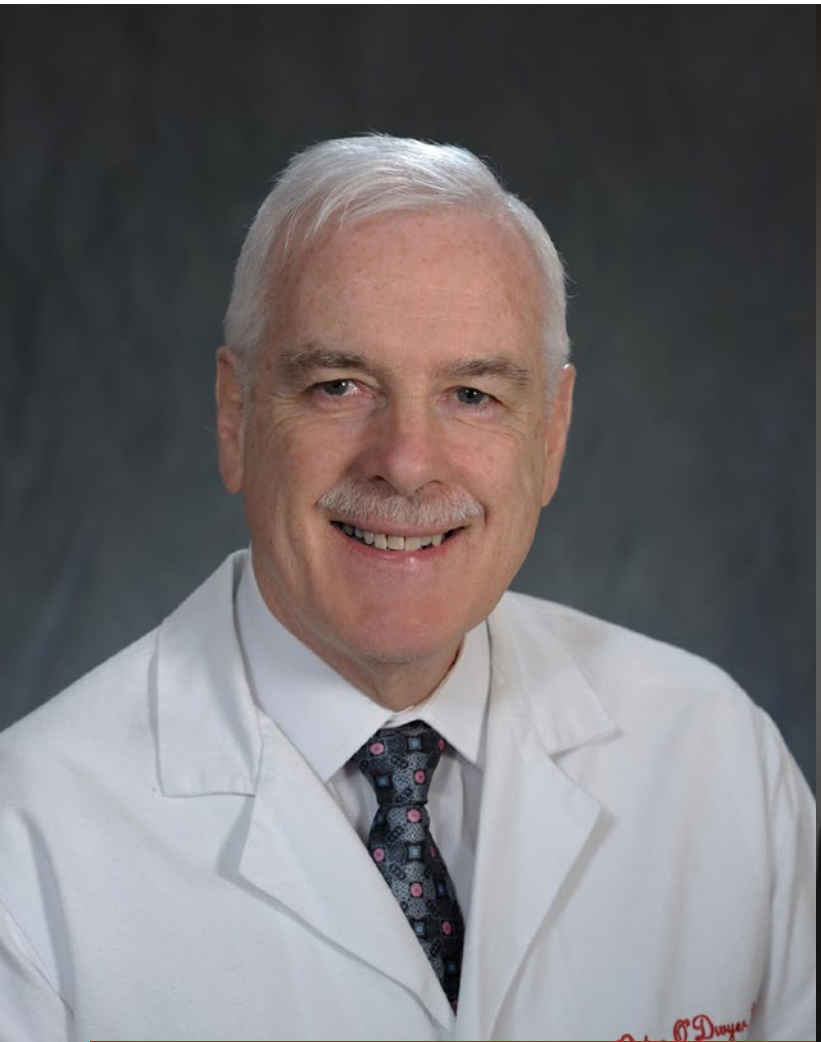
CONVERSATION WITH THE CANCER LETTER

Peter O'Dwyer and Mitch Schnall on the challenges of running screening and prevention trials



Peter J. O'Dwyer, MD
Professor of Medicine, the Hospital of the University of Pennsylvania and the Presbyterian Medical Center of Philadelphia;
Co-chair, ECOG-ACRIN Cancer Research Group

Mitchell D. Schnall, MD, PhD
Eugene P. Pendergrass Professor of Radiology,
Chairman, Department of Radiology,
Perelman School of Medicine at the University of Pennsylvania;
Co-chair, ECOG-ACRIN Cancer Research Group

Prevention and early detection studies frequently require engaging physicians from specialties other than oncologists, said Peter O'Dwyer and Mitchell Schnall, co-chairs of ECOG-ACRIN Cancer Research Group.

The logistical problems this creates can be observed in the case of the ECOG-ACRIN study EA2185, which compares two regimens for monitoring pancreatic cysts.

"The individuals who would put patients on this study are not medical oncologists, who are the drivers of most of the therapeutic studies, and they are often in specialties outside the traditional cancer research specialties, in this case, gastroenterology and surgical specialties, but, to a certain extent, primary care," O'Dwyer said to *The Cancer Letter.*

"And we're trying to figure out what are the best structures to allow this to happen? How much of it needs to occur in CTEP versus in the Division of Cancer Prevention or elsewhere, and could we streamline it in such a way as to have something like a 'registration-lite' for individuals who are not going to be treating patients, who don't need to have their pharmacy information in there, for example, and other aspects that are required by our current registration procedures, so simplifying this, making it easier, ultimately for primary care.

"Our focus should be on primary care physicians, because, if large screening trials are going to ever be implemented, we're going to need the patients—they're not even patients—the subjects to be screened at the level of their local doctor. So, that's a big part of the way that we're thinking about how to engage more people in this process."

Another challenge would be to figure out how money flows through institutions, Schnall said.

"Institutions are becoming very complex these days," Schnall said. "We have to be more agile in how we engage these systems, because the assumption that we can send dollars to the cancer center and they can figure it out, are more complex in this complex environment. And so, we also need the agility to be able to engage the right constituency within systems that are going to be participating in these trials, through contracts and other.

> "One man's cure is another man's overtreatment."
>
> *– Mitchell Schnall*

"And again, we've been talking to NCI about this, with the same groups, as part of this sort of rethinking, because it is a barrier when you're trying to engage a group who is part of a system, who has very arms-length relationships to the cancer center—through the cancer center. We then have to sort of negotiate these internal relationships rather than just say, if they're going to enter the patients, let's just directly contract to them and get it over with."

A video of the conversation is available here.

O'Dwyer and Schnall spoke with Paul Goldberg, editor and publisher of *The Cancer Letter.*

Paul Goldberg: Thank you for agreeing to meet with me, gentlemen. Last March, an ad hoc committee formed by NCI presented a set of recommendations on cancer screening trials. How would you boil down the message of that report? Or maybe there's another way of asking it: What are the key issues surrounding screening and prevention trials in the publicly funded system?

Peter J. O'Dwyer: Mitch, do you want to start?

Mitchell D. Schnall: Sure. To me, among the most important things that the committee concluded was that the [TMIST breast cancer screening] trial was important, and to me that's a statement not just of that trial, but of the importance of screening, prevention, to the armamentarium in the fight against cancer. There's a tendency, naturally, to be focused on patients who are suffering and focused on therapeutics, which are critically important.

But these trials, I think, are equally important in preventing severe disease. And so, I think first and foremost, the statement by the committee that this is an important trial and we should put effort into concluding it was, I think, a very important statement for them to make, and much appreciated. I think much of the other comments made, from my perspective, were fairly high-level comments focusing on the need to do everything to promote accrual and participation in the trial and execution of the trial, as per the protocol, which is frankly a generic comment on any of

the trials that we do. I don't know, Peter, if you want to expand on some of that.

PJO: I think highlighting the importance of screening and prevention was a big part of the main message of the report, and I also liked the recommendation that they look into the framework of the design of these studies, feasibility, and the operations supporting them. I think they put their finger on a difference between the screening and prevention studies and the therapeutic studies, and recognize that they may need to be done a little bit differently.

They also suggested a portfolio analysis, which has implications of prioritization and so on. We have relatively few screening trials in the whole system, so maybe that's not an urgent requirement right now, but it certainly, with the development of new technology, is going to become so.

What's ECOG-ACRIN's history and interest in screening and prevention trials? By the way, we should probably just back up because the report we're talking about focused on TMIST, where I've been talking broader.

PJO: Yes. I should probably address that in terms of ECOG's history. So, ECOG has participated with all of the cooperative groups in the development of prevention trials, which probably had their peak in the late '80s, early '90s, particularly, and we had two major contributions.

One was through [Waun] Ki Hong in a number of ECOG institutions in head and neck cancer, the role of 13-cis-retinoic acid in prevention of second primary tumors, and that was a positive study, and I don't think that it ever wound up in a huge intergroup study, such as, for example, the breast cancer studies, or the prostate cancer prevention trials mounted by NSABP and SWOG.

And we participated in the design of all of those and were involved in those, and our part of that effort, if you like, was for lung cancer prevention, and it was with the selenium trial [E5207], and that was led by Dan Karp, who, as you probably know, came out of Ki Hong's group also.

That didn't turn out the way we wanted it, but it was a very successful study in that it accrued very well, and accrued quickly. It had correlative endpoints that were led by Steve Belinsky, and, of course, he was at a SWOG institution at the time, so it highlighted cross-system collaborations, as there were in the other studies, too.

So, that kind of was the history of our involvement in that, and since the end of those studies, until TMIST came along really... well, no, actually, the other screening studies. Mitch, I should hand over to you to talk about the screening studies of imaging in NLST [National Lung Screening Trial] and so on.

MDS: Right, and we on the ACRIN side, we have a rich history in this space; right? Really starting with our first DMIST trial, the digital mammography trial, which interestingly enough, if you look at the proliferation of digital mammography—and it wasn't a given that it was equivalent even to standard film-screen mammography—there were a lot of concerns. Digital mammography proliferation in the U.S really came concurrent with the release of the results of the DMIST trial, and followed with multiple other screening trials.

We did a CT colonography trial showing that it's relatively effective for centimeter polyps. We did the NLST trial, which obviously had major impact. Since the merger, we've actually done some additional trials.

We did the trial that recently published—the AB-MRI trial for abbreviated breast MR, demonstrating that for patients with radiographically dense breasts seeking supplemental screening, that there was a two-and-a-half fold increase in cancer detection rate by adding an abbreviated breast MR.

So, this screening focus has been part of our history and focus on the ACRIN side for a long time that we brought into, into ECOG-ACRIN together, and sort of culminating both with this TMIST trial as well as the view going forward of an approach to screening that will be much more combined biomarker imaging-based, and the need to sort of integrate blood based biomarkers and imaging approaches together into more effective screening programs, which is something that we're interested in pursuing.

Finally, the other thing that we're interested in is trying to think collaboratively between screening and prevention—for a couple of rationales. One is mechanisms used in prevention might also speak to mechanisms used for screening, particularly for use in molecular-based screening approaches. The second is that the screening component of a prevention trial could represent a way to measure endpoints and serve as a sort of a marker for the effectiveness of the prevention. Peter, any other thoughts?

PJO: Well, yeah, you bring up an important nexus, and I think that my predecessor in this role, Bob Comis and Mitch saw the potential of this—and kudos to both because this is really where [we're interested in] bringing together different biomarkers—in particular imaging biomarkers because they're non-invasive—and clinical markers for trials of various kinds. I think we're really at a remarkable moment when therapeutic advances in genomics and targeted therapies and immunotherapy are set

to influence strategies for prevention and screening.

And our belief is that these interventions may have an even greater impact in that setting, in prevention rather than in treating established cancer. So, this is the time really for a big focus on this area, and I think that probably underlies the CTAC committee's sense of the whole field.

Right, this is not the time to abandon it just because the costs are high. Could we establish the context for another trial, which is really what I'm writing about, which is the EA2185 pancreatic cyst surveillance trial, and screening and surveillance trials require participation of medical specialists other than oncologists. So, what obstacles at NCI may prevent other medical specialty groups from getting involved? I mean, the radiologists have done pretty well, but who else is out there that you need?

PJO: Mitch? Do you want me to take a stab at that first?

MDS: No, go for it. I'll pitch in.

PJO: You know, this study is a multi-level study.

I think that it's really unique in its screening and surveillance focus, because it has a primary imaging entry. It addresses the biology of cancer risk. It has correlative studies that'll come around behind the positives on this study and analyze various aspects of risk in the context of this screening.

So, it has value at a number of levels. I think the context that you bring out, and that is that the individuals who would put patients on this study are not medical oncologists, who are the drivers of most of the therapeutic studies, and they are often in specialties outside the traditional cancer research specialties, in this case, gastroenterology and surgical specialties, but also maybe less for this, but to a certain extent primary care.

And all of these different components of the medical system need to be considered in how the structures are put together to make these trials happen. Historically, the therapeutic approaches have driven those structures, and really a one-size-fits-all to bring in other specialties may not work as well as it could with a different approach.

This is kind of an unintended consequence of the history of where we are in this type of cancer research, and so we've been in discussions with, particularly with Phil Castle, Ned Sharpless, and Worta McCaskill-Stevens, but also on the CTEP [Cancer Therapy Evaluation Program] side, which regulates the registration of investigators, with Jim Doroshow and Meg Mooney.

And we're trying to figure out what are the best structures to allow this to happen? How much of it needs to occur in CTEP versus in the Division of Cancer Prevention or elsewhere, and could we streamline it in such a way as to have something like a "registration-lite" for individuals who are not going to be treating patients, who don't need to have their pharmacy information in there, for example, and other aspects that are required by our current registration procedures, so simplifying this, making it easier, ultimately for primary care.

Our focus should be on primary care physicians, because if large screening trials are going to ever be implemented, we're going to need the patients—they're not even patients—the subjects to be screened at the level of their local doctor. So, that's a big part of the way that we're thinking about how to engage more people in this process.

MDS: There's another corollary to what Peter said, and that is, in addition to the NCTN structure, which assumes broad participation across the whole portfolio of trials, it also sort of has a single point of contact into a health system or into an institution, and institutions are becoming very complex these days; right? I mean, I'm in the University of Pennsylvania Health System.

The University of Pennsylvania Health System is six hospitals, and we've got the academic radiology group, we've got the private group, and same thing in multiple specialties.

And so, we have to be more agile in how we engage these systems because the assumption that we can send dollars to the cancer center and they can figure it out, are more complex in this complex environment. And so we also need the agility to be able to engage the right constituency within systems that are going to be participating in these trials, through contracts and other.

And again, we've been talking to NCI about this, with the same groups, as part of this sort of rethinking, because it is a barrier when you're trying to engage a group who is part of a system, who has very arms-length relationships to the cancer center—through the cancer center. We then have to sort of negotiate these internal relationships rather than just say, if they're going to enter the patients, let's just directly contract to them and get it over with.

Well, let's say I'm a primary care physician. What would be my obstacles in participating in, say, any of the trials? I don't want to choose one, because I'll probably choose the wrong one.

PJO: Under current structures, you mean?

MDS: Yeah. I mean, you'd have to be registered in the NCTN, which basically means you've got to be qualified to do an NCTN study, including—because I go through this as a radiologist—identify the pharmacy they're going to send the chemotherapy agents to.

PJO: The IRB.

MDS: Right. Deal with a ton of paperwork to show that I'm capable of being able to treat patients on NCTN trials. Then I would also have to figure out how I'm going to work with my cancer center, so that if there's accrual [that] happens and the dollars will go to the cancer center, that I actually get my costs reimbursed, for me doing that trial.

So, you can imagine if I'm a primary care doc, this sort of bar that holds. And what it means to us as a group. It means that we've got to put a ton of resources into that primary care doc to educate them on what it is to be in the NCTN, to walk them through a bunch of paperwork, most of which are irrelevant to the trial they're going to go on that they've never seen before, heard before, and really are scared of, to work and try to create a relationship between them and the cancer center that would keep them whole for their costs and participating in the trial. It really creates challenges to getting these folks on these trials.

Are NCORPs going to have an easier time or a harder time? Community docs, non-academic docs.

MDS: I don't think it much matters. What I say is that, the very large institution... I think it has to do, to a large extent, with internally the structure of your organization and how you operate, but if you're an arms-length specialist, in terms of participating, normally in cancer trials, you're going to be, it doesn't matter whether you're in a big or small place, you're going to suffer from these concerns.

PJO: Ultimately, it's really important not to reinvent the wheel here. It's taken us 50 years to get to this point where we have an established nationwide system of cancer research that really works, and so tinkering with the existing system rather than trying to stand up a different but parallel system, and I think that it's logical, seems to us the best way forward. And I think we've embarked on that over the last year or so, and we'll see some results, I think.

MDS: That's worked in the past, right? Before the formal NCTN, there was a little more latitude in how people could get rostered for studies, and there were special rosters developed. We at ACRIN had the latitude to be able to engage sites this way. I know speaking with some of our colleagues in the NCTN, the legacy trials, like the STAR [Study of Tamoxifen and Raloxifene] trial and some of the other breast cancer prevention trials, they were able to separately roster people that way. So, in legacy before the formality of the NCTN, there was some of that flexibility, which was effective.

So, the recommendations sought by NCI prior to this focused on TMIST. How would you apply those recommendations globally to EA2185? We touched on some of this, but maybe there's something we forgot.

MDS: I mean, I think again, we touched on a lot of this. I think a key would be to be able to create a separate, if you will, "registration-lite" program, and to be able to allow direct engagement, in this case [with] gastroenterologists and the GI surgeons that are going to primarily be seeing these patients, and that way we could greatly expand the participant pool and be closer to where these patients are.

And what kind of changes are you making to your studies? I guess we're getting back to TMIST, that's probably where it mostly needs to happen. Where is it now? I haven't looked at it in about six, seven months, so I probably missed a bunch.

MDS: Well, I mean, TMIST is accruing quite well now, we've done some things based on recommendations to the committee and frankly things we were doing ahead of time, and I think you and I may have talked about that.

We started to work on some redesigns and have negotiated some of those out with NCI to decrease the total sample size a bit. The work that I described in getting sort of the non-standard NCTN sites accruing was work that we've been doing all along in TMIST, but you can imagine, each site getting them up and running because of the effort that it takes, was quite a bit delayed. But now we've got, we're solidly accruing between 2,000 and 2,500 patients a month. I don't remember the latest, but I think we're over [56,000] patients in at this point, and so we've been on solid footing on the accrual in TMIST in the last six to 12 months.

So, at this rate, you would be expecting results when, roughly?

MDS: So, we're projecting about two years 'til we finish accrual, so by now probably about 18 or 19 months that we'd be finished and then we've got follow up after that. So we'd be expecting results in about, with all the follow up (it's a funny design, because it's a design that you could end at any

time) but something of the order of four years of follow-up, so probably about six years from now.

What about European data? Can you pool it with Europe or not? Or is that still being discussed?

MDS: It's being discussed. There's a lot of nuance about this design—because it's not diagnostic-based; it's outcome-based, which I think is becoming even more and more important as we think about a lot of the challenges that the next generations of screening are going to create and then how important it is for us to be outcomes-based.

As we become better and better at finding disease, we want to find a disease that matters. So, we're looking and we'll consider anything, but at this point I don't know that we've found some slam-dunk data that we can pool.

Is there anything we forgot?

PJO: Well, I would say that in terms of the other changes that we're making to our studies,[it] is [an] all-in approach, particularly for studies that are going to be challenging or complex. We develop study teams, we tune the composition of those study teams to what skillsets are required to manage them.

I know Diane [Dragaud] is on the call. We have a big focus on communication, and I think we're getting better at communicating with our sites and with potential participants, and that's a lot of resource. But we think it's worthwhile and it's something that what we're doing for EA2185.

Oh, that's interesting. What do you need to do there?

PJO: What we need to do is to get to a critical mass of participants. Within the existing participants, we're looking at novel methods of alerting people to the existence of the pancreatic cyst—because it can be missed, and because there are criteria for how long the cyst has been there that make a patient eligible or ineligible and what kind of other tests they might have had. So, some of this is actually amenable to an algorithmic approach within particular systems, and that's the approach we're developing.

We think that in that way, I don't know if [PI] David [Weinberg] mentioned it, that the potential exists for EA2185 to be a kind of a laboratory environment for what may work in the direction of accruing patients to screening studies. Can we be smarter about it? And that's something we're going to try and work out within that trial.

MDS: Leveraging the EHR to identify candidates in ways that may be valuable, because we're looking through broad populations.

The question, the research question is really fascinating to think about, because, is this stuff benign, or is this going to kill you?

PJO: It's a complex design and those are exactly the issues. And that's why it's valuable.

MDS: And the challenge, and I can tell you, because I do this for a living, is that the imaging studies are becoming so good that, inadvertently, we're finding pancreatic cysts are incredibly common, and we've got to get our arms around figuring out how to manage these. Because every time somebody's getting a workup because of hematuria, we're looking at their kidneys. Every time somebody's getting a workup because of GI distress or because their biliary tract is being worked up, right, we're seeing the pancreas. And there's almost an epidemic of pancreatic cystic lesions, and frankly, this is emblematic. There's corollaries in other areas as well, where imaging is so good, there's a proliferation; of small renal cell carcinomas, for example. And it's not because there's suddenly a proliferation, it's because we're seeing stuff that we've never seen before and trying to figure out how we should be caring for these patients is absolutely crucial.

Yeah. You're talking about Whipples, I mean that's not [trivial].

MDS: That's exactly my point. One man's cure is another man's overtreatment; right?

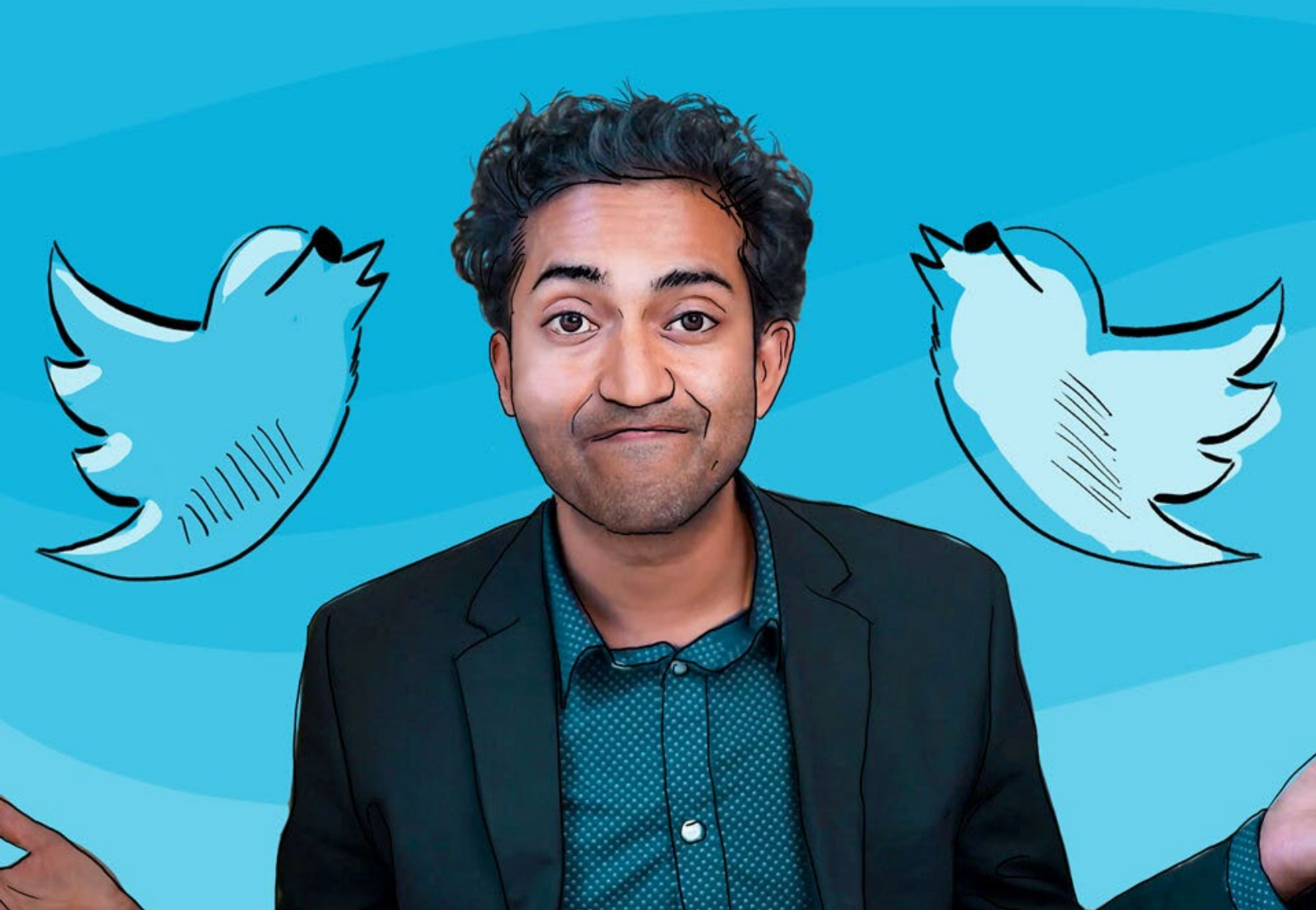
Well, thank you so much for talking with me and I look forward to writing about this.

> Our focus should be on primary care physicians, because if large screening trials are going to ever be implemented, we're going to need the patients—they're not even patients—the subjects to be screened at the level of their local doctor.
>
> – *Peter O'Dwyer*

Did Vinay Prasad need to mention the Nazis to make a point on the U.S. pandemic response?

By Alice Tracey

Vinay Prasad might well have made his contrarian points without invoking the specter of the Third Reich. He didn't have to go there—but he did. Voluntarily.



Prasad, an oncologist and associate professor in the Department of Epidemiology and Biostatistics at UCSF, likes a good Twitter fight. He has incited brawls over FDA's accelerated approval of cancer drugs, efficacy of checkpoint inhibitors, usefulness of next-gen sequencing, and—in recent months—the restrictions aimed at curbing the spread of COVID-19.

In an Oct. 2 Substack blog post, Prasad argues that public health measures may have laid the groundwork for the onset of fascism in the U.S.

The comparison set off a deluge of Twitter controversy, including accusations of anti-Semitism and ignorance of the circumstances that led to the rise of German fascism.

In the blog post and an accompanying video titled "How Democracy Ends," Prasad speculates that in the name of public health and safety, an unscrupulous U.S. government could turn dictatorial and fascist.

"When democratically elected systems transform into totalitarian regimes, the transition is subtle, stepwise, and involves a combination of pre-planned as well as serendipitous events," Prasad wrote. "Indeed, this was the case with Germany in the years 1929-1939, where Hitler was given a chance at governing, the president subsequently died, a key general resigned after a scandal and the pathway to the Fuhrer was inevitable."

Also on Oct. 2, Prasad posted a link to his blog post and video on Twitter, sharing it again the next day. The Twitterverse exploded, with Prasad's detractors battling his defenders while Prasad stood by his original point. Prasad didn't respond to questions from *The Cancer Letter*, and at this writing, the post is still up.

Arthur L. Caplan, a bioethicist at the New York University and an expert on the bioethical implications of fascism, said Prasad's argument is specious and ignorant.

"The notion that public health will lead us to fascism due to efforts to control COVID is ludicrous, dangerous, and offensive," Caplan said to *The Cancer Letter*. "It's anti-Semitic, anti-gay, anti-Romani people. It cheapens the deaths of those who died in camps for political objections, or in the case of Jehovah's Witnesses, religious objections.

"I have to say, rarely will I claim to be the world's expert on much, but I'm up there on the Nazis. I've studied it for decades and I did it, just so you know, because my dad was in the troops that liberated Dachau.

"I have written one of the first books about Nazi medical experiments and the ethics thereof, and early on, I have argued that Trump's rhetoric and his divisiveness, his racism, his homophobia, and his appeals to white nationalism were somewhat analogous to what was going on in Germany in the 1930's.

"I haven't changed my opinion since he became president, nor since his more public looney followers attacked the Capitol," Caplan said.

"But to mix the two—the public health effort to fight a plague with political forces that we ought to be watching carefully—is imbecilic."

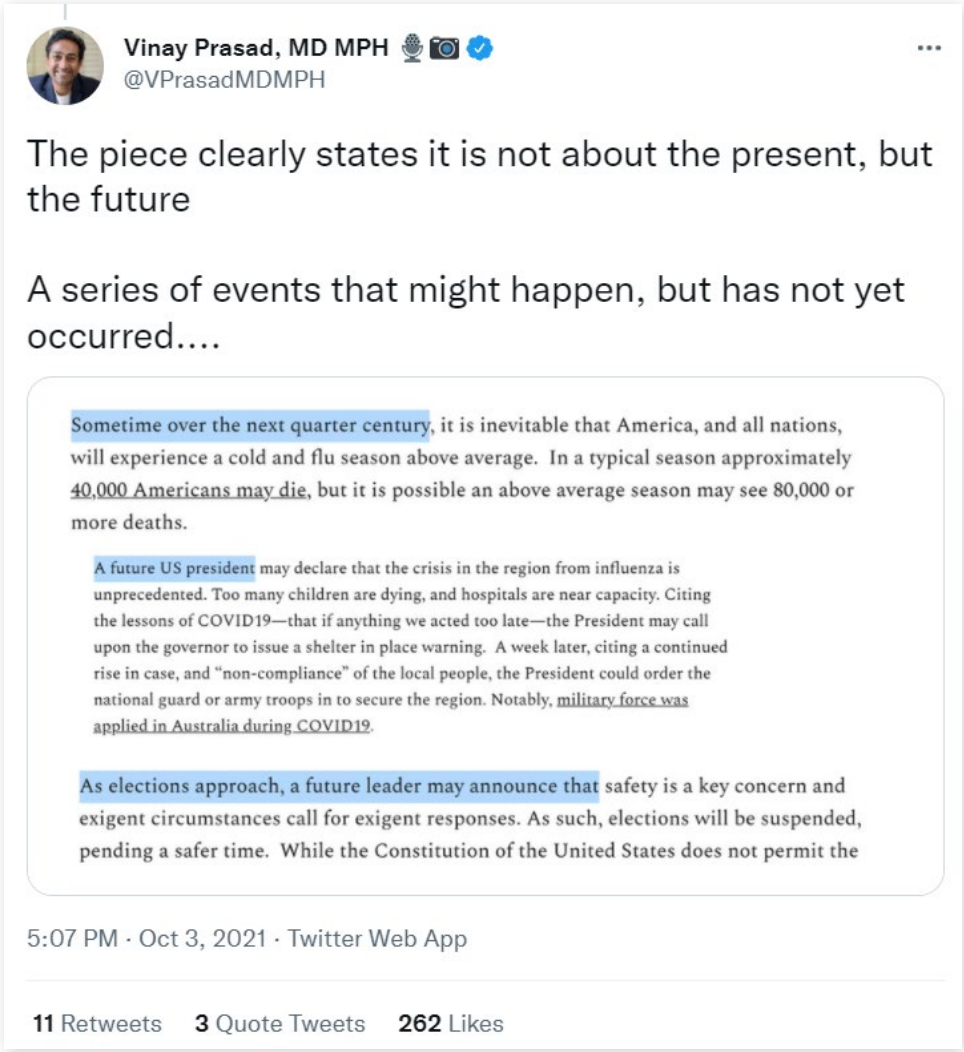
Caplan, the Drs. William F. and Virginia Connolly Mitty Professor and founding head of the Division of Medical Ethics at NYU Grossman School of Medicine, is the editor of *When Medicine Went Mad: Bioethics and the Holocaust*, the authoritative text on Nazi medicine.

Caplan's guest editorial on Prasad's invocation of fascism is published here.

Robert Proctor, professor of the history of science at Stanford University and author of *The Nazi War on Cancer*, another classic book on Hitler's view of public health, said he, too, finds Prasad's words unconvincing.

> But to mix the two—the public health effort to fight a plague with political forces that we ought to be watching carefully—is imbecilic.
>
> *– Art Caplan*

"Dr. Prasad clearly likes to be provocative, and, given all of the problems of modern medicine, I can see where he is coming from," Proctor said to *The Cancer Letter*.



"Comparing a mask or vaccine mandate to the steps taken by Hitler to restrict liberties in 1930s Germany is a misrepresentation of what went on in the Third Reich.

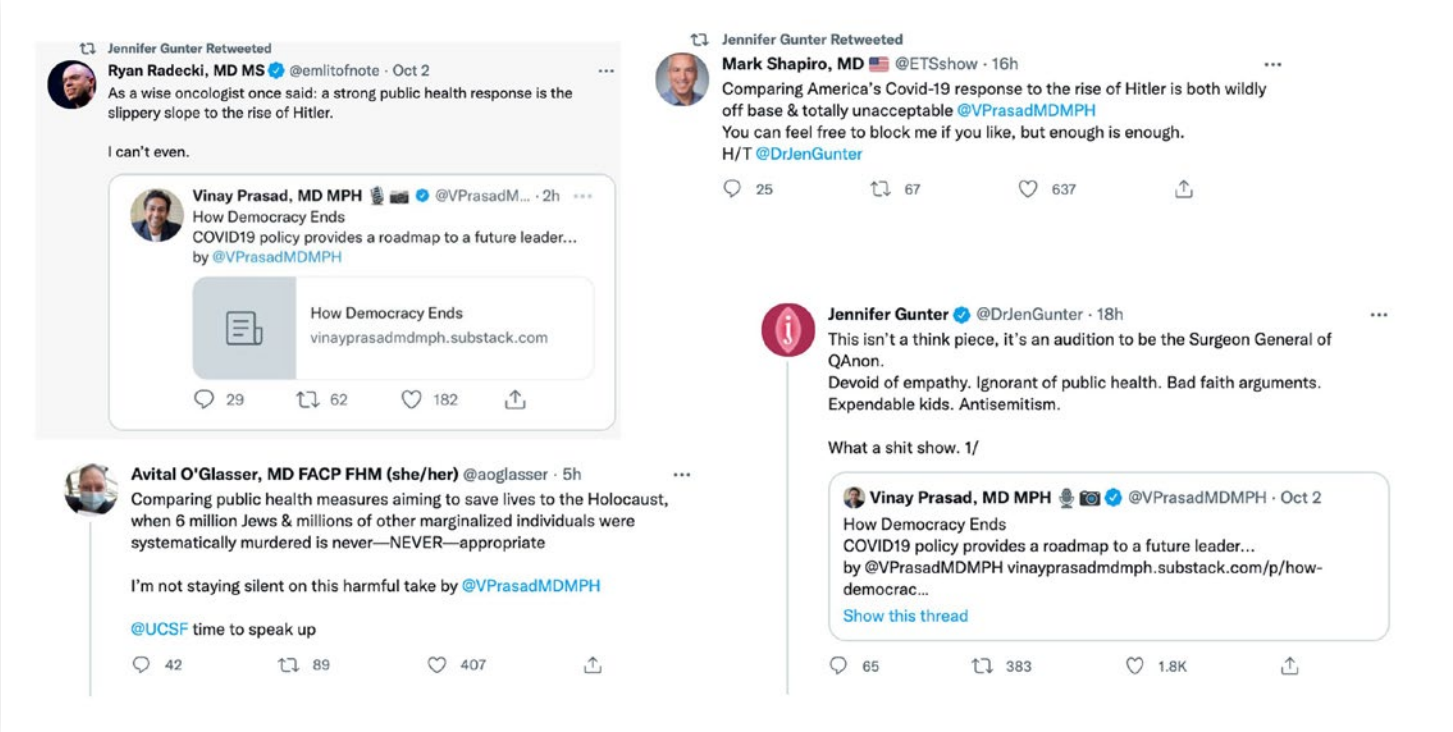
"If you're going to play the Nazi card, you'd better have something to back it up. And in this case, Dr. Prasad is overplaying the dangers of vaccination mandates and trivializing the genuine harms to liberty posed by 1930s fascism.

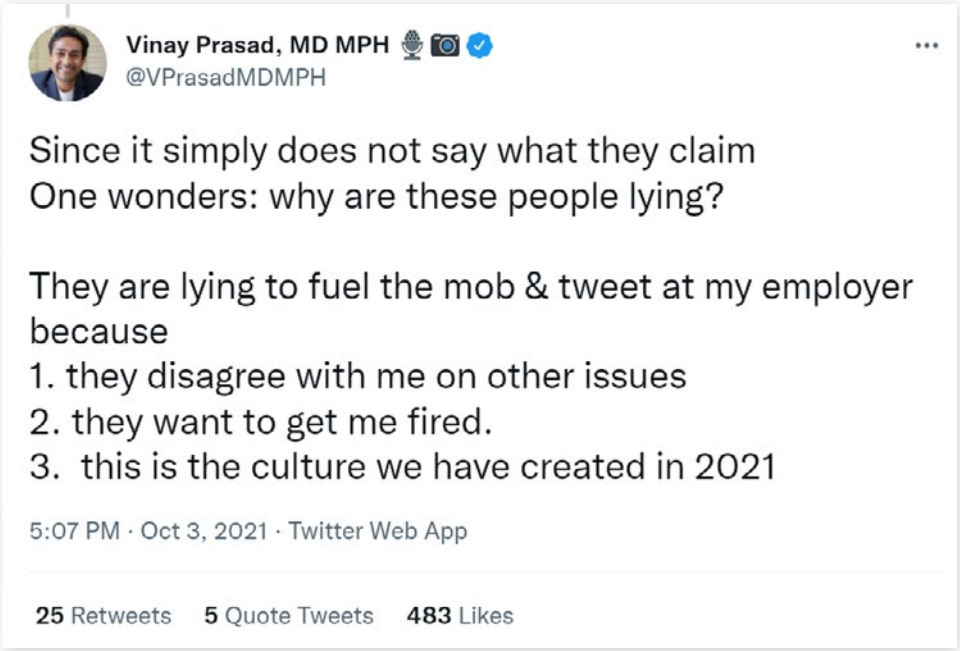
"I'm not too worried about COVID policies leading us onto the path of fascism; the restriction of liberties is nowhere near that great. It goes without saying that a more dramatic epidemic might well lead us to take to more draconian steps, but we are very far from that."

Prasad: "All these people *pointing emoji* are lying"

With 110.8K followers on Twitter and 23.7K Tweets under the handle @VPrasadMDMPH, Prasad is a veteran of countless Twitter debates.

A following this large means Prasad can easily disseminate and amplify his publications when they appear in peer-reviewed journals, turning obscure papers into social media hits.





Three years ago, *The Cancer Letter* talked to Prasad about his vocal criticism of new directions in oncology and his rise to Twitter stardom (*The Cancer Letter*, June 22, 2018).

"Let's be honest, why do I use Twitter? Number one, I find it fun. I find it fun to use Twitter, it's enjoyable, it's interactive, you get to hear from interesting people," Prasad said of his activity on the site (*The Cancer Letter*, June 22, 2018).

Following his comments on fascism, Prasad has doubled down. In an Oct. 3 tweet, he said his critics were "lying about the content of my piece" and clarified, "Its [sic] not a Holocaust analogy."

Prasad attached to this an image of several responses from physicians —all of whom condemned his Hitler reference—including Ryan Radecki, Mark Shapiro, Avital O'Glasser, and Jennifer Gunter.

"This isn't a think piece, it's an audition to be the Surgeon General of QAnon," Gunter, a San Francisco OB/GYN, tweeted.

Yet some Twitter users are stepping up to defend Prasad's remarks, including Daniel Goldstein, an oncologist at the Davidoff Cancer Center of Rabin Medical Center in Israel. Goldstein posted a tweet on Oct. 4 rejecting the notion that "How Democracy Ends" is anti-Semitic.

"I'm a Jew and an Israeli," Goldstein wrote. "Say what you want about @VPrasadMDMPH's most recent piece, but it's not antisemitic. Can agree or disagree with what he's saying - that's fine. But there's no antisemitism there. Just Sayin."

Prasad re-tweeted this cautiously worded exculpation from his own account.

As his original tweet backfired, Prasad, in an Oct. 3 tweet, invoked cancel culture. He said his critics have misinterpreted his statements and are attacking him personally.

This familiar claim of cancel culture victimhood was, according to Caplan, entirely predictable—and represents a shirking of personal responsibility on Prasad's part.

"I'm sure there are going to be complaints by his admirers that this is another instance of cancel culture," Caplan said to *The Cancer Letter*. "But sometimes self-cancellation has to be taken seriously."

Thought experiments

"How Democracy Ends" is just one of many recent attacks Prasad has lobbed at COVID-19 public health measures.

The oncologist has published and re-tweeted several posts critiquing COVID-19 mask and vaccine mandates for school-aged children. Recent op-ed headlines attributed to Prasad include "Scientists Who Express Different Views on COVID-19 Should Be Heard, Not Demonized" and "Why Are Highly Vaxxed Colleges Implementing Strict COVID Policies?" (STAT News, April 27, 2020; MedPage Today, Sept. 30, 2021).

On Sept. 29, in a blog post titled "Progressivism is Dead," Prasad argued that the Left has become "increasingly frenzied and disinhibited" during the COVID-19 pandemic—censoring misinformation, shaming individuals, infringing on personal rights, and instituting policies like school closures, which, according to Prasad, disadvantaged the poor.

"That was the original sin," Prasad wrote. "Closing schools for so long in Democratic stronghold cities, strong union cities, precisely after the President that many disliked pushed for it. But no matter how wrong he was about other matters, he was right on that issue. We should have reopened schools. And the net result has been devastation so catastrophic it will shape this country for the next 100 years, if we survive it."

Prasad is the author of *Ending Medical Reversal: Improving Outcomes, Saving Lives (2015)* and *Malignant: How Bad Policy and Bad Evidence Harm People with Cancer (2020)*. He hosts the Plenary Session Podcast (@Plenary_Session), where he discusses medicine, oncology, and health policy.

Prasad has also published over 300 academic articles, according to his website. In 2018, *The Cancer Letter* shared three reviews of a Prasad "thought experiment" paper on drug prices (*The Cancer Letter*, June 22, 2018). These experts pointed out inaccuracies in the assumptions and methodology used in the paper. Soon after the publication of the three reviews, Prasad retired the Twitter account he was using at the time (*The Cancer Letter*, Sept. 7, 2018).

Also in 2018, Prasad chaired an evidence review committee that recommended denying Medicaid coverage of next-gen sequencing tests for vulnerable patients in Oregon. The effort was unsuccessful (*The Cancer Letter*, Sept. 28, 2018).

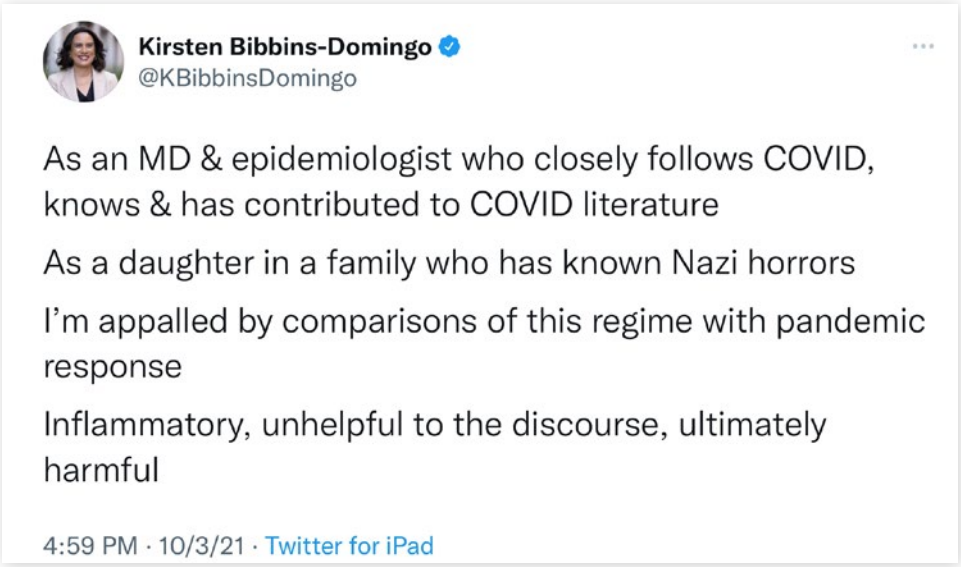
> "I'm not too worried about COVID policies leading us onto the path of fascism; the restriction of liberties is nowhere near that great. It goes without saying that a more dramatic epidemic might well lead us to take to more draconian steps, but we are very far from that."
>
> – *Robert Proctor*

"Inflammatory, unhelpful"

Prasad isn't a member of the UCSF Cancer Center and doesn't see patients at UCSF Health facilities. Officials at Zuckerberg San Francisco General Hospital, where Prasad practices medicine, didn't respond to *The Cancer Letter*'s request for comment.

UCSF Executive Director of Public Affairs Kristen Bole said her institution believes in academic freedom, but condemns misinformation.

"COVID-19 public health measures have saved innumerable lives and minimized



suffering for millions of people," Bole said to *The Cancer Letter*. "UCSF is proud to play its part in the public health response to this global pandemic.

"As a university, we celebrate academic freedom and respect the right of our faculty to express their individual opinions. In some cases, however, we must respectfully disagree. We understand that some may seize upon any opinion to foster misinformation. As an institution, UCSF will continue to advocate for evidence-based public health measures."

Prasad holds a faculty appointment with UCSF's Department of Epidemiology & Biostatistics.

Kirsten Bibbins-Domingo, chair of that department, said that the department and university protect his academic freedoms.

"That doesn't mean, necessarily, that we all agree with him, but I think that people are free to voice their opinions," Bibbins-Domingo said to *The Cancer Letter*.

Bibbins-Domingo is the vice dean for Population Health and Health Equity, the Lee Goldman, MD, Endowed Professor of Medicine, leader of the UCSF COVID Community Public Health Initiative, and co-founder of the UCSF Center for Vulnerable Populations at Zuckerberg San Francisco General Hospital.

"I think we are always trying to balance the importance of free exchange of ideas, which is sort of the lifeblood of a university, as well as the ability to speak out on those ideas with which we disagree," Bibbins-Domingo said.

If her Oct. 3 tweet is any indication, Bibbins-Domingo disagrees with Prasad—strongly, openly, poetically even:

"As an MD & epidemiologist who closely follows COVID, knows & has contributed to COVID literature

As a daughter in a family who has known Nazi horrors

I'm appalled by comparisons of this regime with pandemic response

Inflammatory, unhelpful to the discourse, ultimately harmful."

THE CANCER LETTER | OCTOBER 8, 2021 | VOL 47 | ISSUE 37

GUEST EDITORIAL

Vinay Prasad's Nazi analogy is imbecilic, ignorant, and dangerous

Arthur L. Caplan, PhD
Drs. William F. and Virginia Connolly Mitty Professor;
Founding head of the Division of Medical Ethics,
NYU Grossman School of Medicine

There is reason for concern about fascism rising in the United States. The reason is primarily Trumpism, followed by racism, followed by right-wing seditionist impulses.

The notion that public health will lead us to fascism due to efforts to control COVID is ludicrous, dangerous, and offensive. We have had a very mild response, in my opinion, to COVID, almost irresponsibly respectful of those who do not want to change their behavior from selfishness.

I see no argument made, other than hype by Dr. Vinay Prasad, that would make me worry about Anthony Fauci leading a repressive fascist regime, or the CDC taking over as the Bureau of State Control.

I have written one of the first books about Nazi medical experiments and the ethics thereof, and early on, I have argued that Trump's rhetoric and his divisiveness, his racism, his homophobia, and his appeals to white nationalism were somewhat analogous to what was going on in Germany in the 1930's.

I haven't changed my opinion since he became president, nor since his more public looney followers attacked the Capitol.

But to mix the two—the public health effort to fight a plague with political forces that we ought to be watching carefully—is imbecilic.

Remember, ironically, one of the attributes of National Socialism was a keen concern for public health, including worries about smoking and diet.

Indeed, the race hygiene theory is consumed with the views that genetic threats have to be eliminated to preserve the health of the Volk, the people, as is well-documented by people like Robert Proctor and many others, whether it's the wholesome bread movement or the awarding of prizes to the most eugenically sound parent at various state fairs. The Nazi Party took public health extremely seriously.

What it didn't take seriously was the humanity of all humans. What it didn't take seriously is the equality and fundamental rights of human beings.

Why would Dr. Prasad ignore the former, a public health push of the Nazis, and ignore the latter completely? That's what makes the analogy and his argument not only imbecilic, but ignorant and dangerous. It makes it fundamentally racist.

It's anti-Semitic, anti-gay, anti-Romani people. It cheapens the deaths of those

who died in camps for political objections, or in the case of Jehovah's Witnesses, religious objections.

People today who try to impose mandates for vaccination don't intend to round up anybody and put them in a camp, kill them, and bake them in ovens to destroy the evidence.

So, what I'm saying is this: I don't think the public health side of Germany led to Naziism or to a Nazi genocide. What led to Nazi genocide was racism. They are very different.

Our public health movement is not fueled by racism.

The public health movement today is international. It is deeply concerned with the rights of the poor and those who have very few resources. Many of the groups that it is concerned with—the WHO, UN, various European groups, U.S. groups, and so on—are precisely the groups that the Nazis didn't give a damn about.

I have to say, rarely will I claim to be the world's expert on much, but I'm up there on the Nazis. I've studied it for decades, and I did it, just so you know, because my dad was in the troops that liberated Dachau.

When he finally talked about what he saw there, I started to try and understand what the hell had happened there. That's what led me to study the euthanasia programs, but also the camp experiments. I've been at it for a while. I did get an apology from the German Medical Association about 20 years ago for their roles.

So, I feel pretty comfortable that I understand when the analogies are right and when they're not.

Not only is this egregious, it's unnecessary. You don't need to go down that road to make points. If you think current public health efforts are overbearing or intrude too much on individual rights, what takes you from that position to allege that the next thing we're going to see is a public health movement worldwide under the banner of fascism?

You don't need it. You can get all the traction you want and have an argument without getting to that metaphor.

There are plenty of people who hold opinions like that about mandates or passports, but I rarely hear them mentioning Hitler or fascism or making other allegations of mass human rights violations.

It comes up whenever people really get angry about abortion. It comes up whenever people get angry about assisted suicide.

Sometimes in the animal rights movement, when people get going on the slaughter of animals for science, pretty soon Nazi metaphors are waltzing around. So, I can't say it's the first time I've seen egregious abuse, but it has to be called out and condemned, lest we lose sight of what the issue is with respect to at least fascism in Germany and that is—and I'll say it again—racism.

I'm sure there are going to be complaints by Dr. Prasad's admirers that this is another instance of cancel culture. But sometimes self-cancellation has to be taken seriously.

When you're making the metaphors—and I'm claiming that racism in general and anti-Semitism in particular are the pertinent attributes of German fascism—when you forecast moving from showing a vaccine card to go to a Knicks game, to stormtroopers marching down Pennsylvania Avenue in the name of public health, you're going to find a lot of people, who had relatives die in camps and are very sensitive to the anti-Semitism lurking behind the white nationalism of Trump, fully outraged by what he's saying.

Francis Collins steps down after 12 years as NIH director

By Matthew Bin Han Ong

Francis Collins will step down as director of NIH by the end of 2021, closing out a chapter in his career as the longest-serving presidentially appointed NIH director.

"It has been an incredible privilege to lead this great agency for more than a decade," Collins said in a statement Oct. 5. "I love this agency and its people so deeply that the decision to step down was a difficult one, done in close counsel with my wife, Diane Baker, and my family. I am proud of all we've accomplished.

"I fundamentally believe, however, that no single person should serve in the position too long, and that it's time to bring in a new scientist to lead the NIH into the future. I'm most grateful and proud of the NIH staff and the scientific community, whose extraordinary commitment to life-saving research delivers hope to the American people and the world every day."

As NIH director, Collins has served three presidents over more than 12 years. A physician-geneticist, Collins took office as the 16th NIH director on Aug. 17, 2009, after being appointed by President Barack Obama and confirmed by the U.S. Senate. In 2017, he was asked to continue in his role by President Donald Trump, and in 2021, by President Joe Biden.

Prior to becoming the NIH director, Collins served as the director of the National Human Genome Research Institute (NHGRI) from 1993-2008, where he led the international Human Genome Project, which culminated in April 2003 with the completion of a finished sequence of the human DNA instruction book.

"Few people could come anywhere close to achieving in a lifetime what Dr. Collins has at the helm of NIH," Health and Human Services Secretary Xavier Becerra said in a statement. "It takes an extraordinary person to tackle the biggest scientific challenges facing our nation—and under three presidents, amidst three distinctly different chapters of American history. Dr. Collins, master of scientific breakthroughs and scientific reason—from mapping the human genome to fighting the most devastating pandemic of a century—has routinely broken ground to save countless lives, while unleashing innovation to benefit humanity for generations to come."

Under his directorship, NIH's budget grew by 38%, from $30 billion in 2009 to $41.3 billion in 2021. Collins proposed and established initiatives—from fundamental basic science to translational science and focused projects—to tackle some of the most pressing health issues in the U.S., including Alzheimer's disease, cancer, opioid use disorder, rare diseases and the COVID-19 pandemic.

Collins introduced and led an array of consequential research and public health programs, including these:

- All of Us Research Program, which is on its way to enrolling one million people across the U.S. to provide their health data so that researchers can improve illness prevention as well as treatment for the full spectrum of diseases and conditions.

- Accelerating Medicines Partnership to reduce the time from the identification of biological markers of disease to the development of treatments that target those pathways.

- Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, a multi-billion-dollar effort to develop sophisticated technologies to understand the neuronal networks of the brain and what goes wrong to cause Alzheimer's disease, schizophrenia, psychosis and other serious brain diseases.

- Cancer Moonshot Initiative to fuel innovation and speed new treatments to reduce cancer incidence and improve patient outcomes (*The Cancer Letter*, To The Moon, 2016-2017).

- HEAL (Helping to End Addiction Long-term) Initiative to address the national opioid crisis by improving treatments for opioid misuse and addiction and enhancing pain management.

- Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership that developed a coordinated research strategy for prioritizing and speeding development of promising treatments and vaccines;

- Rapid Acceleration of Diagnostic (RADx) program to create an innovation funnel for COVID-19 testing technologies;

- Community Engagement Alliance (CEAL) Against COVID-19 Disparities to support partnerships in communities hardest hit by the pandemic and reduce health disparities; and the

- Researching COVID to Enhance Recovery (RECOVER) Initiative to identify why some patients don't fully recover from the effects of COVID-19 disease and develop ways to treat these patients or even prevent long COVID altogether.

A new component of NIH, known as the Advanced Research Project Agency for Health (ARPA-H)—proposed by President Biden and supported by Collins—is in the works, pending congressional appropriation.

Modeled after DARPA in the Department of Defense, ARPA-H is envisioned to support and conduct high-risk, high-reward biomedical and health research in a way that is radically different than NIH's grant-based system. ARPA-H would be designed to eliminate silos and catalyze the development of transformative, evidence-based, use-driven

cures for a range of biomedical challenges, from the molecular to the societal.

On the policy front, Collins has tackled long-standing issues that have hampered science, including:

- Creating guidelines for address sexual harassment and structural racism,
- Enhancing accountability and transparency in clinical trials and ensuring broad data sharing, and
- Supporting early-stage researchers, implementing policies to help them succeed in a hyper-competitive research environment.

Collins will continue to lead his research laboratory at the NHGRI, which pursues genomics, epigenomics and single cell biology to understand the causes and means of prevention for type 2 diabetes. His lab also seeks to develop new genetic therapies for the most dramatic form of premature aging, Hutchinson-Gilford Progeria Syndrome.

> “I fundamentally believe, however, that no single person should serve in the position too long, and that it’s time to bring in a new scientist to lead the NIH into the future. I’m most grateful and proud of the NIH staff and the scientific community, whose extraordinary commitment to lifesaving research delivers hope to the American people and the world every day.”
>
> *– Francis Collins*

Cancer, biomedical research groups reflect on Collins’s career

Howard A. “Skip” Burris III, MD, FACP, FASCO
Board chair, Association for Clinical Oncology

The Association for Clinical Oncology congratulates Dr. Francis Collins on his long and impactful tenure as Director of the National Institutes of Health.

Over the past 12 years, Dr. Collins has worked tirelessly to ensure that the United States remains at the forefront of biomedical innovation by spearheading new initiatives to modernize and improve biomedical research. Dr. Collins has been pivotal in the implementation of the 21st Century Cures Act, which gave the NIH new funding and authority to support vital cancer research, including through the Beau Biden Cancer Moonshot.

Under his careful guidance, these initiatives have helped to fuel innovation and speed new treatments to reduce cancer incidence and improve patient outcomes. Through his leadership, the All of Us initiative—which builds on his career of research into the human genome—promises to further revolutionize the way we diagnose and treat cancer so that our treatments are better targeted and more effective.

His passion for science and public service led to new policies and reforms aimed at encouraging and supporting early-career researchers and building a stronger, more robust scientific workforce ready to help tackle the research questions of tomorrow. We also commend his efforts to increase workforce diversity and to increase equity in the way biomedical research is funded. We are hopeful that these efforts will continue long after Dr. Collins steps down from his leadership role at the NIH.

We are extraordinarily grateful for Dr. Collins’ steadfast leadership and wish him well as he returns to the National Human Genome Research Institute. We look forward to close collaboration with the incoming leader of the NIH as we pursue our shared goal of advancing federally supported basic and translational research and publicly funded cancer clinical trials.

Karen E. Knudsen, PhD, MBA
CEO, American Cancer Society; American Cancer Society Cancer Action Network

For more than a decade Dr. Collins has provided exemplary leadership and stewardship as head of the NIH, the nation's top medical research engine and the driving force behind numerous recent breakthroughs in cancer treatment and prevention through the National Cancer Institute.

During his tenure as director Dr. Collins has overseen an increase in NIH funding from $29.5 billion to $43 billion and has successfully shepherded the creation and implementation of numerous significant research initiatives. Among the most significant to cancer is the Cancer Moonshot, which has already funded more than 240 research projects and helped speed the development of improved and new uses for immunotherapies, boosted research efforts into childhood cancer, and worked to expand the use of early cancer detection strategies.

Additionally, Dr. Collins' leadership helped ensure years of NIH research into coronaviruses was quickly put to work developing safe and effective COVD-19 vaccines in partnership with industry. The critical science that led to an accelerated pathway to these vaccines is an essential component to curbing the pandemic and ensuring everyone, including cancer patients, can safely access necessary medical care and build a healthy future.

Before his tenure as NIH director, Dr. Collins worked for decades as a researcher, contributing to critical science, most notably for his leadership on the Human Genome project, that is the direct result of the federal government's essential year over year investment in medical discovery.

We extend our gratitude to Dr. Collins for dedicating his career to the advancement of medical science in public service and look forward to working with the next director to continue the advancement of medical research, cancer breakthroughs, and the lifesaving work of the NIH.

American Association for Cancer Research

AACR
American Association for Cancer Research

The American Association for Cancer Research (AACR) today expressed its gratitude to Francis S. Collins, MD, PhD, for his exceptional service to the American people as Director of the National Institutes of Health (NIH) for the past 12 years.

Collins announced earlier this week that he would step down as NIH Director by the end of 2021 to return to his laboratory at the NIH's National Human Genome Research Institute (NHGRI). Collins served as Director of the NHGRI from 1993-2008.

"Throughout his distinguished career, Dr. Collins has been recognized for both his innovative contributions to basic and clinical research and his extraordinary stewardship of the largest supporter of biomedical research in the world," said AACR President David A. Tuveson, MD, PhD, FAACR, Director of the Cold Spring Harbor Laboratory Cancer Center, Cold Spring Harbor, New York, and chief scientist for the Lustgarten Foundation. "He is a renowned physician-scientist and a distinguished national leader on biomedical research-related issues.

"He is admired and revered by countless members of Congress from both sides of the aisle, as well as the broader research and patient care community."

Collins is the longest-serving head of the NIH since the position became a presidentially appointed one in 1971 following the signing of the National Cancer Act. He has led the agency under three U.S. presidents.

He is lauded for his landmark discoveries of disease genes and for his leadership of the international Human Genome Project, which culminated in April 2003 with the com-

pletion of a finished sequence of the human DNA instruction book.

"During the past 12 years as NIH Director, Dr. Collins has consistently communicated clear, science-based guidance to our elected leaders, and displayed a passion for supporting the professional advancement of young and emerging scientists," said Margaret Foti, PhD, MD (hc), chief executive officer of the AACR. "The entire medical research com+-munity is fortunate to have had Dr. Collins at the helm of the most important biomedical research institution in the world over such a critical period in our nation's history.

"Under his leadership, the NIH has continued to be at the forefront of medical breakthroughs that have improved the well-being of millions and saved lives from countless human diseases, including cancer."

Association of American Cancer Institutes

AACI thanks Dr. Collins for his work over the past 12 years on behalf of the biomedical research community in general, and for cancer research in particular.

During his tenure, he expanded the agency's investment in biomedical research, collaborated with then-Vice President Joseph Biden to launch the Cancer Moonshot Initiative, and championed early-stage researchers, whose discoveries are accelerating progress against cancer.

Most recently, Dr. Collins has supported ARPA-H, the health-focused research agency proposed by President Biden. (AACI leadership participated in the first ARPA-H listening session.)

AACI wishes all the best to Dr. Collins in his retirement and looks forward to partnerships with his successor.

Research!America

Research!America expresses our deepest gratitude to Francis S. Collins, MD, PhD, for his 12 years of service as the director of the National Institutes of Health. His tenure leading the largest supporter of biomedical and health research in the world has been nothing short of extraordinary.

"Dr. Collins has established a legacy as a tremendous advocate for the power of research to lift hope, and constantly expand the possibilities for research to provide answers to the devastation caused by disease," said Mary Woolley, president and CEO of Research!America. "His gift for communicating the value of research to policymakers and the public is among his many superpowers. Research!America is immensely proud to have worked with him throughout his career at NIH."

Dr. Collins has always been a strong voice for how medical research can and does make a substantive difference in the world. At a Research!America event in 2011, he said: "What's the nature of medical research? Let's be clear that a society will be judged in how that society reaches out to those in need… We shouldn't lose sight of that. The economic case for medical research is very strong but so is the humanitarian case."

Under Dr. Collins leadership, the NIH budget grew by 38% from $30 billion in 2009 to $41.3 billion in 2021, forging new ground in collaborative research, taking on such pivotally important roles as driving unprecedented strides in neuroscience through the BRAIN Initiative, fostering new research synergies through public-private partnerships, spurring basic research needed to effectively combat COVID-19 and its lingering health effects, and in many other landmark ways advancing medical, public health, and scientific progress.

"The nation, and the world, owe Dr. Collins a huge debt for his leadership in science across so many domains — from his key role in the Human Genome Project, to spearheading NIH's COVID-19 response, along with so much more," said Susan Dentzer, Research!America board chair. "We will miss him in his role at NIH, but we know his passion for science will lead him to make many ongoing contributions that will truly benefit all of us."

Dr. Collins has had a long history of involvement with Research!America; on several occasions he's even shared his musical talents at our annual Advocacy Awards, most recently closing out our 2021 event

with a duet of "Hallelujah" with Renée Fleming.

Our alliance is grateful for his invaluable contributions to medical and public health progress and looks forward to further partnership as he continues to advance the public good in his lab at the National Human Genome Research Institute.

Federation of American Societies for Experimental Biology

FASEB extends its heartiest congratulations and deepest appreciation to Francis S. Collins, MD, PhD, for his decades of dedicated public service culminating in more than 12 years as Director of the National Institutes of Health (NIH). Having served in three administrations, Collins is the longest-tenured presidentially appointed NIH Director and oversaw the agency during a period of tremendous growth in both public and congressional support for biomedical research.

"FASEB has been extremely fortunate to call Dr. Collins an outstanding colleague and valued friend throughout his time at NIH. His willingness to engage with NIH stakeholders, his remarkable ability to explain complex scientific concepts, and steady leadership in good and bad times will be hard to replicate," said FASEB President Patricia L. Morris, MS, PhD.

FASEB honored Collins with its 2017 Public Service Award in recognition of his ability to convey the excitement, achievements, and promise of biomedical research to broad audiences through his exceptional public outreach efforts.

The award citation noted that Collins' efforts brought research into America's living rooms on the Colbert Report, The Charlie Rose Show, CNN, CNBC, and National Public Radio, in addition to his extensive interviews with magazines and newspapers across the country, informing millions about the extraordinary advances in biomedical research and the critical role NIH plays in this enterprise. He also brought science to social media, including chatting with Astronaut Kate Rubins on the International Space Station, hosting a Reddit Ask Me Anything event and conversing directly with thousands of his followers on Twitter.

In addition, Collins was instrumental in distributing $10 billion in funds from the American Recovery and Reinvestment Act, releasing a detailed five-year NIH-wide strategic plan to capitalize on new opportunities for scientific exploration, and has been a superb advocate for NIH on Capitol Hill.

He testified before Congress more than 20 times and personally met with more than 200 members of Congress to make the case for increasing the federal investment in biomedical research. His ability to earn the trust and confidence of House and Senate leaders as well as powerful committee chairmen have been essential in building and maintaining bipartisan support for NIH especially during periods of great uncertainty, including devastating budget cuts due to sequestration and the 16-day government shutdown in 2013.

A desire to improve conditions for the entire scientific community drove Collins' efforts to hire senior staff responsible for implementing recommendations related to improving the training and diversity of the scientific workforce, address harassment and bullying in science, and expand programs to help young investigators compete for federal funding.

FASEB sends its best wishes to Collins as he steps down from his incredibly demanding role as the head of NIH and returns to his research lab at the National Human Genome Research Institute. The Federation looks forward to continuing to work with him in this next phase of his career.

> "He is admired and revered by countless members of Congress from both sides of the aisle, as well as the broader research and patient care community."
>
> *– David A. Tuveson*

THE CANCER LETTER | OCTOBER 8, 2021 | VOL 47 | ISSUE 37

OBITUARY

Thomas A. Waldmann, renowned immunologist, dies at 91

By NCI Staff

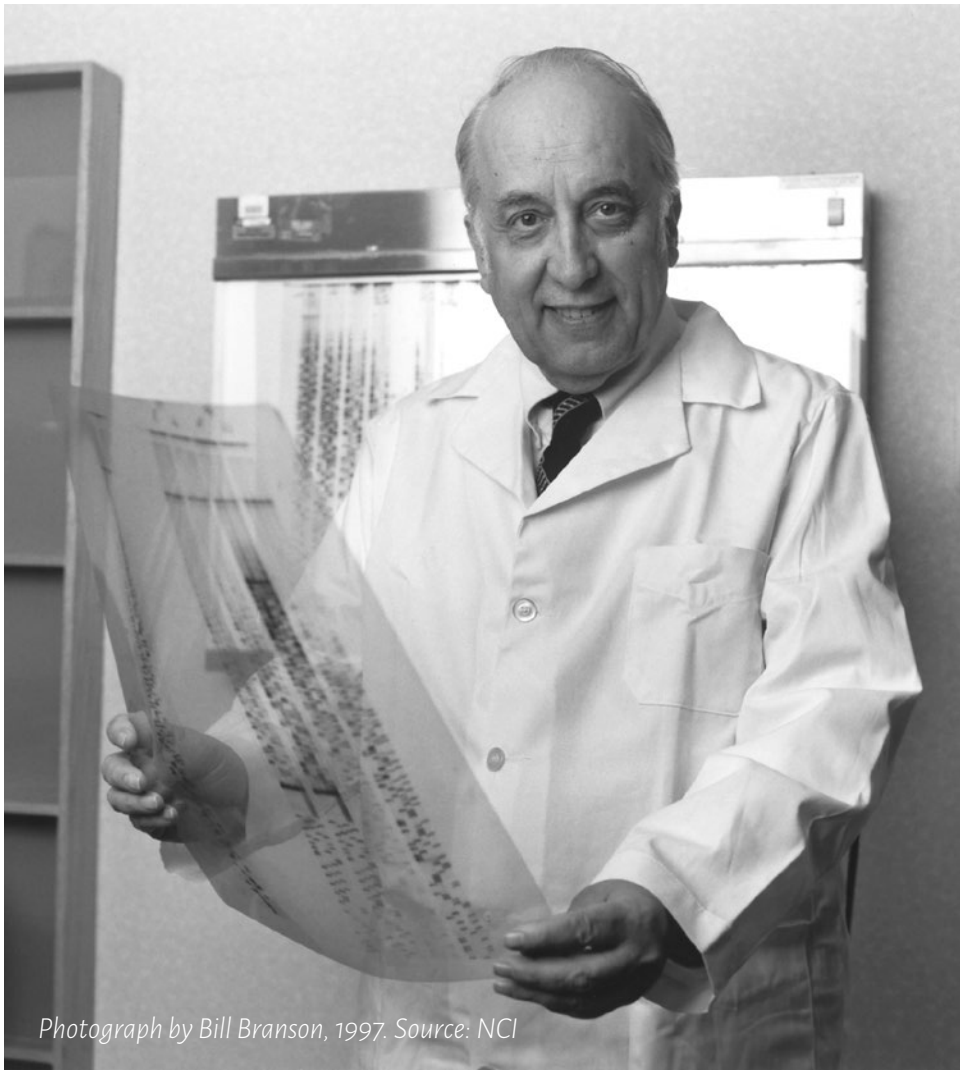
Thomas A. Waldmann, chief emeritus of the NCI Lymphoid Malignancies Branch and NIH Distinguished Investigator, died Sept. 25. He was 91.

Considered a giant in the field, Tom was a renowned immunologist whose more than 60-year career at the National Cancer Institute led to numerous high-impact discoveries that advanced the fields of organ transplantation, autoimmune disease and cancer. He was a leader in the study of cytokines and their receptors and of monoclonal antibodies, now a dominant form of cancer immunotherapy.

He received his MD from Harvard Medical School in 1955 and joined NCI in 1956 after residency at Massachusetts General Hospital. At NCI, he started by studying how the body metabolizes proteins, including immunoglobulins, in the blood.

By 1959, he had become a senior investigator, and his research had expanded to include work with patients with primary immunodeficiency diseases and disorders of lymphatic channels. Tom became Chief of the Metabolism Branch, now the Lymphoid Malignancies Branch, in 1971.

Tom's pivotal studies revolutionized our understanding of the roles played by the interleukin-2 (IL-2) receptor and



Photograph by Bill Branson, 1997. Source: NCI

interleukin-15 (IL-15) receptor cytokine systems in the life and death of T lymphocytes. In characterizing the first cytokine receptor, IL-2, his team set the stage for understanding the biology and biochemistry of this family of molecules and then demonstrated that antibodies specific for the IL-2 receptor were useful in treating adult T-cell leukemia, prolonging survival of transplant recipients, and treating multiple sclerosis.

In 1994, Tom and his team co-discovered the cytokine IL-15. Like IL-2, IL-15 triggers the production of immune cells that attack and kill cancer cells. Tom's group initiated the first-in-human IL-15 clinical trial in 2011. Furthermore, Tom initiated clinical trials to evaluate IL-15's capacity to augment antibody-dependent cellular cytotoxicity when administered with tumor directed monoclonal antibodies. This work exemplifies his passionate pursuit for developing therapeutics for cancer and AIDS.

He is remembered for other accomplishments as well. Prior to 1980, Tom studied the metabolism of serum proteins, which led him to identify a rare disorder of the gastrointestinal tract now known as Waldmann's disease. In 1981, he helped treat the first patient with AIDS at NIH. And in 2016, the Food and Drug Administration approved daclizumab, the antibody he discovered, for use in the therapy of relapsing multiple sclerosis.

While Tom's many landmark contributions are well known, "his greatest legacy may be the vast number of outstanding scientists in their own right who owe their success at least in part to Tom's mentoring," said Jay A. Berzofsky, chief of the Vaccine Branch, whom Tom mentored for nearly 28 years.

"Tom was the consummate scientist's scientist," said Berzofsky. "He was an encyclopedia of knowledge and constantly came up with valuable insights, bringing diverse sources of knowledge to bear on any question. All of us in the branch improved our science as well as our presentations because of Tom's mentoring. He was a great friend, collaborator and father-figure to his entire scientific family. We will all miss him tremendously."

"Tom was one of the most influential mentors in my career," said Louis M. Staudt, chief of the Lymphoid Malignancies Branch. "When I arrived at NCI in 1988, I was a 'dyed-in-the-wool' basic scientist, though I had trained in internal medicine. Tom insisted that I attend his clinical rounds every week where I witnessed his deep commitment to patient-oriented research. It took a while to sink in, but years later I found myself following in Tom's giant footsteps, for which I am grateful."

"Tom was one of the brightest scientists and clearest thinkers I have ever had the pleasure to work with in my many years at the NIH," said Robert Yarchoan, chief of the HIV and AIDS Malignancy Branch. "When I was a fellow in Dr. Waldmann's branch, I came away with a real sense of how to go back and forth between the lab and the patient, and this has been the focus of my career since."

Collectively, Tom's career was full of tremendous originality and scientific novelty. He contributed to the acceleration of progress in cancer research that has major implications for future discoveries.

His over 880 publications and over 100 named honorary lectures or keynote addresses have had an enduring impact on the work of others and has led to his receipt of countless honors, including but not limited to the Health and Human Services Career Achievement Award, the Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research, the Paul Ehrlich Medal, the Abbott Laboratory Prize in Clinical Diagnostic Immunology, the AAI-Ralph Steinman Award for Human Immunology Research, the Milken Family Medical Foundation Distinguished Basic Scientist Award, the Artois-Baillet Latour Health Prize, and the Service to America Career Achievement Award.

Tom was also a member of several societies, including the National Academy of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences, the Hungarian Academy of Sciences, and he was an Honorary Fellow of the Royal Society of the Medical Sciences (UK).

Moreover, Tom was an enthusiastic photographer and former president of the NIH Camera Club. "No matter how busy, he was always happy to share his knowledge of photography with fellow photo enthusiasts," said Berzofsky.

Tom is predeceased by his wife of 62 years, Katharine Spreng Waldmann. He is survived by his children Richard, Robert and Carol and his grandchildren Marina, Kathy, Clarissa, Ember, Jonathan, Orion and Arno. In lieu of flowers, the family requests donations to a memorial fund to benefit the International Medical Corps. Please find Tom's public obituary here for more information about his extraordinary life.

There will be a small, private service at Pumphrey Funeral Home in Bethesda, Maryland, on Oct. 18. The size is limited due to COVID restrictions, so please contact the family at cw@alum.mit.edu if you would like to attend. The service will be followed by the burial at Parklawn Cemetery at 2:30 p.m.

Tom once said in an interview with *The Washington Post*, "Science is a river. You're always building on the past. You might be able to turn over a rock and find something exciting; you don't want to give up and say, 'This is all there is.' . . . It's like planting a fruit tree that has a long duration, and when it comes time to harvest the oranges or whatever, you don't want to leave." A giant in his field, an excellent mentor and a true leader to all who had the privilege of working with him, Tom will be sorely missed.

IN THE ARCHIVES

CANCER HISTORY PROJECT

The Emil J Freireich archive: tributes, primary sources, and videos

Emil J Freireich, a trailblazing oncologist who developed groundbreaking therapies for childhood leukemia, and one of the 60 original members of ASCO, died Feb. 1.

"For more than 60 years, he pushed boundaries and devoted himself to saving young lives and relieving suffering. Dr. Freireich's compassion and empathy, with a focus on the holistic needs of individual patients, was fused with scientific creativity and perseverance. This rare blend of exceptional qualities has created a lasting legacy that will forever be part of the history of cancer research and that of MD Anderson," said Peter WT Pisters, president of MD Anderson.

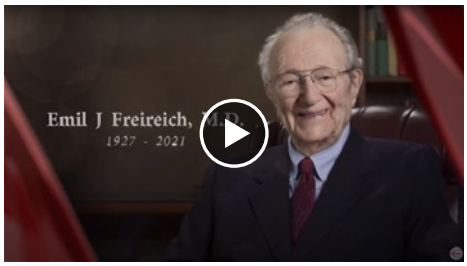
The Cancer History Project has created the Emil J Freireich Archive to collect materials documenting his contributions to oncology. Contributors are invited to submit photos, primary sources, articles, podcasts, videos, and more.

- The Emil J Freireich Archive
  By Cancer History Project | Oct. 7, 2021

Quote of the week

> It is a great human weakness to generalize from exceptions. As scientists, we know that the best solution to a specific problem is a specific solution.
>
> – *Emil J Freireich (The Cancer Letter, May 14, 1976)*

Selected contributions from the Emil J Freireich Archive:



- **Video:** MD Anderson to pay tribute to legendary Emil J Freireich, M.D., in virtual celebration on Sept. 23
  By MD Anderson Cancer Center | Oct. 7, 2021
- **Oral history:** Emil J Freireich interviews
  By MD Anderson Cancer Center | Oct. 7, 2021
- **Obituary:** Pioneer of Combination Chemotherapy Dr. Emil J Freireich
  By ASCO | Feb. 5, 2021
- **Obituary:** J Freireich loved good science and a good fight
  By Moshe Talpaz, MD | Feb. 5, 2021
- **Obituary:** J Freireich was one of the few oncologists to have developed a cancer cure
  By Otis W. Brawley, MD | Feb. 5, 2021
- NCI's Frei & Freireich era Lauded As Researchers Receive First NIH Distinguished Alumni Award
  By *The Cancer Letter* | Sept. 14, 1990

When Emil "Tom" Frei and Emil "Jay" Freireich came to work at NCI in 1955, the time was right for a major breakthrough in treatment research on cancer, a disease previously thought to be incurable. When they left NCI 10 years later, they had demonstrated that at least one form of cancer, childhood leukemia, indeed could be cured. In the

intervening years, their work set the standard by which all other clinical research, even today, is measured.

- Historical vs. Current Controls: Comparability, Ethical Issues Argued By Moertel, Freireich
  By *The Cancer Letter* | April 20, 1979

Ethical issues involved in the conduct of clinical trials have been a source of concern and sometimes frustration for cancer treatment investigators, particularly when it comes to deciding between randomization and historical controls.

As was expected, the confrontation between the two most outspoken investigators on opposite sides of that issue provided plenty of grist for that argument recently at the Second International Conference on the Adjuvant Therapy of Cancer in Tucson.

Charles Moertel, director of the Mayo Comprehensive Cancer Center, believes that not only is randomization ethical in most cases but it is also the only way that reliable comparisons can be made in many phase 3 and 4 studies

Emil (Jay) Freireich, chief of Developmental Therapeutics at M.D . Anderson Hospital, believes that randomization "borders on the unethical," and that historical controls can be at least as reliable as randomization, if not more so.

- Freireich Blasts Prevention Advocates, Defends Treatment
  By *The Cancer Letter* | Sept. 15, 1978

"We aren't making any progress in prevention that I know of. We are in treatment. We're winning there."

Emil (Jay) Freireich, head of the Dept. of Developmental Therapeutics at M.D. Anderson, challenged the popular concept that prevention is the key to substantially reducing the number of cancer deaths. Freireich chaired the session on future developments at the National Conference on Care of the Child with Cancer in Boston this week. His attack on advocates of stepped up prevention research was made at a press conference prior to the session.

- Freireich's Seven Laws To Protect Against Obstacles To Clinical Research
  By *The Cancer Letter* | May 14, 1976

Seven obstacles that "threaten to choke off the significant clinical research which is essential to our ultimate goal of the control of cancer" were described by Emil Freireich in the David A. Karnofsky Memorial Lectureship at the annual meeting of the American Society of Clinical Oncology.

"I think the time has come to change directions to swing the boat 90 degrees back toward the type of clinical research that is more observational, and I propose that such a change will keep us relentless on target to our goal of cancer control," Freireich said.

Recent contributions

- Still CLIMBing: Dr. Nancy U. Lin Envisions a Future of Curative-Intent Approaches for Advanced Cancers
  By ASCO | Oct. 7, 2021

- **Podcast:** Undaunted Dreams: Podcast Interview with Brenda Brody and Stacey White
  By ASCO | Oct. 7, 2021

- ASCO and Conquer Cancer Collaborate With Filmmakers for PBS Documentary
  By ASCO | Oct. 5, 2021

This column features the latest posts to the Cancer History Project by our growing list of contributors.

The Cancer History Project is a free, web-based, collaborative resource intended to mark the 50th anniversary of the National Cancer Act and designed to continue in perpetuity. The objective is to assemble a robust collection of historical documents and make them freely available.

Access to the Cancer History Project is open to the public at CancerHistoryProject.com. You can also follow us on Twitter at @CancerHistProj.

Is your institution a contributor to the Cancer History Project? Eligible institutions include cancer centers, advocacy groups, professional societies, pharmaceutical companies, and key organizations in oncology.

To apply to become a contributor, please contact admin@cancerhistoryproject.com.

IN BRIEF

SU2C Dream Team takes on colorectal cancer disparities

Stand Up To Cancer (SU2C), Exact Sciences, and Providence announced funding for a new Dream Team dedicated to addressing colorectal cancer disparities. The SU2C Colorectal Cancer Health Equity Dream Team will receive a total of $8 million—$6 million from Exact Sciences and $2 million from Providence.

The Stand Up To Cancer-selected Dream Team will consist of robust screening, research, education, and training efforts that will extend across the United States to establish three SU2C Zones: Greater Boston, Los Angeles, and Great Plains Tribal Communities in South Dakota. These zones, which will ideally operate long after the grant period is over, include diverse and distinct communities that are medically underserved and have particularly low screening rates for colorectal cancer.

The multi-disciplinary team selected by SU2C is led by Jennifer Haas, of Massachusetts General Hospital; Folasade P. May of the University of California, Los Angeles; and Anton Bilchik of Providence Saint John's Health Center in Los Angeles. Additional team members are from the Dana-Farber Cancer Institute and the Great Plains Tribal Leaders Health Board.

Under the leadership of Haas and May, the team's wide-ranging goals include: establishing and implementing comprehensive at-home stool-based colorectal cancer screening programs at community health centers to increase screening rates to 80% within the SU2C Zones; ensuring patients who have an abnormal stool-based screening test result receive a follow-up colonoscopy; building a collection of blood and stool samples for future research to ensure that low income and racial/ethnic minority populations are represented in the development of new screening tests and early detection methods for colorectal cancer; and fostering the careers of a new generation of Black, Latino, and American Indian doctors and researchers.

Additionally, under the leadership of Bilchik, Providence will design and deploy a community-based campaign to increase colorectal cancer screening rates in demographically diverse areas within Los Angeles County. Providence will recruit and deploy community health action teams (CHATs)—residents trained and supported to work as health promoters and care navigators within their own neighborhoods—to implement a locally designed and operated colorectal cancer screening campaign.

"During the COVID-19 pandemic, there has been a dramatic drop in colorectal cancer screening," Haas, the Peter L. Gross MD chair in primary care at Massachusetts General Hospital, professor of medicine at Harvard Medical School, and professor of social and behavioral sciences at Harvard T.H. Chan School of Public Health, said in a statement. "While we've seen some colorectal cancer screening rates rebound more recently, overall the impact of COVID-19 on Black, Indigenous, and people of color is dire and compounds the low cancer screening rates and poorer cancer outcomes seen before the pandemic."

A SU2C Colorectal Cancer Health Equity Community Engagement Grant program will roll out in the coming months to support and complement the Dream Team's work. SU2C will provide three-year grants ranging from $5,000 - $25,000 to organizations within the SU2C Zones to develop new or implement existing community programs in colorectal cancer early detection and screening.

Michael Diaz named president, managing physician of Florida Cancer Specialists and Research Institute

Michael Diaz was named president and managing physician at Florida Cancer Specialists and Research Institute.

Diaz succeeds Lucio Gordan, who has held the position since 2018.

Diaz joined FCS in 2011 and provides care at two FCS office locations in St. Petersburg. Since November of 2018, he has worked as assistant managing physician for the statewide practice. Diaz serves on the FCS Executive Board and is the FCS director of patient advocacy.

Gordan is a member of the board of directors for the Community Oncology Alliance and Florida Association of Clinical Oncology. Gordan will continue to practice as a medical oncologist at the FCS Gainesville Cancer Center and serve as chief medical officer of therapeutics and analytics for the statewide practice.

Mount Sinai researchers receive $4M in grant awards for junior scientists

Two Mount Sinai cancer researchers will be awarded $4 million in total costs from the National Institutes of Health Common Fund, which supports high-impact programs and research by junior scientists around the country.

Deborah Marshall, assistant professor of radiation oncology at The Tisch Cancer Institute and The Blavatnik Family Women's Health Research Institute at the Icahn School of Medicine at Mount Sinai, and Jalal Ahmed Khan, assistant professor of radiation oncology at the Precision Immunology Institute and The Tisch Cancer Institute, each received an Early Independence Award worth $2 million given out over five years.

This award, established in 2011, provides an opportunity for junior scientists to skip traditional postdoctoral training and move immediately into independent research positions.

Marshall's study seeks to define novel predictors of female sexual dysfunction and to identify quantitative imaging and microbiome-based biomarker indices associated with damage to specific sexual organs from radiation oncology treatments. Results of the study will rapidly provide transformative data and inform personalized interventions to preserve female sexual function or mitigate the effects of radiation in this understudied population.

Ahmed Khan's study seeks to advance the cancer therapy known as chimeric antigen receptor CAR T-cell therapy for solid tumors by manipulating CAR T cell interactions with the immune tumor microenvironment.

The lab will use tumor models to understand the parameters driving the activity and fate of CAR T cells, and design novel CAR T-cell therapies that capitalize on the immunobiology of solid tumors to form durable anti-tumor responses.

In addition to providing advanced radiotherapy to a diverse population of cancer patients, Marshall directs a laboratory aiming to advance the understanding of the impacts of radiotherapy on sexual function in women and female-bodied cancer patients across the lifespan. The lab applies radiobiological imaging, and multi-omic methods in human research to prevent and mitigate the effects of radiotherapy on sexual function and improve quality of life after cancer treatment.

Ahmed Khan leads the Ahmed Khan lab, which is part of the interdisciplinary Precision Immunology Institute and The Tisch Cancer Institute at Icahn Mount Sinai. The lab is recruiting student and postdoctoral researchers in immunology and immunotherapy.

This work is supported by the NIH Common Fund under award numbers DP5OD031876 and DP5OD031828 to Marshall and Ahmed Khan, respectively.

$1M gift furthers UNC research on breast cancer disparities, barriers to high-quality care

Rich Preyer and Marilyn Jacobs Preyer of Hillsborough, North Carolina donated $1 million to support the latest phase of UNC Lineberger Comprehensive Cancer Center's Carolina Breast Cancer Study, which is investigating how the causes, treatments, and long-term outcomes of breast cancer differ between Black and white women.

Researchers from UNC Lineberger and UNC Gillings School of Global Public Health launched the Carolina Breast Cancer Study in 1993 to identify a wider range of breast cancer risk factors and to better understand how these risk factors contribute to disparities in breast cancer.

The study focuses on the biological and social determinants of health—from pathology, molecular markers, and genetics on the cellular level, to health care access, the financial burden of care, and quality of life following diagnosis.

The next phase of the study, phase IV, will utilize high-end computing to analyze image data from histopathology and mammograms, enabling scientists to develop a more robust model of disparities and breast cancer outcomes. The researchers will also focus on doubling the number of young women and Black women participating in the research.

The private funds will help researchers expand the study to include more participants and lay the foundation for pursuing additional funding sources going forward.

This gift counts toward the Campaign For Carolina, UNC's most ambitious fundraising campaign in history, launched in October 2017 with the goal of raising $4.25 billion by December 2022.

The Carolina Breast Cancer Study is funded in part by the University Cancer Research Fund, the NCI's SPORE in breast cancer, and Susan G. Komen.

THE CANCER LETTER | OCTOBER 8, 2021 | VOL 47 | ISSUE 37

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

One in seven patients missed cancer surgery during COVID-19 lockdowns

One in seven cancer patients around the world missed out on potentially life-saving operations during COVID-19 lockdowns, a study from the University of Birmingham in the U.K. found.

Planned cancer surgery was affected by lockdowns regardless of the local COVID-19 rates at that time, with patients in lower income countries at highest risk of missing surgery.

These findings were published in *The Lancet Oncology*.

Led by experts at the University of Birmingham, almost 5,000 surgeons and anaesthetists from around the world worked together as part of the NIHR-funded COVIDSurg Collaborative to analyse data from the 15 most common solid cancer types in 20,000 patients across 466 hospitals in 61 countries.

The researchers compared cancellations and delays before cancer surgery during lockdowns to those during times with light restrictions only. During full lockdowns, one in seven patients (15%) did not receive their planned operation after a median of 5.3 months from diagnosis—all with a COVID-19 related reason for non-operation. However, during light restriction periods, the non-operation rate was very low (0.6%).

Patients awaiting surgery for more than six weeks during full lockdown were significantly less likely to have their planned cancer surgery. Frail patients, those with advanced cancer, and those awaiting surgery in lower-middle income countries were all less likely to have the cancer operation they needed.

Full and moderate lockdowns independently increased the likelihood of non-operation after adjustment for local COVID-19 case notification rates.

"In order to prevent further harm during future lockdowns, we must make the systems around elective surgery more resilient—protecting elective surgery beds and operating theatre space, and properly resourcing 'surge' capacity for periods of high demand on the hospital, whether that is COVID, the flu or other public health emergencies," co-lead author James Glasbey from the University of Birmingham said in a statement.

Rates of HCC are rising in rural areas while slowing in urban areas

A study from USC Norris Comprehensive Cancer Center, part of Keck Medicine, showed that while cases of hepatocellular carcinoma have begun slowing in urban communities in the U.S., the incidence of the cancer is rising at a rate of 5.7% annually in rural areas, approaching urban rates.

"Considering that one in five Americans live in a rural community, this study suggests that HCC is a critical under-recognized public health issue affecting rural Americans," Kali Zhou, a gastroenterologist and hepatologist with Keck Medicine and co-lead author of the study, said in a statement.

The rural subgroups experiencing a rapid rise in HCC included men ages 60-69, non-Hispanic Blacks, American Indian/Alaskan Natives, and those who live in either the southern part of the country or in a high-poverty area.

The researchers discovered that certain urban subgroups experienced declining incidence rates of HCC starting in 2013, including both men and women, younger individuals ages 40-59, Asian Pacific Islanders, and people who live in the Western United States. No rural subgroups experienced a clear decline during the study period.

Prior research indicates that this rising trend among rural communities is not evident with other common cancers. The rate at which rural residents are developing lung, breast, and colorectal cancer is falling.

Zhou and her colleagues examined HCC trends across rural and urban communities over the past 20 years using the North American Association of Central Cancer Registries database, which covers 93% of the U.S. They looked at cases

diagnosed between 1995-2016 of adults over 20 years of age.

Of the more than 310,000 new cases of HCC, 85% were diagnosed in urban and 15% in rural areas. The researchers tracked new cases per year for both geographic groups to discover that while the average rate of new cases was still lower in rural areas compared to urban ones over the 20-year span, cases increased at a higher average percentage rate per year in rural areas.

The rates of increase were similar for the two groups from 1995-2009. However, in 2009, the pace of new HCC cases in urban America began to slow down, with no corresponding slowing in rural America. By 2016, this meant the number of cases increased 218% from 1995 in rural settings, compared to 118% in urban ones.

The study did not examine the reasons rural America's annual change in new HCC cases is outpacing that of urban communities, but the researchers speculate there may be several factors at play.

"Obesity and alcohol use, both risk factors for liver cancer, may be more prevalent in rural populations," Zhou said.

Residents in rural areas may lack the same access to health care as urban dwellers, Zhou added, leading to a lack of preventive cancer care.

Zhou's previous research showed that people living in rural parts of the country are also more likely to have a late-stage liver cancer diagnosis and worse survival rates than those in urban communities.

NASEM publishes guidance for campus climate surveys measuring sexual harassment

The Action Collaborative on Preventing Sexual Harassment in Higher Education—part of the National Academies of Science, Engineering, and Medicine—published its first collaborative resource: a *Guidance Document on Measuring Sexual Harassment Prevalence Using Campus Climate Surveys*.

The goal of the resource is to help the higher education ecosystem conduct climate surveys that align with best practices identified by research.

Authored by the Action Collaborative's Evaluation Working Group, this guide provides key considerations for collecting population-based data in the form of a large-scale survey such as a campus climate survey, with the goal of measuring the prevalence of sexual harassment.

The guidance document can be found here.

On Oct. 12-13, the Action Collaborative will host its third annual public summit, an open forum for those in the higher education ecosystem to identify, discuss, and elevate approaches to addressing and preventing sexual harassment.

Chronic stress may impact treatment completion, survival outcomes in patients with breast cancer

Researchers at The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James) showed that chronic physiologic "wear and tear" from stress, known as allostatic load, may be associated with a decreased likelihood of cancer treatment completion and lower overall survival.

Samilia Obeng-Gyasi of OSUCCC-James presented these findings at the 14th AACR Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, held online Oct. 6-8.

Allostatic load is caused by lifelong exposure to stressors—such as social isolation, poverty, and racism—many of which are common among racial/ethnic minorities.

"Patient behavior and clinical outcomes cannot be isolated from the effects of their social environment," Obeng-Gyasi, a surgical oncologist and member of the Translational Therapeutics Research Program at the OSUCCC-James, said in a statement.

In this study, Obeng-Gyasi and colleagues in the ECOG-ACRIN Cancer Research Group sought to understand how allostatic load and genetic ancestry (identified by DNA) impact patients' survival and their likelihood of completing chemotherapy. Prior studies suggest that allostatic load and genetic ancestry each play a role in poor breast cancer outcomes; however, no studies have looked at both factors at the same time in a study population.

This study represents a retrospective review of ECOG-ACRIN E5103, a clinical trial evaluating the inclusion of bevacizumab into adjuvant sequential anthracycline and paclitaxel in patients with lymph node-positive or high-risk lymph node-negative HER2-negative breast cancer.

The researchers analyzed data from the ECOG-ACRIN E5103 phase III clinical trial, one of the first large breast cancer treatment trials to assemble a biorepository and database of patient information, including demographics and DNA, for future research.

Using genomic analyses and other patient information from the E5103 re-

pository, Obeng-Gyasi and colleagues examined chronic stress, measured by allostatic load, across three broad categories of genetic ancestry—African, European, and other. Among the 348 patients included in the analysis, approximately 80% had European ancestry, 10% had African ancestry, and 10% had other ancestry.

Allostatic load was measured in patients in E5103 using biomarkers of the cardiovascular, immune, and metabolic systems collected prior to starting treatment. Examples of these biomarkers included body-mass index, blood pressure, creatinine, and several cytokines.

After adjusting for genetic ancestry, the researchers found that each one unit increase in allostatic load score was associated with a 15% reduction in the likelihood of completing chemotherapy and a 14% increase in the risk of death.

Allostatic load appeared better than genetic ancestry at predicting chemotherapy completion and overall survival.

UAMS and Mayo Clinic researchers advance PROTAC technology for targeted molecular therapy

Researchers at the University of Arkansas for Medical Sciences Winthrop P. Rockefeller Cancer Institute and the Mayo Clinic have discovered a way to supercharge molecular cancer treatments to destroy more cancer-causing proteins in cells.

The research findings of UAMS' Hongyu Li, the Helen Adams and Arkansas Research Alliance Endowed Chair in Drug Discovery and professor of medicinal chemistry and chemical biology in the UAMS College of Pharmacy, and Haojie Huang, the Gordon H. and Violet Partels professor of cellular biology at the Mayo Clinic, were published in *Advanced Science*.

Li and Huang's research gives drug makers a new tool for enhancing molecular cancer treatment therapy with Proteolysis Targeting Chimeras technology. PROTACs are genetically engineered molecular compounds that bridge cancer-causing proteins with the molecules that seek to destroy them.

The team found that adding an "oglio," or oligonucleotide, to the PROTAC molecular compound helped degrade the targeted proteins completely, improving on conventional PROTACs.

NCI to study Anktiva + Keytruda as a chemo-free NSCLC therapy in 700-site Lung-MAP clinical trial

The Lung Cancer Master Protocol public-private partnership—which includes the NCI, the National Clinical Trials Network Cooperative Groups (SWOG, ECOG-ACRIN, Alliance, and NRG), Friends of Cancer Research, and the Foundation for the National Institutes of Health—will study the IL-15 receptor superagonist complex Anktiva (N-803) in the Lung-MAP clinical trial.

Anktiva is sponsored by ImmunityBio, Inc.

Anktiva will be given in combination with Merck's Keytruda (pembrolizumab) to participants with non-small cell lung cancer who have failed previous treatments. The combination therapy will be offered as a treatment to patients with tumors that do not have mutations targetable with a drug, as is the case for the majority of NSCLC patients.

The Lung-MAP trial is open at more than 700 sites in the U.S. When fully enrolled, this trial group will include 478 patients.

The trial protocol will enroll patients to a randomization schema of Anktiva + Keytruda versus investigator choice of standard-of-care chemotherapy (docetaxel, gemcitabine, pemetrexed, or docetaxel + ramucirumab). Two cohorts are being studied independently: primary checkpoint inhibitor resistant patients, and previous responders to checkpoint inhibitors who then subsequently progress.

This Lung-MAP study will look at how Anktiva could potentially bolster the effectiveness of Keytruda for patients with non-targetable cancer cell mutations. Current standard of care for patients who progress on Keytruda is chemotherapy with significant toxicities associated. Data presented by the study developers at ASCO 2021 showed the Anktiva/Keytruda combination as a chemotherapy-free alternative that has produced lower rates of adverse events than chemotherapy in the second-line setting.

Gel enhances CAR T benefits in brains surgically treated for glioblastoma

According to researchers from the University of North Carolina Lineberger Comprehensive Cancer Center, pairing a newly developed gel with immunotherapy that was delivered to post-surgical mouse brains with glioblastoma improved the immunotherapy's effectiveness.

These findings appeared Oct. 6, 2021 in *Science Advances*.

In this mouse study, the CAR T-cell gel was placed to fill in the area where a glioblastoma tumor had just been surgically removed. Previous studies have shown that administering T cells alone produces limited benefit.

"We developed a gel made of fibrin, a protein most often associated with helping blood to clot. Applying a gel substance to an area of the brain to aid CAR T-cell therapy is unique in glioblastoma treatment," Edikan Ogunnaike, a biomedical engineer at UNC and first author of the article, said in a statement. "The gel aided CAR T-cell distribution in the brain by acclimating the T cells to the post-surgical wound environment while also stopping the tumor from recurring."

The researchers used concentrations of human fibrinogen, a protein produced by the liver, which was transformed to fibrin with enzymes to develop a porous gel that was mixed with CAR T cells and placed in the post-surgical brain area.

The gel created web-like fibrin scaffolds in the brain, in which the CAR T cells uniformly enmeshed themselves into the pores of scaffolds. The scaffolds are biodegradable and do not cause inflammation, tissue death, or scarring.

Nine of 14 (64%) mice that received the gel and T cells were tumor free 94 days after treatment, compared to two of 10 (20%) mice who only received T cells. The researchers said if these findings can be replicated in human studies—they caution that many early laboratory findings don't lead to clinical studies or new therapies—it would result in a great improvement in current treatment rates.

The investigators are currently looking at injecting CAR T cells to other parts of the brain. The process is being tested in pilot clinical studies to assess safety as well as to see if it elicits a greater distribution of CAR T cells.

"The gel might also allow for local delivery of other biological agents that could sustain T cell growth and counter suppression of an immunotherapy," Ogunnaike said.

NRG Oncology launches FORTE, a colorectal cancer prevention clinical trial

NRG Oncology activated FORTE (Five or Ten Year Colonoscopy for 1-2 Non-Advanced Adenomatous Polyps, or NRG-CC005), a large, randomized trial of surveillance colonoscopy for participants with a first-time diagnosis of 1 or 2 adenomas.

Participants in the study will be assigned to having their next colonoscopy exam at 5 years and at 10 years or their next colonoscopy exam at 10 years. The study is expected to enroll 9,500 participants (about 4,750 people in each study group).

The primary objective of the study is to determine when people who had 1 or 2 small benign polyps removed during colonoscopy should have their repeat colonoscopy exam.

Participants in FORTE are also being asked to submit blood, stool, and tissues from polyps to support research into how colorectal cancer develops from a polyp.

FORTE is being conducted through NCORP, in conjunction with members of the NCTN. The trial will be led by NRG Oncology with the participation of other network organizations: Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, and SWOG.

DRUGS & TARGETS

FDA approves Tecartus for relapsed or refractory B-cell precursor ALL

Tecartus (brexucabtagene autoleucel) received FDA approval for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia.

Tecartus is sponsored by Kite Pharma, Inc.

Efficacy was evaluated in ZUMA-3 (NCT02614066), a single-arm, multicenter trial that evaluated Tecartus, a CD19-directed chimeric antigen receptor CAR T-cell therapy, in adults with relapsed or refractory B-cell precursor ALL. Patients received a single infusion of Tecartus following completion of lymphodepleting chemotherapy.

Of the 54 patients evaluable for efficacy, 28 (52%; 95% CI: 38-66) achieved complete response within 3 months. With a median follow-up for responders of 7.1 months, the median duration of CR was not reached; the duration of CR was estimated to exceed 12 months for more than half the patients.

This application was granted FDA priority review, breakthrough designation, and orphan drug designation.

FDA recognizes MSK database of molecular tumor marker information

The FDA granted recognition to a partial listing of the Memorial Sloan Kettering Cancer Center's Oncology Knowledge Base (OncoKB) as the first tumor mutation database to be included in the Public Human Genetic Variant Databases.

The FDA recognized a portion of the OncoKB as a source of valid scientific evidence for level 2 (clinical significance) and level 3 (potential clinical significance) biomarkers. Under the FDA's database recognition program, test developers can use these data to support the clinical validity of tumor profiling tests in premarket submissions.

Determining the mutation profile of a tumor using DNA sequencing enables the use of targeted therapies and investigational treatment options.

The OncoKB database contains detailed information regarding specific alterations in 682 cancer genes. The information is curated from various worldwide sources, including government agencies, medical professional groups, medical and scientific literature, and clinical trials.

The FDA reviewed the operating and governance procedures and policies, processes for the database and for variant evaluation and curation, and method of assignment of clinical significance. The data are sorted into one of two levels of clinical significance consistent with FDA-authorized tumor profiling tests and displayed on a tab referred to as "FDA recognized alterations."

EMA validates relatlimab + nivolumab application for advanced melanoma

The European Medicines Agency validated the Marketing Authorization Application of the fixed-dose combination of Opdivo (nivolumab) and relatlimab, a LAG-3-blocking antibody, for first-line treatment of adult and pediatric patients (12 years and older and weighing at least 40 kg) with advanced, unresectable or metastatic melanoma.

Both drugs are sponsored by Bristol Myers Squibb.

This application was based on the phase II/III RELATIVITY-047 trial, the first to demonstrate a statistically significant and clinically meaningful progression-free survival benefit of a combination therapy over standard of care anti-PD-1 monotherapy in metastatic melanoma.

Primary results from the RELATIVITY-047 trial were presented in an oral abstract session and selected for the official press program for the American Society of Clinical Oncology annual meeting in June 2021. Data were also presented in an oral presentation during the European Society for Medical Oncology annual meeting in September 2021.

The EMA's validation confirms completion of the submission and begins the centralized review process. The FDA has also accepted for priority review the Biologics License Application for the relatlimab and Opdivo fixed-dose combination.

This is an investigational therapy and is not approved for use in any country.

MD Anderson and Schrödinger announce strategic research collaboration to accelerate development of WEE1 program

The MD Anderson Cancer Center and Schrödinger, Inc. today announced a two-year strategic research collaboration focused on the development of Schrödinger's WEE1 inhibitor program, an investigational therapeutic approach designed to target the WEE1 kinase.

The goal of the collaboration is to accelerate and optimize the clinical development path for Schrödinger's WEE1 program through molecular biomarker-driven tumor type prioritization and patient stratification and to validate biomarkers to predict response or resistance to a WEE1 inhibitor. The joint team will seek to prioritize clinical studies of a WEE1 inhibitor as a single agent in selected cancer indications and in rational combinations for defined clinical subpopulations.

Under the preclinical collaboration agreement, Schrödinger will join forces with researchers in MD Anderson's Translational Research to AdvanCe Therapeutics and Innovation in ONcology (TRACTION) platform. TRACTION is a core component of MD Anderson's Therapeutics Discovery division, an integrated team of clinicians, researchers, and drug development experts.

MD Anderson and Schrödinger will jointly pursue translational studies, and Schrödinger will provide research support funding. As part of the agreement, MD Anderson is eligible to receive certain payments based on the future development and commercialization of Schrödinger's WEE1 inhibitor compounds. Schrödinger will have sole responsibility for the development, manufacture and commercialization of all compounds and products, and sole rights to all novel intellectual property that arises from this collaboration.

WEE1 is a gatekeeper checkpoint kinase that prevents progression through the cell cycle, allowing time for DNA repair to occur before cell division takes place. Thus, inhibition of WEE1 allows for accumulation of DNA damage, triggering DNA breakage and apoptosis in tumor cells.

Schrödinger is developing tight-binding, selective WEE1 inhibitors with optimized physicochemical properties designed to be well suited for combinations with other DNA damage response therapies for the treatment of a broad range of solid tumors.

NEXT Oncology expands phase I program with VCS partnership

NEXT Oncology and Virginia Cancer Specialists have joined forces, launching NEXT Virginia, a cancer clinic, in September 2021.
This partnership will also help expand VCS's phase I and developmental therapeutics cancer research program and bring the latest in new agents and anticancer treatments to the VCS Research Institute.

The expanded phase I program will begin this fall, while the stand-alone NEXT Virginia clinic, adjacent to Virginia Cancer Specialists, is built.

NEXT Virginia is headed by Alex Spira, co-director of the VCS Research Institute, who is the site's clinical director and CEO. Spira is also the director of the VCS thoracic and phase I program and a clinical assistant professor at John Hopkins.

NEXT Oncology has relationships with both Texas Oncology and Virginia Cancer Specialists, both of which are practices in the US Oncology Network. The new clinic will be located at 8613 Lee Highway in Fairfax.

NCI TRIALS

NCI Trials for Oct. 2021

The National Cancer Institute approved the following clinical research studies last month.

For further information, contact the principal investigator listed.

Phase I - 10433
Phase I/Ib Trial Evaluating the Safety and Efficacy of BET Inhibitor, ZEN003694 with PD-1 Inhibitor, Nivolumab with or Without CTLA-4 Inhibitor, Ipilimumab in Solid Tumors

UPMC Hillman Cancer Center LAO
Mahdi, Haider Salih
(216) 445-7069

Phase I - 10440
A Phase 1/1a Study of Venetoclax, MLN9708 (Ixazomib Citrate) and Dexamethasone for Relapsed/Refractory Light Chain Amyloidosis

City of Hope Comprehensive Cancer Center LAO
Rosenzweig, Michael A.
(626) 256-4673

Phase I - PBTC-059
Phase 1 Trial of Autologous HER2-Specific CAR T Cells in Pediatric Patients with Refractory or Recurrent Ependymoma

Pediatric Brain Tumor Consortium
Hegde, Meenakshi
(832) 824-4840

Phase II - 10466
A Phase 2 Study of Bevacizumab, Erlotinib and Atezolizumab in Subjects with Advanced Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) Associated or Sporadic Papillary Renal Cell Cancer

National Cancer Institute LAO
Srinivasan, Ramaprasad
(240) 760-6251

Phase II - 10476
A Randomized Phase 2 Study of Combination Atezolizumab and CDX-1127 (Varlilumab) with or Without Addition of Cobimetinib in Previously Treated Unresectable Biliary Tract Cancers

JHU Sidney Kimmel Comprehensive Cancer Center LAO
Azad, Nilofer Saba
(410) 614-9169

Phase II - A021901
Randomized Phase II Trial of Lutetium Lu 177 Dotatate Versus Everolimus in Somatostatin Receptor Positive Bronchial Neuroendocrine Tumors

Alliance for Clinical Trials in Oncology
Hope, Thomas A.
(415) 353-7065

Phase II - A092001
Phase 2 Randomized Trial of Neoadjuvant or Palliative Chemotherapy with or Without Immunotherapy for Peritoneal Mesothelioma

Alliance for Clinical Trials in Oncology
Mansfield, Aaron S.
(507) 293-0569

Phase II - S1934
NASSIST (Neoadjuvant Chemoradiation +/- Immunotherapy Before Surgery for Superior Sulcus Tumors): A Randomized Phase II Trial of Trimodality +/- Atezolizumab in Resectable Superior Sulcus Non-Small Cell Lung Cancer

SWOG
Osarogiagbon, Raymond Uyiosa
(901) 355-6340