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HOW A FLATIRON HACKATHON TEAM LINKED MEDICAID EXPANSION WITH REDUCTION IN RACIAL DISPARITIES IN TIME TO CANCER TREATMENT

Last December, Flatiron Health convened a "hackathon," an event where programmers, developers, and scientists pitch novel ideas and aggressively crunch data in a competitive sprint.

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Director, Feist-Weiller Cancer Center
LSU Health Shreveport

The LSU Health Sciences Center in Shreveport, LA is seeking a Director for the Feist-Weiller Cancer Center. The new Director will provide leadership to the Cancer Center with the development and implementation of a dynamic agenda for future growth and expansion, while also developing key relationships with the Chancellor, Vice Chancellors, Deans and other institutional Center Directors and Department Chairs.

The Feist-Weiller Cancer Center has diverse clinical settings including the Ochsner LSU Health Shreveport Academic Medical Center, a neighboring Shriners' Hospital for Children, one of eight St. Jude Children's Research Hospital affiliate clinics, and the Overton Brooks VA Medical Center. The Ochsner LSU Health Shreveport Academic Medical Center serves as a regional Level 1 trauma center for North Louisiana, East Texas and South Arkansas.

The position will report to the Vice Chancellor of Research of LSU Health Shreveport. The Feist-Weiller Cancer Center is a designated Louisiana Board of Regents Center for Excellence in Cancer Research, Treatment and Education. This cooperative community/academic partnership at Feist-Weiller Cancer Center serves area physicians, cancer patients and the general public as a resource in the fight against cancer.

The successful candidate must have proven experience as a leader who can inspire faculty and staff to work together to develop future leaders in Cancer Research. It is also important that the candidate have strong management skills with an ability to grow revenues and meet budgets, excellent communication skills, experience and interactions with NCI, and the ability to work collaboratively with a broad range of constituents both internally and externally.

Candidates must meet the following qualifications: MD degree from an LCME accredited medical school with at least 15 years experience in clinical services and administering residency and medical student educational programs. The successful candidate must be able to obtain a valid Louisiana license and be board certified. The candidate should possess a national reputation built upon a distinguished record of achievement in research, teaching and clinical care with national stature.

The search is being led by Dr. Chris Kevil, Vice Chancellor for Research at LSU Health Shreveport. Interested candidates may submit curriculum vitae and/or contact the staff supporting this recruitment to cwinne@lsuhsc.edu.

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Editor & Publisher
Paul Goldberg

Reporter
Matthew Bin Han Ong

Reporter
Claire Dietz

Designer
Jacqueline Ong

Illustrator & Operations Manager
Katie Goldberg

Web Developer
David Koh

Editorial, Subscriptions and Customer Service
PO Box 9905 -
Washington, DC 20016

T 202-362-1809
F 202-379-1787
W www.cancerletter.com

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REAL WORLD EVIDENCE

HOW A FLATIRON HACKATHON TEAM LINKED MEDICAID EXPANSION WITH REDUCTION IN RACIAL DISPARITIES IN TIME TO CANCER TREATMENT

By Matthew Bin Han Ong

Last December, Flatiron Health convened a "hackathon," an event where programmers, developers, and scientists pitch novel ideas and aggressively crunch data in a competitive sprint.

These events, also known as hackfests or codefests, are a staple of tech culture. No two hackathons are the same, and at that particular Flatiron event—the company's 18th—35 teams were challenged to find the best uses for real world data in solving real world problems.

One team, led by health economist and pharmacoepidemiologist Blythe Adamson, proposed using Flatiron's database to ask two big questions:

- Does the Affordable Care Act's Medicaid expansion program reduce disparities between black and white patients?
- Are black patients with metastatic cancer getting timely treatment, compared to white patients, in states that implemented the expansion?

Adamson *et al.* dove into the company's vat of data and emerged with the answers—Medicaid expansion is indeed associated with a significant reduction in racial disparities in states that implemented it.

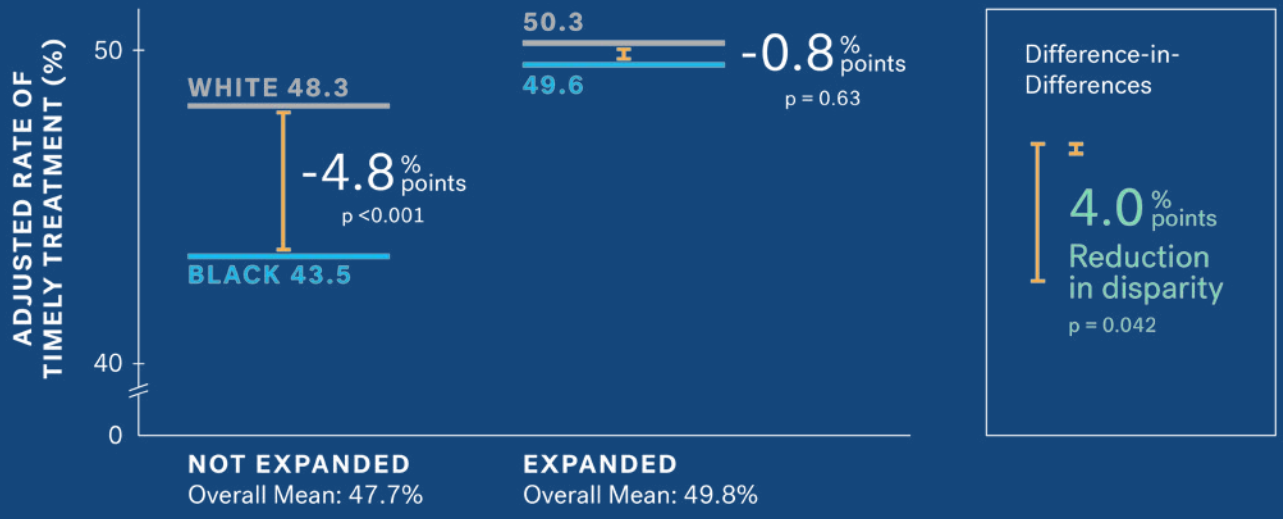
Six months later, the team's project would become the most-discussed plenary session at the annual meeting of the American Society of Clinical Oncology in Chicago. The study comes at a time of continued opposition to Obamacare by congressional Republicans. The broad health care reform initiative narrowly avoided a repeal in 2017, with three Senate Republicans defying their party's efforts to end the ACA without an immediate replacement program.

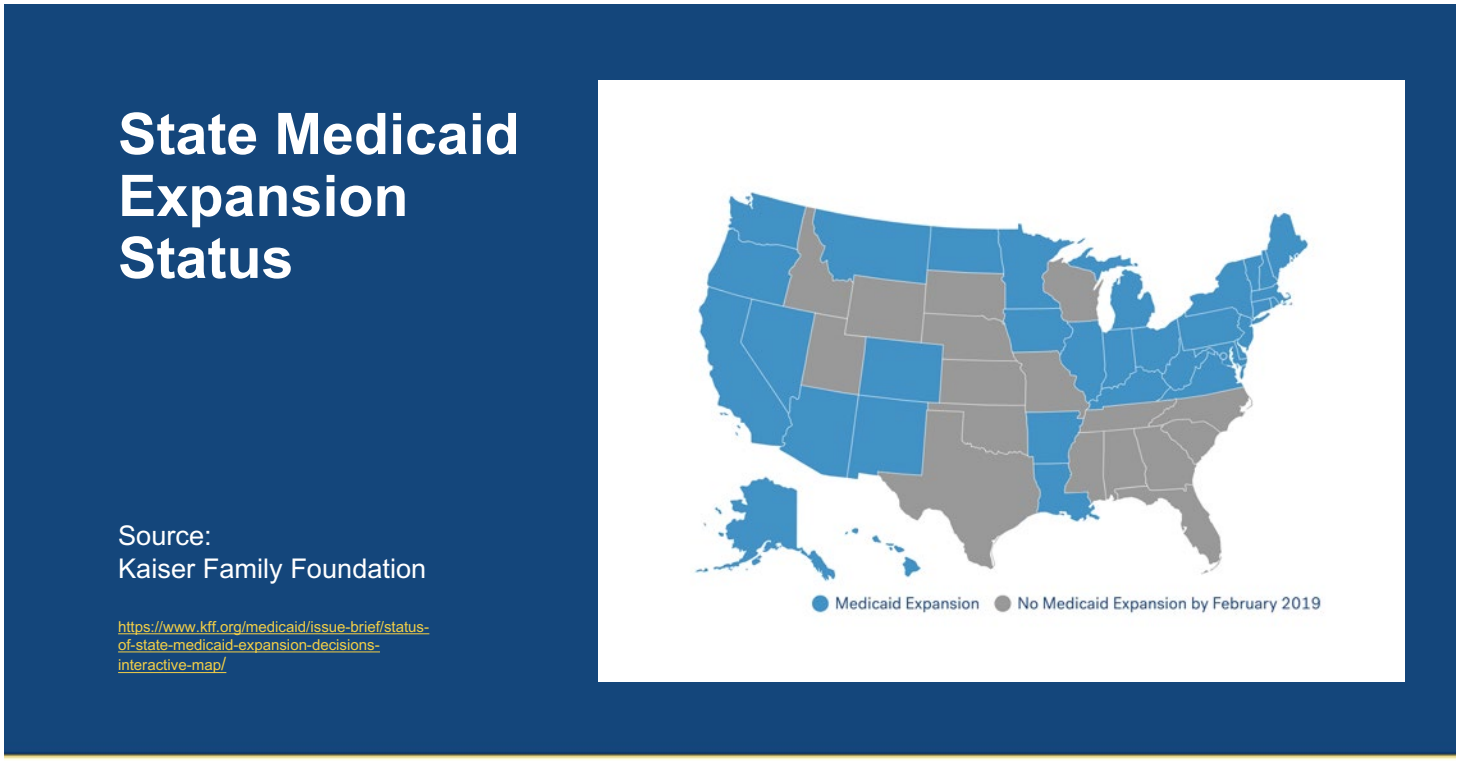
After the results were presented at ASCO, Democrats on Capitol Hill promptly took to Twitter to highlight Adamson's study.

"The Affordable Care Act helped reduce inequity within our country," Senate Democrats wrote June 3 on their official Twitter account. "But the Trump admin and the GOP have continuously worked

Racial Disparities in Cancer-Related Care Remain a Societal Challenge

Results: Change in Racial Disparity





to undermine the law and take away health coverage from American families. Democrats will not stop fighting to #ProtectOurCare."

The three-day hackathon began on Dec. 5, 2018, at Flatiron's headquarters in Lower Manhattan. It was a Wednesday night, and a chilly breeze was blowing outside. Flatiron, taking note, had lined its communal picnic tables with trays of steaming hot dumplings.

One by one, employees announced their hackathon ideas. The next morning, everyone—statisticians, clinical data analysts, machine learning specialists, research oncologists—hunkered down, tapping away at their keyboards for two days, hoping to emerge victorious.

The grand prize? Bragging rights, and a stack of laptop stickers to commemorate the winner of the hackathon.

"They usually last one to three days, and you cancel all of your meetings, and form teams to work, or "hack," on something you're passionate about. And sometimes it can be pretty competitive," said Adamson, a senior quantitative scientist at Flatiron. "Yes, you can motivate a bunch of nerds with something as silly as a laptop sticker.

"I got up on stage and pitched this idea—because I knew I couldn't do it alone—saying that, 'I think we should test this hypothesis. Did Medicaid expansion have an impact on racial disparities?'

"It's pretty incredible to me that we could go from an idea that I had in the shower in November—to the ASCO Plenary stage six or seven months later."

A conversation with Adamson appears on page 13.

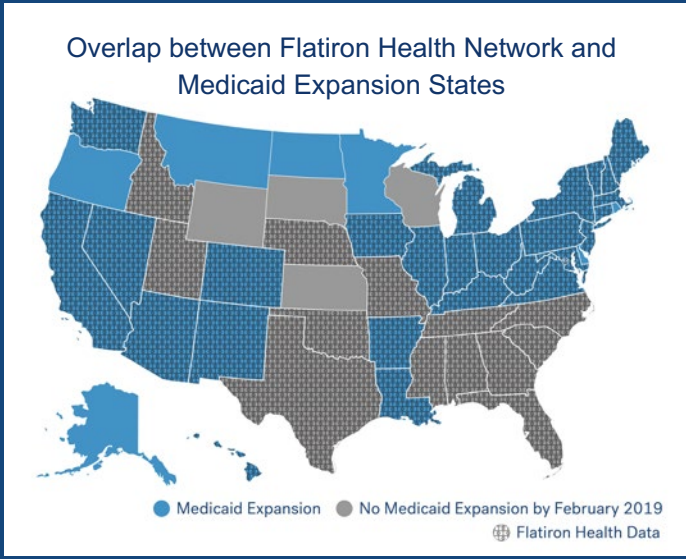
By Monday, Dec. 10, Adamson and her team had made history—their project was the first study to use real-world, real-time data to show that, in states

"I got up on stage and pitched this idea—because I knew I couldn't do it alone—saying that, 'I think we should test this hypothesis. Did Medicaid expansion have an impact on racial disparities?'"

– Blythe Adamson

Data Sources

- Flatiron Health electronic health record (EHR)-derived database
  - De-identified
  - Structured data: demographics including race and medication administrations
  - Unstructured abstracted data: diagnosis date, stage, oral anti-cancer medications
- Kaiser Family Foundation
- U.S. Bureau of Labor Statistics



Expansion and Flatiron Health data as of May 2019

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PRESENTED BY: Amy J. Davidoff, PhD. Amy.davidoff@yale.edu

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that implemented Medicaid expansion, black cancer patients were getting timely treatment, nearly on par with white patients.

The results of the final analysis, presented at an ASCO plenary session, show that Medicaid expansion is associated with a 4% reduction in post-diagnosis time to treatment for black patients with metastatic cancer—effectively a near-elimination of racial disparities in timely treatment in states with Medicaid expansion.

To date, 37 states, including the District of Columbia, have adopted the Medicaid expansion. Of that number, 34 have implemented the expansion. The patient data included in the Flatiron study are sourced from 27 of these states.

"Please note that we didn't even win that hackathon—I believe we came in third place—but the response from people at Flatiron was so moving that we could tell, early on, that it was something that was really meaningful to people," Adamson said to The Cancer Letter. "And when the call came around for ASCO abstracts, we sat back and had to make a decision: 'Should we do this for real?'"

For the project, Flatiron teamed up with two researchers from Yale University:

- Amy Davidoff, a health economist, health services researchers, and senior research scientist at the Yale School of Public Health, Department of Health Policy, and
- Cary Gross, professor of medicine and epidemiology, and director of the National Clinician Scholars Program at Yale.

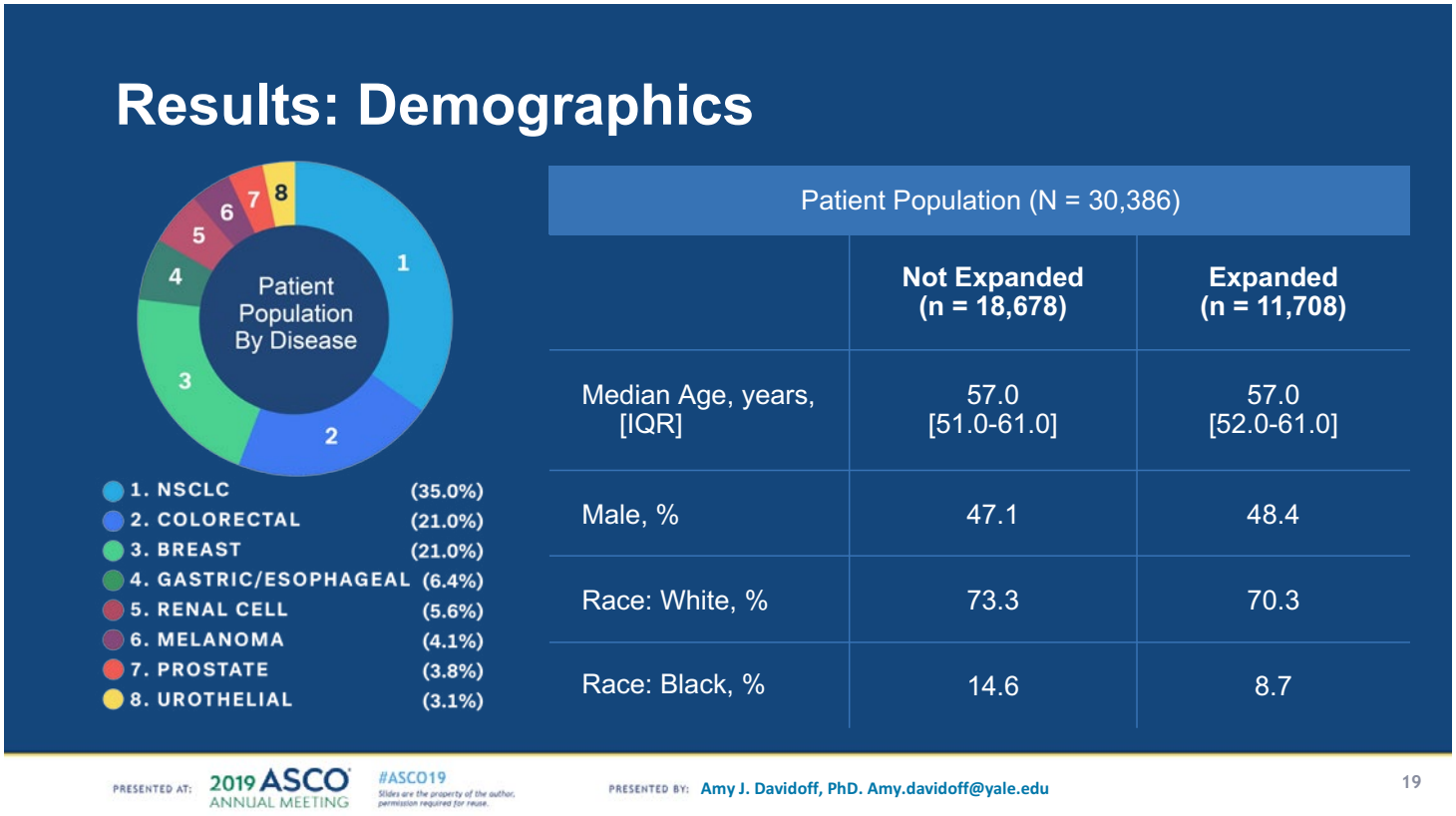
"Cary brought in Amy Davidoff from Yale, who is a famous health econ hero to me, already had published research showing that ACA and Medicaid expansion reduced the rate of uninsured cancer patients and shifted diagnoses earlier stages," Adamson said. "And so, with Amy and Cary, we redesigned the methods to account for all the different potential sources of bias and get close to causal inference."

This was Adamson's first ASCO meeting. She had never submitted an abstract to the professional society before this study.

"In preparing for the ASCO abstract submission, we thoughtfully redid the study with care and rigor," Adamson said. "It was well received."

Rep. Adam Schiff (D-CA), chair of the House Intelligence Committee, and Sen. Dianne Feinstein (D-CA), ranking member of the Senate Judiciary Committee, too, chimed in.

"New research shows that fewer Americans, especially women and people of color, are dying of cancer because of expanded health coverage through the ACA," Schiff wrote in a June 3 tweet. "Health care saves lives. That's why



we're fighting so hard to make sure every American has access to quality care."

"Thanks to the Affordable Care Act, the disparity in access to cancer care for white and African American patients has almost been eliminated," Feinstein wrote in a June 3 tweet. "Further proof that the ACA is saving lives and improving care for millions of Americans."

Andy Slavitt, a former acting administrator of the Centers for Medicare and Medicaid Services who led the turnaround of Healthcare.gov in the Obama administration, called Adamson's study "Great news."

"Since the ACA, African American disparity in advanced cancer diagnosis & treatment has almost entirely caught up to whites where Medicaid has expanded, a near 5% improvement," Slavitt wrote in a June 2 tweet. "There is a right direction. Support those pushing for it."

To study time to treatment, Adamson's team divided Flatiron's data on Medicaid patients into two cohorts—states with Medicaid expansion (n = 11,708), versus states without expansion (n = 18,678). The sample included patients with eight cancer types, with non-small cell lung, colorectal, and breast cancer making up 77% of cases.

"In the case of evaluating health care policy, randomization is almost never possible. States would not allow themselves to be randomized to expansion or not expansion," Adamson said. "We designed the next best thing one could do, using methods to mimic attributes of randomization.

"This is the first study that I've seen where we cut straight to the heart of what mattered to us, which was understanding if health equity improved. By pre-specifying our hypothesis and methods before running the experiment, it strengthened the scientific validity of the results. We certainly demonstrated the possibility to generate real time evidence for policy design."

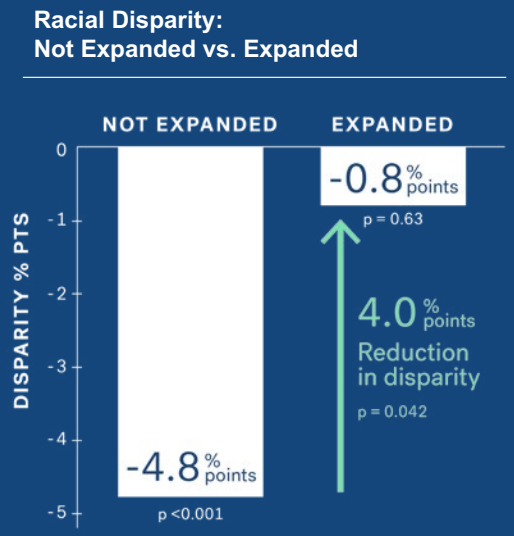
The results of the study, while correlative, builds on prior evidence regarding the effect of ACA expansions on insurance coverage and general access for cancer patients, said Syed Yousuf Zafar, associate professor of medicine and population health sciences at Duke University.

"An important point to make at the outset is, this is not a randomized controlled trial, and the results from the study are indeed correlation, showing association, not causation," Zafar said to The Cancer Letter. "However, there have been experiments close to randomized studies that have actually shown similar benefits with Medicaid expansion. In that sense, I'm talking about the Oregon experiment.

"When Oregon expanded Medicaid access, they had to do so with a random lottery, just because of the number of

Conclusions

- Medicaid expansion was associated with reduced racial disparities in timely cancer treatment
- Extends prior evidence regarding effects of ACA expansions on insurance coverage and general access for cancer patients
- National healthcare policy may reduce disparities in cancer care
- EHR data = valuable research resource



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> Policies that improve access and decrease the time to treatment will serve to drive the value proposition in cancer care. Congress must understand that policies that improve access will not only improve patient outcomes, but drive down costs.
>
> *– John H. Stewart*

people who applied for expanded Medicaid. And that random lottery basically served as a natural randomized study. In the results of that randomized study, they basically found that, in some cases, access to care, care utilization, and certain health outcomes improved with Medicaid expansion."

The expansion of the ACA has several critical consequences that lead to the conclusions in the Flatiron study, said John H. Stewart, professor of surgery at the University of Illinois College of Medicine at Chicago, physician executive for oncology sciences at University of Illinois Health, and associate director for clinical sciences at the University of Illinois Cancer Center

"This study is extremely important as it demonstrates the importance of the Patient Protection and Affordable Care Act in improving cancer care," Stewart said to The Cancer Letter. "First, there is improved access to medical facilities. Second, many institutions have implemented navigation programs to facilitate the delivery of care for these patients across the care continuum and undoubtedly reduces the structural impediments to timely care that factor into racial disparities.

"Although this study is highly significant, it does raise several important questions. First, are there data that show a reduction in the time to treatment for patients with early-stage cancer? I believe that this will be the most important outcome of the PPACA. Second, are there data on differences in the utilization of palliative care? Finally, does Medicaid expansion reduce health care expenditures associated with the care of these patients?"

The results of this study are timely given the improvement in treatments for metastatic disease, Stewart said.

"Policies that improve access and decrease the time to treatment will serve to drive the value proposition in cancer care," Stewart said. "Congress must understand that policies that improve access will not only improve patient outcomes, but drive down costs."

The Flatiron study is proof of principle that real world evidence can be used to examine and inform health policy interventions, said Zafar, who led a discussion of Adamson's study at the ASCO plenary session.

"From a data standpoint, we need better use of real world evidence to help inform population-based outcomes," Zafar said. "Importantly, I don't think real world evidence can, today, replace our gold standard for efficacy, which is randomized controlled trials, but it can inform quality of cancer care and population-based outcomes, very much like this study did.

"They did a really nice job. I believe there has been one other study that has looked at time to treatment with Medicaid expansion. If I remember correctly, that study was done just in Kentucky. The Flatiron study was done in the metastatic setting; that study that was done in just one state was done in the adjuvant setting in early-stage cancer. And that study actually did not see any improvement in time to initiation of chemotherapy with Medicaid expansion."

The impact of Medicaid expansion in North Carolina on cancer patients would be immediate, Zafar said.

"I happen to live in a state that has not expanded Medicaid access," Zafar said. "So, during my plenary discussion, I talked about my patient, Sylvia, who has metastatic pancreatic cancer, applied for Medicaid when she lost her insurance soon after her diagnosis, and unfortunately was told she was not eligible for Medicaid in North Carolina, because her income was too high."

"Now, interestingly, her income was $18,000 a year. And despite that very low income, she's still not eligible for Medicaid. So, I could see the immediate impact Medicaid expansion—in a state like North Carolina—would have on my patients, and how they can afford and access health care."

Under the ACA, Medicaid eligibility is extended to nearly all low-income individuals with incomes at or below 138 percent of poverty—$17,236 for an individual in 2019, according to the Kaiser Family Foundation.

This expansion fills in historical gaps in Medicaid eligibility for adults and was envisioned as the vehicle for extending insurance coverage to low-income individuals, with premium tax credits for the ACA Marketplace coverage serving as the vehicle for covering people with moderate incomes. While the Medicaid expansion was intended to be national, a June 2012 Supreme Court ruling essentially made it optional for states.

"I think this study presents really timely evidence that health policy interventions are needed to improve access to care for our patients," Zafar said. "In terms of moving forward, I would advocate for Medicaid expansion at the state level, obviously, and that would be an important policy step."

Back at Flatiron, Adamson has already started working on her next big hackathon project—using real world data to elucidate the safety and efficacy of cancer immunotherapies in people living with HIV.

"There's absolutely no evidence about the safety or efficacy of these drugs in people living with HIV, which to me is crazy, because with HIV, you're more likely to develop cancer—and then, to have no understanding about whether there's an interaction between the drug efficacy and the virus," Adamson said.

"So, at the Flatiron Hackathon 19 in March, we identified patients with HIV who had used immunotherapy and matched them to patients just like them—diagnosed in the same year with the same stage and disease and type of drug, similar in every way except they don't have HIV. We compared overall survival outcomes for immunotherapy in people with vs without HIV.

"Would anyone ever be incentivized to pay for and run a large randomized trial of this? I doubt it. I designed this to be a companion study to CITN-12, a phase I study looking at safety of pembrolizumab in cancer patients living with HIV.

"So, to have a prospective trial looking closely at safety alongside a retrospective study of effectiveness in the real world, it can give us a whole new and more complete picture of risks and benefits for a marginalized population that matters."

Q & A

Adamson spoke with Matthew Ong, a reporter with The Cancer Letter.

CONVERSATION WITH THE CANCER LETTER

Flatiron's Adamson: Medicaid disparities study shows real world data is valuable for assessing policy

Blythe Adamson
Senior quantitative scientist, Flatiron Health

"I could see that this needed to be done and Flatiron is the only group that could do it. And you might have heard in the presentation at ASCO on June 2, we learned from and shared the experiences of patients treated as recently as February 28, 2019. This was real-time policy evaluation."

Before 2019, Blythe Adamson, a senior quantitative scientist at Flatiron Health, had never attended an annual meeting of the American Society of Clinical Oncology.

In the shower, sometime in November 2018, Adamson came up with an idea for future research: "I think we should test this hypothesis: Did ACA Medicaid expansion have an impact on racial disparities?"

At a Flatiron hackathon last December, she pitched the idea.

"This is Hackathon 18, and it kicks off on a Wednesday night in December, where they order dumplings for the whole company. So, I got up on stage and pitched this idea to recruit a team—because I knew I couldn't do it alone."

Three days later, Adamson and her team produced compelling preliminary results, which would be further developed to demonstrate that black patients with advanced cancer received timely treatment in states with Medicaid expansion, compared to white patients.

The study, conducted in collaboration with researchers from Yale University, showed a 4% reduction in racial disparities in time to cancer treatment—nearly eliminating the overall gap between black and white Medicaid patients in 27 states.

On June 2, at the ASCO annual meeting, Adamson's project was the opening presentation in the lineup of plenary session.

"It's pretty incredible to me that we could go from an idea that I had in the shower in November—to the ASCO Plenary stage six or seven months later," Adamson said. "Being able to rapidly generate evidence and efficiently spread it with this large audience was an incredible honor.

"To me, academic researchers are the key to identifying and answering questions to improve health. I hope investigators try to replicate my work in this study and extend the research to look at other outcomes and interventions."

Adamson spoke with Matthew Ong, a reporter with The Cancer Letter.

Matthew Ong: How did this study come about and what was your role? I hear this grew out of a hackathon.

Blythe Adamson: It did. It's pretty amazing. It's really the converging of many things at the same time. First, before coming to Flatiron, I had noticed that in the field of health economics, there was a lot of research attempting to understand if the Affordable Care Act and Medicaid expansion had an impact on health outcomes.

I saw a lot of posters and presentations using beautifully designed difference-in-difference methods, and the researchers had clearly spent time thinking about the right methods to understand the impact. But all of the results were limited by not enough follow-up data. They didn't have recent enough data to understand what happened in the years after expansion. And so, they couldn't answer it yet.

In my prior work as an HIV researcher, I'd worked with marginalized populations and seen real racial disparities in health.

And then I came to Flatiron. Many studies had described the existence of racial disparities in cancer. But I was frustrated that there wasn't much evidence of interventions that made it better, that made things more equitable.

So, at my first hackathon, those three things converged to reveal this incredible opportunity to use Flatiron data. We recognized that there's probably no other dataset in the world that could answer this question, because you need individual patient level data with the clinical depth and recency.

I could see that this needed to be done and Flatiron is the only group that could do it. And you might have heard in the presentation at ASCO on June 2, we learned from and shared the experiences of patients treated as recently as February 28, 2019. This was real-time policy evaluation.

Very cool. Could you describe how this happened at the hackathon?

BA: So, hackathons are really common at tech companies and in tech culture. They usually last one to three days, and you cancel all meetings, and form teams to work, or "hack," on something you're passionate about. And sometimes it can be pretty competitive.

This one was an internal hackathon. We do these three to four times a year. The prize at Flatiron for hackathons, besides just the glory of winning, are laptop stickers to commemorate the win. Yes, you can motivate a bunch of nerds with something as silly as a laptop sticker.

This is Hackathon 18, and it kicks off on a Wednesday night in December, where they order dumplings for the whole company. So, I got up on stage and pitched this idea to recruit a team—because I knew I couldn't do it alone—saying that, "I think we should test this hypothesis. Did ACA Medicaid expansion have an impact on racial disparities?"

I had spoken with Cary Gross from Yale, counting him as one of our team members for that original hackathon. By the end of the first night, we had a 30-page analysis plan. The next day, we crushed through coding it up for eight

cancer types. On the third day, we had preliminary results showing significant evidence of Medicaid expansion impact.

I remember walking out of the conference room, saying to my colleague, "We just did the equivalent of a three-year doctoral dissertation over the course of three days."

Please note that we didn't even win that hackathon—I believe we came in third place—but the response from people at Flatiron was so moving that we could tell, early on, that it was something that was really meaningful to people.

And when the call came around for ASCO abstracts, we sat back and had to make a decision: "Should we do this for real?" Cary brought in Amy Davidoff from Yale, who is a famous health econ hero to me, already had published research showing that ACA and Medicaid expansion reduced the rate of uninsured cancer patients and shifted diagnoses earlier stages. Our study built on her prior work.

We brought Amy in for her expert eye, and she just totally tore apart the analysis plan, pointing out all the holes, and limitations. After that, I thought, if we really can work together to overcome these critiques and together design the most valid, rigorous way to answer this, then, it would be a really, really strong study.

And so, with Amy and Cary, we redesigned the methods to account for all the different potential sources of bias and get close to causal inference. And in preparing for the ASCO abstract submission, we thoughtfully redid the study with care and rigor. It was well received.

So, it's pretty incredible to me that we could go from an idea that I had in the shower in November—to the ASCO Plenary stage six or seven months later. Being able to rapidly generate evidence and efficiently spread it with this large audience was an incredible honor.

I mean, "well received" is a complete understatement, in my opinion. Everyone at ASCO was electrified by the results, because you showed a near-elimination of time to treatment disparities for the Medicaid population in states with expansion. I do notice, nevertheless, the cautionary disclaimers about how correlation doesn't equal causation. How are you and the other authors framing that part of the conversation?

BA: Well, two things. One is that real world data can, to me, be extremely valuable when a randomized trial is not feasible or ethical. And in the case of evaluating health care policy, randomization is almost never possible. States would not allow themselves to be randomized to expansion or not expansion.

We designed the next best thing one could do, using methods to mimic attributes of randomization. There's a lot changing over time. There are differences between states, differences within states. And we can use and leverage those differences to help us isolate change that is really attributable to a health care policy like Medicaid expansion.

In the study, you compared the expanded cohort to a non-expanded cohort. What might be some confounding variables that could explain the decline in time of treatment for black patients in the expanded cohort?

BA: In observational research there are measured and unmeasured confounders. In this study, income was an unmeasured confounder. A purer way to understand the effect of Medicaid expansion could have been a narrow focus on only the patients who are poor or near poor. And we weren't able to do that in the study because we did not have income data.

By including all persons less than 65 years old, it likely diluted the real effect that we could see. Including lots of patients that have high incomes and have commercial health insurance in our study probably biased the results towards observing no effect at all of the intervention.

Is this is the first study of its kind on disparities in the Medicaid population and how Medicaid might actually affect access to cancer care in real time?

BA: Many other researchers are working on important questions like this one. Previously, others have explored Medicaid expansion association with health outcomes and included sensitivity analyses that break down results into subgroups by race.

This is the first study that I've seen where we cut straight to the heart of what mattered to us, which was understanding if health equity improved. I think what is unique here, one strength of this study, is that we focused only on one purposeful question to answer.

By pre-specifying our hypothesis and methods before running the experiment, it strengthened the scientific validity of the results. We certainly demonstrated the possibility to generate real time evidence for policy design.

> This is the first study that I've seen where we cut straight to the heart of what mattered to us, which was understanding if health equity improved. I think what is unique here, one strength of this study, is that we focused only on one purposeful question to answer.

What are other significant findings in the study? Are there any other issues that you've learned, through this process, that you'd like to highlight?

BA: You know, time to treatment is one outcome. But there are many other outcomes that we could have looked at.

We selected timely treatment, because it's important to patients. We consider it to be a patient-centered outcome. Sometimes timely treatment is related to overall survival.

We've seen this in some early cancers. But not all the evidence is consistent. I think it would be valuable to do a similar analysis to understand how Medicaid expansion affected racial disparities in other outcomes.

I'm a purist, and so, I really don't want to speak to the significance beyond our primary hypothesis testing. One aspect of the data that we learned more about in this study was new depth into understanding the representativeness of patients in the Flatiron Health network and new ways we can approach understanding the generalizability of evidence.

Does this study merit congressional attention? I mean, I expect your results will attract political debate, if it hasn't already.

BA: As a health economist and data scientist, I strive to do research that meaningful, actionable, and informs decision-making and policy. It was satisfying to see that, in this case, the results rapidly reached government officials with influence on the design of healthcare policy.

I was shocked how many leaders learned about the study from Twitter. I hope that it is seriously received and weighed as a part of a larger body of evidence.

I wonder if folks from the Obama administration looked at this and thought, "See? Told you so." Have you heard from the people that helped design the ACA or any other proponents of the ACA really?

BA: There's been quite a bit of discussion on Twitter from policymakers and leaders that were involved in ACA implementation.

And so, it's been great to see that. We saw Andy Slavitt, who was one of the architects behind the Affordable Care Act, tweet out one of the stories. So, I would say it's good to see it's getting on those radars and getting the attention from some of the people that were involved early on in the policy.

Sen. Dianne Feinstein sent out an excellent tweet about it. And I really hope that it demonstrates the future potential of what we can use electronic health records for: this type of real-time policy evaluation.

Because, there are often times when policies are designed with the best intentions, but once they're rolled out and implemented, there can be winners and losers in any health care policy, and there can often be unintended consequences.

So, even ones that are designed with the purpose—the ACA was designed to improve access, quality and equity.

And your study showed it does.

BA: Yes. Specifically, that of those three goals—access, quality and equity—this study is one of the first to focus on equity. We're not trying to claim that time to treatment is the best representation of quality.

We see that, in evaluating the policy, it was working in cancer. I hope that it encourages others to use the opportunity that we have to figure out if policies are working—to understand if they're worth fighting for, or need to be redesigned.

What are your next steps for the study? Where are you going to publish the manuscript?

BA: We are working on the publication right now. It's under review and we're looking forward to sharing. Many of the questions that we're receiving are answered with sensitivity analysis that we've run so far, and so, I'm excited for that to become available.

The other part that I am excited about is the growing number of talented health disparities researchers and the increasing appreciation of their work. There are seven academic medical centers, universities, and non-profit cancer centers that partner with Flatiron and their faculty members have free access to all of the national data used in this study.

Equipping academic researchers to answer important questions with good data is one of the most rewarding aspects of my job as a scientist at Flatiron. When I came, I knew that, gosh, there are a ton of questions that are really important to patients that no other data source can answer. Who is going to answer these? There aren't enough scientists at Flatiron to answer all these good questions.

To me, academic researchers are the key to identifying and answering questions to improve health. I hope investigators try to replicate my work in this study and extend the research to look at other outcomes and interventions.

At Flatiron, we want to learn from the experience of every cancer patient. And it makes me feel so hopeful to see how many researchers are interested in learning from all these patients, whether they're uninsured so they've never been captured in a cleaned database, or they're under 65, so they're not in Medicare, or they don't meet clinical trial exclusion criteria, so they're not captured in the effectiveness data we understand.

We have an important chance to deeply understand these populations and their health.

Beyond these upcoming multitudes of collaborations, what's your next big idea or project that you want to work on? Have you gone there yet?

BA: Oh, we have. You should see what I did in my second hackathon. So, cancer patients that are living with HIV are always excluded from cancer clinical trials.

For the promising new, life-extending immunotherapies, there's absolutely no evidence about the safety or efficacy of these drugs in people living with HIV, which to me is crazy, because with HIV, you're more likely to develop cancer—and then, to have no understanding about whether there's an interaction between the drug efficacy and the virus.

So, at the Flatiron Hackathon 19, in March, we identified patients with HIV who had used immunotherapy and matched them to patients just like them—diagnosed in the same year with the same stage and disease and type of drug, similar in every way except they don't have HIV. We compared overall survival outcomes for immunotherapy in people with vs without HIV.

Would anyone ever be incentivized to pay for and run a large randomized trial of this? I doubt it. I designed this to be a companion study to CITN-12, a phase I study looking at safety of pembrolizumab in cancer patients living with HIV.

So, to have a prospective trial looking closely at safety alongside a retrospective study of effectiveness in the real world, it can give us a whole new and more complete picture of risks and benefits for a marginalized population that matters.

Did we miss anything?

BA: I don't think so. What I was really, really proud of watching Amy present on stage was that title slide showing the names of the co-authors, because it stuck to our original hackathon team.

We had research oncologists, a clinical data analyst, machine learning data scientist, pharmacoeconomist, and two outcomes researchers from Yale volunteer time, nights, and weekends to doing this research because we knew it was important.

That hackathon gave me the opportunity to work with people I would not normally, ever work with before. We shared a mutual passion and learned a lot from each other and the experience. I am proud of the teamwork, motivation, and dedication of Aaron Cohen, Melissa Estevez, Cary Gross, Erin Williams, Kelly Magee, Neal Meropol, and Amy Davidoff.

We stuck together from that first late night sharing dumplings during hackathon, all the way to sitting side-by-side in the front row of the plenary session. It was an incredibly proud moment.

It wasn't just a plenary, it was the first item in the plenary line-up, and also the first item that ASCO sent out in a press release on top studies at ASCO 2019, ahead of the meeting.

BA: It was my first ASCO meeting. First abstract I've ever submitted to ASCO.

That's awesome.

House bill gives NIH a $2B increase, but battle over budget caps looms

By Paul Goldberg

The House of Representatives June 19 passed a package of four appropriations bills for fiscal year 2020.

The $982.8 billion package, nicknamed the "minibus" bill and passed on a 226 to 203 vote, gives $41.1 billion to NIH, an increase of $2 billion above the 2019 level and $6.9 billion above the President's budget proposal.

Centers for Disease Control and Prevention gets $8.3 billion, $938 million above the 2019 enacted level and $1.7 billion above the President's budget request.

According to a statement by the Democratic majority on the committee, the legislation, H.R. 2740, "rejects the proposed slashing and outright elimination of critical programs in President Trump's budget request and instead invests in important priorities like health care, education, clean energy, infrastructure, national security, and restoring America's standing abroad.

"Additionally, the legislation provides robust oversight of the administration, including blocking it from diverting Defense and Army Corps funds to build a border wall, keeping the United States in the Paris Climate Agreement, and permanently repealing the global gag rule."

A division-by-division summary of H.R. 2740 is posted here. Amendments to each division of the bill are posted here.

"In terms of the FY2020 Appropriations process, and specifically in regard to our efforts to ensure another robust funding increase for NIH, the medical research advocacy community is becoming accustomed to watching the events in DC play out in sort of a split-screen manner," said Jon Retzlaff, chief policy officer and vice president of science policy and government affairs of the American Association for Cancer Research. "For example, this week, we watched (and applauded) as one of the screens showed the House passing the Labor, Health and Human Services, Education and Related Agencies (Labor-HHS-Ed) Appropriations Bill as part of a broader package of bills (where five FY2020 spending bills were combined into one bill). This "minibus" bill included a $2 billion funding increase for NIH in FY2020."

"However, we also paid close attention to the other screen, which showed top Senate Republicans, including Senate Majority Leader Mitch McConnell (R-KY) and Senate Appropriations Chairman Richard Shelby (R-AL), as well as top Congressional Democrats, including House Speaker Nancy Pelosi (D-CA), and House Majority Leader, Steny Hoyer, meeting with President Donald Trump's negotiating team (acting White House chief of staff Mick Mulvaney, Treasury Secretary Steven Mnuchin, and acting director of the Office of Management and Budget Russ Vought) in an attempt to restart the previously stalled bipartisan budget negotiations."

"The bottom line is that without a broader budget deal to raise the spending caps for FY2020 (that are currently in place as a result of the 2011 Budget

> The bottom line is that without a broader budget deal to raise the spending caps for FY2020 (that are currently in place as a result of the 2011 Budget Control Act), this week's actions in the House will end up being a futile effort by House leaders to continue the sustained funding momentum of the past four years for one of our nation's top national priorities, specifically the lifesaving medical research that is supported by NIH.
>
> *– Jon Retzlaff*

Control Act), this week's actions in the House will end up being a futile effort by House leaders to continue the sustained funding momentum of the past four years for one of our nation's top national priorities, specifically the lifesaving medical research that is supported by NIH. And most concerning is the fact that failing to reach a budget deal could result in a cut to NIH's budget of ten percent in FY2020 if the sequester (across-the-board cuts in discretionary domestic and defense spending) is allowed to take effect."

Mary Woolley, president of Research!America, said the bill bespeaks congressional commitment to medical and public health priorities.

"We applaud the $2 billion increase for the National Institutes of Health, which will enable it to support more researchers across the nation to make the discoveries that will lead to better health for everyone," Woolley said. "This legislation also provides investments of almost $1 billion for the Centers for Disease Control and Prevention, which works around the clock protecting our nation from global and domestic health threats. It also increases funding by $20.2 million for the Agency for Healthcare Research and Quality, which is playing a pivotal role in maximizing healthcare quality and squeezing costly inefficiencies out of healthcare delivery.

"We were also heartened that the House passed the amendment led by Congressman Pocan that aims to reduce the negative impact of the administration's recent attempts to stifle life-saving fetal tissue research. While we hoped the minibus would go further to prevent these progress-slowing policy changes, this amendment is an important statement in support of responsible research that plays a unique role in understanding and combating lethal health threats."

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REVIEW

Chernobyl, the HBO miniseries: Fact and fiction (Part IV)

Readers will be pleased to learn this is the final installment of my reviews of the HBO Chernobyl miniseries, which just ended its TV run June 3. The series, which has received extraordinary critical acclaim, had a vast global audience.

By Robert Peter Gale
Visiting Professor of Hematology, Imperial College London
Executive director of clinical research in hematology and oncology, Celgene Corp.

Some have called it the best TV of the year, and one or more Emmys are surely in store. Lest I seem a curmudgeon, I join the critics and most viewers in thanking Craig Mazin and his colleagues for bringing the story of Chernobyl NPF accident back to public attention.

Although the story presented was generally accurate, there were important conceptual and factual errors, some of which I discussed in previous reviews. Are these errors important? No, and yes.

No, because the 10,000-meter view of the accident is what really matters. Screenwriters need a simple storyline: A really *bad* thing happened in a *bad* place and now, thousands or millions of people, maybe all of us, will suffer for decades from birth defects, genetic abnormalities, cancer and more (try three-headed goats).

But is this really the message we should take from the Chernobyl accident? I would argue no. What it shows is the fallibility of humans, not physics, something we see every day—design a complex machine poorly, override safety controls, allow politicians to ignore science, etc. Sound familiar? A Ferrari is amazing technology, but a potentially dangerous machine if you put a 6-year-old in the driver's seat. Should we ban Ferraris, or restrict who can drive them?

There is a second reason the errors in the miniseries are important. Many readers of The Cancer Letter have written questioning several technical details. For example, were the emergency personnel dangerously radioactive? No. Their predominant exposure was to external radiations. After surface decontamination, they posed little threat to us or to the public.

The Chernobyl situation is unlike the accident we faced Goiania, Brazil,

where victims ingested large amounts of 137-cesium and were highly-radioactive. Initially, we treated them behind lead shields wearing protective gear. We quickly found we could not care for these critically-ill persons properly, especially the children. Moreover, we found the shielding protection was offset by the longer time it took us to deliver care, because the shielding was heavy and slowed our movement. Off it went. As you know, physicians are invincible (until they're not).

The most common question I received was about the pregnant wife of a firefighter, who supposedly lost her child from radiation she received whilst caring for her injured and supposedly highly radioactive husband. Earlier, I described how this is impossible for many reasons.

First, none of the firefighters was dangerously radioactive. Obviously, we should never expose a pregnant woman, or anyone, to even a low radiation dose, unless there is a perceived benefit. We use ultrasound rather than abdominal X-rays in pregnant women, unless absolutely needed.

However, a pregnant woman's body is a reasonably effective shield against low-dose external radiations to the fetus, especially radiations from alpha particles (stopped by a piece of paper) and electrons, as portrayed in the scenes from the Chernobyl miniseries. I also discussed the rarity of birth defects in children of pregnant women exposed to the A-bombs: that these abnormalities were limited to cognitive disability, and that they occurred only in children exposed to radiation in the second trimester.

In the miniseries, the woman is told her child received 25 roentgens. What exactly does this mean, and does it make sense? A roentgen (an antiquated term) is a measure of radiation in air (the electric charge freed by radiation in a specified volume of air divided by the mass of that air). Obviously, it's the dose absorbed in a tissue or organ, which determines the amount of damage caused by radiation—a dose is measured in gray (the absorbed dose) or sievert (equivalent dose adjusted for the type of radiations), not the dose in air. If we stick with the miniseries, we can very roughly calculate that 25 roentgens is about 250 millisieverts.

If the fetus received this dose, the dose to the mother would have had to be substantially higher, more than the average A-bomb survivor. This is, of course, somewhere between highly unlikely and impossible. More importantly, in utero radiation exposure does not cause liver fibrosis or congenital heart defects in animals or humans.

Why focus on this issue? Because readers may be asked by a pregnant woman about radiation risks to a fetus in the event of a nuclear terrorist attack or radiation accident. They need to give advice based on scientific data, not a book (even from a Nobel laureate) or TV miniseries.

I'm very sorry this woman's child had these birth abnormalities and died, but these problems are extraordinarily unlikely to have anything to do with radiation exposure. Readers should recall, about 3% of normal births in the U.S. are associated with congenital/birth defects according to the U.S. Centers for Disease Control and Prevention. Congenital heart disease occurs in about 1% of *normal* births in the U.S. resulting in about 20% of infant deaths. Because the liver receives about 25% of the heart output, congenital heart defects are sometimes associated with liver abnormalities from, for example, portal hypertension.

A third common question was whether there was or will be an extraordinary increase in cancers, especially amongst the mitigation workers (dare I say *liquidators*), as portrayed in the miniseries. Are these men (and some women) really doomed?

> “Screenwriters need a simple storyline: A really bad thing happened in a bad place and now, thousands or millions of people, maybe all of us, will suffer for decades from birth defects, genetic abnormalities, cancer and more (try three-headed goats). But is this really the message we should take from the Chernobyl accident?”

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Source: HBO

Obviously, no. A worst-case scenario is a 1% increase in lifetime cancer risk above baseline from 43% to 44% in men and from 39% to 40% in women. Hardly a death sentence, and nothing compared with other health risks such as cigarette smoking and excessive drinking, both common amongst the liquidators.

I recall lecturing a group of Fukushima-Daiichi mitigation workers concerned about health consequences of exposure to 50 millisieverts of radiation (emergency worker limit in Japan). Everyone in the room was a smoker and most reported smoking two or more PPD for many years. I pointed out their 10-20-fold increased risk of lung cancer, many other cancers, chronic obstructive pulmonary disease (COPD), and arteriosclerotic cardio-vascular disease (ASCVD). I also mentioned lung cancer in smokers is caused, at least in part, by radiation by inhaling 210-polonium, which contaminates tobacco leaves.

No one seemed impressed by this information (perhaps my Japanese is not as good as I think), and certainly no one stopped smoking during my lecture, even though the risk of death from smoking three cigarettes (total, not per day) is equivalent to the risk of death from one chest X-ray.

Most readers are likely to have been trapped behind someone at airport security refusing to go through a screening device. First, screening devices at most U.S. airports use millimeter wave scanners, which do not emit ionizing radiations. Second, the amount of radiation this person is exposed to every 2 minutes from background sources—like radionuclides in granite or marble floors (thorium, radium, uranium) and cosmic radiations—whilst arguing with the TSA supervisor, is equivalent to the radiation dose they will receive from 2 seconds of flying at 12,000 meters (if they make it through security).

If you're afraid of radiation, don't worry about screening. Don't fly. And don't get me going on porcelain tooth veneers, which are also radioactive. A prolonged kiss with someone with these has a risk equivalent of death due to skydiving (which, admittedly, I do).

These examples illustrate the exaggerated fear most people, educated or not, have about radiation, including makers of the Chernobyl miniseries. Are they fearmongers? I doubt it. Misinformed is more likely.

But back to the final episode of the HBO Chernobyl miniseries. The last topic requiring correction is the mostly inaccurate portrayal of the Soviet government officials, scientists, and health care workers.

With a few exceptions (Legasov and Khomyuk), the portrayals are caricatures of evil, mean-spirited, deceptive nincompoops. Were most people in the Soviet Union like this, it's unlikely they could have built an atomic bomb, launched Sputnik, contributed importantly to mathematics, physics and computer science, and much more. Were we to take the persona in the miniseries as real, it's a wonder the Soviet Union survived much beyond Oc-

tober 1917, or avoided blowing up the planet, perhaps several times, with nuclear disasters (bombs and NPFs) over the next several decades.

Was the Soviet Union really an Evil Empire bent on destroying America? Not in my opinion. Yes, there was repression of human rights, forced labor camps, exile to Siberia, and the Gulag archipelago so dramatically portrayed by Solzhenitsyn; a police state.

But read Russian literature, say Dostoevsky, Tolstoy or, my favorite, Bulgakov, and you will see nothing really changed over hundreds of years. When Brezhnev became General Secretary of the Communist Party and told his mother how he lived in the Kremlin, she said: "I'm happy for you, Leonid, but what will happen if the communists come to power?"

NPF accident. Sure, the Soviet government tried to conceal the accident, but let's consider what happened when their cover was blown. Ask yourself how many governments would have accepted my offer to try to save lives of the accident victims. Details of a nation's nuclear program are typically secrets. No American had ever entered the Institute for Biophysics or Hospital 6, certainly not one with a KGB dossier.

I discussed this unexpected openness with my Soviet colleagues, and eventually, with General Secretary (later President) Gorbachev. What they told me was they could not conscience these brave young firefighters dying, when there might be medical interventions which might save at least some. How many governments would have acted similarly?

"I knew each of the firefighters intimately, including the 29 who died. I never heard one of them express regret over what they had done to contain the Chernobyl disaster. These men are the real heroes."

Were Soviet citizens fundamentally different than us? Not really. Sadly, they got stuck with a terrible political system doomed to failure. Marx and Lenin's target for communism was England, not Russia, but politicians take what they can get. The rest is history. As Winston Churchill said: "Democracy is the worst form of Government except all those other forms that have been tried from time to time."

I'm certain many, if not most, readers will disagree with my view of the Soviet Union, but let me try to defend my position in the context of the Chernobyl

Of course, not everyone was on board with this decision. One government newspaper described me as the greatest spy since Kim Philby, a left-handed compliment at best.

And another example: In Part II, I described a previously untried therapy for radiation damage (sargramostim) and how I offered to inject myself with it to convince the Soviets to let us use it. Although I knew the biology of this drug, academician Andrei Vorobiev, a distinguished hematologist and 20 years my senior, did not. Yet, he insisted I also inject him. He almost died, but that's a different story.

There is insufficient space to fully describe the tireless efforts of Soviet physicians and nurses on our team over many months, including my late colleagues, Profs. Angelina Guskova and Alexander Baranov, whom I miss dearly. And I was not the only foreigner quickly admitted following the accident, including Hans Blix and a team from the U.N. International Atomic Energy Agency.

Try to imagine these invitations after a major nuclear event during the current U.S. administration. Forgetaboutit. A 4 month-old Mexican infant was recently separated from his parents.

I knew each of the firefighters intimately, including the 29 who died. I never heard one of them express regret over what they had done to contain the Chernobyl disaster. These men are the real heroes.

In the miniseries, the liquidators are portrayed as being coerced into their mission. I interviewed many of them at the time of the accident, not 30 years later. Almost everyone I spoke with volunteered. Anyone with knowledge of Russians will recognize how these people respond to adversity. Recall Napoleon's 1812 excursion into Russia, or the Nazi invasion of the Soviet Union in WWII. These people are tough; 20 million Soviets died fighting the Nazis. The notion that most liquidators were conscripted against their will shock people who know Russians respond to adversity: they thrive on it.

About six weeks after the accident, I felt a press conference was needed to brief the world on what was really going on with the victims and at the NPF. I suggested this to several Soviet officials. I warned them that rumors were flying of thousands of deaths and other nonsense. Absent credible information, people create their own facts.

To my surprise, the government asked me to speak at the press conference, without

restriction. Again, I ask readers to consider the likelihood of similar invitation to this happening to a Russian physician after a huge U.S. nuclear accident. So, there I was on the podium, facing more than 1,000 foreign journalists, unscripted.

In the Soviet Union at that time, reporters had to write their questions on slips of paper, which were given to the speaker. I received a stack of about 50 questions, the first of which said, "Why are Americans lying about consequences of the Chernobyl accident, claiming thousands of people died?" An obvious plant by the KGB or some government official. However, I had the microphone and quickly realized no one else could see what was written on the first note. So, I turned it around and said, "The first question is: Why, despite the Cold War, are Americans so willing to help the Soviet people respond to this tragedy?" My point is, the Soviets were not perfect, but neither were they monsters.

The scene I just described repeated itself when I met with President Gorbachev in the Kremlin a few weeks later. After some pleasantries, he pulled out the front page from the New York Daily News with the headline banner, "Thousands Dead From Chernobyl," and asked me, "Why your government publishes such lies?"

I responded that the U.S. government doesn't control the press in America (despite recent attempts), which I'm sure he knew. He then showed me about 20 envelopes he'd received from American citizens with notes of sympathy—some containing donations of $5 or $10. He was clearly touched, as was I.

The point of all of this is to try to give viewers of the Chernobyl miniseries a more nuanced, accurate impression of what really happened during the days, weeks, and months after the Chernobyl NPF accident.

Did the Soviet government initially try to hide the accident? Yes. But when they realized this was hopeless—a radiation cloud does not respect international boundaries—they acted in what I regard as a decent, humane way, and not terribly differently from other governments I've dealt with, such as Brazil and Japan.

And so my review of the HBO Chernobyl miniseries ends. I thank the editors of the The Cancer Letter for the invitation to set the record straight, and give readers facts about the accident and background about ionizing radiations, which I hope they enjoyed and will share with others. Chernobyl was a unique NPF accident which could not occur at a Western nuclear reactor. Some will immediately say I'm wrong, "Look at Fukushima."

As I tried to explain, what happened at Fukushima is entirely different than what happened at Chernobyl. The medical consequences are also extraordinarily different. But NPFs are not the real problem, global warming is. There is no realistic alternative to reversing or at least slowing global warming other than using nuclear energy. We should, of course, develop alternative energy sources, conserve energy, and pray someone can figure out how to harness nuclear fusion, but there is no other immediately available energy choice. It always surprises me environmentalists are not the strongest advocates for nuclear energy.

But I want to close with two equally urgent challenges: nuclear terrorism and nuclear war. Prof. Jim Armitage and I discussed the imminent threat of nuclear terrorism recently, in an article in The New England Journal of Medicine for those wanting more information.[1]

More troubling is the increasing threat of a nuclear war. The U.S. recently withdrew from the Joint Comprehensive Plan of Action (JCPOA), unofficially known as the Iran Nuclear Deal. In response, Iran threatened this week to restart uranium enrichment and increase its stockpiles. And after decades of nuclear arsenal downsizing, the U.S., Russia and most other nuclear states have committed to upgrading their nuclear weapons capabilities and their missile delivery systems.

And it gets worse. In February, the U.S. gave official notice of withdrawal from the INF treaty in six months; Russia responded in kind. Other risks are continued development of nuclear weapons by North Korea, and China's increasing nuclear arsenal. Even more worrisome is Pakistan's dispersion of its nuclear warheads throughout the country. The recent conflict between India and Pakistan over Kashmir has brought two nuclear-armed nations into active conflict. And the Middle East with a nuclear-armed Israel is a mess.

Prof. David Nathan and I review these issues in a forthcoming article in the ASCO Post.[2] Our conclusion: physicians need to focus on this extraordinary threat to mankind and re-engage in efforts to prevent a nuclear war, especially a new Cold War between the U.S. and Russia and/or China.

In closing, I apologize for covering some complex radiation-related issues so superficially, but this is The Cancer Letter, not the Bulletin of the Atomic Scientists and I was asked to review a TV miniseries, not produce a nuclear physics textbook. Readers wanting a more detailed description of several topics I discussed can start with a recent book by Eric Lax and me: Radiation: What you need to know.[3]

I get 5 cents for every copy you buy. With six children, I need it.

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NCI advisors approve 23 concepts at joint NCAB/BSA meeting

By Claire Dietz

The NCI Board of Scientific Advisors has approved 23 new and reissue concepts: five Requests for Applications/Requests For Proposals and 18 PARs, program announcements reviewed in the institute.

The following six concepts, presented at a June 10 joint meeting with the National Cancer Advisory Board, were approved:

Clinical Trials Information and Management and Support Contract Proposal (New RFP)

The CTIMS is designed to provide project management, organizational and information management support to NCI-sponsored clinical trials, related scientific programs, and their scientific evaluation process.

The RFA was submitted by the Clinical Investigations Branch at the NCI Cancer Therapy Evaluation Program.

The CTIMS contract supports the Division of Cancer Treatment and Diagnosis and the Coordinating Center for Clinical Trials. The intended outcomes of the contract are to facilitate efficient and effective development, review, and completion of NCI-supported clinical trials and related scientific projects.

The project management for CTIMS supports new clinical trials initiatives by:

- Using project teams to involve extramural investigators in CTEP drug development planning: PMs for 19 early-phase project teams lead to 78 Letters of Intent
- Increasing ETCTN accrual in disease-specific clinics:
  - Creating and analyzing over 30 surveys to ETCTN investigators to assess accrual feasibility
  - Developing and maintaining web-based tools for physicians to identify appropriate disease-specific trials
    - These initiatives contributed to a 100% increase in ETCTN trial accrual over two years
- Managing clinical trial accrual:
  - Managing and monitoring over 50 early-phase Corrective Action Plans to slow accruing trials
- Supporting new NCI precision medicine initiatives:
  - Coordinating working groups and committees for NCI-MATCH and Pediatric MATCH
  - Assisting with onboarding over 25 labs into the NCI-MATCH laboratory network, including SOP development, coordination of lab application review, and orientation of labs
  - Providing organizational support for the new Pediatric Early Phase Clinical Trials Network

CTIMS accomplishments include:

- New NCI Cancer Moonshot initiatives required additional PM support
  - Cancer Immunotherapy Monitoring and Analysis Centers and Cancer Immunotherapy Data Commons
  - Drug Resistance and Sensitivity Network
  - NCORP Biospecimen Procurement Protocol
- Established a second NCTN Core Correlative Sciences Committee (NCTN-CCSC) due to increased workload and supported 57 proposals reviewed by the NCTC-CCSC as of February 2019

The information management's accomplishments include:

- NCTN/NCORP Data Archive
- Clinical Trials Stewardship Committee

- Provided support to over 10 publications, including:
  - "The Current Understanding of the Endocrine Effects from Immune Checkpoint Inhibitors and Recommendations for Management" in JNCI-CS (July 2018)
  - "Seamless Designs: Current Practice and Considerations for Early-Phase Drug Development in Oncology" manuscript published in JNCI (December 2018)
  - "FACTS: Factors Affecting Combination Trial Success" (ASCO abstract 2544 2018; publication submitted to Frontiers in Medicine, January 2019)

The future of CTIMS project management is intended to support new and ongoing trials and projects by:

- Providing and enhancing PM support to current clinical trials networks and new precision medicine trials as identified
- Providing flexible, high-quality PM support to ongoing and evolving scientific programs
- Maintaining and optimizing information management support to facilitate data sharing and harmonization
- Maintaining and enhancing PM support and coordination of NCI scientific steering committees

The budget for the contract reissue is for a 7-year contract period. The requested budget is $6.5 million for the initial year, with the total contract estimated to cost $49 million over 7 years.

This represents an 18% increase over the current contract year related to increased project management needs of new scientific projects and growth of complex precision medicine trials. Industry funding through DCTD's Cooperative Research and Development Agreements is anticipated to cover the increase. This also includes an allowance for cost of living adjustments.

Co-Infection and Cancer (New PAR)

The purpose of the program is to enhance mechanistic and epidemiologic research in co-infection and cancer and identify markers for early detection and prevention.

Co-infection is defined by the occurrence of infections by two or more infectious (pathogenic or non-pathogenic) agents, either concurrently or sequentially, and includes both acute and chronic infections by viruses, bacteria, parasites, and other microorganisms. For the purpose of the FOA, co-infection with HIV was excluded.

This PAR was submitted by NCI's Center to Reduce Cancer Health Disparities.

Infection-driven carcinogenesis shows most infected individuals are chronic carriers and rarely develop the associated cancer.

However, infection-driven cancer initiation and progression may require additional co-factors. Questions raised include:

- What factors act cooperatively with the pathogens to produce cancer?
- What are the mechanisms that underpin that cooperation?
- What is the involvement of other pathogenic agents and non-pathogenic agents in the development and progression of cancer?

Evidence suggests that co-infection is associated with cancer risk, but the direct role in causation in unknown, and mechanisms are speculative.

Infections with another infectious agents may be the necessary co-factor for infection-related cancer initiation and progression:

- Etiologic role of co-infection in cancer risk is suspected, but largely unknown
- Mechanisms of co-infection in carcinogenesis is unclear
- Identification of risk profiles may lead to targeted interventions and prevention strategies

There was no associated budget.

U.S and Low- and Middle-Income Country (LMIC) HIV Malignancy Research Networks (New RFA/Coop. Agr.)

The goals of this RFA include: accelerating scientific knowledge in HIV-associated cancers, developing research capacity, supporting collaborations between U.S. investigators and LMIC investigators, and fostering the development of early career investigators.

The RFA was submitted by the AIDS Malignancy Program in the NCI Office of HIV and AIDS Malignancy.

Phase I and II of LMIC consist of collaborative consortia in HIV associated cancers. The collaborative consortia in HIV-associated cancers include:

- Phase I U54 (limited to Africa)
  - RFA-CA-13-010: Sub-Saharan African Collaborative HIV and Cancer Consortia (U54)
- Phase II U54 (expanded to include other LMICs)
  - RFA-CA-16-018: Collaborative Consortia for the study of HIV-associated cancers: U.S.

and Low- and Middle-Income Country Partnerships (U54)

The consortia conduct research projects that address high-priority research questions in HIV-associated cancers, and accelerates basic, translational, population, and implementation research.

By enhancing the ability of LMIC institutions to serve as a national and regional resource for training and career development of scientific leaders in cancer research, the consortia improve research infrastructure in the partnering country towards becoming independent research centers.

The consortia include:

- 11 consortia partnerships between a U.S. institution and a LMIC institution
  - 10 in sub-Saharan Africa
    - Tanzania, Kenya, Uganda (3), Rwanda, Botswana, Malawi, Zambia, and Nigeria
  - 1 in South America
    - Argentina

The leadership would be shared between U.S. investigators and LMIC investigators.

Some examples of research project topics in LMIC include:

- HPV/cervix/anal
  - HPV typing for rural vs urban women
  - HPV natural history and modifiable risk factors
  - Cervix treatment outcomes
- KS/Kaposi sarcoma-associated herpesvirus (KSHV)
  - Predictors of KS recurrence or progression
  - KSHV genomic variability
  - KSHV Ab response in KS patients
- Lymphoma
  - Biomarkers and tumor characteristics that lead to better lymphoma treatment outcomes
  - Sequencing the T cell receptor repertoire in patients with lymphoma
- Liver cancer
  - HIV's role in HCC and early detection
- Other
  - Cancer burden using HIV-cancer record linkage

Some accomplishments of the collaborative consortia in HIV-associated cancers:

- Developed regional hubs for translational research in HIV-associated cancers
  - Publications (49)
  - New grant submissions from young LMIC investigators (2 K43)
  - Submission of R01 and K08 grants using data and/or samples
- Developed a novel model for career development centered around peer mentoring (Journal of Global Oncology 2018 41-11)
- Training includes:
  - Inter-consortia training
  - Community sensitization in early detection of KS
  - Cryotherapy and Loop Electrosurgical Excision Procedure (LEEP)
  - Laboratory assays (e.g. immunohistochemistry, HPV typing, KSHV, PCR)
  - Anal pap and High Resolution Anoscopy (HRA)
  - Transient elastography using Fibroscan

The main features of the proposed phase III RFA include partnerships between U.S. and LMIC investigators—which are open to all investigators, phase II investigators are eligible as long as they propose new projects—and research projects that address questions in one related topic area, amongst others.

For example, possible research topics include:

- Research that addresses gaps in knowledge in the pathogenesis of cancers that are relatively rare in the U.S. but frequent in people living with HIV in an LMIC (e.g., Kaposi sarcoma, cervical cancer, ocular surface squamous neoplasia)
- Research to better understand the pathogenesis of cancers that affect people living with HIV and differences between analogous cancers in people without HIV
- Research that provides new insights into the role of social determinants in cancer risk, cancer care, and adherence to care and how it impacts survivorship in the era of combination antiretroviral therapy in LMICs
- Research that seeks to identify novel interactions of HIV with other co-factors (biological, environmental or exogenous) that modulate risk to cancer
- Research focused on development of novel, low cost and technologically feasible approaches for the prevention, diagnosis, and treatment of HIV-associated

cancers particularly those that can be implemented in LMICs

- Research that evaluates optimal approaches that will guide strategies to improve the integration of cancer care with HIV care in the public health settings of LMICs

The FY2018 funding was $8.3 million. The proposed budget can request up to $800,000 direct costs per year for 5 years. The F&A costs to LMIC institutions are limited to 8% of modified total direct costs. The requested set-aside is $6 million per year for 5 years (for a total of $30 million, which can support 5-6 networks).

These funds will come from NCI's HIV/AIDS allocation that must be used to support HIV/AIDS research. From ending phase I projects, this will generate $5.7 million. It will require $300,000 new HIV/AIDS dollars, but the Fogarty International Center may be interested in co-funding.

The concept is tentatively approved by the NIH Office of AIDS Research as a FY2020 NCI initiative and identified as a priority by the NCI BSA Ad Hoc Subcommittee on HIV/AIDS Malignancy.

Biospecimen Banks to Support NCI National Clinical Trials Network (NCTN), NCI Community Oncology Research Program (NCORP) and CTEP-Supported Early Trials/Studies (Reissue RFA/Coop. Agr./ Limited Competition)

The Biospecimen Banks is designed to support NCI Clinical Trials by collecting, processing, storing, and distributing well-annotated NCI Clinical Trials biospecimens for research.

The RFA was submitted by Pathology Investigations & Resources Branch, in NCI's Cancer Diagnosis Program.

From all organ sites in adult and pediatric cancer, over 400,000 samples were distributed. Approximately 410,000 of these samples are solid tumors. Specimens used for research have been a part of over 500 publications.

NIH policies include requirements for data sharing and public access to publications from NCTN clinical trials. De-identified patient-level data from all NCTN phase III and phase II/II trials must now be submitted to the NCTN/NCORP Data Archive after publication of the trial's primary results (which may also include results from any integral biomarker included in the trial).

Data submission to the archive includes the dataset, data dictionary, and relevant metadata, along with a de-identified code for each patient that can be used for future linkage to genomic, imaging, or other specimen data contained in other database.

Current funding consists of:

- 5 NCTN banks ($11.1 million a year) and ETCTN bank pilot ($650,000 a year)
- 5 Awards for NCTN Biospecimen Banks (totaling $15.2 million)
  - Infrastructure and operations
  - NCTN Biospecimen IT Navigator & Front Door Service curation - "Legacy" specimens retrieval, processing, QA/QC
  - Specimens for CIMAC (specialized processing/handling)
  - Specialized kits and tubes for collection sites & processing
  - Digital whole slide images storage/scanning
- NCORP cancer prevention trials biospecimens (totaling $1.8 million)
- New PEP-CTN Biospecimen Banking in COG NCTN Bank (totaling $230,000)
- 1 Award for Early Clinical Trials Bank (ETCTN, CITN, & CIMAC) (totaling $2.5 million)

The total cost for six banks per year is $19.73 million.

Pediatric Brain Tumor Consortium (Reissue RFA/Coop. Agr./ Limited Competition)

The Pediatric Brain Tumor Consortium, supported through successive Funding Opportunity Announcements since 1999, is the primary source of NCI-sponsored clinical trials for children with relapsed and refractory brain tumors.

The RFA was submitted by the Clinical Investigations Branch at the NCI Cancer Therapy Evaluation Program.

From 2014 to 2019, two of four Children's Oncology Group phase III clinical trials were based on PBTC results. Two other COG CNS Tumor Committee protocols are under review by CTEP are based on the results of PBTC-029.

The results from PBTC and COG phase II trials that treated recurrent malignant brain tumors were combined in a meta-analysis to generate information that can be used in future study designs.

The PBTC has shared its disease assessment criteria with COG, which, in turn, has modified some of the language in its templates based on COG trial guidance. The PBTC has taken active steps to encourage its member institutions to enroll on the Pediatric MATCH study that is being run by NCI and COG.

The PBTC RFA plan consists of several enhancements:

- Increased capacity for clinical trials

- Increased number of member institutions
- Enhanced ability to continue collaborative interactions with COG CNS Committee

The budget is $2,218,314 in direct costs and $2,711,850 in total costs.

With the budget request of $3.3 million in direct costs and total costs of $4 million, PBTC would be able to:

- Have additional member institutes (6 sites at $80,000 per site)
- Increase support for OBD-MC ($400,000)
- Leadership funds to support participation of COG CNS Committee members ($125,000)

Chronic Pancreatitis, Diabetes, and Pancreatic Cancer Consortium (Reissue RFA/Coop. Agr.)

The purpose of the joint NCI-NIDDK Chronic Pancreatitis, Diabetes and Pancreatic Cancer Consortium is to gain insight into the pathophysiology of chronic pancreatitis and its sequelae: chronic pain, pancreatic insufficiency, T3cDM, and the diabetes and pancreatic cancer association.

The RFA was submitted by the Cancer Biomarkers Research Group in the Division of Cancer Prevention.

The consortium currently has four projects:

- Chronic Pancreatitis—Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies
- Pediatric pancreatitis—International Study Group of Pediatric Pancreatitis: In Search for a Cure
- Type 3c Diabetes—Evaluation of a Mixed Meal Test for Diagnosis and characterization of Pancreatogenic Diabetes Secondary to Pancreatic Cancer and Chronic Pancreatitis
- New-Onset Diabetes

Ancillary CPDPC studies consist of small short or intermediate term exploratory studies that are hypothesis driven, utilize existing consortium resources, and provide future validation in prospective cohorts.

Some CPDPC exploratory studies include:

- Immune profiling in patients with RAP, CP, and PDAC Associated DM
- Investigating NMU (Neuromedin U) roles in type 3c DM associated with CP and PDAC

The New-Onset Diabetes study consists of new-onset diabetics, aged 50-85, who are at elevated risk of pancreatic ductal adenocarcinoma:

- Cumulative incidence rate over 3 years- 0.85%
- 6-8-fold higher risk of being diagnosed with PDAC within 3 years of developing diabetes
- 25-40% of patients with PDAC develop diabetes between 6 and 24 months prior to PDAC diagnosis

A cohort of 8,000 NOD patients will be recruited to the study with these goals:

- Estimating the probability of PDAC in a cohort of new onset diabetes
- Establishing a biobank of clinically annotated biospecimens, to establish a reference set of specimens for pre-diagnostic PDAC and other diabetics
- Performing validation studies of promising biomarkers for identification of occult PDAC
- Providing a platform to develop future interventional and screening protocols for early diagnosis
  - Early detection of PDAC will require asymptomatic subjects in a high-risk population
  - New-Onset Diabetics is a high-risk population

When it began in 2018, the NOD study faced difficulty in accruing patients, including delays in IRB approval and the lack of multilingual consent forms. However, recruitment pace is improving and appears promising, based on the current numbers and projection for the future.

To address the challenge of accrual, high volume sites are being identified and prioritized for greater responsibility, patient incentives are included to improve participation, and translations are provided for patient consent forms.

The goals of renewing the CPDPC Consortium include:

- Maintaining infrastructure and core facilities
- Providing a platform for clinically relevant studies using the biospecimens and cohorts accrued during the first grant cycle
- Completing enrollment and collection of biospecimens in the prospective cohort studies
- Following-up to assess clinical outcomes

The proposed budget for the RFA is $2.3M per year for supporting infrastructure—$1.8 million for 9 U01 grants for clinical centers and $500K for 1 U01 grant for a coordinating center, including institutional and personnel costs. This adds up to $11.5 million over five years.

IN BRIEF

Cathy Eng named co-leader of GI cancer program at Vanderbilt

Cathy Eng, professor of gastrointestinal medical oncology at MD Anderson Cancer Center, was recruited to Vanderbilt University Medical Center as co-leader of the VICC Gastrointestinal Cancer Research Program.

She will oversee an expansion in the clinical and research activities of the medical oncology gastrointestinal cancer disease group at Vanderbilt, as well as develop programs for adolescent and young adult oncology services.

Eng will co-lead the multi-disciplinary Gastrointestinal Cancer Research Program at VICC with Daniel Beauchamp.

Eng's work has led to numerous practice-changing outcomes, particularly with regard to the use of immunotherapy in metastatic anal cancer.

She has been at MD Anderson for 17 years, where she has served as the associate director of the Colorectal Center, chair of the Clinical Research Committee, and chair of the Multidisciplinary Colorectal Cancer Tumor Board. She has also served as the section leader for the Rare Cancers Subsection for the MD Anderson HPV Malignancies Moonshot Program.

Eng is serving a second term as NCI Rectal/Anal Cancer Task Force chair. She is the lead contact principal investigator for the NCI National Clinical Trials Network Leading Academic Participating Sites grant for two terms.

She was recently elected to the position of co-chair of the Rectal/Anal Subcommittee for the Southwest Oncology Group and serves on the ECOG-ACRIN Cancer Research Group gastrointestinal committee.

Mark Bonnen named chair of radiation oncology at UT Health San Antonio

Mark Bonnen was named chairman of the department of radiation oncology in the Long School of Medicine, effective Sept. 1.

Bonnen joins UT Health San Antonio from Baylor College of Medicine, where he founded the Department of Radiation Oncology in 2012. Since 2014, he has served as the inaugural interim chair of radiation oncology at the Dan L. Duncan Comprehensive Cancer Center at Baylor College of Medicine.

Bonnen replaces Nikos Papanikolaou, who served as interim chair of the department.

Steven Shak to receive Leadership in Personalized Medicine Award

Steven Shak, co-founder, chief scientific officer, Genomic Health, was named recipient of Personalized Medicine Co-

alition's 15th annual Leadership in Personalized Medicine Award.

After beginning his career as an assistant professor at NYU, Shak discovered and cloned the human DNase I gene during the first half of his 14-year tenure at Genentech. This discovery provided the foundation for Genentech's development of dornase alfa (Pulmozyme), the first treatment for cystic fibrosis. The therapy helped extend the life expectancy of cystic fibrosis patients significantly.

Shak turned his attention to personalized medicine while leading development of Genentech's trastuzumab (Herceptin). He spearheaded the first regulatory approval of a personalized medicine in the U.S. by shepherding trastuzumab through the FDA in 1998, five years before scientists spurred the development of additional personalized therapies by finishing the first complete sequence of a human genome.

Trastuzumab is now part of the standard of care for the 20-30% of breast cancer patients whose tumors overexpress HER2 genes.

Shak co-founded Genomic Health, where he led the development of the Oncotype IQ portfolio of diagnostic tests and services, which analyzes the genomic characteristics of cancer cells to predict how aggressively the cancer might spread, thereby sparing patients and health system from unnecessary side effects and costs.

Kim Popovits, chair of the board, CEO, president, Genomic Health, said Shak is focused on personalized medicine enabled by real-world evidence.

PMC will present Shak with the Leadership in Personalized Medicine Award during the Personalized Medicine Conference at Harvard Medical School, from Nov. 13-14.

Upal Basu Roy named vice president of research at LUNGevity

Upal Basu Roy was named vice president of research at LUNGevity Foundation.

In this role, Basu Roy will be responsible for setting the strategy and overseeing LUNGevity's scientific research awards programs, including the Translational Research Program, the Career Development Award program, research funded through the ALK Positive partnership, and LUNGevity's Patient Focused Research Center.

Under Basu Roy's leadership, LUNGevity launched the Patient-Focused Research Center in 2017, which conducts qualitative and quantitative studies on patients' unmet needs, values, and preferences.

Currently, he is managing several multi-year, patient-focused research projects in Patient FoRCE, including Project ACTs, a study with the University of Kentucky and Moffitt Cancer Center to identify barriers to adherence to lung cancer screening and developing shared-decision aids; Project Transform, a patient preference study with Johns Hopkins and Ohio State University; and Project PRIORITY, a study with the EGFR Resisters patient group to uncover the treatment experience of EGFR-positive lung cancer patients.

Thomas J. Smith awarded ASCO/ Walther Cancer Foundation palliative and supportive care award

ASCO has awarded Thomas J. Smith with its Walther Cancer Foundation Palliative and Supportive Care in Oncology Endowed Award and Lecture. Smith will accept his award and deliver a keynote address at the 2019 Supportive Care in Oncology Symposium in Oct. 25-26 in San Francisco.

"I have always felt that palliative care was simply part of oncology, and that oncologists are especially suited to providing primary palliative care," Smith said in a statement. "We know our patients and their families and are best positioned to help them cope with the successes, failures, and symptoms of cancer and its treatment. Palliative care is just good medicine and nursing—better care at a cost we can afford."

Endowed by the Walther Cancer Foundation, the award recognizes an individual who has made significant contributions to palliative care practice and research in oncology. The Walther Cancer Foundation is a private foundation that supports and promotes interdisciplinary and inter-institutional bench and clinical cancer research, with a special commitment to supportive oncology.

Work by Smith and his colleagues was the first to show palliative care at the end of life improved patient symptoms and helped patients to maintain their quality of life, while also demonstrating a significant cost savings for palliative care programs through reduced hospital admissions and other factors.

Smith is a professor of oncology at the Johns Hopkins University School of Medicine, director of Palliative Medicine for Johns Hopkins Medicine and the Harry J. Duffey Family Professor of Palliative Care.

Smith has contributed to the development of clinical guidelines; most notably he was the senior author of ASCO's guideline on the Integration of Palliative Care into Standard Oncology Care. He is also co-chair of ASCO's clinical practice guideline on the use of white blood cell growth factors.

ASCO announces Health Policy Leadership Development Program fellows

ASCO announced the Health Policy Leadership Development Program Fellows for the 2019-2020 class. Wendy Allen-Rhoades of Baylor College of Medicine, and Laura LaNiel Tenner of the Mays Cancer Center, home to UT Health San Antonio MD Anderson Cancer Center, will spend the next year developing leadership skills and healthcare policy expertise.

During their fellowship, Allen-Rhoades and Tenner will participate in ASCO efforts to shape cancer-related policies that directly affect individuals with cancer and the oncology practice environment.

ASCO's Health Policy Leadership Development Program launched in 2016 to build policy and leadership expertise among the members and volunteers. Fellows receive practical experience working with ASCO Policy and Advocacy staff and policy counsel in crafting policy positions and statements; training in communication, leadership, and advocacy; and a mentored project that advances an ASCO policy initiative. Fellows will also be full members of the ASCO Leadership Development Program.

Tenner is a medical oncologist specializing in gastrointestinal malignancies and assistant professor at The Mays Center. Her clinical focus is gastrointestinal cancers, predominantly liver, gastric, and colorectal cancers. She also has specialized training in ethics in oncology and population sciences research, with a specific focus in health care systems and cancer care improvement.

Allen-Rhoades is a pediatric oncologist, researcher, and medical director of the Adolescent and Young Adult Oncology and Soft Tissue Sarcoma Programs at Baylor College of Medicine. Her clinical research interest includes investigating ways to improve outcomes for adolescent and young adult oncology patients and her translational research efforts focus on investigating the role of microRNAs in osteosarcoma including using microRNAs as biomarkers and studying the functional roles of microRNAs in tumor and metastases development. She completed her fellowship training in pediatric hematology and oncology at Baylor College of Medicine and Texas Children's Cancer Center.

The Health Policy Leadership Development Program is open to all ASCO members who have completed their final subspecialty training between 2010 and 2015. The application period for the 2020-2021 program will open on July 1.

This program is supported by the Mission Endowment of Conquer Cancer, the ASCO Foundation.

Stephanie Dutton receives Susan G. Komen Greater Pennsylvania award

Stephanie Dutton, UPMC Hillman Cancer Center chief operating officer and vice president, received the distinguished Susan G. Komen Greater Pennsylvania Terri L. Chapman Award.

Dutton has been involved in Komen since the early 2000's and has served on the Komen Greater Pennsylvania Board for the past six years.

"My work in cancer care and at UPMC Hillman Cancer Center allows me to play a small part in the work to advance breast cancer research and provide quality patient care from an administrative standpoint," said Dutton. "I am in awe of our team and our partnership with Komen Greater Pennsylvania as we work together to bring awareness to this disease."

The Chapman award, established in 2010, is presented to individuals who demonstrate leadership qualities, impact and influence decision makers, and who support Susan G. Komen Greater Pennsylvania.

The award is named in honor and memory of Terri Chapman, a long-time leader of the Board of Directors of Komen Pittsburgh, who was instrumental in establishing Pittsburgh's full affiliation with Susan G. Komen, an organization

with a $2 million annual operating budget, serving people within a 53-county area in Pennsylvania.

Northwell opens Pancreatic Cancer Center

The Northwell Health Cancer Institute announced the opening of its new Pancreatic Cancer Center, featuring a multidisciplinary team of surgical, medical and radiation oncologists, gastroenterologists, interventional radiologists, pathologists, endocrinologists, genetic counselors, social workers, nutritionists, and pain management and palliation specialists.

Northwell clinicians leading the program were joined by a Long Island native who recently underwent surgery to remove a tumor within her pancreas, as well as representatives from Cold Spring Harbor Laboratory and the Lustgarten Foundation, which are collaborating with Northwell in the fight against pancreatic cancer.

As an integrated health system, Northwell is able to collaborate with physicians in multiple specialties and handle any other medical conditions patients may have.

At the new center, patients and their families work closely with an experienced nurse navigator who facilitates communication and guides them every step of the way, officials said.

As part of their strategic affiliation with Cold Spring Harbor Laboratory, Northwell's pancreatic cancer specialists are working closely with David Tuveson, director of the CSHL Cancer Center and chief scientist at the Lustgarten Foundation, and one of the pioneers of organoid research.

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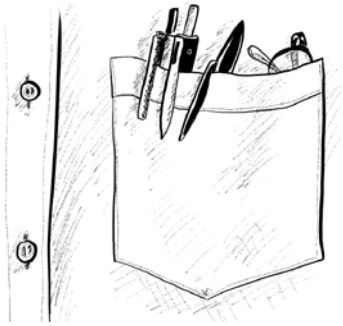
THE CLINICAL CANCER LETTER



TRIALS & TRIBULATIONS

Lessons from the front lines of value-based care: The OCM's impact on community oncology

By Charles Saunders
CEO, Integra Connect

Nearly three years after its introduction, the CMS's Oncology Care Model (OCM) remains the most ambitious and far-reaching initiative to shift cancer care toward value-based models.

The impact on community oncology, where almost 55% of U.S. cancer patients receive treatment[1], has been especially pronounced. Our experiences supporting the success of one of the largest OCM cohorts—approximately 900 providers and 25,000 patients—has enabled us to aggregate their experiences into a snapshot of the program's positive impacts, its challenges, and the broader implications for providers, pharma, and payers.

OCM participants often cite 2018 as the year that value-based cancer care became a financial and clinical reality for them. That's when they received results for their first two performance periods, covering episodes that started July 1, 2016 through 2017.

What were the primary takeaways?

- **Positive momentum in cost and quality performance.** Practices made steady progress in closing the gap between CMS's target price for chemo episodes and their actual expenditures. We saw an average 46% improvement among our cohort between the first two performance periods. This resulted from successful efforts to reduce unnecessary ER visits and inpatient stays through interventions such as care navigation and extended office hours, along with positive adjust-

> In a recent survey of practices representing 530 community oncologists, nearly two-thirds of respondents told us that pharma was not yet helping them to understand the value—and not just the cost—of their drugs.

ments for use of novel therapies and improved risk adjustments for patients with comorbidities, which was influenced by more accurate and complete coding.

- **Widespread challenges to manage drug spend.** The continued rise of exciting novel therapies—and their accompanying price tags—meant that drugs grew to more than half, and often more than 60%, of total episode costs among our client practices.
- **Difficulties identifying qualifying episodes.** The CMS paid out $160 per beneficiary per month for qualifying 6-month episodes of chemo care, enabling OCM practices to fund new staff, skills, and technology to support success. In 2018, many practices had a rude awakening when CMS deemed episodes unqualified for payments and issued demands for recoupment—on average 30% of their total payments. The disconnect stemmed from an absence of real-time patient data across care settings and inability to recreate CMS attribution logic. For example, a practice may not have known that a chemo patient generated a plurality of E/M codes with another provider treating his or her co-morbid conditions.
- **Unclear performance bonus calculation.** OCM practices found that performance-based payments were inconsistently tied to high performance on cost and quality metrics and instead were influenced more by novel therapy and local trend factor adjustments. The inclusion of claims, but not clinical data, to compare participants was also a concern.

Community oncology practices quickly internalized the lessons of OCM results in 2018 to solidify their priorities for the new year. We now see the following actions at the top of their lists.

- **Shaping the OCM's future, while applying current lessons to commercial contracts.** Community OCM practices have largely "kept the faith" about the inevitability and desirability of value-based cancer care. And the OCM, regardless of its shortcomings, remains their primary reference point. Therefore, they are banding together with leading industry groups such as the Community Oncology Alliance, Association of Community Cancer Centers, and American Society of Clinical Oncology to aggregate feedback and prescribe improvements to help the model work more sustainably. At the same time, they are bringing the basic OCM framework—episode payments plus performance bonuses when cost and quality targets are achieved—to commercial payers to launch complementary programs.
- **Implementing new programs to further decrease episode cost.** With a first wave of transformation under their belts, practices are ramping up a series of initiatives to take cost and quality to the next level. The use of care pathways, while far from new, has taken on a tangible urgency as practices seek to address the rising cost and importance of chemo and novel therapies, as well as their impact on the overall economics of cancer care and improved survival rates—especially among high-volume cancer types with high cost variance. In addition, practices are implementing risk prediction models and analytics that proactively identify patients most requiring engagement to facilitate targeted care interventions and reduce avoidable resource utilization.
- **Better managing end-of-life resources.** End-of-life care is rising in importance among OCM practices, as they improve guidelines and capabilities to care for cancer patients in the advanced stages of life-threatening illness. This includes reconsidering aggressive therapies with little hope of improving survival and instead referring appropriate patients to palliative care, hospice, or in-home care resources.
- **Considering the holistic value, not just cost, of drugs.** Community OCM practices are committed to ensuring their patients receive the right treatment at the right time, regardless of cost. However, they are now assembling a more complete and nuanced understanding of a drug's holistic value across the episodes of care for which they are now accountable. They are specifically looking for data that sheds light on quality of life alongside clinical outcomes and total cost of care.

What should other community oncology stakeholders—particularly pharma and payers—take away from OCM

participants' experiences and outlook for the year ahead?

For starters, the boundaries between the three domains are blurring. As providers assume financial as well as clinical risk, opportunities are arising to partner in new ways to achieve the quality and cost improvements that value-based care requires.

In a recent survey of practices representing 530 community oncologists, nearly two-thirds of respondents told us that pharma was not yet helping them to understand the value—and not just the cost—of their drugs. Providers are seeking new information from pharma to make informed treatment decisions, an opportunity to partner and differentiate drugs in a way that improves choice.

Likewise, pharma is also beginning to express interest in outcomes-based pricing arrangements with payers that would tie drug reimbursement rates to actual health outcomes. Moreover, commercial payers are increasingly looking for value-based care models that create real impact beyond the tacit agreements to abide by guideline-directed drug choices. In collaboration with community-based practices, payers are discussing how to leverage the Oncology Care Model's lessons to design and collaboratively launch commercial equivalents targeted at their highest-risk populations.

The OCM reaches a critical milestone in mid-2019, with participating practices required to demonstrate savings in order to proceed to two-sided risk or exit the program. Regardless of how or whether this scenario plays out, by reinforcing the core principles of the Oncology Medical Home, the OCM's impact on community oncology is established.

It has irrevocably shaped expectations for the components of fee-for-value reimbursement models; created a roadmap of practice transformation to support these expectations; influenced the implementation of enhanced services such as patient-centered care coordination; and created opportunities for new partnerships with pharma and commercial payers in order to realize value-based care's promise.

“In collaboration with community-based practices, payers are discussing how to leverage the Oncology Care Model's lessons to design and collaboratively launch commercial equivalents targeted at their highest-risk populations.”

References

1. *Fact Sheet: What is Community Oncology, Community Oncology Alliance (COA), August 2017.*

CLINICAL ROUNDUP

Study finds one in six cancer survivors reported pain restricting daily functioning

A new report finds about one in three cancer survivors (34.6%) reported having chronic pain, representing nearly 5.4 million cancer survivors in the U.S. The report, appearing as a Research Letter in JAMA Oncology, finds one in six survivors (16%), representing about 2.5 million people in the U.S., reported suffering from high impact chronic pain that restricts daily functioning. Those rates are about double the rates in the general population.

Chronic pain is one of the most common long-term effects of cancer treatment and has been linked with an impaired quality of life, lower adherence to treatment, and higher health care costs. Nevertheless, there is a paucity of information regarding the prevalence of, and risk factors for, the development of chronic pain among cancer survivors.

To gain a better understanding of the epidemiology of pain in cancer survivors and help inform future health care priorities and policies, investigators led by Changchuan Jiang of Mount Sinai Hospital, with researchers from Memorial Sloan-Kettering Cancer Center, University of Virginia, and the American Cancer Society investigated the prevalence of chronic pain among cancer survivors in the U.S. using data from the National Health Interview Survey (2016-2017).

The survey collects information related to chronic pain (pain on most days or every day in the past six months) and high impact chronic pain (chronic pain limiting life or work activities on most days or every day in the past 6 months).

Overall, 1,648 of the 4,526 cancer survivors identified in the survey (34.6%) reported having chronic pain; 768 of the survivors (16.1%) reported having high impact chronic pain. Applied to the nation as a whole, those rates equal approximately 5.39 million and 2.51 million cancer survivors, respectively, in the U.S.

Time since diagnosis was not significantly associated with the prevalence of either chronic pain, but a higher prevalence of chronic and high impact chronic pain was reported among survivors with less than a high school education (39.2% for chronic pain and 18.5% for high impact chronic pain), low household income (44.6% and 22.8%, respectively), public insurance among those aged 18-64 years (43.6% and 27.1%, respectively), or no paid employment (38.5% and 20.4%, respectively).

"Because socioeconomic status and employment are associated with insurance coverage and access to care in the United States, the patterns of chronic pain that we observed in cancer survivors may be explained by barriers to cancer care and pain management as well as by the type and extent of cancer treatment received," said Xuesong Han, American Cancer Society investigator and co-author of the report. "The prevalence of chronic pain and high impact chronic pain among cancer survivors in our study was almost double that in the general population, suggesting there are important unmet needs in the large and growing community of people with a history of cancer."

Radiation + chemo doesn't improve endometrial cancer recurrence-free survival

The standard of care for women with stage III/IVA endometrial cancer following surgery has been chemotherapy and radiation to prevent recurrence. But in a new finding, radiation combined with chemotherapy did not increase recurrence-free survival in these women.

The findings were published in the *New England Journal of Medicine*, the results of a NCI-sponsored Gynecology Oncology Group study led by Daniela Matei co-leader of the Translational Research in Solid Tumors Program at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

"The trial was supposed to be a positive trial demonstrating that the combined regimen was superior to chemotherapy given alone," said Matei, the Diana, Princess of Wales Professor of Cancer Research, a professor of Medicine in the Division of Hematology and Oncology, and a Northwestern Medicine gynecological oncologist. "Our results indicate the combined regimen of radiation and chemotherapy did not result in an improvement in recurrence-free survival, and that chemotherapy alone remains the standard of care for stage III uterine cancer."

The phase III trial randomly assigned 736 eligible patients to one of two possible treatment arms. A group of 346 received a combined treatment consisting of chemotherapy and radiation over 21 weeks, a second group of 361

women received chemotherapy alone over 17 weeks.

A median follow-up of six months after the randomized phase III trial showed the recurrence-free survival for the two arms of the trial were very similar: 59% for the group that got chemotherapy and radiation and 58% for chemotherapy alone.

Patients who received both chemo and radiotherapy had fewer recurrences in the pelvis; however this did not translate into improved recurrence-free survival, because there were relapses outside of the radiation field.

"For patients at high risk of a local relapse, radiation may be occasionally necessary to prevent pelvic recurrences," said Matei, professor of Obstetrics and Gynecology in the Division of Gynecologic Oncology.

Radiation can cause immediate as well as chronic side effects that impact the quality of life of treated patients. These include diarrhea, low blood counts, and urinary symptoms, among others.

"An important consideration is the fact that concomitant delivery of chemo and radiotherapy can result in decreased tolerance of the treatment and incomplete delivery of chemotherapy," Matei said. "More than 25% of patients assigned to the combined arm were not able to complete chemotherapy on this study."

Radiation was historically used first, before it was recognized chemotherapy has a role in the treatment of endometrial cancer. After chemotherapy was added to the treatment, radiation continued to be used as a standard approach.

The study was supported by grants CA 27469, CA 37517, 1 U10 CA180822, U10CA180868, and UG1 CA189867 from NCI.

Mount Sinai researchers show first link between exposure to dust from 9/11 attack and prostate cancer

World Trade Center responders with prostate cancer showed signs that inflammation was activated in the prostate after exposure to dust from the World Trade Center site, possibly causing chronic inflammation that contributed to their cancer, according to a study by Mount Sinai researchers in Molecular Cancer Research in June.

Inflammation has long been considered an important factor to consider in prostate cancer progression. Researchers looked into the inflammatory and immune system underpinnings of the World Trade Center responders to help prevent new prostate cancer cases in first responders and to understand how other large-scale environmental exposures to multiple carcinogens may develop into cancer.

This is the first study of people who were exposed to the World Trade Center dust and who subsequently developed prostate cancer. This research and further study of the expression of genes and pathways in other patients whose environmental exposures caused inflammation could lead to clinical trials that offer anti-inflammatory or immune targeted therapies in similar cases.

"World Trade Center responders show an overall increase in cancer incidence, and specifically of certain cancer types such as prostate cancer," Emanuela Taioli, director of the Institute for Translational Epidemiology at the Icahn School of Medicine at Mount Sinai and associate director for Population Science at the Tisch Cancer Institute, said in a statement.

"It is important to address the reasons why this is happening in order to prevent new cases in this aging cohort. Our findings represent the first mechanistic link between exposure to World Trade Center dust and prostate cancer."

This work pairs data from first responders and from a study of rats exposed to actual dust from ground zero. The dust samples, which contain metals and organic compounds, such as polycyclic aromatic hydrocarbons and polychlorinated biphenyl, are unique because they are the only samples taken on Sept. 11, 2001, that exist. All other dust samples were collected after a significant storm on Sept. 14, 2001.

Both the human and rat prostate cancer tissues show an increase in cells that indicate inflammation, specifically immune cells called T helper cells. The Sinai researchers believe that inflammation started occurring in the prostate after exposure to the World Trade Center dust, and that may have triggered chronic inflammation that contributed to prostate cancer.

"Several years ago, I saw a first responder in his 40s who began having symptoms of prostatitis, a painful condition that involves inflammation of the prostate, soon after exposure to the World Trade Center dust," William Oh, chief of the Division of Hematology and Medical Oncology at the Icahn School of Medicine at Mount Sinai and deputy director at The Tisch Cancer Institute, said in a statement.

"He ultimately developed a high grade prostate cancer several years later. It suggested to me that there might be a link between his exposure and cancer, but I knew that I would need to examine it systematically."

The study was sponsored by grants from the Centers for Disease Control and Prevention, the National Institute for Occupational Safety and Health, NIH, and the National Institute of Environmental Health Sciences.

DRUGS & TARGETS

FDA approves pembrolizumab for metastatic SCLC

FDA has granted accelerated approval to pembrolizumab (Keytruda) for patients with metastatic small cell lung cancer with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

The drug is sponsored by Merck.

Efficacy was investigated in 83 patients with SCLC who had disease progression on or after two or more prior lines of therapy enrolled in one of two multicenter, multi-cohort, non-randomized, open label trials:

- KEYNOTE-158 (NCT02628067) Cohort G;
- KEYNOTE-028 (NCT02054806) Cohort C1.

Patients received either pembrolizumab 200 mg intravenously every 3 weeks (n=64) or 10 mg/kg intravenously every two weeks (n=19). Treatment continued until documented disease progression, unacceptable toxicity, or a maximum of 24 months.

The main efficacy outcome measures were overall response rate and duration of response (modified RECIST v1.1) assessed by blinded independent central review. The ORR was 19% (95% CI: 11, 29); the complete response rate was 2%. Responses were durable for 6 months or longer in 94%, 12 months or longer in 63%, and 18 months or longer in 56% of the 16 responding patients.

Adverse reactions in patients who received single-agent pembrolizumab for previously treated SCLC were similar to those occurring in patients with other solid tumors who received pembrolizumab.

Pembrolizumab was previously granted orphan drug designation and priority review for the SCLC indication.

FDA approves Amgen and Allergan's Kanjinti, Herceptin biosimilar

FDA approved Amgen and Allergan Kanjinti's (trastuzumab-anns) for all approved indications of the reference product, Herceptin (trastuzumab) for the treatment of HER2-overexpressing adjuvant and metastatic breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Kanjinti is a biosimilar to trastuzumab, a recombinant DNA-derived humanized monoclonal immunoglobulin G1 kappa antibody. The active ingredient of Kanjinti is a humanized monoclonal antibody that has the same amino acid sequence, structure, and function as trastuzumab. Kanjinti has the same pharmaceutical dosage form and same strength after reconstitution as trastuzumab.

"Kanjinti is the third biosimilar from our portfolio to receive FDA approval, highlighting our long-term commitment to providing patients with serious illnesses access to high-quality biological therapies," David M. Reese, executive vice president of research and development at Amgen, said in a statement.

At the time of approval, Kanjinti is the only trastuzumab biosimilar to incorporate the evaluation of a single transition in the clinical study, demonstrating similar safety and immunogenicity in patients who were previously on Herceptin, the company said.

Amgen has a total of 10 biosimilars in its portfolio, three of which have been approved in the U.S. and three that are approved in the EU.

Kanjinti is currently not available commercially.

Lynparza approved in EU for ovarian cancer

The European Commission has approved Lynparza as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

The drug is sponsored by AstraZeneca and Merck.

The EU approval was based on data from the randomized, double-blinded phase III SOLO-1 trial which evaluated Lynparza as maintenance monothera-

py compared with placebo in patients with BRCAm advanced ovarian cancer following first-line platinum-based chemotherapy.

The trial results showed Lynparza reduced the risk of disease progression or death by 70% versus placebo following response to platinum-based chemotherapy (HR 0.30 [95% CI 0.23-0.41], p<0.001).

This is the third indication for Lynparza tablets in the EU. AstraZeneca and Merck are exploring additional trials in ovarian cancer, including the ongoing phase III PAOLA-1 trial, which is testing Lynparza in combination with bevacizumab as a first-line maintenance treatment for women with advanced, stage IIIB-IV high-grade serous or endometrioid, fallopian tube, or peritoneal ovarian cancer, regardless of BRCA status.

Lynparza is approved in 64 countries, including those in the EU, for the maintenance treatment of platinum-sensitive relapsed ovarian cancer regardless of BRCA status. It is approved in the U.S. as first-line maintenance treatment in BRCAm advanced ovarian cancer following response to platinum-based chemotherapy.

It is also approved in 38 countries, including the U.S., countries in the EU and Japan, for germline BRCAm HER2-negative metastatic breast cancer previously treated with chemotherapy; in the EU this includes locally advanced breast cancer. Regulatory reviews are underway in other jurisdictions for both ovarian cancer and breast cancer.

SOLO-1 was a phase III, randomized, double-blinded, placebo-controlled, multi-center trial to evaluate the efficacy and safety of Lynparza tablets (300 mg twice daily) as maintenance monotherapy compared with placebo in patients with BRCAm advanced ovarian cancer following first-line platinum-based chemotherapy.

The trial randomized 391 patients with a deleterious, or suspected deleterious, germline or somatic BRCA1 or BRCA2 mutation who were in clinical complete or partial response following platinum-based chemotherapy.

Patients were randomized (2:1) to receive Lynparza or placebo for up to two years or until disease progression. Patients who had a partial response at two years were permitted to stay on therapy at the investigator's discretion.

The primary endpoint was progression-free survival and key secondary endpoints included time to second disease progression or death, time to first subsequent treatment, and overall survival.

Lynparza is a first-in-class PARP inhibitor and the first targeted treatment to potentially exploit DNA damage response pathway deficiencies, such as BRCA mutations, to preferentially kill cancer cells, the companies said.

Lynparza approved in Japan for ovarian cancer

Japan's Pharmaceuticals and Medical Devices Agency has approved Lynparza as a maintenance treatment after first-line chemotherapy in patients with BRCA-mutated ovarian cancer.

The drug is sponsored by AstraZeneca and Merck.

The approval in Japan was based on data from the randomized, double-blinded phase III SOLO-1 trial which evaluated Lynparza as maintenance monotherapy compared with placebo in patients with BRCAm advanced ovarian cancer following first-line platinum-based chemotherapy.

Results from the SOLO-1 trial showed Lynparza reduced the risk of disease progression or death by 70% versus placebo following response to platinum-based chemotherapy (HR 0.30 [95% CI 0.23-0.41], p<0.001).

Lynparza is the only PARP inhibitor approved in Japan. AstraZeneca and Merck are exploring additional trials in ovarian cancer, including the ongoing phase III PAOLA-1 trial, which is testing Lynparza in combination with bevacizumab as a first-line maintenance treatment for women with advanced, stage IIIB-IV high-grade serous or endometrioid, fallopian tube, or peritoneal ovarian cancer, regardless of BRCA status.

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Patients who had a partial response at two years were permitted to stay on therapy at the investigator's discretion. The primary endpoint was progression-free survival and key secondary endpoints included time to second disease progression or death, time to first subsequent treatment and overall survival.

The data were presented on Oct. 21, 2018, at the Presidential Symposium of the ESMO 2018 Congress in Munich, Germany and published simultaneous-

ly online in the New England Journal of Medicine.

The SOLO-1 safety profile was in line with that observed in prior clinical trials, the sponsors said.

Myriad receives second insurance reimbursement decision for its BRACAnalysis in Japan

Myriad Genetic Laboratories Inc. said the Japanese Ministry of Health, Labour, and Welfare has granted a second manufacturing and marketing approval for Myriad's BRACAnalysis Diagnostic System as a companion diagnostic with the PARP inhibitor, Lynparza (olaparib).

Lynparza is marketed by AstraZeneca and MSD.

The decision allows physicians to use BRACAnalysis to identify women with ovarian cancer who have a germline BRCA mutation and are eligible for first-line maintenance therapy with Lynparza.

BRACAnalysis previously was approved in Japan for use in patients with unresectable or recurrent breast cancer and is the only companion diagnostic test for a PARP inhibitor to receive regulatory approval in Japan.

Myriad is commercializing BRACAnalysis in exclusive partnership with SRL Inc., a subsidiary of Miraca Group, and one of the largest laboratory service providers in Japan. According to Japan's National Cancer Center, there are approximately 10,000 patients diagnosed with ovarian cancer each year.

BRACAnalysis is a diagnostic system that classifies a patient's clinically significant variants in the germline BRCA1 and BRCA2 genes. Variants are classified into one of the five categories; "Deleterious," "Suspected Deleterious," "Variant of Uncertain Significance," "Favor Polymorphism," or "Polymorphism."

Once the classification is completed, the results are sent to medical personnel in Japan for determining the eligibility of patients for treatment with Lynparza.

Myriad has been collaborating with AstraZeneca since 2007 on the development of companion diagnostics for Lynparza. BRACAnalysis CDx was approved by FDA in December 2014 for patients with advanced ovarian cancer and again in January 2018 for patients with HER2-negative metastatic breast cancer. The test is marketed in the U.S. as BRACAnalysis CDx.

Lynparza is the first approved oral poly ADP-ribose polymerase inhibitor and the first targeted treatment to potentially exploit DNA damage response pathway deficiencies, such as BRCA mutations, to preferentially kill cancer cells.

Specifically, in vitro studies have shown Lynparza-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and cancer cell death.

Lynparza is being investigated in a range of DDR-deficient tumour types and is the foundation of AstraZeneca's industry-leading portfolio of compounds targeting DDR mechanisms in cancer cells. Lynparza is a registered trademark of AstraZeneca.

In July 2017, AstraZeneca and Merck announced a global strategic oncology collaboration to jointly co-develop and co-commercialize Lynparza.

Gilead, Nurix form collaboration to develop cancer therapies

Gilead Sciences Inc. and Nurix Therapeutics Inc. formed a collaboration to discover, develop, and commercialize a pipeline of innovative targeted protein degradation drugs for patients with cancer and other challenging diseases.

Nurix's technology platform is focused on the manipulation of the ubiquitin system and its component E3 ligases, the key enzymes responsible for controlling protein levels in human cells.

Under the collaboration, Nurix will utilize its proprietary drug discovery platform to identify novel agents that utilize E3 ligases to induce degradation of specified drug targets.

Gilead will have an option to license drug candidates directed to up to five targets resulting from the work. Nurix will retain the option to co-develop and co-detail up to two programs in the U.S. The collaboration excludes Nurix's lead degradation program, for which Nurix retains all rights.

Under the agreement, Nurix will receive an upfront payment of $45 million and will be eligible to receive up to approximately $2.3 billion in total additional payments based on the successful completion of certain research, pre-clinical, clinical, regulatory, and commercialization milestones as well as up to low double-digit tiered royalties on net sales.

For those programs that Nurix opts in to co-develop and co-detail, the parties will split development costs as well as profits and losses 50/50 for the U.S., and Nurix will be eligible to receive royalties on ex-U.S. sales and reduced milestone payments.