



TCL

THE CANCER LETTER

Inside information on cancer
research and drug development

Vol.

45

No.

10

MARCH 8, 2019

www.cancerletter.com

TRUMP'S PROPOSAL FOR PEDIATRIC CANCER HAS NCI ENVISIONING THE FIRST DATA FEDERATION OF ITS KIND

In anticipation of an infusion of funds from Congress, NCI is developing a blueprint for a comprehensive cancer data federation—starting with pediatric cancer.

→ PAGE 4

SHARPLESS: WITH \$500 MILLION, NCI CAN CREATE DATA FEDERATION THAT WOULD CHANGE RESEARCH IN CHILDHOOD CANCER

→ PAGE 10

NEEDED: A FULLY FUNDED DATA FEDERATION FOR PEDIATRIC CANCER WITH DEEP GENOMIC SEQUENCING AND CLINICAL RECORDS

→ PAGE 28

NEWS ANALYSIS


GOTTLIEB RESIGNS AT FDA, RECOMMENDS SHARPLESS AS SUCCESSOR

→ PAGE 30

IN BRIEF

RAYMOND DUBOIS RECEIVES AACR MARGARET FOTI AWARD

→ PAGE 33



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COVER STORY

- 4** Trump's proposal for pediatric cancer has NCI envisioning the first data federation of its kind
-

CONVERSATION WITH THE CANCER LETTER

- 10** Sharpless: With \$500 million, NCI can create data federation that would change research in childhood cancer
- 17** CHOP's Resnick: Big data will transition from research to the standard of care in the clinic
- 24** St. Jude's Roberts: "No single institution can maximize cures and minimize toxicities alone"
-

GUEST EDITORIAL

- 28** Needed: A fully funded data federation for pediatric cancer with deep genomic sequencing and clinical records
-

NEWS ANALYSIS

- 30** Gottlieb resigns at FDA, recommends Sharpless as successor
-

IN BRIEF

- 33** Raymond DuBois receives AACR Margaret Foti Award
- 33** Charles Sawyers to present AACR Princess Takamatsu memorial lecture
- 34** Alberto Mantovani receives Pezcoller Foundation-AACR Award

- 34** Jeffrey Bluestone to receive AACR-Irving Weinstein Foundation lectureship award

- 35** Manuel Hidalgo named chief of hematology and medical oncology at Weill Cornell

- 35** Greg Delgoffe to receive Sy Holzer Endowed Immunotherapy Research Fund
-

FUNDING OPPORTUNITIES

- 36** FDA Oncology Center of Excellence publishes research contract opportunities

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

- 37** Genentech submits sNDA for Venclexta plus Gazyva for previously untreated CLL
- 37** Study: AI may perform as well as radiologists
-

DRUGS & TARGETS

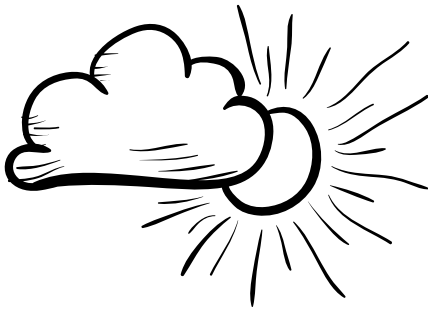
- 38** Paige.AI receives FDA Breakthrough Device designation
- 38** Lynparza receives positive EU CHMP opinion in breast cancer
- 39** Breast Cancer Index receives expanded Medicare coverage
-

NCI TRIALS

- 40** NCI Trials for March

TRUMP'S PROPOSAL FOR PEDIATRIC CANCER HAS NCI ENVISIONING THE FIRST DATA FEDERATION OF ITS KIND

By Matthew Bin Han Ong



In anticipation of an infusion of funds from Congress, NCI is developing a blueprint for a comprehensive cancer data federation—starting with pediatric cancer.



“I think data aggregation, data federation, is something we need throughout cancer research, but it’s a particularly pressing need in pediatric cancer research,” NCI Director Ned Sharpless said to The Cancer Letter in his first detailed comments on this issue.

The data federation that NCI has in mind would allow researchers to move seamlessly between types of data—clinical records, genomic information, pathology and outcomes data—as well as through different platforms where databases are stored, be they in Bethesda, Philadelphia or Memphis.

“We envision this to be a very high-grade dataset that will be useful for real cutting-edge translational and basic research,” Sharpless said. “This quality, this size, this scope doesn’t exist in any area of biomedical research.

“And so, this is an important first step in learning how useful radical data sharing and aggregation can be. Therefore, we really expect it to inform not just childhood cancer, but every kind of cancer.”

A conversation with Sharpless appears on [page 10](#).

NCI’s plans, developed over the past month with key players in childhood cancer, are a response to a pledge by President Donald Trump to dedicate more federal funds to pediatric cancer research (The Cancer Letter, [Feb. 8](#)).

“Many childhood cancers have not seen new therapies in decades,” Trump said at his State of the Union address Feb. 5. “My budget will ask the Congress for \$500 million over the next 10 years to fund this critical life-saving research.”

Trump is expected to release his budget proposal on March 11. If congressional appropriators concur with his request, insiders anticipate that these funds would be added to NCI’s budget. At this writing, it’s not publicly known whether the president will seek an increase for

NIH and NCI, or whether he will propose dramatic cuts, as he has in the past two years (The Cancer Letter, [Feb. 16](#), 2018, [May 26](#), 2017).

“The support [for pediatric cancer research] that the president suggests—\$500 million over 10 years—is wonderful and appreciated, but that is not enough money to boil the ocean in terms of big data,” Sharpless said. “But \$50 million a year for 10 years is a significant investment. I mean, that would help a lot. Certainly, Congress decides the appropriation, were they to give us more, we’d find a use for it. I mean, NCI could always use more support for great cancer research.

“For this to be successful, we have to leverage existing investments and make sure we use the datasets that are already out there and try and link them, and get data and pull data from them to get into this common aggregated and federated dataset that lives in the cloud.”

The pediatric cancer community is in universal agreement that the data needs for childhood cancer research are not currently met, said Adam Resnick, director of the Center for Data Driven Discovery in Biomedicine at the Children’s Hospital of Philadelphia and scientific chair for several consortia-based efforts, including the Children’s Brain Tumor Tissue Consortium and Pacific Pediatric Neuro-Oncology Consortium.

“Through such integrative efforts that look at leveraging a tremendous opportunity to think about pediatric cancer anew—in ways that leverage emerging data-science supportive technologies, cloud-based resources, and community engagement—I think this can really transform the research landscape in terms of its capacity to accelerate discovery, diagnostics, and have immediate impact in the context of clinical translation, potentially prospectively for each and every individual patient

across the U.S.,” Resnick said to The Cancer Letter.

“For us, it’s extremely exciting to hear and see both the NCI and the administration and other community partners and patient groups really coming together and reconsidering, ‘What are the unmet needs that can inform in new ways through new approaches of integration?’

“This is a time of new technologies, new initiatives and efforts, the emergence of an NIH data commons landscape, the ongoing growth of efforts of the NCI in terms of establishing and developing a data commons framework, the proposed new resources and influx of funding provide, and just-in-time opportunity for our community to engage in defining how all these parallel and intersecting efforts can be brought to bear in the context of the pediatric enterprise and the translation to impact.”

A conversation with Resnick appears on [page 17](#).

Sharpless said the data federation would build on existing initiatives at NIH and NCI—including the Cancer Research Data Commons, the Genomic Data Commons, TARGET, the pediatric version of The Cancer Genome Atlas, as well as the Gabriella Miller Kids First Pediatric Research Program, a trans-NIH initiative that receives \$100 million over 8 years through the Kids First Research Act.

The institute would also leverage collaborations with academic institutions and research networks, including St. Jude Children’s Research Hospital, the Children’s Oncology Group, and CHOP.

“None of these existing things are perfect,” Sharpless said in an interview. “They all have some aspects of the elements we want, but by putting them all together and making them searchable—the vision is that you would just go in as a researcher and look for, say,

who with neuroblastoma responds to adriamycin. And you would know if that was a St. Jude's patient, or a COG patient, or wherever the source came from."

Private sequencing companies, including Foundation Medicine, would likely play a role in the data federation as well.

"I think everything's on the table as to how we build this out. It is unimaginable to me, given the expertise that exists for data analysis and data aggregation in the private sector, that we wouldn't be relying heavily on industry partners for some aspects," Sharpless said. "Once the common structure is there, it allows everybody to contribute data to the sandbox and all things work better."

Among international stakeholders, The World Health Organization would be a key partner—in September 2018, St. Jude and WHO formed a collaboration that aims to cure at least 60 percent of children with cancer worldwide by 2030 (The Cancer Letter, [Oct. 12, 2018](#)).

St. Jude launched its own data-sharing platform, St. Jude Cloud, in April 2018. To date, the platform is the largest public repository of pediatric cancer genomics data, with 5,000 whole-genome, 5,000 whole-exome, and 1,200 RNA-seq datasets. The Memphis, TN, hospital expects to make 10,000 whole-genome sequences available later this year.

"St. Jude Cloud is the world's largest repository for pediatric cancer genomics data, including pediatric cancer and cancer survivorship data," said Charles Roberts, executive vice president, director of the Comprehensive Cancer Center, and director of the Molecular Oncology Division at St. Jude. "This also reveals the thirst for data sharing as, since its launch less than a year ago, more than 800 people from over 400 institutions have registered. They get immediate access to data in the cloud that previously would have taken weeks to download."

A conversation with Roberts appears on [page 24](#).

The data federation should complement other existing efforts through coordination of resources, since NCI is already dedicating over \$2 billion over 10 years for pediatric cancer, including funding from the Beau Biden Cancer Moonshot, said Vincent Miller, chief medical officer of Foundation Medicine.

"One of the key things in any of these efforts is not to let perfection be the enemy of excellence," Miller said to The Cancer Letter. "And that being said, the pediatric space is unique in that patients tend to be cared for in a much more manageable and more uniform way as far as number of institutions, number of EMRs, clinical trial participation, etc., than in the adult oncology ecosystem."



We envision this to be a very high-grade dataset that will be useful for real cutting-edge translational and basic research. This quality, this size, this scope doesn't exist in any area of biomedical research.

— Ned Sharpless



"Certainly, at Foundation Medicine, we provide genomic data on a large number of patients dealing with pediatric cancer. A couple of thousand patients are actually on our website. They're formatted for researchers as part of a portal."

In July 2016, Foundation contributed 18,000 cases to NCI's Genomic Data Commons, without remuneration (The Cancer Letter, [July 29, 2016](#)).

"We've been big supporters of these types of initiatives on the pediatric front," Miller said. "We've got the ap-

propriate template agreements in place. We've got precedent for doing this. We've shared and worked through some of the glitches that are always common in large data transfers. So, we're certainly excited to both contribute to the discussion but also contribute meaningfully on the data front."

The childhood cancer community will benefit from NCI's vision to create a broader data federation for cancer research, said Peter Adamson, chair of the Children's Oncology Group and professor of pediatrics at CHOP.

"I don't think there's any question that there's going to be some return on the investment to do that," Adamson said to The Cancer Letter. "Part of this discussion, which is an important discussion to have, is it's always great that the

president brought childhood cancer and the problem of childhood cancer to the forefront, which is always welcome.

"But, we also need to have a robust budget for the NCI as a whole. If we're unable to grow the NCI budget as a whole, I think childhood cancer is going to be challenged, along with other cancers. So, I don't think you could do one without the other, and obviously doing both would be ideal. But I don't think you can shrink the NCI budget and have as much of an impact with \$50 million a year for childhood cancer."

NCI needs to invest more in epigenetics and research on outcomes of children with cancer, Adamson said.

“There are still many cancers where we don’t know the drivers. It’s not revealed

Sharpless said. “But I think it’s also important to say that this initiative would not only facilitate and improve survivorship research and biospecimen analysis, but I think it really helps with every area of pediatric cancer research.”



One of the key things in any of these efforts is not to let perfection be the enemy of excellence. And that being said, the pediatric space is unique in that patients tend to be cared for in a much more manageable and more uniform way as far as number of institutions, number of EMRs, clinical trial participation, etc., than in the adult oncology ecosystem.

– Vincent Miller



by sequencing and it may as well be in the epigenome,” Adamson said. “So, I do think there’s a need to build upon some existing infrastructures that do capture biospecimens and outcomes and making sure that we are able to learn from every child with cancer in the country by building up.

“And that’s part of the related STAR Act: Survivorship, Treatment, Access, and Research. It’s to make sure that we have a biorepository system that can help feed investigator-initiated research as well as other initiatives.”

NCI’s new data initiative will also build upon survivorship and biospecimen collection efforts funded through the STAR Act, which authorizes NCI to spend up to \$30 million per year over 5 years, beginning in 2019.

“I think the STAR Act is, in some ways, a great taking-off point for this initiative,”

The genomic characterization of pediatric cancers has allowed researchers to understand, in reasonable detail, what drives childhood malignancies both at diagnosis and at relapse.

“There’s plenty of evidence in the pediatric context that targeted-based approaches or precision-based approaches that are defined by molecular context are extremely effective,” CHOP’s Resnick said.

“What we’re now finding is that what has been pathologically described as one disease is potentially five or six or 11 different diseases, when you start looking at the detailed molecular biology,” Resnick said.

“And that presents a challenge for a whole new type of way of thinking about creating the kinds of clinical trials where the right patients are selected for the trials in ways, that with smaller

numbers, are more likely to actually achieve meaningful, statistically significant results, as supported by molecular definition of disease.”

With funding support from the Moonshot, NCI is investing in fusion oncoproteins, a driver for many childhood cancers, COG’s Adamson said.

“One of the classic ones is in Ewing sarcoma with EWSR1,” Adamson said. “We still haven’t come up with a therapeutic approach, even though we’ve known about this for well over 20 years.

“Because childhood cancers don’t undergo a long evolutionary period, many occur within a short developmental period and not from years or decades of exposure. When you do find an aberration, it’s more likely to be fundamental to the malignant process than for potentially cancers that have accumulated many, many aberrations and knowing what the drivers are is far from trivial.

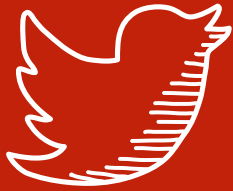
“What we often argue, in part, is when we find something in a childhood cancer that is a target in driving a cancer, it’s often fundamental and can apply more broadly than to the rare childhood cancer. So, I do think defining that landscape often points to clear drivers.

“I think what we’ve also learned is that the initial sequencing efforts are not going to uncover everything we wanted to know as far as what the drivers are. And I think that’s right now where there’s increasing interest in the epigenome.”

There is likely a need for more comprehensive clinical genomics that can be linked directly to clinical care and implementation, Resnick said.

“I think what we’re finding more and more is that more comprehensive processes that essentially look at the entire genome—like a whole-genome sequencing, as opposed to a whole-exome or a panel—provide a larger amount of

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information that can complement current clinical efforts,” Resnick said.

“I think there’s a lot of interest, by our community, in thinking about comprehensive clinical data generation, and this is driven in part by the recognition that the cost of large-scale clinical data generation is now dropping in ways that it will indeed be feasible for clinical whole genome sequencing, for example, to occur within a short period of time. Big data is set to transition from largely occurring in the context of research to, in the very near future, be the standard of care in the clinical context.

“And so, many in our community recognize that it won’t be too long before, for example, clinical whole genome sequencing combined with RNA-seq is the starting digital footprint of an electronic health record in ways that would suddenly make big data a daily reality that right now is still largely restricted by our community to research-grade data sets.”

At St. Jude, whole-genome sequencing and whole-exome sequencing have a minimum of 30X and 100X coverage, respectively, which is the standard used for cancer genomic research, said St. Jude’s Roberts.

“The current coverage provides us with 90 percent of the power for identifying mutations present in 20 percent of the bulk tumors and deep sequencing by panel may enable discovery of additional variants present in smaller sub-clones,” Roberts said. “For others, provision of panel data or exomes enables new discoveries. We are in the process of learning tumor heterogeneity by performing single-cell DNA and RNA sequencing.

“While in 2019 we understand the genetics of cancer so much better than a few years ago, we still have a long way

to go. Increasingly we’re learning that there are numerous cancer-driving mutations that can only be identified via the combination of RNA-seq and/or whole genome data. And additional information can come from methylation and ATAC-seq analyses.”

In his State of the Union address, Trump seemed to make a significant personal commitment to the \$500 million, said Nancy Goodman, founder and executive director of Kids v Cancer.

“He brought out a beautiful girl who survived cancer, inspirational Grace,” Goodman writes in a guest editorial for The Cancer Letter. “The president asked us to be emotionally invested in Grace, as he was. He told us that ‘nurses and doctors cried when Grace finished chemo.’ He concluded: ‘Grace—you are an inspiration to us all.’”

Goodman’s guest editorial appears on [page 28](#).

“NCI has a terrific project for the funds—a clinical database of pediatric cancer with deep genomic sequencing, clinical records, and data federation,” Goodman writes. “The private genomic sequencing and big data industry’s expertise and resources could be used to help design, build and populate this dataset.

“If we don’t get new funds—meaning the \$50 million per year above the \$30 million Congress authorized under the Childhood Cancer STAR Act, then Grace was just emotional bait. That would be really lousy. The president’s offer will have been a cheap shot, an exploitation of Grace and of all of us whose children have been treated for or have died of cancer.”

A large, white, serif capital letter 'Q' is positioned in the upper right quadrant of the page. The letter has a classic, slightly rounded top and a long, elegant tail that curves downwards and to the right.A large, black, serif ampersand (&) is positioned in the middle left quadrant of the page. The ampersand is highly stylized, with a prominent loop on the left side and a sharp, pointed tail on the right.

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

A large, white, serif capital letter 'A' is positioned in the lower right quadrant of the page. The letter is a classic, slightly flared serif 'A' with a clean, balanced design.



CONVERSATION WITH
THE CANCER LETTER

Sharpless: With \$500 million, NCI can create data federation that would change research in childhood cancer

“

If this effort is highly successful for childhood cancer, then we'll broaden the efforts to other cancers next. This is an important first step in learning how useful radical data sharing and aggregation can be.

”



Norman E. Sharpless
Director, NCI

Matthew Ong: The White House has promised \$500 million over 10 years for childhood cancer—whether or not Congress appropriates these funds, it sounds like the pediatric cancer community is in agreement that greater investment is needed in data aggregation and sharing. Are the data needs for childhood cancer being met currently?

Ned Sharpless: This is an area of unmet need. Not solely for childhood cancer, but across all cancers. I think that radical data federation involves multi-level aggregation of data from a variety of sources—genomics, clinical data, radiology, histology.

We don't really have datasets like that for any population of cancer patients. And I would argue we need it, particularly, if you think about every childhood cancer being a rare cancer, essentially. If cancer is a heterogeneous disease, we really need information on small populations.

I think pediatric cancer's a great place to start out, because the number of cases is lower—it's about 16,000 a year. Also, I think there's tremendous frustration in the pediatric advocacy community that we haven't been doing a better job of data aggregation and data sharing. And so, there's a real desire to do more here, and this is a population that is engaged in the issues related to data sharing and data privacy that are important in an effort like this.

And, importantly, it's hard to do clinical trials and traditional sorts of studies in these populations, where every childhood cancer is a rare cancer. So, you really have to learn from every child with cancer. That's critical. There's no luxu-

ry of saying, "Well, we can just study part of the population, because it's so large." That's not the case with childhood cancer. I think data aggregation, data federation, is something we need throughout cancer research, but it's a particularly pressing need in pediatric cancer research.

What are some challenges that are unique to aggregation of data in pediatric cancer?

NS: I think there are a number of challenges to data aggregation in general. There are rules about data sharing and data privacy. There is the issue of data hoarding that groups have with data. I think that problem is probably over-advertised. It's not as bad a problem as maybe some people believe, but it is still a problem.

Probably the biggest challenge about data aggregation in general—and this is not unique to pediatric cancer data—it's just a lot harder to do than you might imagine.

There are a bunch of weedy, complex issues that make sharing data hard. Even when everybody wants to share, and we're allowed to share, and the consent is proper, and all these kinds of complex issues are okay, getting all the data in a way that you want it, that you can link it to the various sources and abstract from electronic health records and put those clinical data in, and making all of those pieces talk to each other in a way that's safe and secure, and ensures patient privacy, that's just really hard to do.

But when you do that, the thing you get out of that effort is greater than the sum of its parts. You get these abilities to see what genetic lesions correlate with what histologic features of the tumor, correlate with what sorts of outcomes in the patients. And so, you really can

get a lot more out of the data when it's aggregated and federated in this way.

You know, we have a demonstration project, if you will, of the utility of big data in cancer research, and that's The Cancer Genome Atlas. TCGA has been wildly successful from NCI's point of view.

But that's just genomic data. It's been used for thousands of publications for research efforts that we never even imagined that it would be used for—going even beyond cancer research.

And so, the next level of that experiment is if genomic data's good, what happens when you take genomic data to the 10th power?

So, that's really the intent of this effort. And we think pediatric cancer's a great place to start, because the system is already set up to care for these kids in a more networked manner than adult patients, and it's an unmet need.

If the funding comes through, would NCI and the community be aiming for a clinical-grade database, or a research-grade data commons?

NS: I don't think I would call it solely a pediatric data commons, because when I think of the cancer research data commons that we've been working on hard—including with Moonshot funding—that is a set of datasets.

If we called each one of those datasets a "node," The Genomic Data Commons is one node.

There are several others—there's the clinical data, the genomic data, the imaging, cohort data, and other sorts of data. Each one of those nodes can be looked into and searched by a com-

mon overarching metadata aggregator that can then pull out the radiology and histology and clinical outcomes and genomics of a specific patient, for example—or specific set of pediatric cancer patients.

I don't think you would want to create a special little pediatric node that would be walled off and separate from that greater ocean of data, because the problem with that is that it won't be used to the same extent as that greater ocean of data.

So, rather than create its own special walled off node, the idea is to make that infrastructure, that framework I described to work better, and then to actually get a lot of the data. We need to sequence the tumors. We need to extract the clinical charts. We need to upload the medical images. We need to get all those data and put it in a place where researchers can use it.

We envision this to be a very high-grade dataset that will be useful for real cutting-edge translational and basic research.

It would be data de-identified, private and secure, and so, it would be a research-grade dataset to stimulate clinical research in some settings.

To make sure I understand this correctly: we're talking about a broad vision here, but with childhood cancer as an entry point, right?

NS: Right.

I think one could argue that if this effort is highly successful for childhood cancer, then we'll broaden the efforts to other cancers next.

But in a way, it turns the clinical trials framework on its head.

When you have a lot of patients with the same disease, it's easier to test therapies. And in that setting, complexity is the enemy; right?

You want to have all the patients be alike and as similar as possible and get the same therapy, plus/minus one modest change to test, if it works. And that's how we've made progress in more common diseases for decades.

But when you're talking about the other end of the spectrum of rarer cancers and molecularly defined subtypes, and that's where we're going in oncology for all kinds of cancer, not just childhood cancer.

As we talk about molecular defined subtypes that are rarer and rarer, it's harder to use that traditional clinical trials framework.

What you need to do instead is follow every patient, learn as much about every patient as you can, and this sort of real world evidence framework.

And then, figure out why they respond, from analyzing these sort of aggregated datasets. We think this is the frontier of cancer research in general, and as I said, pediatric cancer's the right place to start.

What are some of the existing initiatives that NCI can currently link? Within NCI, or maybe beyond NCI?

NS: That's a really good question.

I mean, the support that President [Donald Trump] suggests—\$500 million over 10 years—is wonderful and appreciated, but that is not enough money to

boil the ocean in terms of big data. As I said, big data's much more expensive than you might imagine. And the NCI has a lot of experience with these data initiatives, and we know what this costs.

So, really, for this to be successful, we have to leverage existing investments and make sure we use the datasets that are already out there and try and link them and get data and pull data from them to get into this common aggregated and federated dataset that lives in the cloud.

So, there are things like the TARGET dataset, that's the pediatric version of The Cancer Genome Atlas, that's 3,400 sequence cases. That's genomic data.

There's the Gabriella Miller Kids First data resource, which has got some germline data in it and first-degree relatives. St. Jude [Children's Research Hospital] has a lot of patients that are sequenced with some clinical annotation, and so, we've been having a lot of discussions with them.

The Children's Oncology Group has Project:EveryChild that NCI supports. That's got a lot of stored samples and some clinical annotation, and most of those children were treated on clinical trials.

None of these existing things are perfect. They all have some aspects of the elements we want, but by putting them all together and making them searchable—the vision is that you would just go in as a researcher and look for, say, who with neuroblastoma responds to adriamycin.

And you would know if that was a St. Jude's patient, or a COG patient, or wherever the source came from.

We also, by the way, are thinking about how we would collaborate with international stakeholders. There are a lot of other countries that want to do better with their pediatric cancer data. The

World Health Organization has a major initiative.

And because the cases in pediatric cancer are rare, getting more data from other countries is a useful thing. There are some challenges unique to global data sharing, but for pediatric cancer, some uses of international data will be important, too, we think.

And might this also be an opportunity for public-private partnership, if the money comes through?

NS: I think everything's on the table as to how we build this out.

It is unimaginable to me, given the expertise that exists for data analysis and data aggregation in the private sector, that we wouldn't be relying heavily on industry partners for some aspects—be that as a contractor to help us extract the data from the charts, or as a cloud resource provider to help support some of the systems, or a machine learning company to help do cutting-edge analysis.

I think we will have specific tasks that will require industry partnerships, as well as many academic partnerships, and partnerships with the cancer advocacy community.

I think all of those things are likely to be an important part of this. Once you have the infrastructure built, say, you want to get some sequencing data, it's possible for a separate initiative.

Companies and organizations that sequence tumors, they can put their data in our dataset. So, once the common structure is there, it allows everybody to contribute data to the sandbox and all things work better.

Where is NCI currently in terms of its capacity to do sequencing? Would it be useful to have really deep genomic sequencing, whole genome and exome sequencing?

NS: We have sequenced a number of patients, and we have access to sequences done by others for a number of patients.

But I think you're right, some of the money for this effort would also be used to pay for additional sequencing.

But I want to be clear, not most of the money.

This is not TARGET II, a sequencing effort. This is just to fill out some key datasets where we feel like the sequencing data were missing.

I think the kinds of sequencing we would need would be minimum analysis of DNA, which could be for kids a whole genome is more important, because they have structural variance and other things that are harder to find with whole exome.

I think we'll need some germline sequencing, and already have a lot of germline sequencing, but we'll need to do that as well.

But I think, importantly for kids, the tumors tend to have fewer mutations and often, certain subtypes the driver mutation tends to be the same thing over and over again. So, DNA sequencing is not generally enough for this population.

You need some assessment of the epigenetic state of the tumor through either RNA sequencing, and/or dedicated analysis of chromatin.

So, we think some sequencing will be required. Obviously, we have a lot of sequencing data already that we will use and aggregate in these datasets.

And, of course, other groups will sequence and contribute those data. But it's likely we'll continue to need more sequencing, particularly to get at the epigenetics data of the cancer. That'll be really important.

How would you describe the impact of in-depth genetic analysis in the pediatric space? Have we long ago moved past establishing proof of principle as we know it, and is the impact meaningful and substantive?

NS: I think there has certainly been successes from genomic characterization from pediatric cancer.

So, the appreciation that there are rare responders to pediatric immunology approaches—these kids with microsatellite instability, the MSI-high tumors.

Usually, pediatric cancers don't respond to those drugs, but there are rare patients that do, they're identified through sequencing.

I think the appreciation of out translocations and certain neuroblastoma, and other kinase targets that were identified for adult cancer were then validated as pediatric targets through sequencing efforts.

But something that still happens today is, you have drugs that work in kids, where the children respond—in some cases very nice responses—and we don't know why. It's not really specified by any DNA mutation.

So, there are patients that respond to a drug like adriamycin or a treatment like radiation therapy, and we can't predict that solely by analyzing the DNA.

So, there is more molecular information we need about those patients to really predict who's going to respond—to solve this key question in clinical oncology, this decision problem of, how do you decide what drug to give a patient first?

That is a huge problem not only for kids, but also adults. And we really can't answer it. Our ability to predict response is still very limited, and as you know, highly impure.

We treat people two months, we get a CAT scan and see that the tumor didn't shrink. That's the most frustrating thing in the world as an oncologist, to give someone months of ineffective therapy.

So, I think this is an opportunity to try to figure out: What do you need to know about a child's tumor, what molecular information do you need to know?

Or maybe it's not just molecular information. Maybe radiology helps. Maybe clinical features help, etc.

What set of information do you need to know to predict what therapy's going to work best?

Since this is all going to require significant investment—and we have a proposed \$50 million a year—if you could submit a budget request, what would be the ideal amount?

NS: As I said, big data's very expensive. But \$50 million a year for 10 years is a significant investment. I mean, that would help a lot.

Certainly, Congress decides the appropriation, were they to give us more, we'd find a use for it. I mean, NCI could always use more support for great cancer research.

I think one part of the portfolio that would be really important is the ability to give some research grants. So, some of the funding would go to research initiatives both in terms of analyzing data using novel techniques, so fund people to do cool machine learning or artificial intelligence approaches to data analysis.

But also, to use these datasets we create for specific purposes, like try to understand response to therapy, or try and find a new target for drug development using these federated datasets.

And to that grants portfolio, that could be augmented with additional funds. The more we could spend on investigator-initiated research in the community, the better we do, I think, in cancer research.

So, that's part of it. I think there are lots of other portions of the data initiative that could be built out based on what Congress decides to appropriate.

This might be a question for Congress as well, but as you know, the STAR Act is authorized to spend \$30 million per year over 5 years for the creation of a biorepository. Should that money be separate, or used together with this? What are the chances that the \$500 million might come through as new cash?

NS: The STAR Act has some broad direction for HHS, and NCI's part is fo-

cused on biospecimen and survivorship research.

We have already begun implementing the STAR Act with specific funding opportunities in FY 2019 and have some great stories that we'll be able to talk about as those funding announcements get a little further along, and when some of the new projects are really built out.

And that's really a great thing. We needed a better survivorship portfolio and better biospecimens collection.

But this effort, this new initiative will then build upon that framework, that foundational work. And really be sort of a force multiplier, if you will, for that effort.

Because, if you think about it, you collect all these biospecimens, but then you need additional money to sequence them and to clinically annotate them, and to get the radiology images, and to put all the data somewhere where people can use it.

That's why data sharing's so expensive; just having the piece of tumor is a very early part of the whole analysis. And we need to do everything.

And so, I think the STAR Act is, in some ways, a great taking-off point for this initiative. But I think it's also important to say that this initiative would not only facilitate and improve survivorship research and biospecimen analysis, but I think it really helps with every area of pediatric cancer research.

If you're interested in response to therapy or pathogenesis, you're interested in why kids got these cancers to begin with, or you're interested in disparity populations within pediatric cancer.

These are all things that are hard to study because pediatric cancers are rare. But a big data initiative allows you

to work on almost any area of childhood cancer research, including the laudable goal of advancing survivorship research.

What are the next steps towards making this an effective initiative?

NS: We are already working on these ideas—NCI has a robust portfolio of childhood cancer research and we're already starting to meet internally and with stakeholders to talk about how we can really facilitate the big data initiative in childhood cancer.

Of course, dedicated funding is important and we won't know that until the FY 2020 appropriations process is complete.

We plan to convene a meeting asking stakeholders as well as data experts to come to the NCI sometime in the next couple of months to talk about where are the opportunities?

And hopefully as we have a better idea of what type of funding might be possible, the size of the opportunity will come better into focus.

But this is an area the NCI's really focused on.

As you know, one of my key focus areas when I came here—that I've been talking about non-stop for 15 months—has been data, using big data better. And we think pediatric cancer's a really great place to apply some of those principles.

So, we're going to do this to some extent, but obviously, new funding from Congress would really be appreciated and speed things along.

Did I miss anything?

NS: Let me say one other very important thing, which is that we've never really had a dataset like this.

This quality, this size, this scope doesn't exist in any area of biomedical research. And so, this is an important first step in learning how useful radical data sharing and aggregation can be.

Therefore, we really expect it to inform not just childhood cancer, but every kind of cancer.

I think that studies done with these multimodal datasets will benefit non-malignant disease, will have implications for things that aren't even cancer, just the way that The Cancer Genome Atlas has been used for lots of purposes that have nothing to do with cancer.

So, I think these big datasets are very valuable and useful, and I think childhood cancer is the pilot phase. But we envision that what we learn from this effort will be useful well beyond childhood cancer.

And also doing it in a federated way, which would also be a new way of doing things.

NS: Yes, the machine learning community's really coming to us, and they're saying, "We can't use our cool artificial intelligence technology if you just have radiology and no clinical information. Or you just have pathology and no response data. Or you just have the genomics."

Their modern, cutting-edge analytic tools really work better in these robust multi-modal datasets, and I fully agree with that. I think as you start adding these things together, it's not really just additive, it's sort of an exponential growth and utility.

I think this effort could be a game changer for childhood cancer patients, and I'm excited about what we can achieve.

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Resnick spoke with
Matthew Ong, a reporter with
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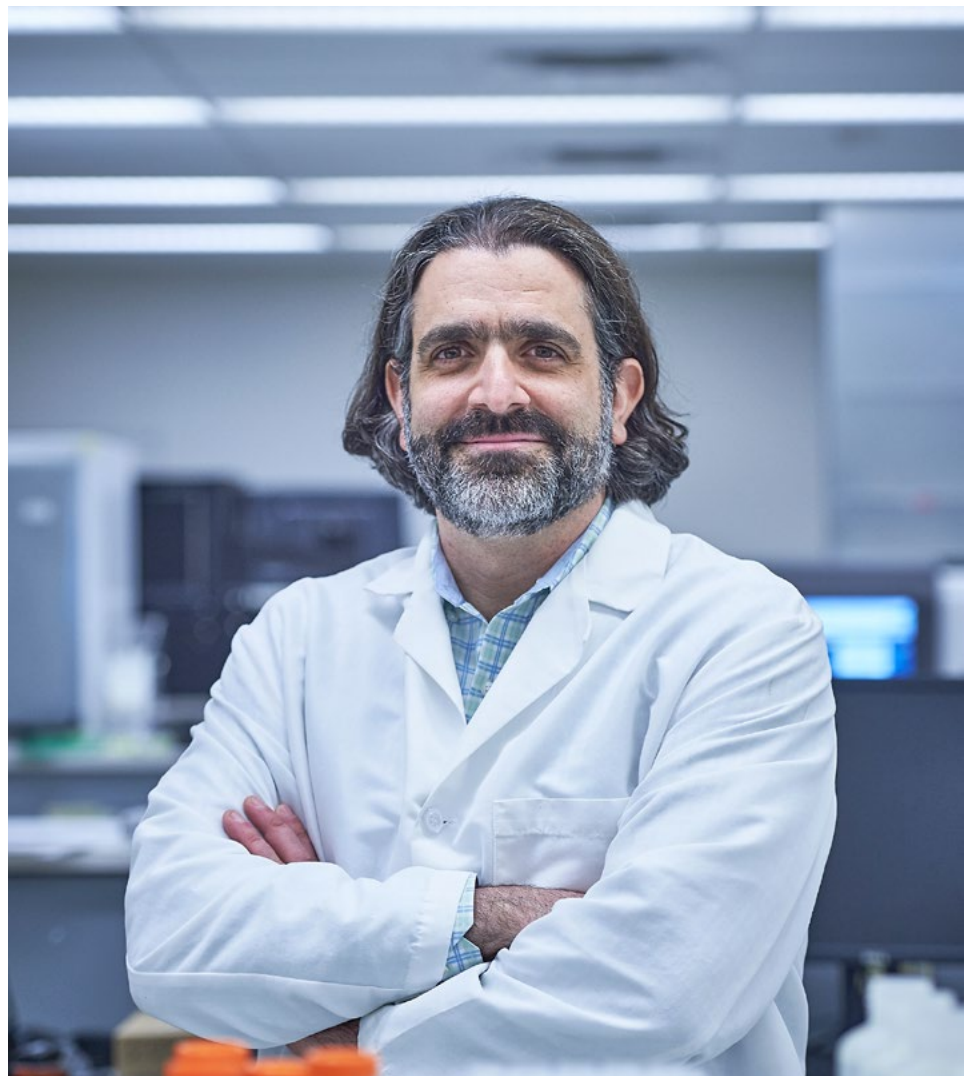
CONVERSATION WITH
THE CANCER LETTER

CHOP's Resnick: Big data will transition from research to the standard of care in the clinic

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It's extremely exciting to hear and see both the NCI and the administration and other community partners and patient groups really coming together and reconsidering, 'What are the unmet needs that can inform in new ways through new approaches of integration?'

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Adam Resnick

Director, Center for Data Driven Discovery in Biomedicine, Children's Hospital of Philadelphia; Scientific chair, Children's Brain Tumor Tissue Consortium and Pacific Pediatric Neuro-Oncology Consortium

Matthew Ong: Is there a need for a consolidated data commons for pediatric cancer? What are you hearing from the childhood cancer community?

Adam Resnick: I think this would be a universal answer in the pediatric cancer community: the data needs are not currently met, and it's for a variety of different reasons that are distinguished in the pediatric setting, compared to the adult cancer landscape.

Centralization is one approach, especially as supported by disease-specific efforts or NIH entities, but there is also a likely need for federation across a decentralized data commons landscape.

Can you describe what you've learned in your work on data-driven discovery, and how that approach could inform the creation of a larger, federated model for databases?

AR: One of the main challenges, obviously, in the pediatric cancer landscape is that no single institution sees enough patients of a particular kind to collect enough specimens or generate enough data to analyze it independently, or fully interpret the datasets on their own, or even generate sufficient the data on their own to drive the accelerated impact for patients that data-driven processes can impart.

And so, if any one entity wanted to actually undertake such an effort, it would take a very long time, just because the pediatric cancer landscape, by definition, ends up being a rare disease research context, despite the fact

it's currently the leading cause of disease-related death in children.

By definition, the pediatric community has to undertake a different form of consortia or collaborative-based efforts in order to aggregate or connect either specimens or datasets in order to empower them for meaningful analysis.

A second layer of challenge is that there are much fewer of us in the pediatric research community undertaking the analysis of such datasets or sufficient numbers of us focused on the analysis of specific cancers.

And what I mean by that is that the data can be just as complex and just as challenging to understand as a melanoma cancer dataset or a lung cancer dataset as require similar levels of infrastructure and resources.

But by comparison, there are very few focused domain experts, let's say for certain types of pediatric cancer, like medulloblastoma or neuroblastoma researchers, to fully explore, mine and interpret and iteratively re-contextualize the data.

And so, in the context of the modern, technologically evolving landscape of new types of data and their analysis, whether it's a different modality from genomics to proteomics to single-cell datasets, or even how such data get intersected in the clinical trial context, there's a need for the pediatric community not only to collaborate amongst themselves, but also to undertake engagement and recruitment of data-type specific domain expertise into our research community for communities who may not have yet defined pediatric cancers as a research objective.

I think it represents what we think of and what others have also recently contextualized as the opportunity and need for models of convergence research across the disparate knowledge domains and research efforts,

meaning that as a community we must have infrastructure and mechanisms to provide access and use of the data in a way that's non-local, that functions to bring together, one, the disease-specific community itself with their domain expertise, but two, also attracts and brings other research community members who may not even be researchers in the pediatric disease context, but have other expertise to inform, connect, and analyze data.

This is the transformational power of a data commons or data federation approach in accelerating translational impact.

You can imagine genomicists or proteomicists or computer scientists who may not necessarily have received their training or have ever had access to pediatric data in the past.

How can we bring them into the fold and provide them the capacity to inform pediatric cancer datasets partnering in non-local environments with disease-specific domain experts?

To accelerate discovery and translation, it's clear that the data generator is not the only user who should inform analysis. This is in part because of the diversity of expertise required, but also because other data sets and their connectivity, immediately impart new paths to knowledge not evident in the initial investigatory-specific cohort.

Diversifying the community of expertise and its access and utilization of data will only accelerate our capacity to interpret it, just because we don't currently have enough pediatric cancer researchers and are unlikely as a community to be able to scale our resources in a community-specific way.

And, certainly, in the data-driven research component, the NIH as a whole, I'd say, and as has been defined recently by the NIH's strategic plans, faces a critical shortage of data scientists. Data sci-

entists with particular expertise in pediatrics are therefore even more limited.

We have to actually think about our community in a much broader scope, and through strategic investments in pediatric cancer research, look for how such efforts can support growth via convergence and integration.

I think the challenge that the pediatric community faces is that there's tremendous power and impact that can be harnessed by focusing, centralizing efforts in a pediatric disease entity, or perhaps even in a broader pediatric cancer-specific effort, but there's also the risk of potentially siloing the pediatric community in doing so.

This is the critical balance data commons infrastructure and data-driven efforts must navigate. We must harness and empower community efforts through the lens of domain experts, but also recognize the design principles required to fully harness acceleration of discovery from data to information to knowledge and impact through the elimination of such domain-specific boundaries and control.

In addition to data science specific approaches, I also think there's a strategic space, supported by new technologies and resources, for our community to look at not only bringing in other domain experts into the field in support of convergence research, across pediatric data types and modalities, but especially in cancer we also need to really think of pediatric cancer as part of the continuum of research across pediatrics, adolescents and young adults, and ultimately adult cancers, recognizing that these are indeed different and likely have different origins or causes, as kids don't typically get cancer, because they smoke or overeat, or because of any of the other major lifestyle drivers of adult cancers.

But as a community, we've begun to recognize that there are many opportuni-

ties for looking at cancer more broadly and integratively across this continuum of research across ages and across cancer types.

In the pediatric cancer landscape, especially, there are additional opportunities to also expand this continuum even beyond cancer, recognizing that pediatric cancer is occurring in the context of childhood development.

That is indeed the context of the efforts being undertaken by the NIH Gabriella Miller Kids First Pediatric Research Program, which is a trans-NIH initiative, as the Kids First Data Resource Center, we're trying to make headway in looking at ways in which cross-disease analyses across cancer and structural birth defects can also support the discovery process and its acceleration towards translational impact, recognizing that many childhood disease and syndromes have both a structural birth defect component and a cancer component connected through shared biology.

Through such integrative efforts that look at leveraging a tremendous opportunity to think about pediatric cancer anew—in ways that leverage emerging data-science supportive technologies, cloud-based resources, and community engagement—I think this can really transform the research landscape in terms of its capacity to accelerate discovery, diagnostics, and have immediate impact in the context of clinical translation, potentially prospectively for each and every individual patient across the U.S.

For us, it's extremely exciting to hear and see both the NCI and the administration and other community partners and patient groups really coming together and reconsidering, 'What are the unmet needs that can inform in new ways through new approaches of integration?'

"This is a time of new technologies, new initiatives and efforts, the emergence

of an NIH data commons landscape, the ongoing growth of efforts of the NCI in terms of establishing and developing a data commons framework, the proposed new resources and influx of funding provide, and just-in-time opportunity for our community to engage in defining how all these parallel and intersecting efforts can be brought to bear in the context of the pediatric enterprise and the translation to impact."

What's in the works at CHOP?

AR: At CHOP, within our center, there are largely two broad efforts underway, but intrinsic to these is the recognition that CHOP, like all pediatric research hospitals, must work in the context of a community of hospitals.

One are consortia-based initiatives where again, groups of investigators and hospitals have come together independent of, let's say, NIH funding or specific initiatives, to support centralized biorepository-based efforts or data generation efforts in a disease specific manner.

My own experiences really began with and have largely benefited from a pediatric brain tumor initiative called the Children's Brain Tumor Tissue Consortium. In that context, we have recruited more than 3,000 patients on a longitudinal, observational study.

We have just finished sequencing and released via the Kids First Data Resource more than 1,000 whole-genomes along with RNA-seq and deep clinical and phenotypic data for such subjects. We'll continue to generate additional data from such specimens and will be releasing such consortia-based data in near real-time without embargo.

We're also part of new NCI-supported initiatives, that again, generate other new data types beyond bulk sequenc-

ing, including single cell sequencing efforts that are leveraging our collaboration network amongst pediatric enterprises, but also creating new partnerships with adult efforts.

One such pilot initiative that was launched at the end of last year is called Project HOPE and Project CARE, looking at single-cell sequencing at least in one disease type. Here, it's gliomas, in pediatrics, adolescents and young adults, and then adult GBMs.

Additionally, a separate pilot is underway with the NCI's [Office of Cancer Clinical Proteomics Research] effort. This is a proteomics-based initiative in pediatric brain tumors across multiple histologies with new data being release in the coming months. I think that the community is now poised to leverage some of these emerging centralized resources, evaluating existing approaches in these collaborative efforts while looking for such efforts can be broadened and scaled.

And again, at CHOP, every one of these efforts is a partnership, and while we may be the coordinating center for some of these consortia-based or NIH-based initiatives, the reality is that it's a shared resource across a broad community. And there's parity of ownership and responsibility across more than 18 institutions who have partnered in across consortia-based initiatives like the Children's Brain Tumor Consortium.

The other side of the equation for data generation efforts are NIH-sponsored initiatives that are fairly recent in the context of the data sciences, and for us at CHOP this has been in the context of the Gabriella Miller Kids First Program or Kids First DRC or Data Resource Center for which CHOP is the prime recipient along with several key partners.

This effort is only a year and a half in and is an NIH Common Fund-supported effort that includes the NCI and looks at

creating centralized environments for cross-disease analysis integration and data empowerment, initially focused on whole-genome sequencing and germline contributions to disease, especially across childhood cancer and structural birth defects.

That program includes also data generation efforts where individual investigators from a variety of institutions submit grants, essentially, on behalf of certain cohorts, and then receive allocated funding for sequencing. Or actually, I think they just receive the commitment to the sequencing. They don't actually get any funding themselves.

The Kids First Program includes data generation efforts where individual investigators from a variety of institutions submit application, essentially, on behalf of certain, well defined disease cohorts, and then receive allocated sequencing commitments for the cohort that will become part of public datasets on the Kids First DRC platforms.

That Kids First program is staged to have more than 30,000 whole-genomes, by the end of 2019, split largely evenly between pediatric cancer and structural birth defects cohorts.

Those represent my own center's direct efforts that are part of a much larger community of pediatric cancer efforts. And really, the key to the success for these types of efforts is also, as I mentioned before, ensuring that we're not siloed.

We're working very hard on partnering the Kids First DRC with efforts at the NCI, particularly as it relates to the Genomic Data Commons and the data commons framework, ensuring that users can interact between such spaces, because, as I mentioned, the pediatric cancer context is slightly unique in the context of syndromic diseases and ensuring that we can both integrate vertically across, particularly, NIH IC's

efforts for pediatric data, as well as horizontally across different institutes and centers within the NIH is key to our community's success.

These efforts are still at the early stages, but I think there's tremendous momentum in the program across our community.

In creating a data federation that isn't only clinical-grade, but also research-grade, how deep does the sequencing need to be in order for the data to be effective or useful?

AR: I think there are a couple of different ways to think about these questions. One of the challenges of, and I think this is what you're pointing to this space, is the difference between let's say, clinical-grade sequencing and research-based sequencing. One type of difference that you noted is in the depth of coverage of sequencing and its use.

But one of the key challenges that the community still faces is that the approach of using panels or targeted-based efforts is largely derived from creating such clinical platforms in ways that can be directly linked to existing actionability. And because the actionable space can be limited in pediatric cancers, clinical panels can also be limited in advancing new knowledge.

I think what we're finding more and more is that more comprehensive processes that essentially look at the entire genome—like a whole-genome sequencing as opposed to a whole-exome or a panel—provide a larger amount of information that can complement current clinical efforts.

It's true that not all the information and perhaps not even a majority of

WGS data may necessarily be clinically actionable at that particular moment, but through the right types of infrastructure and community engagement and resources, those efforts can become a living, breathing data set that continues to grow in understanding through reanalysis, secondary use, and data-sharing practices in ways that can be immediately translatable to the patients in the clinic or in the context of either new clinical trial designs or emerging therapeutics.

I think this is why there is likely a need for more comprehensive clinical genomics that can be linked directly to clinical care and implementation. For example, particularly in the context of the emerging immunotherapy landscape, where a vaccine-based approach or neoantigen-based approaches may be less constrained than the small molecule-based targeting approaches in the drug development process, such data-driven clinical resources could be transformative.

I think there's a lot of interest, by our community, in thinking about comprehensive clinical data generation, and this is driven in part by the recognition that the cost of large-scale clinical data generation is now dropping in ways that it will indeed be feasible for clinical whole-genome sequencing, for example, to occur within a short period of time. Big data is set to transition from largely occurring in the context of research to, in the very near future, be the standard of care in the clinical context.

And so, many in our community recognize that it won't be too long before, for example, clinical whole-genome sequencing combined with RNA-seq is the starting digital footprint of an electronic health record in ways that would suddenly make big data a daily reality that right now is still largely restricted by our community to research-grade datasets.

But because costs are dropping, that's going to happen, and it's going to happen fast along timelines our community may not be fully prepared to harness, and we as a community need to think about what is the right infrastructure and workflows and standards around which we can continuously empower the use of such data on behalf of patients, and how we can support its implementation in the clinical setting in ways that, I think, right now are still going to be fairly challenging for most oncologists and clinical environments to fully harness.

So really, building the right tools and environments to iterate around multimodal data analysis, its integration with the longitudinal, clinical, phenotypic, and genotypic data collection processes is poised to be transformative.

Recognizing that layering longitudinal, clinical, EHR data along with molecular clinical grade data across time and along with imaging data like MRIs or digital pathology—that's extremely key, but again, I think that it has been challenging historically to implement especially across a federated landscape across institutions and hospitals. But this is likely what will be required for pediatric cancer research to succeed.

However, from a data driven and technology perspective, there is a huge amount of opportunity. And the pediatric community, I think, is itself extremely well-poised because of our historical existential need to already collaborate and partner across consortia and clinical trials.

I'm sure Peter [Adamson] talked about the COG and the unique context under which a very high percentage of pediatric patients end up on clinical trials comparatively to the single digit percentages of adult cancer patients. The community is extremely well-poised for such initiatives to be undertaken and be supported.

Have we definitively reached a point at which genomic characterization of pediatric cancer is the standard approach to thinking about research and treatment in a meaningful way?

AR: I think for sure. Some of the best-case scenarios and use cases that the entire cancer community utilizes around molecularly driven or precision-based approaches are actually in the pediatric context.

The impact is phenomenal and measured in slightly different ways, potentially, than in the adult community, largely because the number of patients is smaller.

But being able to have precision-based approaches driven by a molecular definition of the disease has a number of different constraints that are especially important in a pediatric context.

And I'll provide you the brain tumor context, especially, as a use case.

Non-selective treatment approaches, let's say, radiation therapy, that target a specific cancer in the central nervous system, in the context of a young child, while it may be curative for the cancer, the approach can also damage and oftentimes does damage the central nervous system itself of the developing child.

In the context of development, where you have cell proliferation both across cancer and non-cancer contexts, non-specific approaches have severe side effects for children in ways that essentially can impart Pyrrhic victories for the child, where parents are faced with decisions of loss of IQ vs. survival.

And so, precision-based approaches are especially salient for the pediatric context where you're trying to minimize long-term side effects, toxicities, and downstream harm to what hopefully is a very long life still ahead of a child.

And one that's likely distinguished from an aged population who is being treated for cancer and that has somewhat different side effects independent of development.

I think many of us in the pediatric community try to enunciate what is a really high unmet need for leveraging precision-based approaches in the pediatric context to ensure that we are not only curing, but also providing for a happy and long-lived normal life for a child as a fully functional member of humankind. In the pediatric context, survival is key, but the ultimate goal of most parents is lifelong normalcy.

I think therefore the answer to your question is obviously, "Yes." There's plenty of evidence in the pediatric context that targeted-based approaches or precision-based approaches that are defined by molecular contexts are extremely effective.

However, what is also informative to remember is that in the pediatric cancer context, one of the biggest challenges we face is that if we don't have large numbers to support the kinds of traditional clinical trials that have been run historically in other cancer types, and so it's extremely important that when we do run clinical trials, the patient populations are very well defined.

And so, what we're now finding is that what has been pathologically described as one disease is potentially five or six or 11 different diseases, when you start looking at the detailed molecular biology.

And that presents a challenge for a whole new type of way of thinking about creating the kinds of clinical trials where the right patients are selected for the trials in ways, that with smaller numbers, are more likely to actually achieve meaningful, statistically significant results as supported by molecular definition of disease.

I think it's along those two contexts—precision-based therapies and molecular definition of disease—that I think there's tremendous opportunity for applying data generation-based efforts.

In one, guiding a path to sub-classify and better classify diseases in ways that can define the kind of clinical trials that we need to innovate around, in the context of smaller numbers of patients.

And then secondarily, in engaging targeted or precision-based approaches that can mitigate the harm and toxicities that traditional chemotherapeutic or radiation-based approaches impart in the developing context of childhood cancer.

It sounds like NCI and the community are pretty much on the same page about where this needs to go and how potential new federal funding could be used in this space.

AR: Yes. And I think it's a unique opportunity and time, because of the synthesis of new technologies, new ways to empower communities to come together around data commons-like environments and infrastructure that supports truly non-local, federated, convergence-based research through collaboration, and shared resources bringing new and diverse communities together.

Is there anything I've missed?

AR: No. I think, by and large, hopefully most of us that you've interviewed, really are sounding the same message of unprecedented opportunities, clear unmet needs, and really strategic alignment between the community, hospital systems, clinical trial organizations, the NIH, and the U.S. government.

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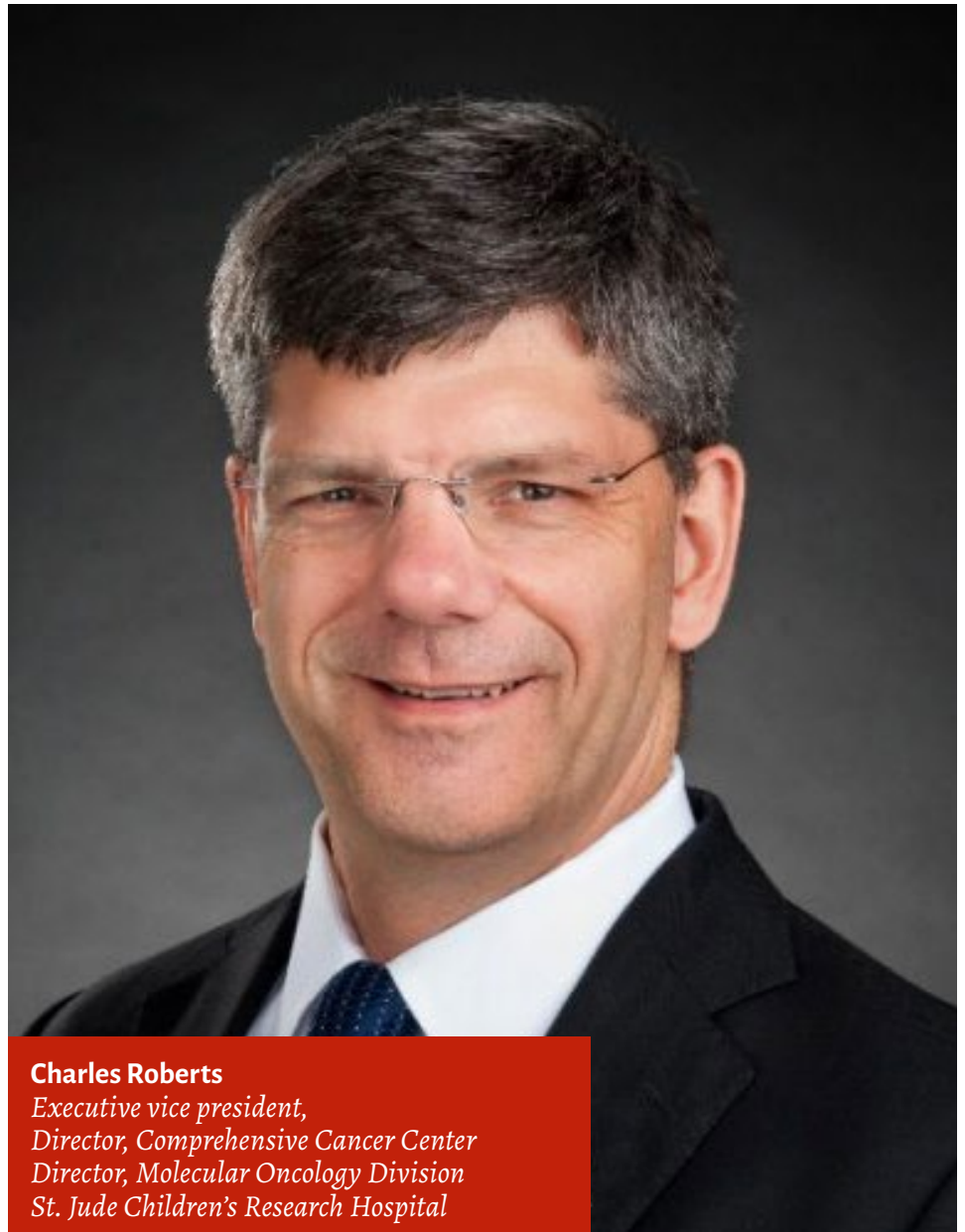
CONVERSATION WITH
THE CANCER LETTER

St. Jude's Roberts: “No single institution can maximize cures and minimize toxicities alone”

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Historically, cancer research drug development has largely been focused upon adult cancers with drugs trickling down to pediatric trials over time. But we now know that 55 percent of the driver mutations are unique to childhood cancers. So, relying upon that old model is not going to serve children well.

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Charles Roberts

*Executive vice president,
Director, Comprehensive Cancer Center
Director, Molecular Oncology Division
St. Jude Children's Research Hospital*

Matthew Ong: You have a pretty comprehensive database at St. Jude, but overall, as a community of pediatric researchers, is there a need for something bigger, better?

Charles Roberts: I think there is a substantial unmet need.

This year, Jinghui Zhang from Computational Biology at St. Jude, working with the National Cancer Institute and Children's Oncology Group, performed genomic analysis of 1,699 childhood cancers and found that 55 percent of the genetic mutations that drive pediatric cancer are not found in adult cancers.

Historically, cancer research drug development has largely been focused upon adult cancers, with drugs trickling down to pediatric trials over time.

But we now know that 55 percent of the driver mutations are unique to childhood cancers. So, relying upon that old model is not going to serve children well.

How do we best serve children fighting cancer? First and foremost it is collaboration across institutions and across areas of expertise, spanning from basic to translational and clinical research.

The greatest impact will require a combination of laboratory investigation to reveal the mechanisms by which these unique mutations drive cancer, focused efforts on pediatric cancer translate into clinical trials specifically for children, and robust data sharing.

Given the many pediatric-unique mutations and that differential therapeutic responses are affected by heterogeneity within cancer types and driven by sub-class specific mutations, getting

samples and data shared are essential for advancing the field.

With respect to biopsy samples, the number of cases is smaller compared to adult cancers, the biopsies are often small, so samples are limiting and can be gone quickly.

To address this limitation, one of the approaches we've been taking is to systematically put samples into mouse models and to comprehensively characterize both the original tumor and the mouse PDX samples via whole genome and whole exome sequencing, paired with RNA-seq, methylation profiling. And then make all of the PDX samples and genomic data freely available.

Demand is clearly there as our Childhood Solid Tumor Network has sent out over 1,300 vials to 194 investigators at 93 institutions in 15 countries. And our PROPEL resource has more than 200 samples of leukemias to share free of charge.

The need for sharing goes beyond samples—its big data, too. We developed the St. Jude Cloud for this purpose. It provides researchers around the world access to the world's largest public repository of pediatric cancer genomics data.

This also reveals the thirst for data sharing, as since its launch less than a year ago, more than 800 people from over 400 institutions have registered.

They get immediate access to data in the cloud that previously would have taken weeks to download.

How many cases do you have in the cloud thus far?

CR: The St. Jude Cloud already has more than 5,000 whole genome, whole-exome, and 1,200 RNA-seq datasets from more than 5,000 pediatric cancer patients and survivors.

We continue to add more whole genome sequences and expects to make 10,000 of those available at AACR this month.

At ASCO, we're going to be announcing that comprehensively sequenced and clinically annotated patient-derived data will be made available to others in real time, rather than holding them back for months or years in order to accompany a publication.

Is the St. Jude's database currently the most well-annotated, well-aggregated and most comprehensive database on childhood cancer?

CR: St. Jude Cloud is the world's largest repository for pediatric cancer genomics data, including pediatric cancer and cancer survivorship data.

This data includes whole-genome sequencing, not just whole-exome sequencing. With whole-genome, whole-exome and RNA-seq data, we are already making novel discoveries.

A St. Jude study published in *Nature Medicine* last week found whole genome sequencing led to the discovery of gene fusions common in childhood melanoma.

St. Jude Cloud also has a collection of bioinformatics tools to help both experts and non-specialists gain novel insights from genomics data.

These tools include validated data analysis pipelines and interactive visualization tools to make it easier to make discoveries from large datasets. Data and results can be securely shared with collaborators within the platform.

One of the biggest choke points in advancing cancer research is the need for computational biologists. Often, scien-

tists and physician scientists have good questions and ideas but don't have access to dedicated computational biologists as they're expensive.

What the St. Jude Cloud provides is brilliant. The tools and designed to be accessible and user-friendly and displaying results in a way that biologists and physicians can understand the impact without needing a computational biologist. Indeed this was a major driver behind why we created St. Jude Cloud, and I do think it's world-leading.

Another major advance is providing all of the data in the cloud so that analyses can be performed without having to download the data.

Scott Newman, one of our Bioinformatics Group leaders, prior to coming to St. Jude found that it took over seven months just to download 10TB data of 92 high grade gliomas from the Pediatric Cancer Genome Project.

With the advent of the St. Jude Cloud, investigators can analyze data directly in the cloud.

Indeed, if they choose, they can upload their own tools, choosing whether to share them, and immediately analyze all of the PCGP data.

How much has St. Jude spent on this in total, to get the cloud to where it is today? And how much do you continue to spend every year? What's your annual budget?

CR: We spent \$3.3 million to develop and launch the St. Jude Cloud, which included \$500,000 in support from DNANexus and \$2 million from Microsoft.

We have budgeted \$14.6 million and 15 positions to support it over the first five years, through 2023.

Additionally, on an annual basis DNANexus has been providing \$500,000 and Microsoft over a million dollars in storage and computational cost.

Equipping not just the scientists and doctors at St. Jude, but, in real time equipping investigators at Dana-Farber, Memorial Sloan Kettering, Stanford, Seattle Children's Hospital, and people in Princess Máxima in the Netherlands, and around the world to have access to this data, that will facilitate so many more advances.

For something like this to be useful, it has to be research-grade; right?

CR: Yes. Absolutely. Most of the tools are published in peer-reviewed journals including ProteinPaint which was published in *Nature Genetics* in 2015.

What does it take to make a database like this research-grade? Do you need deep sequencing?

CR: There are some questions that have yes/no answers, such as whether a patient carries a particular mutation. Our whole-genome sequencing and whole-exome sequencing have a minimum of 30X and 100X coverage, respectively, which is the standard used for cancer genomic research.

The current coverage provides us with 90 percent of the power for identifying mutations present in 20 percent of the bulk tumors and deep sequencing by

panel may enable discovery of additional variants present in smaller subclones.

For others, provision of panel data or exomes enables new discoveries. We are in the process of learning tumor heterogeneity by performing single-cell DNA and RNA sequencing.

While in 2019 we understand the genetics of cancer so much better than a few years ago, we still have a long way to go.

Increasingly, we're learning that there are numerous cancer-driving mutations that can only be identified via the combination of RNA-seq and/or whole -enome data.

And additional information can come from methylation and ATAC-seq analyses.

Say, for instance, if you're looking at germline mutations and you're looking for new, actionable targets that are unique to pediatric malignancies, do you have to do whole genome sequencing to get there? Or is this a clinical-grade question?

CR: For current, actionable clinical questions, typically targeted panels are sufficient. But we know that the list of recognized germline predisposing mutations will continue to grow.

There are interesting correlations between germline variations and genome-wide somatic alteration profile. For example, BRCA-like mutational signature has recently been reported to be a good predictor for sensitivity to PARP inhibitors.

Given the low mutation burden of pediatric cancer, a genome-wide approach is required to ensure robust result of mutational signature analysis.

Furthermore, germline copy number alterations and structural variations

have rarely been explored and variants in regulatory regions will also need a genome-wide approach.

For this reason, to account for both current clinical needs and continued discovery research we perform all of these on each new cancer patient at St. Jude.

As you know, the White House promised \$500 million—of course it's unclear whether that's coming through just yet—but with \$500 million over 10 years, what can we realistically achieve, and is that enough?

CR: As I mentioned, we now know that while pediatric cancer shares some features and mutations with adult cancers, for the majority of mutations pediatric cancer is different.

Any investment is welcome. There's no question that the field of pediatric researchers can put that scope of investment to good use.

This funding will facilitate better data sharing, which is critical for researchers nationwide and around the world to understand the unique nature of pediatric cancer.

As a field, it will enable us all to be able to better identify problems and enable people to develop new ideas about how we can best intervene.

Do we need a federated model of data sharing in terms of infrastructure, and would NCI be in a good position to facilitate that?

CR: I think the federated model is absolutely the way to go.

Past efforts to set up central databases haven't always worked. The reason is the field is in evolution. The type of data we need is changing. The questions we're asking are changing.

Just like in any innovative field, whether it be Silicon Valley or similar industries, people are thinking and collaborating and competing and new ideas come up and you suddenly say, "Oh, that's much better," and the whole field changes.

That innovation enables a number of experiments and different approaches to develop rapidly.

St. Jude is developing new tools and new ways of thinking that we think are revolutionary for our field, and we want the community to have access to those resources.

That's why we want to provide everything for free and enable other researchers. It's critical, and part of our mission, to share these innovations with our peers.

And others are interested in focused sharing of pediatric cancer data too. The NCI-supported Gabriella Miller Kids First Data Resource Portal has substantial genome data.

We have been collaborating with HudsonAlpha Institute for Technology and developed a genome sequencing center for the Kids First program with the focus on generating and uploading the high quality genomic sequencing data for pediatric cancer.

The UCSC Treehouse has RNA-seq data and we have already shared our RNA-seq data with the UCSC Treehouse team.

Additionally, we have discussed with the Kids First team on multiple occasions

the feasibility of developing methods that will make the model of federated data sharing a reality.

We do think that this federated model is important in order to support advances most rapidly and we're excited about the idea of NCI further supporting data sharing.

However, this is technically challenging and will require dedicated effort to tackle this problem.

Who else has full capacity to be able to generate high grade data and do the sequencing that required? Or, perhaps, it's truly a team effort.

CR: Beating pediatric cancer will clearly take a team effort. At St. Jude, we're fortunate to we have the ability and capacity to make a major impact. It's intrinsic to our mission.

Danny Thomas didn't say, "No child should die in the dawn of life in Memphis, TN" or "No child should die in the dawn of life in the United States."

He said, "No child should die in the dawn of life." And I think that is a mission that everyone can support.

We know that no single institution can maximize cures and minimize toxicities alone.

In collaboration with COG and many other institutions, if our scientific expertise, our data and our analysis tools speed advances in research and answer important questions, that's the goal.



GUEST EDITORIAL

Needed: A fully funded data federation for pediatric cancer with deep genomic sequencing and clinical records



By Nancy Goodman

Founder and executive director of Kids v Cancer

It was a thrilling moment for me when, sitting on my living room couch, listening to the State of the Union address, I heard the president say:

“Many childhood cancers have not seen new therapies in decades. My budget will ask the Congress for \$500 million over the next 10 years to fund this critical life-saving research.”

The next day was even better, when I read a Politico article reporting Speaker Nancy Pelosi’s retort:

“\$500 million over 10 years—are you kidding me? . . . Who gave him that figure? It’s like the cost of his protection of his Mar-a-Lago or something.”

Fantastic. At last, we, parents who have lost our children to cancer, are getting real political attention for our kids. My son, Jacob, died of a pediatric cancer when he was 10 years old.

Of course, Ms. Pelosi has a point—\$500 million over 10 years might not get us to cures for childhood cancer. PhRMA claims it costs five times as much. I don’t know. But, dedicated to the right project, \$500 million could still have significant impact.

President Trump seemed to make a significant personal commitment to this new \$500 million in his State of the Union address. He brought out a beautiful girl who survived cancer, inspirational Grace. The president asked us to

be emotionally invested in Grace, as he was. He told us that “nurses and doctors cried when Grace finished chemo.” He concluded: “Grace—you are an inspiration to us all.”

So—was the use of Grace and the offer of \$50 million a year really an intention to give children with cancer funds for new research? Or was it a cheap shot to pull on our heart strings and ask for kind feelings toward Mr. Trump? Will the president and his administration invest the political capital necessary to make the additional commitment of resources to pediatric cancer a reality, or was it just an applause line in a very long speech?

We will have our first answer when the president publishes his fiscal year 2020 budget, which is expected to be next week. Presidential budgets are only recommendations to Congress and are only provided in broad strokes. While we would expect Mr. Trump's budget to specify a funding number for the NCI, it's not necessarily clear that it will specify funding for smaller programs within the NCI, such as a new \$50 million pediatric cancer program.

And, if the president proposes instead an across-the-board cut in the NCI's budget, then his offer of an additional \$500 million for pediatric cancer research becomes magical math. In this world of magical math, we do not know if his \$50 million per year is intended as an increase in pediatric cancer research funds or as compensation for any fiscal year 2020 cuts in pediatric cancer research funds.

There may be smoke and mirrors even if we see an additional \$50 million or more in the president's NCI budget. It is still unclear how the president's \$500 million relates to the Childhood Cancer STAR Act, which added \$30 million per year to the federal budget for pediatric cancer research. Will the pediatric cancer programs be upped by only \$20 million instead?

The pediatric cancer community will be pushing hard for new and incremental funding for the NCI. And it would be disingenuous for the president to talk about increasing spending for pediatric cancer research if he then requests a cut in NCI's budget. That means robbing Peter to pay Paul.

But whether or not the president's budget proposes an increase to NCI's budget, we will urge the NCI to follow his prioritization and fund incremental pediatric projects however they can to the \$50 million marker above the \$30

million authorized under the Childhood Cancer STAR Act.

NCI has a terrific project for the funds—a data federation for pediatric cancer with deep genomic sequencing and clinical records. This platform needs to add value in both the clinical and research settings. Private industry's resources and expertise in deep genomic sequencing and big data industry's expertise and resources could be used in the design, construction, and population of this dataset.

Fully funded, with the \$50 million plus-up, in addition to the portion of the \$30 million of STAR Act funding dedicated to this project, whatever incremental Speaker Pelosi wants to contribute, and the participation of private companies, we could create one of the most robust datasets for any cancer population.

It could serve as a clinical and research tool to accelerate pediatric cancer research and draw in researchers, even from outside the pediatric cancer community, for years to come.

If we don't get new funds—meaning the \$50 million per year above the \$30 million Congress authorized under the Childhood Cancer STAR Act, then Grace was just emotional bait. That would be really lousy. The president's offer will have been a cheap shot, an exploitation of Grace and of all of us whose children have been treated for or have died of cancer.

I remain hopeful. NCI has lined up a terrific project. And, with NCI Director Ned Sharpless taking the lead, we have someone who is effective, who has the stature and who has the commitment to get it done right. Fully funded, this would be a transformational project.

Let's get this done.

“

The pediatric cancer community will be pushing hard for new and incremental funding for the NCI. And it would be disingenuous for the president to talk about increasing spending for pediatric cancer research if he then requests a cut in NCI's budget. That means robbing Peter to pay Paul.

”

NEWS ANALYSIS

Gottlieb resigns at FDA, recommends Sharpless as successor

By Paul Goldberg



Scott Gottlieb has submitted a letter of resignation from his job as FDA commissioner, reportedly recommending that NCI Director Ned Sharpless be appointed as his successor at the agency.

Sharpless's name was first mentioned in *The Wall Street Journal* as a possible candidate to replace Gottlieb, and knowledgeable sources told *The Cancer Letter* that Gottlieb has indeed mentioned to the administration that Sharpless would be his choice for the job.

If Sharpless were indeed to move to the top job at the regulatory agency, he would be the second NCI director to do so. That said, the circumstances were extremely different in 2005, when Andrew von Eschenbach received a battlefield promotion to FDA commissioner.

Von Eschenbach's predecessor at the agency, Lester Crawford, was fired after two months on the job, when he was found to have failed to disclose ownership in food, beverage, and de-

vice companies (The Cancer Letter, [Sept. 30, 2005](#)).

By contrast, Gottlieb, a 46-year-old physician and cancer survivor, has completed a successful near-two-year stint as commissioner, and it appears that he really is leaving largely in order to put an end to his weekly commute from Connecticut and spend more time with his family, which includes three young children.

Gottlieb is resigning from a controversial administration with his reputation intact. He has been viewed as a level-headed regulator and has focused on genuine public health issues, including increasing oversight of vaping and other tobacco products.

Gottlieb's opportunity costs—measured in consulting gigs and seats on company boards—were high when he took the job. Now, with the words “former FDA commissioner” added to his CV, these opportunity costs would be even higher.

Several friends acknowledge that Gottlieb had told them privately that he wouldn't stay in his job through the end of President Donald Trump's term in office. However, FDA officials said they weren't expecting his resignation.

There were no publicly visible warning signs about Gottlieb's plans. On Jan. 3, social-media-savvy FDA commissioner [tweeted](#): “I've heard from friends contacted by an online pharma news pub that's preparing a story speculating that I'm leaving #FDA. I want to be very clear—I'm not leaving. We've got a lot [of] important policy we'll advance this year. I look forward to sharing my 2019 strategic roadmap soon.”

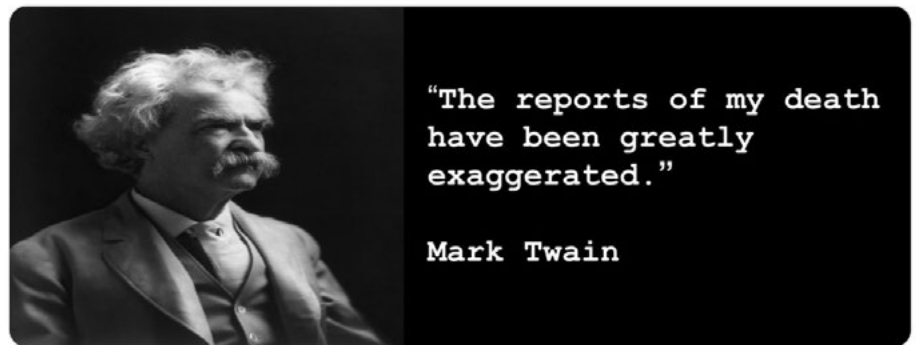
Late last year, Gottlieb recruited Amy Abernethy, an expert in generating and applying real-world evidence, to the job of principal deputy commissioner, mak-



Scott Gottlieb, M.D. ✓
@SGottliebFDA

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I've heard from friends contacted by an online pharma news pub that's preparing a story speculating that I'm leaving #FDA. I want to be very clear - I'm not leaving. We've got a lot important policy we'll advance this year. I look forward to sharing my 2019 strategic roadmap soon



3:00 PM - 3 Jan 2019

Earlier this year, on Twitter, Gottlieb invoked Mark Twain in an effort to quell rumors of his impending departure.

ing her the second-highest ranking official at FDA. (The Cancer Letter, [Jan. 4](#)).

Abernethy came to the agency from her job as chief medical officer at Flatiron Health, a unit of Roche. Since deputy commissioners have in the past stepped in to take over as commissioners, Abernethy is also regarded as a potential successor to Gottlieb.

While the Trump administration has placed conservative ideologues in many key position, FDA and NCI have been spared. Gottlieb has a solid Republican pedigree. His background is in the pharmaceutical industry, drug regulation and Wall Street, not libertarian ideology.

NCI's Sharpless, whose political views aren't publicly known, is clearly not driven by politics, either. A former cancer center director and biotechnology entrepreneur, Sharpless has sought not only to protect investigator-initiated research, but also to commercialize discoveries (The Cancer Letter, [Feb. 15](#)).

Tellingly, as soon as he stepped into the job at NCI, Sharpless commissioned a review of the Small Business Innovation Research program, one of the institute's lesser-known activities that years ago provided seed capital for a company Sharpless had co-founded (The Cancer Letter, [Feb. 22](#)).

Sharpless has also forged friendly, informal relationships with FDA oncology staff members, regularly playing basketball with and against them.

In one such game involving FDA players, Sharpless broke his ring finger, a mishap that gives “new meaning to ‘breakthrough designation,’” he said in a [tweet](#) at the time.

The von Eschenbach situation was different. He was a Bush family friend whose vision for NCI was focused on the goal to end “suffering and death due to cancer” by the year 2015. His actions at the institute included reviewing all programs based on their potential to contribute to the 2015 Goal (The Cancer Letter, [May 19, 2006](#)).

After being tapped to take the FDA job, von Eschenbach vowed that he would run both NCI and FDA (The Cancer Letter, [Oct. 9, 2005](#)). He abandoned that idea, presumably after the Bush administration explained to him that FDA regulates NCI trials, and thus the two entities cannot be directed by the same individual.

It’s telling that after taking the FDA job—where Gottlieb served as his political minder—von Eschenbach was apparently directed to stop talking about his 2015 goal (The Cancer Letter, [Feb. 17, 2006](#)).

As a presidential appointee, Sharpless has gone through clearance and sold all stocks that could pose conflicts.

The NCI job doesn’t require confirmation by the Senate; the FDA job does. If Sharpless is shifted to the agency, the institute could face considerable uncertainty.

At a time of rising appropriations, the stakes for NCI are high. Funding increases boost the probability of boundary clashes with other entities at NIH, and a



Norman Sharpless

@nes047

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Results of B-ball with @FDAOncology. New meaning to “breakthrough designation”.



8:36 AM - 23 Feb 2018

Sharpless has forged informal relationships with FDA oncology staff members. In this tweet, he shows off a ring finger broken in a basketball game vs. FDA.

permanent director is better positioned to deflect incursions that may arise.

That said, Sharpless’s deputy director, Douglas Lowy, who has already served as acting NCI director prior to Sharpless taking the job, would have the capacity to provide continuity to the institute.

Lowy doesn’t lack scientific oomph. At the end of his stint as acting director, he shared the 2017 Lasker-DeBakey Clinical Medical Research Award for research that led to development of the human papillomavirus vaccine (The Cancer Letter, [Sept. 29, 2017](#)).

IN BRIEF



Raymond DuBois receives AACR Margaret Foti Award



The American Association for Cancer Research has recognized Raymond DuBois with the 13th Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research during the AACR annual meeting, to be held March 29-April 3 in Atlanta.

DuBois is dean of the College of Medicine at the Medical University of South Carolina and professor in the departments of biochemistry, molecular biology and medicine. He is recognized for contributions to early detection, interception, and prevention of colorectal cancer.

DuBois discovered the mechanistic function of prostaglandins and cyclooxygenase in colon cancer initiation and progression and clarified the role of PGs in the tumor microenvironment, spearheading the consideration of aspirin and other non-steroidal anti-inflammatory mediators for cancer prevention.

The Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research was established in 2007 to recognize a “champion of cancer research whose leadership and extraordinary achievements in cancer research have had a major impact on the field.”

DuBois is known for discoveries elucidating the connection between inflammation, inflammatory mediators and early changes responsible for progression of colorectal cancer. His work in this area demonstrated the role of anti-inflammatory agents in the tumor microenvironment, resulting in the design of various clinical trials outlining a role for anti-inflammatory agents in the reduction of cancer risk and progression.

DuBois is past president of the AACR, chairman and president of the AACR Foundation, and a Fellow of the AACR Academy. He has served as a member of the AACR board of directors.

He is a co-editor-in chief of *Cancer Prevention Research*, and has served as an editorial board member of *Clinical Cancer Research* and as an associate editor of *Cancer Research*, all journals of the AACR. He serves as vice-chair of the Stand Up To Cancer Scientific Advisory Committee.

Charles Sawyers to present AACR Princess Takamatsu memorial lecture



The American Association for Cancer Research will honor Charles Sawyers with the AACR Princess Takamatsu Memorial Lectureship at the AACR Annual Meeting.

Sawyers is a Howard Hughes Medical Institute Investigator, chair of the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center, and professor of medicine at the Weill Cornell Medical College.

He is being recognized for work on cancer drug resistance mechanisms, specifically those involving the tyrosine kinase inhibitor imatinib (Gleevec) in patients with chronic myeloid leukemia and in prostate cancer patients with resistance to hormone therapy.

Sawyers' research into identifying treatments for cancers that have become resistant to established therapies has led to the development of dasatinib (Sprycel) for patients with imatinib-resistant CML and enzalutamide (Xtandi) and apalutamide (Erleada) for metastatic prostate cancer.

Sawyers will present the award lecture on April 1.

The AACR Princess Takamatsu Memorial Lectureship, now in its 13th year, is awarded to a scientist whose novel and significant work has had or may have a far-reaching impact on the detection, diagnosis, treatment, or prevention of cancer, and who embodies the dedication of the princess to multinational collaborations.

Princess Kikuko Takamatsu was instrumental in promoting cancer research and encouraging cancer scientists. She became a champion for these causes following her mother's death from bowel cancer in 1933 at the age of 43.

Sawyers is a past president of the AACR, a Fellow of the AACR Academy, chair of the AACR Project GENIE Steering Committee, and co-leader of the Stand Up To Cancer/Prostate Cancer Foundation Dream Team "Precision Therapy of Advanced Prostate Cancer."

Alberto Mantovani receives Pezcoller Foundation-AACR Award



The Pezcoller Foundation-AACR International Award for Extraordinary Achievement in Cancer Research will be presented to Alberto Mantovani at the AACR Annual Meeting.

Mantovani is being recognized for his work identifying tumor-associated macrophages as mediators of cancer progression, highlighting the role of inflammation and the immune system in tumorigenesis.

His research demonstrating the interplay between inflammation and cancer represents a fundamental paradigm shift in the field and has contributed to the emergence and further development of tumor immunology.

Mantovani will deliver his award lecture on March 31.

The Pezcoller Foundation-AACR International Award, now in its 22nd year, was established in 1997 to annually recognize "a scientist who has made a major scientific discovery in basic or translational cancer research." The awardee must be active in cancer research, have a record of recent noteworthy publications, and be conducting ongoing work that holds promise for continued substantive contributions to progress in the field of cancer.

Mantovani is professor of experimental medicine and pathophysiology at Humanitas University in Milan. He serves as senior editor of *Cancer Immunology Research*, a journal of the AACR.

Mantovani is president of International Union of Immunological Societies and is past president of the Italian Society of Immunology and the International Cytokine Society. He has also served on the board of the Global Alliance for Vaccines and Immunization and IUIS. He is a member of Academia Europea (2017), Robert Koch Stiftung (2016), Accademia dei Lincei (2016), the Henry Kunkel Society (2002), and the European Molecular Biology Organization (2000).

Before his tenure at Humanitas, Mantovani was head of the Department of Immunology and Cell Biology at Istituto di Ricerche Farmacologiche, and professor of general pathology at the School of Medicine at the University of Brescia.

Jeffrey Bluestone to receive AACR-Irving Weinstein Foundation lectureship award



Jeffrey Bluestone has been awarded the 15th AACR-Irving Weinstein Foundation Distinguished Lectureship by AACR.

The AACR-Irving Weinstein Foundation Distinguished Lectureship was established in 2004 to acknowledge "an individual whose outstanding personal innovation in science and whose position as a thought leader in fields relevant to cancer research has had, and continues to have, the potential to inspire creative thinking and new directions in cancer research."

The recipient of this award is selected annually by the AACR president.

Bluestone is being recognized for his scientific contributions to the fields of molecular biology and immunology, specifically his work involving the characterization of CD28 and CTLA-4 function, and subsequent studies demonstrating the role of T-cells in modulating autoimmunity and organ transplant rejection.

Collectively, his research accomplishments have revolutionized the understanding of T-cell biology and have been

essential to the development of countless studies dedicated to understanding the role of the immune system in cancer initiation and progression.

Bluestone is president and CEO of the Parker Institute for Cancer Immunotherapy and the A.W. and Mary Margaret Clausen Distinguished Professor at University of California San Francisco. He is also director of the Hormone Research Institute in the Diabetes Center at UCSF.

Most recently, Bluestone used preclinical models to facilitate the development of biological treatments and cell-based therapies for patients with autoimmune disease. He continues to initiate new projects to determine Treg stability control mechanisms, with the goal of developing therapeutics aimed at targeting Tregs in autoimmunity and cancer.

Prior to joining UCSF and the Parker Institute, Bluestone was director of the Ben May Institute for Cancer Research at the University of Chicago. He also spent time as a senior investigator at the NCI.

Manuel Hidalgo named chief of hematology and medical oncology at Weill Cornell



Manuel Hidalgo was named chief of the Division of Hematology and Medical Oncology in the Weill Department of Medicine at Weill Cornell Medicine and New York-Presbyterian/Weill Cornell Medical Center, effective June 1.

Hidalgo will succeed David Nanus, who has led the division since 2004, first as co-chief with Barbara Hempstead until 2012, then as division chief. Nanus will remain on Weill Cornell Medicine's faculty and serve as director of New York-Presbyterian and Weill Cornell Medicine's Healthcare Services' Cancer Program.

Recruited as the E. Hugh Luckey Distinguished Professor of Medicine, Hidalgo comes to Weill Cornell Medicine and New York-Presbyterian/Weill Cornell Medical Center from Beth Israel Deaconess Medical Center in Boston, where he served as chief of the division of hematology as well as clinical director of the Rosenberg Clinical Cancer Center. He is also the Theodore W. and Evelyn G. Berenson Professor of Medicine at Harvard Medical School and deputy associate director for clinical sciences at the Dana-Farber/Harvard Cancer Center.

Greg Delgoffe to receive Sy Holzer Endowed Immunotherapy Research Fund

UPMC Hillman Cancer Center immunologist, Greg Delgoffe is the first recipient of the newly established Sy Holzer Endowed Immunotherapy Research Fund to advance innovative research in cancer immunotherapy.

The fund was established to honor Holzer's philanthropic work as president

of PNC Financial Services and years of service as chair of UPMC Hillman Cancer Center Council.

The fund has been supported through leadership gifts made by individuals, foundations and corporations, including Robert and Christina Pietrandrea, Jay Cleveland and Cleveland Brother Equipment, the Heinz Endowments, the Hillman Foundation, the Buncher Foundation and the Stanley M. Marks, Research Fund.



Delgoffe, assistant professor of immunology at the University of Pittsburgh, also is a research scientist at UPMC Hillman Cancer Center's Tumor Microenvironment Center.

His laboratory seeks to understand how cancer cells use fuel from their local environment, starving infiltrating immune cells and preventing them from attacking cancer cells.

FUNDING OPPORTUNITIES



FDA Oncology Center of Excellence publishes research contract opportunities

The FDA Oncology Center of Excellence seeks white papers to award contracts for oncology regulatory science research through a Broad Agency Announcement, [FDABAA-19-00123](#).

Research areas are described in the BAA document, but specific OCE interests include analysis of symptoms, physical function, immunotherapy biomarkers, non-clinical studies to evaluate new targeted therapies in children, real-world data endpoints, and external controls for pediatric studies.

Submit quad charts and whitepapers to FDABAA@fda.hhs.gov by March 30.

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THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP



Genentech submits sNDA for Venclexta plus Gazyva for previously untreated CLL

Genentech announced the submission of a supplemental New Drug Application to FDA for Venclexta (venetoclax) in combination with Gazyva (obinutuzumab) in people with previously untreated chronic lymphocytic leukemia and co-existing medical conditions.

Genentech is a unit of the Roche Group.

FDA is reviewing the application under the Real-Time Oncology Review pilot program, which aims to explore a more efficient review process to ensure safe and effective treatments are available to patients as early as possible.

Venclexta is being developed by AbbVie and Genentech. It is jointly commercialized by the companies in the U.S. and commercialized by AbbVie outside of the U.S.

Breakthrough Therapy Designation was granted based on results of the randomized phase III CLL14 study, evaluating the fixed-duration combination of Venclexta plus Gazyva, compared to Gazyva plus chlorambucil, in people with previously untreated CLL and co-existing medical conditions. The study met its primary endpoint and showed a statistically significant reduction in the risk of disease worsening or death (progression-free survival as assessed by investigator) compared to standard-of-care Gazyva plus chlorambucil.

Safety for the Venclexta plus Gazyva combination appeared consistent with the known safety profiles of the individual medicines, and no new safety signals were identified with the combination. Data from the CLL14 study will be presented at an upcoming medical meeting. The CLL14 study is being conducted in cooperation with the German CLL Study Group, headed by Michael Hallek, M.D., University of Cologne.

CLL14 (NCT02242942) is a randomized phase III study evaluating the combination of fixed-duration Venclexta plus Gazyva compared to Gazyva plus chlorambucil in patients with previously untreated chronic lymphocytic leukemia and co-existing medical conditions.

Altogether, 432 patients with previously untreated CLL were randomly assigned to receive either a 12-month duration

of Venclexta alongside six-month duration of Gazyva (Arm A) or six-month duration of Gazyva plus chlorambucil followed by an additional six-month duration of chlorambucil (Arm B).

The primary endpoint of the study is investigator-assessed progression-free survival. Secondary endpoints include PFS assessed by independent review committee, minimal residual disease status, overall response, complete response (with or without complete blood count recovery), overall survival, duration of response, event-free survival, time to next CLL treatment and safety. The CLL14 study is being conducted in cooperation with the German CLL Study Group, headed by Michael Hallek, University of Cologne.

Study: AI may perform as well as radiologists

A [paper](#) published in the *Journal of the National Cancer Institute* suggests that artificial intelligence systems may be able to perform as accurately as radiologists in the evaluation of digital mammography in breast cancer screening.

Breast cancer screening programs using mammography are effective in reducing breast cancer-related mortality. However, current screening programs are highly labor intensive due to the large number of women that have to be screened.

Considering the increasing scarcity of breast screening radiologists in some countries, many researchers believe

other screening methods may be worth investigating.

Since the 1990s, computer-aided detection systems have been developed to detect and classify breast lesions in mammograms automatically. However, no studies to date have found that these systems directly improve screening performance or cost effectiveness. This has precluded their use as a method for screening mammography.

In this study, researchers compare, at a case level, the cancer detection performance of a commercially available AI system to that of 101 radiologists who scored nine different cohorts of mammography examinations from four different manufacturers as part of studies previously performed for other purposes.

Each dataset consisted of mammography exams acquired with systems from four different vendors, multiple radiologists' assessments per exam, yielding a total of 2,652 exams (653 malignant) and interpretations by 101 radiologists (28,296 independent interpretations).

The performance of the artificial intelligence system was statistically not-inferior to that of the average of the 101 radiologists. The evaluated system achieved a cancer detection accuracy comparable to an average breast radiologist in this retrospective setting.

"Before we could decide what is the best way for AI systems to be introduced in the realm of breast cancer screening with mammography, we wanted to know how good can these systems really be," Ioannis Sechopoulos, one of the paper's authors, said in a statement. "It was exciting to see that these systems have reached the level of matching the performance of not just radiologists, but of radiologists who spend at least a substantial portion of their time reading screening mammograms."

DRUGS & TARGETS



Paige.AI receives FDA Breakthrough Device designation

Paige.AI, a start-up in computational pathology focused on building artificial intelligence received the Breakthrough Device designation from FDA.

According to Paige.AI, this is the first such designation for AI in cancer diagnosis publicly announced by any company.

"Paige.AI is focused on providing artificial intelligence tools to pathologists that will enable them to become faster and more accurate in their diagnosis and treatment recommendations for the care of cancer patients," Leo Grady, CEO of Paige.AI, said in a statement.

The FDA's Breakthrough Device designation is granted for technologies that have the potential to provide for more effective diagnosis or treatment for life-threatening or irreversibly debilitating diseases, where timely availability is in the best interest of patients because no approved alternative exists or because the technology offers significant advantages over existing approved alternatives.

The Breakthrough Device program was created by the 21st Century Cures Act.

Paige.AI was launched in early 2018 based on technology developed by Thomas Fuchs, co-founder of Paige.AI, and his colleagues and a license agreement with Memorial Sloan Kettering Cancer Center. MSK began digitizing its pathology slides four years ago.

Under the license agreement, Paige.AI receives de-identified images of digitized slides—more than one million such slides to date—and is funding the digitization of an additional four million archive slides, which in total will create the largest digital pathology dataset.

Paige.AI is working with this de-identified dataset to develop a comprehensive portfolio of AI products across cancer subtypes to serve the needs of pathologists around the world.

Lynparza receives positive EU CHMP opinion in breast cancer

AstraZeneca and Merck said the Committee for Medicinal Products for Human Use of the European Medicines Agency has adopted a positive opinion, recommending the use of Lynparza tablets, as monotherapy for adult patients with germline BRCA1/2-mutations, who have human epidermal growth factor receptor 2–negative locally advanced or metastatic breast cancer.

Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor–positive breast cancer should also have progressed on or after

prior endocrine therapy, or be considered unsuitable for endocrine therapy.

The positive opinion is based on data from the randomized, open-label, phase III OlympiAD trial, which tested Lynparza against the physician's choice of chemotherapy.

Lynparza is approved in over 60 countries, including those in the European Union, for the maintenance treatment of platinum-sensitive relapsed ovarian cancer regardless of BRCA status.

It is approved in the U.S. for first-line maintenance therapy in BRCAm advanced ovarian cancer following response to platinum-based chemotherapy. It is also approved in several countries, including the U.S. and Japan, for germline BRCAm HER2-negative metastatic breast cancer previously treated with chemotherapy – regulatory reviews are underway in other jurisdictions.

OlympiAD was a global, randomized, open-label, multi-center phase III trial of 302 patients, assessing the efficacy and safety of Lynparza tablets (300 mg twice daily) compared to physician's choice of chemotherapy (capecitabine, eribulin or vinorelbine). Two-hundred and five patients were randomized to receive Lynparza and 97 patients were randomized to receive chemotherapy.

Patients in the OlympiAD trial had germline BRCA1 and/or BRCA2-mutated, HER2-negative (hormone receptor-positive or triple-negative) breast cancer and received Lynparza for treatment in the metastatic setting.

Prior to enrollment, all patients were treated with an anthracycline (unless it was contraindicated) and a taxane in the neoadjuvant, adjuvant or metastatic setting. Previous treatment with platinum chemotherapy in the neoad-

juvant, adjuvant or metastatic setting was allowed (28% of patients).

In the trial, Lynparza provided patients with a significant median progression-free survival improvement of 2.8 months (7.0 months for Lynparza vs 4.2 months for chemotherapy). Patients taking Lynparza experienced an objective response rate of 59.9 percent, which was double the response rate for those in the chemotherapy arm (ORR 29%).

Data from the OlympiAD trial can be found in the Aug. 10, 2017 issue of the New England Journal of Medicine.

Breast Cancer Index receives expanded Medicare coverage

Biotheranostics Inc. said its Breast Cancer Index test has received a new Medicare Local Coverage Determination [L37822] by Noridian, effective April 16.

Based on additional studies and inclusion of BCI in clinical practice guidelines, the new LCD provides significantly broader coverage for patients with hormone receptor positive, early stage breast cancer than previously issued for the test in 2014.

Under the new criteria, BCI will be covered for post-menopausal women diagnosed with early-stage, node negative, non-relapsed, ER and/or PR positive, HER2 negative breast cancer to help physicians determine treatment management of the patient for chemotherapy and/or extended endocrine therapy.

For patients diagnosed with HR+, early-stage breast cancer, results across multiple clinical trials investigating the optimal duration of extended endocrine therapy remain inconclusive, and

support the increasing role of genomic tests, including BCI, to help individualize patient selection.

Most recently, the American Society of Clinical Oncology Clinical Practice Guideline Focused Update on Adjuvant Endocrine Therapy for Women with Hormone Receptor Positive Breast Cancer reinforces this solution, endorsing genomic tests such as BCI, to aid in decisions regarding extended adjuvant endocrine therapy with aromatase inhibition for post-menopausal patients with early-stage, HR+ breast cancer.

BCI is the only test validated to predict the likelihood of benefit of extended endocrine therapy to help physicians with recommendations related to treatment of their patients beyond five years.

Breast Cancer Index is a molecular, gene expression-based test uniquely positioned to provide information to help physicians individualize treatment decisions for patients with early stage, ER+ breast cancer. This breakthrough test helps oncologists and patients navigate the difficult trade-off between taking steps to prevent recurrence of their disease and facing significant side effects and safety challenges related to unnecessary treatment.

Breast Cancer Index holds guidelines designation from the American Joint Committee on Cancer for cancer staging based on molecular profile; ASCO, NCCN, European Group on Tumor Markers, and St. Gallen to inform the chemotherapy decision; and ASCO and EGTM to inform the extended endocrine treatment dilemma.

NCI TRIALS



NCI Trials for March

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

For further information, contact the principal investigator listed.

Phase I - 10214

Immune Checkpoint Blockade for Kidney Transplant Recipients with Selected Unresectable or Metastatic Cancers

JHU Sidney Kimmel Comprehensive Cancer Center LAO

Lipson, Evan Jacob
(410) 502-5977

Phase I - 10241

Phase 1 Trial of Human IL-15 (rhIL-15) and Obinutuzumab for Relapsed and Refractory Chronic Lymphocyte Leukemia

NCI Center for Cancer Research
Miljkovic, Miloa
(301) 250-5216

Phase I - 10246

A Phase 1 Study of MLN4924 (Pevonedistat) and Belinostat in Relapsed/Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome

University Health Network Princess Margaret Cancer Center LAO
Shafer, Danielle A
(804) 628-0279

Phase I/II - 10195

A Phase 2 Study of Copanlisib (BAY 80-6946) in Combination with Fulvestrant in Women with Metastatic Breast Cancer Progressing After Aromatase Inhibitor Plus CDK 4/6 Inhibitor

Duke University - Duke Cancer Institute LAO
Dees, Elizabeth Claire
(919) 843-7714

Phase I/II - ABTC-1801

Phase I/II Study of BGB-290 with Temozolomide in Recurrent Gliomas with IDH1/2 Mutations

Adult Brain Tumor Consortium
Bindra, Ranjit S
(203) 200-3749

Phase I/II - PBTC-053

A Pediatric Brain Tumor Consortium Phase I/II and Surgical Study of CX-4945 in Patients with Recurrent SHH Medulloblastoma

Pediatric Brain Tumor Consortium
Salloum, Ralph
(513) 636-1281

Phase II - A091802

Phase II Randomized Trial of Avelumab Plus Cetuximab Versus Avelumab Alone in Advanced Cutaneous Squamous Cell Carcinoma of the Skin (cSCC)

Alliance for Clinical Trials in Oncology
Zandberg, Dan Paul
(410) 328-6373

Phase II - AAML18P1

Stopping Tyrosine Kinase Inhibitors (TKI) to Assess Treatment-Free Remission (TFR) in Pediatric Chronic Myeloid Leukemia - Chronic Phase (CML-CP)

Children's Oncology Group
Chaudhury, Sonali
(312) 227-4863

Phase II - ANBL1821

A Phase 2 Randomized Study of Irinotecan/Temozolomide/Dinutuximab with or Without Eflornithine (DFMO) (IND# 141913) in Children with Relapsed, Refractory or Progressive Neuroblastoma

Children's Oncology Group
Macy, Margaret Ellen
(720) 777-6458

Phase II/III - NRG-G1005

Phase II/III Study of Circulating Tumor DNA as a Predictive Biomarker in Adjuvant Chemotherapy in Patients with Stage IIA Colon Cancer (COBRA)

NRG Oncology
Morris, Van Karlyle
(713) 792-2828

Phase III - A021703

Randomized Double-Blind Phase III Trial of Vitamin D3 Supplementation in Patients with Previously Untreated Metastatic Colorectal Cancer (SOLARIS)

Alliance for Clinical Trials in Oncology
Ng, Kimmie
(617) 632-4150

Phase III - EA5163

EA5163/S1709 INSIGNA : A Randomized, Phase III Study of Firstline Immunother-

apy Alone or in Combination with Chemotherapy in Induction/Maintenance or Postprogression in Advanced Non-squamous Non-Small Cell Lung Cancer (NSCLC) with Immunobiomarker SIG-Nature-Driven Analysis

ECOG-ACRIN Cancer Research Group
Borghaei, Hossein
(215) 214-4297

Phase III - NRG-BR004

A Randomized, Double-Blind, Phase III Trial of Paclitaxel/Trastuzumab/Pertuzumab with Atezolizumab or Placebo in First-Line HER2-Positive Metastatic Breast Cancer

NRG Oncology
Geyer, Charles Edward
(804) 628-6435

Phase III - NRG-G1006

Phase III Randomized Trial of Proton Beam Therapy (PBT) Versus Intensity Modulated Photon Radiotherapy (IMRT) for the Treatment of Esophageal Cancer

NRG Oncology
Lin, Steven H.
(713) 563-8490

Phase III - S1803

Phase III Study of Daratumumab/rH-uPH20 (NSC- 810307) + Lenalidomide or Lenalidomide as Post-Autologous Stem Cell Transplant Maintenance Therapy in Patients with Multiple Myeloma (MM) Using Minimal Residual Disease to Direct Therapy Duration (DRAM-MATIC Study)

SWOG
Krishnan, Amrita Y.
(626) 256-4673 X 63974

Phase Other - AAML16B9-Q

Role of Cohesin in Hematopoiesis and Myeloid Leukemia in Children with Down Syndrome

Children's Oncology Group
Pati, Debananda
(832) 824-4575

Phase Other - ANBL19B1-Q

Proteogenomic Profiling of High-Risk Neuroblastoma for Telomere Maintenance and Patient Outcome

Children's Oncology Group
Lau, Loretta
+612-9845-3115

Phase Other - AOST19B1-Q

Interrogating the Osteosarcoma Micro-environment to Identify Critical Pathways for Therapeutic Intervention

Children's Oncology Group
Davis, Lara E.
(503) 494-8423

Phase Other - AREN18B3-Q

Development of Liquid Biopsy Assays for Wilms Tumor

Children's Oncology Group
Walz, Amy Leanne
(312) 227-4090

Phase Other - WF-1804CD

Assessing Effectiveness and Implementation of an EHR Tool to Assess Heart Health Among Survivors (AH-HA)

Wake Forest NCORP Research Base
Weaver, Kathryn E.
(336) 713-5062

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