

Remarks\* by

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Thank you for that kind introduction, Dr. [Mike] Caligiuri.

As I join you here for the first time as NCI Director, I feel it's appropriate to extend a word of appreciation on behalf of NCI. First, thank you to AACR and its 40,000 members from across the globe, many of whom are in the room today or are joining us online via the Facebook live stream, for your pioneering research and dedication to progress against cancer.

Thank you to the cancer research advocates for your informed voice that helps drive policy change. A big thank you to the members of Congress and the President who clearly appreciate the important work of NCI. With the recent passage and signing of this year's Omnibus spending bill we have seen 4 years of budget increases, including a terrific \$275 million increase to the NCI budget in 2018, as well as continued full funding for the Cancer Moonshot.

And I'd be remiss if I didn't acknowledge my immediate predecessor, Dr. Doug Lowy, who paved the way for my tenure with his steady and professional leadership as NCI acting director over the past 2 years. I'm grateful that he continues to be a driving force at NCI.

Finally, and most importantly, thank you to the cancer survivors and patients. Your experiences are the ones that ultimately matter the most. You continue to lend vital inspiration and help shape how the research enterprise works to better prevent, diagnose, and treat cancer.

NCI is a large and complex organization with tremendous scale and capabilities. I show a few parts of NCI here on this slide. I was sworn in as NCI director in October of 2017. Given the scale of the job, I decided I would spend the first 6 months on the job on what I've been calling my “listening and learning tour.”

\*This text is the basis of Dr. Sharpless's oral remarks. It should be used with the understanding that some of the material may have been added or omitted during final presentation.

And I did exactly that, engaging with, listening to, and learning from the people across the cancer community including students, scientists, patients, advocates, federal employees, and former NCI directors. Although the official tour has ended, I have realized it should never really end, that is, I should keep listening and learning from these same groups throughout my tenure as NCI director.

Today, I'm pleased to share with you key insights I've taken away from this time and what I view as the critical focus areas for NCI. But let me first take a moment to share a bit about my personal experience with NCI and how I arrived there.

My first job as a scientist was at NIH nearly 30 years ago, between my second and third years of medical school. I took a year off to live on the NIH campus and work in an HIV lab as part of the NIH–Howard Hughes Medical Institute program. I loved that experience.

I'd been a math major in college and so this was the first time I'd actually done anything useful. I realized I loved basic investigation, keeping your own hours, studying a topic of your choosing, and poring over data you generated. After my year at NIH, I did return to medical school and then residency at Massachusetts General Hospital, followed by a medical oncology fellowship at Dana-Farber. But throughout my clinical training, I remained that sort of resident who would sneak away from his shift in the ER to go read the latest issue of *Cell* in the hospital library. I was that guy.

Returning to the lab after clinical work was hard, but I recall exactly why I did it. I felt back then that I was letting my patients down. I felt like our tools back in the late 1990s were inadequate for the cancers we faced.

Like so many of you, I have numerous patient stories about how I came to this realization, but will share one from a favorite patient who had breast cancer. A delightful, 40-ish-year-old woman, she had widely metastatic disease—what I suspect we would call, today, “triple negative disease.” But, back then, it was just “breast cancer.” She had lost all of her hair from the chemotherapy I gave her, but she remained positive and upbeat at all times.

During one visit, as it was becoming clear that the initial chemotherapy was no longer working, I had that “goals of therapy” conversation. She told me her main goal for therapy was not to get cured, because she knew was not going to happen, but rather to live long enough to see her 11-year-old daughter, the youngest of her three kids, graduate from high school. Just 6 more years, she asked. It did not seem like too much to ask. But I knew that wasn't going to happen, given the limited options for therapy we had.

That was a hard day. That patient, and many others like her, taught me something: that as much as I enjoyed patient care and clinical oncology, what we really needed were better ways to prevent and treat cancer.

And, like many others, I figured that the largely empirical approach to finding good cancer treatments employed back then was not adequate. Instead, more effective therapy and

prevention would only come from a better understanding of the biology of this disease. And, I realized I wanted to work on that.

So, I decided to become a mouse geneticist and molecular biologist in earnest, so I could find better ways of addressing cancer to help patients. I did that for many years and found, with great collaborators, interesting things about tumor suppressor genes and aging and circular RNA and novel therapeutics.

And along the way I got to train a lot of junior scientists and found I really liked that. And I got to turn some of our basic science ideas into commercializable intellectual property and found I liked that too. And then I became director of a cancer center charged with organizing the cancer research activities in basic, clinical, and population sciences of a large, multidisciplinary center in a diverse and complex catchment area. And I liked that job a lot.

Then the White House called about this job and, well, so far so good!

Through all this, my resolve to prevent and treat cancer has only become stronger. I know that each of you also shares this passion. And I find this energizing, charging...this sense that all the brilliant people working together, we can get things done!

I would now like to turn to my vision for NCI. I have identified four key focus areas where I think NCI can be particularly important to the cancer research enterprise. These are not new areas for NCI. However, I believe the time is ripe for a laser-sharp focus on these four areas, based on where we are today in terms of the developing science and technology, where the mass and heft of the NCI can play a unique role, and where NCI's resources, convening power, and leadership can act as catalysts.

Let me explain the overarching principles that guided my thinking to arrive at these four key areas.

First, cancer is not one disease but many diseases. Take lung cancer, for example. It started as just plain old lung cancer. Then we had non-small cell lung cancer. Then non-small cell lung adenocarcinoma, or RAS mutant non-small lung adenocarcinoma, and RAS mutant non-small cell lung adenocarcinoma with low tumor mutational burden or PD-L1 expression. And each of these new levels of distinction is important in terms of clinical behavior, response to therapy, risk factors, etc.

So, what once was one disease—lung cancer—is now more than 100 clinically distinct entities. This same fragmentation has occurred in every major cancer and, what this means, is even a common cancer like lung cancer really comprises many far less common but highly relevant subtypes. And each of these clinical subentities occurs in a patient who is entirely unique. But features about each patient apart from their disease—their education, their beliefs, their socioeconomic status, etc.—are all critical to the success or failure of therapy too.

A second guiding principle in this effort is the realization that we owe it to patients to make progress against all cancers—not just some of them—which is a real challenge since

cancer is so heterogeneous. But we must work on all the difficult problems and intractable challenges in cancer research. We cannot work on just the easy cancers or the common ones or the best-understood ones. We have to work on all of them.

And a third guiding principle—this staggering heterogeneity of cancer and need to work on all types of cancer—demands new approaches: new understanding of the molecular and cellular biology of cancer, new ways of conducting clinical trials, scientists with different training, and new ways of harnessing data to learn from every patient.

So, those were the principles that shaped my thinking as I considered where NCI should focus priorities now.

The first key focus area is about who is doing the science, the patient care, the work in cancer research, and how they are trained to do it. One of our most important jobs at NCI is to ensure a talented and innovative research workforce for the decades ahead. That means making sure that the best and the brightest don't get discouraged, that researchers continue to work to further science and fuel the discovery of new approaches and technology that will benefit patients.

NCI wants to strengthen and enhance opportunities at every career level from budding high school scientists, fellows, and early-stage investigators (ESIs) to seasoned researchers and staff scientists. We do this by providing funding for training at all stages of the career path. But more than funding, we must focus also on developing the right skills for today's cancer researcher. That means training people with the right expertise to match the heterogeneity of cancer. For example, it requires training in basic immunology, disparities research, prevention methodologies, and data science.

Here are a few examples of how our workforce development efforts must evolve. We must continue to press for a diverse workforce with regard to background, interest areas, ethnicity, and gender. We must encourage the right skill set through dedicated funding of training grants and opportunities. For example, create additional slots on awards focused on patient-oriented research (the K12), new research experiences (R25s), and other grant mechanisms that open new pathways to independence.

Although we are looking at ways to help cancer researchers at all stages, we have appreciated that there are particular problems for newly independent early-career investigators—what NCI calls ESIs. Congress, has asked NIH to pay particular attention to this group of scientists.

As many of you know, one of the biggest hurdles for ESIs is obtaining their first R01, the most common award for investigator-initiated grants. Given the strong support from Congress, as demonstrated by the increase they provided to NCI's 2018 appropriation, we have been provided the resources to decrease this hurdle a bit. Specifically, I am directing our extramural funders to set aside in 2018 a significant amount of additional new funding to increase the total number of first R01s given to ESIs by at least 25%.

To also support the ESIs, we have created a new mechanism to support their first grant—the R37. Under this change, ESIs who receive an R01 will be eligible to have their grant transitioned to an R37 award and, as a result, have the opportunity for extended funding for up to 2 years. In other words, a 5-year R01 grant could become a 7-year R37 grant with minimal extra work.

The R37 has “gone live” and further info is available on the NCI website. We hope 2 years of extra funding will allow ESIs to focus on doing their best research and building their careers.

So, to recap, we will not only train a diverse group of scientists and clinicians to ensure the expertise they need to be successful. We will especially target support for ESI investigators with more R01s this year and a lengthened initial period of funding

A second key area for NCI focus is the foundation, that is, renewing our commitment to basic science to increase understanding and drive novel approaches and technologies. It would not be fair to say that NCI has turned away from basic science in the recent past. Far from it. But there are some voices who feel we have done so well in a few cancer areas that this basic biological focus is no longer needed.

These people may argue for more and more spending to address a specific type of cancer, claiming the need in one tumor type is greater than others. And I understand this perspective. There can be a sense that the great ship of cancer research is passing one by when progress is made in treating some cancers but not the ones you personally care most about. Watching the TV ads for highly effective therapies in lung cancer and melanoma can feel like a fist to the stomach if your loved one has pancreatic cancer or certain types of refractory pediatric brain cancer.

I understand this frustration, and the ferocious desire to see progress in all cancers. It is also important to note that NCI has a large investment in translational and disease-specific research, but we can't afford to bypass the basic science step. An apt quote that is often attributed to Abraham Lincoln goes, “Give me 6 hours to chop down a tree and I will spend the first 4 sharpening my axe.” We must sharpen our axes and maintain a committed focus on fundamental science, because there is still very much about cancer that remains unknown.

While we have made tremendous progress in some cancers, we have to acknowledge that little or no progress has been made in other types. If you most want to see progress in one of these types of cancer, basic science provides hope.

Take, for example, NTRK inhibitors, which work against the fusion oncoproteins of the TRK kinases. These fusion events are very rare, but the kids and adults with cancers driven by these fusions have marvelous responses to NTRK inhibitors, as recently shown in *New England Journal of Medicine* and *Lancet Oncology* papers, with response rates exceeding 90% in one trial.

We should celebrate the success of these new agents, but we should also ask where did they come from, and how do we find more like them? The answer, in this case, comes from basic

science studies in the 1980s at NCI—in fact, at what is now the national lab at Frederick, where Mariano Barbacid was trying to clone the “OncD” oncogene he had discovered. And it turned out to be this weird fusion protein containing the TRK kinase.

I doubt Dr. Barbacid expected to find a new treatment for childhood cancers at the time he did this, but that is what his work ultimately accomplished.

So, if we accept that we still really need basic science, how can NCI help? First, I believe a top down approach is not the way to go here. Focus has to be on investigator-initiated discovery. NCI has some role in identifying topics for specific focus, but once we have done that, we have to sit back and let the magic happen. One of the best ways to support investigator-initiated science is through the funding of Research Project Grants—the RPG pool. This pool funds the vast majority of investigator-initiated awards—the R01s I already mentioned and the even larger program project grants, such as P01s.

In addition to the set-aside specifically for ESIs I already described, we will also put another \$100 million into investigator-initiated science in 2018. This is the largest increase to the RPG pool since 2003. This is possible thanks to increases in the past three years in our congressionally appropriated budget. While this is not solely for basic science—there are lots of laudable clinical trials and health services research funded from the RPG pool—this is the most straight-forward way to assure we continue to fund investigator-initiated basic science.

We also need to minimize the administrative burden on scientists. We understand that the grant application and management process is grueling, and I also understand that NIH bureaucracy is particularly challenging for young investigators. One initial step in the right direction has been longer, for example, 7-year, award periods, such as the Outstanding Investigator Award and the R37 I mentioned earlier. These are steps that have already been taken, and we’re actively looking at other approaches.

Finally, we must help provide great scientific infrastructure to allow cutting-edge science. This includes things like the Cryo-EM facility at the Frederick National Laboratory for Cancer Research, the SEER registry and the Genomic Data Commons. We have several new initiatives underway in this area that I will discuss at a future date.

For the third key focus area, we must catalyze technologies, specifically data technology, to add speed and dimension to our work across the cancer enterprise. If you consider that more than 90% of all digital data created to date across all fields was produced in the last 2 years, you get the idea.

And this brings up the idea of a data lake. They sound so great. You imagine them peaceful and serene. But really, they don’t work as you might imagine. I grew up in the South, and lakes are where you’d commit your old pickup truck. And they are a great place to hide a sea monster. My problem with the data lake concept is that it allows passive data sharing. Just upload your data in some unusable format and you have complied with the data sharing policy. No one else without a PhD in computer science can use it.

We must move from passive data sharing to data aggregation—establishing linkage and interoperability of diverse, complex data sets to understand cancer care and provide real world evidence. For example, linking the genomic data with the path data with the radiology data with clinical data mined by machine learning from an EHR in a large number of patients, in a way that assures data privacy and security.

I would argue that almost no matter what your interest is in cancer research, data aggregation helps your research. Say you want to know the effects of diet or exercise on cancer risk. Or say you want to know why a certain cancer disparity in outcome exists. Or you want to know why some rare patients with melanoma still have a good response to an old, and usually ineffective drug, like dacarbazine.

Such questions are almost intractable by traditional means. But all are addressed by large, annotated multimodal datasets.

So how are we going to harness big data? This is a place where we need to pay special attention to the workforce, attracting young data scientists into cancer research. We will focus on the linkage of many large datasets maintained by NCI to provide interoperability. There are several interesting efforts in this area that range from linking genomic data to clinical data in specific patient datasets. Toward that end, many different groups have begun contributing large datasets into the Cancer Research Data Commons.

This also includes efforts on much larger numbers of patients like novel methods of data linkage within the SEER registry. And we are working with partners, such as the DOE, who have novel capabilities, or FDA and CMS, who have rich datasets.

These data are supported by a developing NCI Cancer Data Ecosystem, which is being significantly amplified with significant new targeted funding from the Cancer Moonshot. This includes highly successful cloud resources for storage and computing.

NCI can lead in standards setting and we have efforts underway to solve the problems of unique identifiers, common ontologies, and a data thesaurus. We need to change our practices to reward and incentivize data sharing and aggregation, for example, by making aggregation possible by smart consenting and good trial design.

We have to do this because the costs of not having big data are too great.

For the last area of key focus, we turn to the vexing problem of clinical trials. Clinical trials are the fundamental means whereby progress is made in cancer therapy and prevention, and we need clinical trials to work for the researchers, clinicians, and our patients. But, we have to admit that the performance of clinical trials has been deeply affected by the fact that cancer is so heterogeneous. Gone are the days when the cardiology paradigm of clinical trials reigned and when we enrolled hundreds of patients in a large phase 3 randomized study with slightly different treatment protocols.

Since there are so many types of cancer, this approach no longer works, and now we are in the era of precision oncology. But, this has caused some major problems. Enrollment is poor with approximately 5% of adult patients enrolled on a clinical trial. And one in five cancer clinical trials for adults is never completed because of accrual issues.

The endeavor is also incredibly expensive which means many good ideas never get tested. And it means the costs of drug development are skyrocketing, and such costs get passed on to patients. While enrollment is better on pediatric cancer trials, it is clear pediatric oncology trials also have some problems.

There have been difficulties getting great new ideas tested in kids with cancer. Pharma has come late to this. Pediatric trials also share the increasing cost issues. And the present system does not work for patients. They have trouble finding trials and having trouble getting access to trials.

So, how to modernize clinical trials given these new realities of cancer care? NCI can promote better design of clinical trials. We have to get rid of unnecessary exclusion criteria and confusing consent forms. We need to adopt central IRBs. We need trials with innovative design to find inactive agents quickly and thereby prioritize good drugs for further testing.

A great example of modern trial design is the NCI-MATCH trial. This precision oncology trial allocated patients to one of 30-plus arms of therapy based on somatic genetic testing. While the efficacy of agents tested in NCI-MATCH will be presented at a later date, this trial enrolled over 6,000 patients at 1,100 sites. This is the fastest-accruing trial in the history of NCI.

We are also employing this same approach through the Pediatric MATCH Trial. Working with the Children's Oncology Group, NCI has brought Pediatric MATCH to 200 sites across the country with 8 arms currently open.

In adult oncology, 85% of patients are not treated at Comprehensive Cancer Centers, and to boost enrollment, we need to accrue patients to clinical trials in the community setting. As NCI-MATCH has made it clear, it is possible to accrue patients to fairly complex trials in community settings. Many of the patients on NCI-MATCH were enrolled at sites within the NCI's Community Oncology Research Program (NCORP). NCORP comprises seven research bases and 46 community sites across the United States, 12 of which are situated to serve minority or underserved populations.

While industry funds more clinical trials than government agencies do, we will always need NCI to support certain kinds of large trials that don't work well in industry, such as complex multimodality approaches including surgery, radiation oncology, etc. This is why I am eager to work with the National Clinical Trials Network (NCTN), which represents NCI's major effort to conduct studies across many academic institutions. I look forward to working with the five clinical trials groups making up the NCTN to conduct trials more quickly and more effectively.



NCI has also created the Experimental Therapeutics Clinical Trials Network (ETCTN), a collaboration among the pharmaceutical industry, academic institutions, and individual investigators to conduct early-stage trials of innovative cancer treatment therapies in high-priority areas of unmet medical needs.

I am aware that the NCTN and related NCI networks have been undersupported. And I am committed to looking at the funding models and to search for additional per-patient funding for NCI network trials in order to maintain critical NCI clinical trials networks.

Lastly, we have to admit that trials done the old way are inefficient. Rather than testing one specific variable in a trial, by aggregating data at greater scale, we can learn from every patient. This will require thinking about trials differently, seeing drug development through the lens of a health service researcher, and using the tools of big data and data aggregation, as I mentioned before.

So, these are the four key focus areas for NCI while I am at the helm: workforce development, basic science, big data, and clinical trials.

It should be clear that these four areas are highly related. For example, workforce development is a big issue for big data, which directly benefits clinical trials, and all of this is underpinned by basic investigation.

Also, let me assure you that focus on these areas does not mean that other areas not explicitly included here will be forgotten. NCI is responsible for the entire National Cancer Program, for research and progress that spans the entire research continuum. And we will remain committed to that mission. As I see it, these are areas of particular opportunity where we need to focus now.

In a moment, I'll continue the conversation with two esteemed colleagues here on stage. But let me finish as I began, by talking about patients.

I started today with the story of a patient that I cared for a long time ago, a patient for whom our therapies back then did not provide much hope. Memories of her and patients like her have provided my motivation. They keep the devastating effects of cancer at the forefront of my thinking. I believe we can work together to lessen these awful burdens of cancer in our patients' lives. And to be sure, we have already made tremendous progress since those bad old days of limited options and a poor understanding of the biology of cancer.

I believe by applying focus in these areas now, we can further accelerate the pace of that progress. We need to honor every patient and realize that those we successfully treat as well as those we are unable to help all have experiences that are valuable for progress against cancer.

We owe it to them to work together to see this potential realized.

Thank you.