Remarks* by

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Good evening! It's an honor to be here. I would like to thank Dr. Alexis Thompson for the invitation. I'd like to start off with a patient's story.

As Dr. Thompson mentioned, I am a medical oncologist, and prior to my role at NCI, I used to treat patients with acute leukemia on the inpatient service at the University of North Carolina Medical Center in Chapel Hill.

In March 2016, I was asleep at home, when I got a call around three in the morning. The medical oncology fellow told me that a previously well, 60-year-old man was in the ER and that I had better come see him quickly. He was febrile, possibly infected, and had low platelets and anemia—signs of an obviously failing bone marrow.

As is often the case in this business, I went to the hematology lab, drinking coffee, where I met the patient's blood smear before I actually met the patient. One quick look at the peripheral smear provided the diagnosis: few platelets, few granulocytes, lots and lots of ugly, immature, obviously myeloid blasts…acute myelogenous leukemia, or AML.

I then went up to see the patient and his family in his hospital room. His name was Mike. He was an African-American guy—a husband, a father with two kids, and a journalist. Even though he was quite sick and must have felt terrible, he was handling it with a real dignity.

We did the usual stuff to stabilize him: IV fluids, antibiotics, transfusions; and we obtained a bone marrow biopsy and put in a central line. But having seen this particular movie many times before, that is, treating patients in this situation, at this age with this sort of AML, I assumed from the get-go that this was not going to end well. I guessed that his would likely end up being another one of those too-common stories of the inpatient leukemia service: a good guy eventually dying from a bad cancer.

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I am a big believer in providing hope for all patients. But, I am also a big believer in frank conversations and realistic expectations, and so I started in this way right away. I warned him and his wife that this was a tough disease. He was going to need very aggressive therapy.

I prepared to treat him with a chemotherapy regimen, 7+3, that was considered old even back when I was in medical school. If he were lucky, we might be able to get him into a remission, and then likely we'd be talking about a bone marrow transplant, which would be his only, but slim, chance at a long-term remission.

All we needed to get started with his therapy were the early molecular results from the bone marrow biopsy, which nowadays, at a good hospital with good hematopathologists, does not take very long at all. Just waiting a little while…

The waiting period for results—this is such a classic hospital moment. *Everything* hangs in the balance.

But have you ever thought about it this way? What happens to that patient after that period of waiting, what happens next, depends on *us*.

What we do at NCI, and through care and research organizations like the American Society of Hematology, is what changes what these test results mean. Our scientific studies, our collective research efforts—these are what determine how we will act on those results when they finally come back. This work means everything to patients like this, and to their families.

I'll come back to Mike's story in a bit.

Today, I will take the opportunity to discuss the status of blood cancer treatment and research and my vision for the National Cancer Institute.

As NCI Director, my role involves overseeing the NCI research portfolio, both intramurally and extramurally, and keeping my finger on the pulse of what's happening across the spectrum of cancer prevention, treatment, and research.

Now, more than a year into this job, I have heard from a lot of the various stakeholders in cancer care and research. I have met with many patients, advocates, doctors, nurses, other caregivers, and scientists, and I have learned a tremendous amount about the Nation's progress against cancer.

And the first thing that I have learned, a clear fact to emerge from all those efforts, is that it is a great time to be a cancer physician or cancer scientist.

This is probably not news to members of ASH, as it is undeniably also a great time to be a blood cancer physician or a blood cancer scientist.

We are making progress at a rate that is greater than at any point in my career as an oncologist. Just look at all the new stuff we've got.

There are exciting new basic science discoveries in chromatin, stem cell biology, etc. There's this cool and emerging new topic of clonal hematopoiesis, demonstrating a direct mechanism to link cancer and aging. And our ever-growing understanding of cancer is turning into new therapies.

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We have approved CAR-T cells for CD19+ cancers: last year's approvals of Yescarta and Kymriah have paved the way for more research in this area for both adults and children. Exciting CAR-T approaches for Hodgkin lymphoma, myeloma and other leukemias will be presented at this meeting.

The FDA just approved a new drug for hairy cell leukemia—Moxetumomab is the *first new therapy for HCL in more than 20 years*. We are especially proud of it since it represents a few decades of work in the NCI intramural program, with Ira Pastan coming up with the idea for this antibody-drug conjugate, and then the initial studies for the agent being led by Robert Kreitman in the NIH Clinical Center.

Look at this year's ASH meeting. I'm blown away. I looked at a couple hundred of the abstracts, I have heard some of the early news about exciting new results, I even listened to John Leonard's *Leonard List* podcast. And there are exciting developments.

For example, at this meeting we'll hear about two NCI- supported trials carried out by ECOG-ACRIN and Alliance that I think revolutionize the care of CLL. Both results describe a chemo-free approach to this disease: using Rituximab + ibrutinib for CLL instead of drugs like fludarabine and bendamustine. This is a really common cancer, and now we have pretty gentle therapy for these patients that works really, really well. These are two trials among hundreds going on now that will make a difference for patients.

And what an extraordinary period for AML. After decades of little progress in this disease, I think we have seen *eight* new FDA approvals for AML in the last year and a half. Both targeted agents (e.g., against FLt3 and IDH mutations), as well as a liposomal formulation of 7+3, a first-in-class Hedgehog pathway inhibitor, the return of Mylotarg, and venetoclax.

So much progress in a refractory disease like AML, after so much time spent wandering in the wilderness. Well, this just suggests that all that detailed and elegant basic science, all that work that we needed to do—well, those efforts are now paying off.

And by the way, this progress is not limited to blood cancer: we have seen great progress this year in breast cancer, in lung cancer, in head and neck cancer, in melanoma, in ovarian cancer. At the last ASCO conference, we even had a wildly positive, large, randomized trial in resected pancreatic adenocarcinoma, which is the first I can recall of my lifetime.

Now, some of you will certainly say that while this progress is impressive, it is not enough. Many of these new approaches are only moderately effective and not curative. Many of these advances represent only singles, or maybe doubles, and we still need some home runs. We still have too many patients dying from cancer, including hematologic cancer, in the United States.

This is true, but from my perspective, it is important to be very clear-eyed on this topic. While we must admit that we still have a long way to go to realize our goal of ending cancer suffering for all patients, at the same time, we also have to admit that the rate of progress is impressive.

I maintain that it is important to be forthright about both statements. One reason for this is that I, as NCI director, routinely have people coming to me advocating radical change as to how the NCI funds research: "Put all the money in the Cancer Centers or the SPORES; the NCI should completely end the Cancer Centers and the SPORES." "Put all the money in R01s; stop funding R01s." "Do more Prevention; the NCI does too much Prevention." And so on.

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To these people, I say that of course we could, and will, make some changes to how we operate. There is no doubt that some things about the NCI could be changed or modernized to better meet our goals. But it is also true that progress against cancer is really strong right now. And so, job number one of the NCI Director is to make sure that positive momentum continues.

Let's take a closer look at where we are now.

The Annual Report to the Nation on the Status of Cancer was published in May. The ARN is an update of rates for new cases and deaths as well as trends for the most common cancers in the United States. These incidence and prevalence statistics show that what we are doing across the cancer research community, in academic and community settings, and in public health, is having a positive effect. We still have a way to go, but overall, progress has been strong. And these are real improvements with real outcomes that mean something to real people.

Some good news is that deaths due to blood cancers from 2011–2015 either decreased or stayed the same.

Myeloma death rates for women stayed the same, while those for men decreased by almost 1%. Death rates for non-Hodgkin lymphoma decreased 2% for men and 2.7% for women, and leukemia death rates dropped 2.2% for men and 2.3% for women.

These results are not a coincidence. I believe these changes are due to sustained research, investment, and discoveries in blood cancers. Study by study, patient by patient, these numbers are a result of the diligent work of many of the people in this room. Let's congratulate those of you in the audience who have made it your life's work to produce this terrific progress.

I find myself pointing out a lot these days that there has been amazing recent progress against cancer, and that the pace of that progress now is faster than ever before, but ALSO that this progress has been highly uneven. Consider the amazing recent advances in CLL and myeloma, where new drugs have revolutionized care in these diseases. And then compare our efforts in acute leukemias, where progress has been more incremental against a really terrible cancer of children and adults.

This informs my decision making as NCI Director and is reflected in the areas we have identified for key focus. The NCI believes we have to learn from every patient so that we can make progress for patients with all types of cancer.

We are extremely grateful for increases to our Congressional appropriations in recent years. And I think it's important to note that this support isn't just about funding. NCI can use its convening power, expertise, and infrastructure to facilitate conversations and collaborations across the community that I think will make a meaningful difference to the future of cancer research and care.

The Cancer Moonshot was announced in 2016 with three overarching goals: accelerate progress in cancer research, encourage greater collaboration, and improve the sharing of data. More than 2 years later, the Moonshot is well on its way to achieving these goals.

A critical component of that foundation was the Moonshot Blue Ribbon Panel, which engaged in a thoughtful and thorough process to develop a comprehensive report that laid out a series of 10 recommendations to get us to those goals. Many funding opportunities were issued and awarded, and several are still open now.

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Of particular interest to the hematology community are two groups of research teams that NCI is funding: the Immuno-oncology Translational Network, or IOTN, focused on immunotherapeutic approaches in adults, and the Pediatric Immunotherapy Discovery and Development Network, or PIDDN, focused on children.

The Pediatric Fusion Oncoprotein Cancer Moonshot initiative includes a request for applications related to NUP98 fusions that occur in young children with AML. Applications are due in next week with awards to be announced mid-year in 2019.

After being sworn in as Director in October 2017, I spent the first 6 months on the job on what I have called my "listening and learning tour." I engaged with a diverse range of stakeholders and arrived at four key areas of focus: workforce development, basic science, big data, and clinical trials. To be sure, these are not new areas for NCI. However, based on where we are today in terms of scientific and technological trends, I believe we need to sharpen our focus on these four areas, as they are foundational to progress. To make the most of recent research advances and emerging opportunities, we have to work strategically in these areas. If we don't, we risk missing critical opportunities for achieving rapid and meaningful progress.

I'd like to mention a few specific areas that may be of interest to the membership of ASH.

WORKFORCE DEVELOPMENT: In 2018, the RPG pool had the largest increase since FY 2003. Also, NCI exceeded its goal of funding 25% more Early Stage Investigators, and the FY 2019-enacted appropriation is a $179M increase over FY 2018. By attracting and retaining the best and the brightest from a diversity of backgrounds, we hope to develop new crops of scientists trained in the latest approaches and technologies.

BASIC SCIENCE: A continued commitment to basic science will broaden our understanding of cancer and hasten progress toward better therapies for the blood cancers for which we have less understanding.

A point I like to make about cancer in general is well-illustrated by blood cancers. I believe the most important fact to come from cancer research in the last two decades has been the appreciation that cancer is not one or a few diseases but, in fact, hundreds—maybe even thousands—of clinically distinct diseases in terms of pathogenesis, therapeutic response, and prognosis. We no longer have just "lymphoma," but now have myriad varieties of B- and T-cell lymphoma, with effective, targeted approaches, depending on things like RNA subtype, CD19 expression, ALK status, BRAF mutation, etc. This fact has had tremendous implications for the entire cancer research enterprise, from drug discovery to prevention to clinical trials and to survivorship.

CLINICAL TRIALS: Every one of today's therapies for malignant hematological disease is available because of a successful clinical trial, but we need to bring these trials up-to-date. This includes increased funding for certain types of clinical trials, as well as incentivizing clinical trials data sharing and access. Improving clinical trial design will help prioritize good drugs for more testing. This includes modernizing the clinical trials infrastructure to support investigations of highly active therapies in small, molecularly defined subsets of different cancer types.

BIG DATA: I will share a story that shapes how I think about the need to focus on big data—one that really bothers me to this day. While we're good at telling people the costs of aggregating data, we're not as good at articulating the costs of **not** aggregating data.

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For 20 years, I would do a month a year on rounds treating AML and, as many of you know, you basically give two drugs or two therapies. You give 7+3, daunorubicin and cytarabine (Ara-C) or decitabine or a hypomethylating agent.

The choice can be hard to make. 7+3 has a better chance of curing, but it's more toxic. In general, we use the hypomethylating agents for the older patients who we think are frailer. But in some patients, the decision was more or less a coin flip. The therapies were interchangeable.

And then a single-institution study with a hundred patients at Washington University showed that if you had a p53 mutation, which is a very common genetic event, present in half the patients, then the response to chemotherapy is as different as black and white.

In other words, the molecular genetics in the tumor should drive therapy. I had never done that.

This paper upset me. I had been treating patients with AML for 20 years. I can close my eyes and see the faces of actual patients that I gave 7+3 to and who did very poorly and had very bad outcomes, which is not at all uncommon with AML. In retrospect, I'm confident we gave what we now know is the wrong regimen.

I see this as a clear failure of data aggregation. If we'd aggregated data and we'd start putting large collections of AML patients together that had been genetically sequenced, this result, and many other results, would have been apparent almost immediately.

I am concerned that we are still doing this for other cancer subtypes today, especially in cases where the genetic event that predicts response is rarer.

Think about it…if we had so much trouble seeing the impact of a common event like p53 mutation, the most common event in human cancer, what else are we missing? Aggregating data will create great opportunities for cancer research and care, but also new challenges.

One challenge is in the area of data standardization. This effort takes many forms, including trying to increase the clinical annotation of the Cancer Genome Atlas, augmenting our available large datasets of annotated imaging data, and developing new linked datasets to the SEER registry.

We must also move beyond passive data sharing to intentional data aggregation in order to fully leverage the power of data, establishing linkages and interoperability of diverse, complex data sets to understand cancer care and provide real world evidence.

We have to do these things because the costs of not harnessing big data are too great. I am certain this will save lives.

So, back to my story about Mike. He came in with AML and we did a bone marrow biopsy. And then the result came back.

To my surprise, he came back with "good cytogenetics." Mike had inv(16), core-binding AML. This meant he would just get the usual 7+3 chemotherapy. He had a good chance of going into remission. He wouldn't need a bone marrow transplant. He had a pretty good chance of being cured.

One of the greatest privileges of being a cancer doctor is getting to deliver good news to a patient. I got to tell him and his family that the results of the bone marrow were actually surprisingly good. What a lovely

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moment. His two adult daughters were there, and they were crying and happy, and his wife was crying and happy, and the patient was a little overwhelmed. It was a good moment, and a surprise.

We treated him with standard 7+3 chemotherapy, and it wasn't a terribly difficult induction. And then he promptly went into remission. He then got his consolidation without much drama, and he's been in complete response for more than 2 years.

Here's a picture of us. We had coffee together a few months ago when he came to visit me at NIH. He is doing really well.

A few lessons from this story:

First, patients will surprise you. A disease that you might assume is incurable can turn out to be very curable. That gives me a lot of hope.

Second, this reminds me to comment on the role of malignant hematology research on the topic of precision oncology. In many ways, precision oncology started with acute leukemia, as we learned that patients had different prognoses and responses to therapy if they differed in things like inv(16), monosomy 7, the Philadelphia chromosome.

This is so well-established that it is now commonplace and the standard of care. So, when people tell me they are scared of precision oncology, or they don't think it will work so well, I tell them to consider AML.

And lastly, note I deliberately chose the word "cure" as the goal for Mike. Now, I know enough about AML to know that after only 2 years in complete response, it is too soon to call him "cured." But, I think we can all talk frankly about that goal.

I have spoken about this issue before, about how sometimes there is fear in our professional community of using the word "cure" when it comes to cancer.

We get worried: what if we fail? What if it comes back? And, of course, the word "cure" should be used cautiously with vulnerable patients. Maybe we should just talk about extending progression-free survival or enhanced quality of life or reduced costs—or whatever measure we might pick. I understand these concerns.

But, my friends, if we've become scared to say "cure," what exactly are we trying to do? And, undoubtedly, we *are* curing some kinds of cancer. We *are* curing more people than ever before, including people with advanced disease and solid tumors. Disease by disease, mutation by mutation—make no mistake. We are helping patients with cancer and, sometimes, we *can* cure them.

Thank you.

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