Remarks* by
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Thank you so much for having me here today! It's a pleasure to join you to talk about pediatric precision oncology!

I'd like to thank Javed Khan and Jeff Trent, and other organizers for inviting me, and for all the effort required to make a conference like this happen.

Over the past several decades, substantial progress has been made in pediatric oncology. Whereas 50 years ago a child with cancer had a low chance of being cured, most children with cancer today will live 5 years past their diagnosis, and many are cured.

But, we know that this is an average and that there are many children with cancer who still die far too soon of their disease. And we also appreciate the burgeoning population of pediatric cancer survivors, of which we are closing in on 500,000 in the U.S! This rapid increase in the survivors of pediatric cancer is good news but also provides the challenge of addressing the long-term toxicity of the drugs we use to cure these cancers.

Let me share a bit of my background. First, perhaps most importantly, I am the son of a pediatrician. This gave me an interesting perspective into several issues that turn out to be relevant to the NCI Director. For example, I have insight into the plight of the young female physician who wants to have a family and a career. I lived that, which is probably why I feel so passionately about workforce issues for young, female researchers today.

More to the point of today's talk, growing up the child of a pediatrician also cemented my unshakeable admiration and love of pediatricians, whom I know to be some of the greatest people alive. I have literally loved pediatricians all my life. There we go, starting with some shameless pandering to the audience. But, in this case it is true.

So, after negotiating childhood, I eventually trained as a medical oncologist at the Massachusetts General Hospital-Dana Farber Cancer Institute and in molecular biology in the DePinho lab there.

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

I went to the University of North Carolina (UNC) in 2002 where I ran my own lab studying activation of tumor suppressor genes and their role in preventing cancer, but untowardly causing aging.

I saw patients with leukemia and lymphoma that whole time and took care of lots of 17-to-20-year-olds trying to navigate that complex intermediate land between pediatric and adult oncology that has come to be known as adolescent and young adult or AYA oncology.

I became the director of the UNC Lineberger Comprehensive Cancer Center in 2014. A few things of relevance I did as Cancer Center director:

Using $20 million of donor and state money, I built a CAR-T Good Manufacturing Practices facility and launched studies in hematological cancers (CD19 ALL, CD30+ lymphoma). I developed novel vectors, not industry designed, which is key to further innovation in that area. I learned a lot about the clinical and regulatory challenges of cell immunotherapies from those efforts.

I started a clinical trial in 2011 using next generation sequencing to guide cancer therapy. We sequenced 3,000 patients, including children, and had many examples of how such results could drive therapy. We also rapidly appreciated we had several Big Data problems and were among the first to try to use AI to make since of clinic genomic data.

I learned a lot about the clinical trial enterprise in pediatric oncology from running a large university hospital protocol office, from helping the departments and divisions recruit in this area, as well as from being on the executive advisory board of St. Jude Children's Research Hospital and MD Anderson Cancer Center.

Some of my relevant research interests included:

We discovered how the activation of cellular senescence contributes to organismal aging. Since DNA damaging agents such as chemotherapy and ionizing radiation activate senescence in healthy cells, one of the first human clinical trials we tried was a collaboration with St. Jude's researchers Les Robison and Melissa Hudson to look at organismal aging in long-term survivors of therapy for pediatric cancers in the St. Jude Life Cohort, which I have called a national treasure on more than one occasion.

So, I was studying long-term pediatric oncology survivorship research long before it was cool. And one thing that frustrated me about survivorship research was how little science there was in this area.

Symptom management is an important and laudable area for study, but I always found the "why" of this long-term survivorship quite interesting. That is, the molecular and cellular biology of long-term toxicity: Why does chemotherapy cause premature gonadal failure years later? Why do the heart or kidneys seem to recover magnificently from all the adriamycin and platinum, etc., but then give up the ghost prematurely decades later? How do they remember what they went through so long ago? Why do people treated for cancers have increased incidence of certain secondary malignancies years to decades later?

Can we not just describe these things but actually understand why they occur and then prevent that from happening?

In my lab's case, we were not just trying to monitor this form of accelerated aging induced by DNA damaging agents using senescence markers, but also to prevent these long-term toxicities. At some point we hit that wall between basic science and clinical research and I was frustrated by this.

We heard from Lee Helman yesterday about how frustrating it can be to have a good clinical idea that cannot go forward because of pharma decision making, and I ran smack into that. So, I founded a company to study the mechanism to induce the long-term protection of stem cells from the toxicity of DNA damaging agents. That company, G1 Therapeutics, has raised more than $200 million and has three drugs undergoing human clinical testing at present.

The lead program is in chemoprotection to prevent DNA damage in patients treated with cytotoxic agents and just reported positive data from a randomized Phase II trial this morning. Because Nancy Goodman is here I want to point out that our initial trials were restricted to adults with small cell lung cancer because of strong biologic rationale, and not the typical pharma routine about not testing drugs in children. If these initial studies continue to be successful, however, I hope and expect trials in children with retinoblastoma-deficient solid tumors, who could really benefit from chemotherapy protection, to happen soon.

And then in October of last year, I became 15th director of NCI. And I have spent my first 5 months as NCI director on a "listening and learning tour," which continues today and is a big reason I am here now.

So, that's a bit about my background and my interests in pediatric oncology.

The big question and the reason we are all here at this conference is to learn how precision medicine approaches can improve outcomes for children with cancer and childhood cancer survivors? And, what do precision medicine strategies and research look like for pediatric cancer?

The basic fact of cancer that we have learned over the last 30 years through basic and translational research is that cancer is not one or 10 diseases, but hundreds or thousands of diseases.

This has direct implications for how one might prosecute a "war on cancer" and especially has implications for pediatric oncology, which comprises many rare and heterogeneous tumor types.

This fact is a real challenge to the clinical trials enterprise, and we will need new paradigms.

NCI has begun to embrace this fact—and I hope to accelerate that process—and the ensuing need for precision approaches, and has several large-scale programs to address this issue.

As many of you know, the TARGET (Therapeutically Applicable Research to Generate Effective Treatments) initiative, for example, is all about discovery. TARGET is a collaboration between NCI and COG, the Children's Oncology Group.

TARGET researchers use comprehensive genomic sequencing to identify genetic alterations in certain childhood cancers. They use whole genome and whole exome sequencing, as well as mRNA, miRNA, and epigenetic profiling, and these are applied to high quality tissue samples that are clinically annotated.

The goal is to uncover the oncogenic drivers of these cancers, which can hopefully serve as drug targets, as well as alterations that have prognostic value.

Acute lymphoblastic leukemia (ALL) was TARGET's first project. It started off as a proof-of-concept study to determine if a large comprehensive genomic sequencing study could work for pediatric cancer like it did for adults with TCGA. The concept has been successful and TARGET has been expanded.

The ALL project not only showed that the sequencing could be done, but that it could change how patients are treated. For example, TARGET researchers appreciated Philadelphia (Ph) chromosome-like ALL, ALL that is like Ph+ ALL, but does not obviously harbor the Ph chromosome.

Ph-like ALL is thought to be driven by activation of Abelson murine leukemia (ABL)-like kinases, and therefore based on this discovery, trials of tyrosine kinase inhibitors, ruxolitinib and dasatinb, are being tested in this population.

The TARGET neuroblastoma team confirmed the presence of recurrent ALK mutations in children with neuroblastoma tumors. This and other studies led to a clinical trial of an ALK inhibitor, crizotinib, in children with relapsed or refractory neuroblastoma.

For Wilms tumor, TARGET identified recurrent mutations in genes associated with adverse outcomes such as relapse.

The acute myeloid leukemia (AML) studies led to several noteworthy findings, but to my mind the AML results become especially interesting when compared with the TCGA's adult AML, showing significant differences in the molecular genetics underlying this cancer in adults and children.

For years, pediatricians have said that when it comes to cancer treatment, "kids are not little adults," and now we have plenty of genomic data to support that concept. In particular, targeted treatments that are developed for adult cancers may not be effective for younger patients with similar disease, even when the drug target exists in both pediatric and adult tumors.

It's the BRAF colon cancer problem, as it has come to be called.

Hopefully, that statement is often going to be not true, and I think we heard about one promising counterexample in NEJM last week with larotrectinib, where a driver event found in both pediatric and adult cancers predicts significant response to a highly targeted therapy.

Segueing to fusion oncoproteins, which are important in several types of pediatric cancers, in some childhood cancers, fusion proteins are the defining genetic driver—and sometimes one of the only identifiable lesions in a genomically quiet tumor.

That observation was the motivating force behind the Cancer Moonshot^{SM} initiative to identify and understand the roles of fusion oncoproteins in pediatric cancer.

In principle, fusion oncoproteins can make good targets because they are exclusive to cancer cells, for example, TRK activation in pediatric sarcomas. But many of these protein targets are transcription factors, which have been a challenge to target therapeutically.

So, the idea of this Moonshot initiative is to interrogate the key dependencies of these fusion proteins—maybe the transcriptional complexes they form or the downstream genes they regulate—and see if there are any potential targets there.

Grants were awarded in 2017 to promote research collaborations on fusion oncoproteins. And in the fall of 2017, an RFA opened to support multidisciplinary collaborative teams taking a comprehensive approach to understanding the biology and developing therapeutics for fusion oncoproteins. This consortium, called the Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium, will start this summer.

Another Moonshot activity of interest is the NCI Formulary, where NCI and Pharma reached an agreement to share drugs to qualified academic investigators.

Investigators hold the Investigational New Drug application, but crossreferencing of pharma data is allowed. It is aimed at preclinical and clinical studies, especially combination drug trials. So far, there are nine companies, 27 agents, in an initiative that recently started.

As a long-term modeler of cancer in mice, I really appreciate the importance of good preclinical models. Peter Houghton and I used to be an act, where he would talk about the role of xenografts and I would talk about genetically engineered mouse models. Especially in rare cancers, we need validated and credentialed preclinical models to investigate the roles of specific oncogenic drivers and, therefore, I believe such models are especially important in the preclinical development of anticancer agents for pediatric populations. The Moonshot also calls for the development of relevant models to specifically study fusion oncoproteins.

An especially important resource in this regard is the NCI-supported Pediatric Preclinical Testing Consortium, or PPTC, which has developed over 230 xenograft models of childhood cancers. These models can be used for the testing of candidate agents prior to moving forward into clinical trials.

In particular, these resources help to de-risk a program in pediatric cancer, allowing biotech and pharmaceutical companies to get needed data that will allow them to take on clinical trials in childhood cancers.

These PPTC models are molecularly characterized, so investigators can identify genetic features that make certain cancer types sensitive to an agent and others resistant to it.

And agents tested by PPTC have transitioned to the clinic for evaluation in children with cancer.

The MEK inhibitor, selumetinib, in being tested in young patients with recurrent or refractory low-grade glioma in a phase I/II clinical trial.

Immunotherapy has been at the forefront of cancer therapeutic research these days. The first CAR T-cell therapy was approved for children and young adults with relapsed or refractory ALL, with an overall remission rate of 83%. And that's an incredible achievement.

But what we don't know about the interplay between the immune system and pediatric tumors is far greater than what we do know.

We don't have a full understanding of how pediatric cancers evade the immune system. We don't know if there is an underlying anticancer immune response that can be boosted in young patients. So, we don't know if immunotherapies, like checkpoint inhibitors, can be used to treat children with cancer.

We know that most pediatric cancers have a low mutational burden and, therefore, few neoantigens. But, are there other kinds of antigens that the immune system can be trained to recognize?

And though we have a few approaches for pediatric hematological cancers, we don't have much to offer for solid tumors.

NCI's Pediatric Immunotherapy Discovery and Development Network was formed based on another Cancer Moonshot recommendation, with the goal of answering many of these questions. The Network aims to identify immunogenic targets that are unique to cancer cells and then develop therapies that go after those targets. And again, as in other areas of pediatric oncology research, we also need representative preclinical models to carry out these discovery experiments.

Funding opportunities for this initiative, in the form of collaborative and individual grants, were released last September. And awarded projects will begin in July.

All of these efforts I've mentioned so far—TARGET, the Fusion Oncoproteins in Childhood Cancers Consortium, the NCI Formulary, the Pediatric Preclinical Testing Consortium, and the Pediatric Immunotherapy Discovery & Development Network—these are mainly discovery and infrastructure efforts that have led to many clinical trials.

But the bulk of NCI's effort to apply precision medicine approaches in clinical care is of course NCI–COG Pediatric MATCH. Through MATCH, we're starting to apply what we've learned about genetic susceptibilities and targeted therapies on a larger scale. The overarching goal is to determine if using precision medicine to match young patients to targeted therapy is an effective approach.

Let me summarize the results of adult MATCH.

The infrastructure works. We learned how to adapt the trial mid-cycle, adding new tests and treatment arms as new data became available. Six thousand patients were accrued at 1,100 sites. There was a 15% match rate and 10% allocation-to-treatment rate. There were multiple positive arms including nivolumab in MSI positive cancers.

Pediatric MATCH was launched in July 2017 at 200 sites nationwide. The trial assigns children and young adults to one of eight treatment arms based on genomic alterations identified by targeted sequencing of more than 160 genes.

The trial is for relapsed or refractory solid tumors, including histiocytoses, non-Hodgkin lymphoma, and brain tumors (gliomas). A committee including members from COG, FDA, and NCI recommended genetic targets and paired targeted therapies for inclusion in the trial.

Pediatric MATCH also seeks to learn more about pediatric cancers, specifically, how do they change during treatment? To that end, matched tissue samples from diagnosis and relapse will be analyzed by whole exome sequencing and compared. This might tell us about how resistance develops, which could ultimately inform combination treatments to prevent or overcome resistance.

There are many completed and ongoing pediatric cancer precision medicine trials, but Pediatric MATCH is the first trial of this scope. It is expanding the frontier of what is possible in pediatric precision oncology.

What's notably impressive about the trial is the level of cooperation between NCI, COG, FDA, and several different pharmaceutical companies. And pharmaceutical companies supplied the drugs being tested in Pediatric MATCH. The response from these companies has been truly amazing. This level of collaboration and cooperation would be very difficult to logistically manage at a different institute, and emphasizes the NCI's strength to lead in pediatric precision oncology.

I would be remiss if I did not highlight the role of COG in all of these efforts and many more.

COG is an NCI-funded clinical trials group and the world's largest organization devoted solely to childhood and adolescent cancer research. They are the reason we are able to translate basic genomic discoveries into a clinical research setting so quickly. They are also the reason we have collected relatively large numbers of tissue samples.

What NCI, COG, and others have accomplished so far is outstanding. With these ongoing consortia and trials, we're bound to make even more advancements.

It has to be said, though, that there are still many challenges to address.

We're just beginning to understand the biology of certain childhood cancers at a molecular level. And the biologic fact that cancer is not one disease but many diseases rears its ugly head here.

As much as we have made progress in certain pediatric cancers, there are a few where our understanding of the disease is very immature, where we don't really have any good ideas. These are the cancers that we can't cut out, which are sensitive to radiation or chemo, and have no neoantigens to drive a tumor response.

For these children, we need new ideas. And new ideas come from investigator-initiated basic science.

Recall, the success of CAR-T cells started 30-plus years ago with the efforts at adoptive cellular immunotherapy in Building 10 at NIH. Steve Rosenberg did not really know how to make that work back then because of an imperfect understanding of T cell biology and the immune response, but he persevered.

Another great therapeutic success story started at NCI Frederick in the early 1980s when Mariano Barbacid, hunting oncogenes, found one he called OncD. It turned out later that OncD was really a fusion of two genes, one of them tropomyosin and the other a kinase that they called TRK.

In neither case were the investigators trying to develop therapies specifically for pediatric cancer, yet two of the most active agents we have seen in a long time came from those endeavors.

So, basic science can save the day for children who have no other hope and, therefore, we need to press that investment.

We must push forward with such things as comprehensive genomic, transcriptomics, epigenomics, proteomic characterization. We need Big Data efforts with linked clinical annotation to understand these complex data sets. We must do studies to understand what drives relapse and resistance to standard therapies. We need fundamental studies in structural biology, cell biology, and medicinal chemistry to allow for the development of new agents, alone or in combination, specifically designed for children with cancer.

Basic investigation benefits all patients with cancer, including children with cancer.

Given this fact, to the people who say NCI does not invest enough in pediatric cancer research, I point out that the NCI investment in basic science is robust and significant, and for some types of pediatric cancers, is the only hope.

In summary, I have stated that cancer is not one disease but many, which is why we need precision oncology.

At every step of the way, we need to remember that "kids are not little adults." Are all of the technologies, protocols, and models that we're currently using optimized to study cancer in children?

I've discussed important NCI-led efforts like TARGET, MATCH, fusion oncoproteins, COG, and the Moonshot.

I have called for continued investment in basic science.

We're on our way and the momentum is there. The data are there. We have opportunities to build on what we've already worked diligently to uncover to help reduce cancer suffering in children.

Thank you for the opportunity to present today.