

“Ending Cancer as We Know It: Building the Bridge to Get Us There”

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Thank you, Dr. Ribas, for that kind introduction. I look forward to our conversation after my remarks! Let me also thank AACR and its 48,000 members worldwide. Thank you for your incredible resilience during difficult times, for your pioneering research, and for your dedication to patients.

I am joining you live – that is, I am not pre-recorded – as you tune in from your homes and offices. I wanted to do this live because there is so much going on right now, that I could not pre-record my remarks even a few days ago. I’ll touch on those recent developments today. I am now in a conference room at the National Cancer Institute in Rockville, Maryland. We are, of course, following proper safety protocols and social distancing.

I guess we have all gotten somewhat used to these video meetings by now, but I miss real life. I suspect everyone will agree with me that it will be wonderful to gather in person again sometime very soon for these meetings.

We’ll cross that bridge when we get there, as they say.

That’s a common expression, but bridges have been on my mind a lot lately. We think of physical bridges as feats of engineering, as being the products of hard work and sacrifice, which is somewhat like cancer research. On the other hand I have spoken at length about how cancer is decidedly not solely an engineering problem—that the engineering mindset that put astronauts on the moon won’t necessarily get us a cure for cancer. We will still need basic investigation for that.

But I think the notion of a bridge that we build together, to take us to someplace new, is a good metaphor the work before us. When we consider where we need to go in cancer research, it’s clear that the bridge we must complete must be strong enough and long enough to connect the present with the future, where we are today, and where we want to go.

Today, I’ll propose a blueprint for our work in the years ahead. I’ll describe what it will take to get us there – a bridge, if you will, to progress against cancer.

We are clearly living in an historic time. Not just for cancer research, or even public health, but for our nation, and the whole world. We are now 14 months into a once-in-a-century global pandemic. We are seeing the greatest social unrest in more than fifty years. We are confronting economic uncertainty and climate change. But despite the obstacles presented by these challenging events, we continue to push forward with a true revolution in cancer research, one that has allowed us to deliver hope for our patients.

I think humanity will come to look back on this productive period, these few decades right now, as a Golden age of cancer research, in much the same way that we look on the early 20th century as a period of remarkable progress against infectious diseases.

We've seen consistent and meaningful declines in cancer mortality, and exciting new technologies across the spectrum from prevention to diagnosis to treatment to survivorship, record numbers of FDA approvals in cancer, providing new drugs and devices that really benefit patients steady progress in prevention measures, like tobacco control and vaccination efforts.

We are living in dizzying and challenging times, but we're still making remarkable progress. And now, we have a new administration in Washington that has declared that making progress against cancer is one of its top priorities. In fact, President Biden has said more than once that he wants to end cancer as we know it. And I believe we can.

The President and the First Lady know cancer. They know the terrible toll that a cancer diagnosis can take. Cancer robbed them of their son. They know cancer.

And today, all of us know cancer too, we all know as well. Estimates are that in 2020, 1.8 million people in the United States were diagnosed with cancer. And more than 600,000 Americans died from cancer. That's more than 1,600 deaths each day.

And globally—particularly in many low- and middle-income countries – cancer incidence and mortality rates are increasing. Already, approximately 70% of cancer deaths occur in low- and middle-income countries. And that is likely to get worse. In sub-Saharan Africa, for example, cancer incidence is projected to increase by more than an 85% by 2030. So I'm not telling you anything you don't already know, when I say our biggest challenges still lay ahead of us.

But as I said, I think we are up to this. This is the golden age of cancer research. Here's why I think that:

First and foremost, cancer mortality rates have been declining over the past 30 years – and the rate of that decline has been accelerating. Although many factors contribute to this trend, more effective treatments are definitely a driving force in recent years. Therapeutic development has rapidly accelerated.

Take for example just since 2017 (the period I have been in federal government), over that time, there has been a string of remarkable productivity in terms of therapeutics. In that period more than 240 new, supplementary or biosimilar approvals have been issued by the FDA for drugs and

biologics for oncologic indications, including more than 80 new medicines. The number of new devices for cancer cleared during this period is similarly mind-blowing. Many of these new products deliver long-lasting patient benefit, even cures in some settings, often with greatly reduced toxicity compared to prior approaches. Almost all of these new therapies are used in molecularly targeted cancer subsets, the modern way of doing things in cancer care.

It's also important to highlight that many new supportive-care therapies have been approved, including new agents for treating pain, bone marrow suppression, nausea and other side effects caused by cancer and its treatments. The importance of these approaches, as well as efforts to make cancer treatment less toxic, must also continue to be a top priority.

This remarkable productivity is a testament to the translation of the great basic science that NCI has been supporting for decades. Often, but not always, this successful translation requires extensive help from industry, which is also highly focused on cancer. So this progress is a testament to the work of basic and translational cancer researchers, working in whatever setting—whether in academia, industry or government. In sum, this progress is a testament to the work of people like you, the members of AACR.

Beyond therapeutics, we are also seeing progress because of prevention and screening. The impact of decades of progress in tobacco control is well-known, but there are lots of other areas of success too.

One of these other areas, of global significance, is the remarkable impact HPV vaccination is now starting to have on cancer incidence. A recent analysis conducted country-wide in Sweden showed that vaccination among those 17 and under led to a 90% decrease in the incidence of invasive cervical cancer. This bodes well for the prevention of other HPV-related cancers, including oropharyngeal cancer, which has reached epidemic levels in the United States. This is a big deal, especially when coupled with NCI's emerging data showing that a single dose of the HPV vaccine can provide lasting protection against neoplasia. A single dose vaccine will be a massive boon for cancer prevention worldwide, particularly for low- and middle-income countries, where cervical cancer kills far too many women.

As an aside, I will point out this achievement really represents the life's work of two NCI intramural scientists: Dr. Doug Lowy and John Schiller, who invented this vaccine and are in the enviable position of getting to watch their basic science efforts now save millions of lives.

In recent years we have created the foundation for facilitating rapid progress. This foundation rests on ongoing initiatives and programs like the Cancer Moonshot, the Cancer Research Data Commons, the Childhood Cancer Data Initiative, and the National Clinical Trials Network, to name just a few. All of these are well positioned to accelerate progress.

Take the Cancer Moonshot, for example, which has created interdisciplinary teams working together to facilitate cutting-edge immunotherapy trials for children and adults.

The Cancer Research Data Commons and Childhood Cancer Data Initiative offer unprecedented access to biospecimens, clinical and molecular data, and research tools that are creating opportunities for studies that could not have been done before.

There isn't time today to walk through all of the ways NCI is facilitating research, but our portfolio is very strong.

And as I mentioned, another major factor is a new administration in Washington that strongly want to make progress against cancer, and that has a real personal connection with cancer. Most of you are familiar with the President's story and the loss of his son, Beau, to glioblastoma. It was this experience that drove then-Vice President Biden during the Obama Administration to launch the Cancer Moonshot. But this personal connection to cancer research also extends to Vice President Harris, whose mother was a breast cancer researcher. In fact, probably like many of us in AACR, the Vice President's first job as a teenager was working in a lab: in her mother's lab cleaning pipettes.

And the First Lady, Dr. Jill Biden, is a fierce advocate against cancer. One of her first acts as First Lady was to visit us at the NCI virtually, and then she also accompanied me on a visit to the Massey Cancer Center in Richmond, Virginia. She spoke about her experience with cancer. In addition to losing her son Beau, Dr. Biden has shared the pain of losing both her parents to cancer.

And, finally, we continue to see tremendous support from the public for scientific research. I have felt this strong bipartisan support for cancer research among members of Congress since my very first day on the job. Everyone wants this effort to succeed.

This brings me to an important event: the release on Friday of the President's Budget for fiscal year 2022. This is the discretionary request, a high-level outline of the President's budgetary priorities. Of particular interest to the biomedical research community, this budget proposal has two exciting parts for those of us interested in cancer research:

First, it suggests a total increase in funding to the NIH of \$9 billion in 2022. This includes \$2.5 billion for the institutes of the NIH, of which NCI is the largest. Such an increase would translate into a substantial increase in the NCI's base budget for 2022. Over the last several years, NCI has had steady increases on the order of \$100 to \$200M, but 2022 would likely be a much larger increase than that, if the President's budget were taken up as is.

This would be key to allowing the NCI to continue to increase pay lines and success rates for grant applications. Increasing pay lines has been my top priority at NCI. These are now up to the 11th percentile from a nadir of the 8th percentile for established investigator R01's, which is good progress, but 11 is still too low. I have been very clear in my goal to get our paylines up to the 15th percentile by FY 2025. We have a slogan for this: 15 by 25.

The type of support proposed in the President's budget would allow NCI to continue to invest robustly in investigator-initiated science. And investigator-initiated science is how we make the basic and translational discoveries that really move the needle for our patients.

In addition to what would be a hefty increase in our base budget, the President's budget includes \$6.5 billion to fund a new national effort: the Advanced Research Projects Agency for Health, or ARPA-H.

It's modeled on the Defense Advanced Research Projects Agency, or DARPA – known for, among other things, establishing the Internet and for making GPS usable. ARPA-H is envisioned as a major investment in federal research to drive innovation—focused on cancer and other diseases and would reside within the NIH. How this would fit with the ongoing efforts in cancer at the NCI is still something to work out, but I think having ARPA-H as part of the NIH is good for the NCI.

These are exciting developments but let me be clear about one thing: what the administration has released is only a budget proposal. It will have to work its way through the U.S. Congress – where lots of interesting things can happen.

As an example, I'll note that in my first year at NCI, the President's budget called for a 26% cut to NCI's budget, but when all was said and done that year, the appropriation from Congress provided a nice increase. Congress controls the power of the purse, and the President's budget is just a suggestion to Congress. But as I said, I think there is strong bipartisan support for cancer research in Congress.

Given these developments, now is the time for all of us in the cancer research community to figure out something important. The President has provided this goal to end cancer as we know it. But what would that mean? And once we figure that out, how do we make it happen?

My view is that given the fundamental links between cancer and aging, I think a world that is totally free of cancer death is an unrealistic goal, at least any time soon. And the President did not say we should eradicate cancer, but instead end what we know to be the tragedy of cancer.

When I think of the tragedy of cancer, I think of real patients, people I have known. I think of a 6-month-old child, dying of a CNS rhabdoid tumor, leaving a yawning and unfillable hole in the lives of loving parents and grandparents. I think of a young mom with metastatic breast cancer, telling me her goal is not to be cured, she did not expect that, but it was only to live a few more years so she could see her children grow up and graduate from college. But even such a modest goal is one that we are unable to meet. I think of a 62-year-old gentleman on the inpatient medical service, dying of small cell lung cancer, wracked by unremitting pain that could not be controlled even with a morphine infusion pump.

So when I think of ending cancer as we know it, I think of ending that, of ending those episodes of the tragedy and unfairness of cancer. I don't expect to end all cancer death, but I think that

eradicating a vast majority of cancer—especially in young, otherwise healthy people—I think that is doable.

How to get there: this is a place for solid metrics as opposed to gauzy, ill-defined goals. And I think one good metric for progress in this vein is age-adjusted cancer mortality—something the NCI, the CDC, the American Cancer Society and the North American Association of Central Cancer Registries measure and report each year.

And for that metric, I think a huge step in the right direction on the path to ending cancer as we know it—would be to cut cancer mortality in half, from its peak of the 1990's. This would be the sort of clear and indisputable result we'll have to see on our way toward ending cancer as we know it.

To be clear about this, the peak cancer mortality in the U.S. occurred in the early 1990's at around 215 deaths per 100,000. Right now, it is about 150 deaths per 100,000, which represents a 30% decline over the last three decades. So that has been good progress, but this number is still way too high, and a 30% decline over 3 decades is way too slow. Reaching a halfway point from that 1990's peak mortality will require a considerable acceleration of what we've been able to achieve in the past few decades.

For most of the last few decades, the rate of mortality decline has averaged about 1.5% per year. Then, in the most recent two years for which we have statistics, good news: we have seen the largest single year declines in cancer mortality since we've been tracking that metric—at 2.2% and 2.4%. So the rate of decline has been speeding up in recent years, but even this rate of annual decline is still not fast enough. To cut cancer mortality in half from its peak in 1990, at the historical decline rate would take until 2040. That's too long. At a rate of 2.5% decline per year, about where we have been in the last few years, this would take till 2031. Not good enough.

But if we continue to accelerate this rate of decline, using all our many tools of prevention, screening, and therapy, I think we can get there by 2026, five years from now. This would require an average reduction in cancer mortality of about 4% per year, which is a considerably faster rate of decline than we have ever done before. But such a reduction will be important, this will represent a huge advance towards ending cancer as we know it.

How do we bridge that distance between what we've been able to achieve and where we want to go?

I am sure, given what we know about cancer today, that it won't be through one smashing breakthrough, or one big discovery, or one major initiative. There will be no silver bullets.

Instead, we need a concerted effort with lots of complex parts, coming together to build that bridge that I spoke about. A bridge from toxic and marginal therapeutic modalities of the past to new approaches of the future. We need a bridge from the place where remarkable, long-term responses – even cures – go from being uncommon to being the expectation.

A bridge that builds from the important gains in prevention through things such as tobacco control to effective approaches for all the main drivers of cancer risk. And by the way, we still have more work to do on tobacco control too.

And perhaps the most importantly: a bridge from the visionary researchers of the past whose science led to the breakthroughs and progress of recent decades to the enterprising young investigators whose work today will lead to future advances, ones we can't even imagine yet.

So what would it take to do this, to build this bridge? Well, doing this will be hard. And the path forward is not obvious. Figuring this out will take a lot of our collective efforts over the years to come.

But there are, I believe, a few directions and activities that hold so much promise that they will undoubtedly be part of our work ahead. These are things we should do in addition to the significant investments in investigator-initiated research that I already mentioned.

Here are some things we could do, using a vehicle like ARPA-H working with the NCI:

One idea is a large national trial or trials of multi-cancer early detection tests. These are blood-based screening tests that have the goal of finding early cancer in healthy adults. Such screening tests will have to be evaluated with appropriate power and endpoints to determine if any of the new technologies being advanced for this purpose can really reduce mortality at the population level. I believe these technologies hold immense promise, but cancer screening is tricky, and we all know about the problems of over-diagnosis and over-treatment. So we have to do this right. I think the first large NCI-sponsored trials of multi-cancer early detection tests will start as soon as 2022.

Another idea would be to devote significant new resources to government sponsored clinical trials. The NCI enrolled around 30,000 patients on clinical trials in 2020, but that number could be much higher. We could double that number. To do this, we would have to do trials not just in the major centers, but also in the community, and we'd have to focus specific effort on underserved populations. We'd have to further expand eligibility criteria for patients, and we'd have to take on new ways to enhance matching efforts; to connect patients with the right trials.

We have an important opportunity here to leverage data science approaches, so that we can learn from every patient with cancer. I have talked a lot about this in the past with regard to childhood cancer, and I already mentioned the Childhood Cancer Data Initiative. But we could do this for adult cancers with regard to data aggregation what we are doing for pediatric disease.

And the idea in expanding clinical trials is not to compete with industry for patients, but to do the sorts of trials at the NCI that are vitally important, but which industry won't or can't take on. Things like prevention trials, and de-escalation trials, and complex multi-modality trials, using novel adaptive designs with regulatory endpoints in mind. There are plenty of patients who are not enrolling on any trial right now, and this is a tremendous opportunity to accelerate progress, by reinvigorating trials with ARPA-H capabilities.

And a final idea would be a new commitment to advancing drug discovery through accelerated approaches to structural biology and medicinal chemistry. The idea here is for NCI to lead large efforts to identify protein structure through technologies like cryo-EM, while also developing new analytics for drug discovery. For example, machine learning approaches to predict protein folding and small molecule binding. And molecular dynamic simulations to identify dynamic binding pockets, and other targets for novel therapeutics in heretofore “undruggable” targets. And then to marry all these approaches with novel ways to make small molecule drugs and biologics, whether PROTACs or molecular glues or multivalent antibodies.

We could create a national network of GMP foundries for novel cellular therapeutics, such as CAR-T cells, natural killer cells, and beyond. We could really explore the entire range of therapeutic approaches on difficult molecular targets using a variety of technologies. This type of work has been a focus of the RAS initiative, which is now leading to promising drugs in the clinic. I think this approach could be vastly scaled to other targets using ARPA-H approaches.

So that’s three ideas for new progress, but there are many, many more. And I think progress toward our goal will require success in many different areas. As I said, there will be no silver bullets.

Importantly, though, let me stress that underlying all of this new work must be intensive efforts to address health equity. The President did not say he wanted to end cancer as we know it for some people. The goal is to make this progress for all people, regardless of race, ethnicity, wealth, or access. The COVID pandemic has put a bright spotlight on the disparities and inequities in American health care. These problems are very familiar to cancer doctors. Cancer progress has long been severely hampered by health disparities.

We have known for some time that taking on health equity and disparities will be a critical part of ending cancer as we know it. But that means more than just doing more of the same things we have been doing to address cancer health disparities. It means baking equity into everything we do. It means addressing systemic racism and all the structural barriers that have blocked our progress.

We can’t leave huge portions of society behind and expect to make meaningful progress against cancer.

I’ve described some of the key aspects of our work that I expect to be important in the years ahead, and that would be possible with new support for the NCI and a new entity like ARPA-H. You might think about these as parts of this bridge I keep talking about– the bridge we’ll build together, to take us from where we are today to where we want to be in the not-too-distant future.

I’d like to close with a recommendation for a book. Not coincidentally, it’s called *The Bridge*, and it was written in the late 1960s, by the journalist Gay Talese. The book describes the construction of the Verrazano-Narrows Bridge in New York City, completed in 1964,

connecting Brooklyn to the then burgeoning suburb of Staten Island. It's a suspension bridge of more than two and a half miles.

In the book, Talese describes a traveling group of workers called the Boomers—iron workers, riveters, welders—who traveled around the country, city to city, from one bridge-building job to the next. The book, it turns out, isn't really about this enormous feat of engineering, or the bridge itself.

Rather, it's the story of the people who made the bridge. The people whose lives and work made that achievement possible.

Likewise, the story of our bridge to the next revolution in cancer won't be so much about new molecules to treat cancer or new ways of doing radiation therapy or better telemedicine or machine-learning data analysis or whatever other piece of technology you favor.

Those things will be important, just like steel and rivets are an important part of a bridge.

But what this story will really be about, the really important part, is that it will be about all of us who work on cancer, and about our patients and about their loved ones.

And the key moments in that story will be about meetings like this, where we come together to talk about what works, and what does not work, and slowly—or not so slowly—together make progress against malignant disease.

And, most importantly, it will be about what we are going to do next.

Thank you for your work, for your vision, your commitment, and for having me today.

I look forward to our conversation.

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