Reflecting on the golden age of cancer research

50 years after the National Cancer Act was signed into law, *Nature Cancer* spoke with the National Cancer Institute Director Dr Ned Sharpless about the progress in cancer research and care, the complications of the pandemic and what to expect in the future.

The National Cancer Act (NCA) was signed into law 50 years ago. What were the milestones in cancer research in the last 50 years?

NS: The 50th anniversary of the NCA is a good time to be having this discussion. The NCA did not create the National Cancer Institute (NCI)— the NCI dates to the 1930s — but, in some ways it created the modern NCI, by providing funding that allowed us to support more science, and by providing for new authorities and capabilities, such as the Frederick National Laboratory and the Surveillance, Epidemiology, and End Results (SEER) program, which is the most widely used database of cancer statistics. The Cancer Center program also existed before the NCA, but the NCA really made it into the modern-era Cancer Center program. It also created the modern National Clinical Trials Network that we have in the United States for cancer research. Most importantly, the NCA made cancer a disease we could talk about as a nation. It removed a lot of the stigma surrounding cancer and changed it into something that politicians and advocates would speak about emphatically. You could also say that the NCA introduced modern cancer advocacy in the United States.

In some ways the NCA was very visionary. It created a great foundation for future cancer research through its broad reach and scope, the funding capabilities it provided, and the path it paved for advocacy. In other ways, though, it was also quite naive — primarily in its understanding of the molecular biology of cancer. For example, some in the cancer community, including Sidney Farber, had told President Nixon that we could have a cure for cancer in five years. That would have been by 1976, and of course that didn't happen, because back in 1971 we did not know what we did not know about cancer. Over the past 50 years we have filled in that knowledgebase through detailed basic and translational science that has given us a very good understanding of the biology of cancer. Now we know where the gaps are that we still need to fill, to make progress. We understand that cancer is not one disease, but that each cancer, in some ways, is almost unique to the patient, and that to really make progress, one has to approach each cancer as a unique entity.

Credit: National Cancer Institute (NCI)

Appreciating the heterogeneity of cancer and understanding the driver events that underlie each cancer has been a major development in the past 50 years that has allowed us to now talk about ending cancer as we know it, as President Biden has stated.

Would all this have been feasible in the absence of the NCA?

NS: How would cancer research have fared without the NCA? We don't know. But if you read the work of individuals involved at the time, and then talk with people who have followed the work of the NCI since, there is a strong feeling that the legislation transformed cancer research nationally. I'm talking about capabilities such as SEER and the Cancer Center network, both unique biomedical research tools that only exist in their purest form as tools for cancer research. That can largely be ascribed to the NCA and in that sense, I think it's fair and accurate to say cancer research would not have been nearly as successful had the NCA not been passed into law. One piece of evidence that cancer research has proceeded at a steady pace is the excitement around cancer therapeutic agents and device development, the massive increase in cancer-relevant FDA approvals, the many new ideas for clinical trials and approaches to treating and diagnosing cancer. At the NCI we're inundated with applications, with requests for funding having doubled since 2013. I think that is because scientists from disparate disciplines are converging on the NCI with great ideas from disciplines such as physics and mathematics, computer science and health services research, nursing and pharmacy, just to name a few, because there is a feeling that we can make considerable progress given our very sophisticated understanding of this disease. Cancer is leading the way in biomedicine and that success, which is evident today in so many ways, is attributable to the NCA.

Do you think that the NCA shaped the NCI in a different way than what might have been without it?

NS: A way to consider that question is by looking at what is different at the NCI compared with other National Institutes of Health (NIH) institutes that didn't have

anything equivalent to an NCA. One of the most obvious differences is that, unlike at other institutes, the Director of the NCI is a presidential appointee. That has pluses and minuses, as it assures that the NCI Director's position changes a lot more. For example, Anthony Fauci has been running the National Institute of Allergy and Infectious Diseases (NIAID) for nearly 40 years, and I'm the seventh NCI Director that he's worked with.

In addition, the framework now known as the National Clinical Trials Network doesn't exist to the same extent for non-cancer disease areas, and that was enabled by the NCA. The Cancer Center program is also very different, which was surprising to me when I started at NCI. As an academic, I thought that there must be similar centers for other diseases and that the cancer centers were the cancer-specific version of the NIH Center grants, but that is not the case. The center programs of other NIH institutes are much smaller in scope, not organized in the same way, and are more like program project grants. The NCI Cancer Center program has the attention of Congress and was essentially created by federal statutes. Centers wanting to demonstrate a certain standard in cancer research can pursue NCI designation and medical institutions advertise whether or not they have NCI designation. As an example, the state of Oklahoma passed a state law about 20 years ago that asked the University of Oklahoma to seek NCI designation. Because of this desire to have an NCI designated center in the state, they worked for 17 years, raising approximately US$400 million from philanthropy, state funding and other sources to build the Stevenson Cancer Center that now exists in Oklahoma. So, the Cancer Center grant is a program like no other across the United States, and it was created by the NCA.

You mentioned that the NCA was visionary, but perhaps a bit naive. President Nixon at the time had stated that "the time has come in America when the same kind of concentrated effort that split the atom and took man to the Moon should be turned toward conquering this dread disease". 50 years from that, how close are we to conquering cancer? This is similar to President Biden's promise to "end cancer as we know it". It's inspiring, but is it achievable? Is there a future 50 years from now when cancer is no longer a major health issue and a global challenge?

NS: It is a tough question to answer, but I'll give an example from the time in my career when I was involved in the preclinical drug development for melanoma. There was a 50-year period of great melanoma science, during which we were learning more and more about the disease, but not much was happening in terms of new therapies being approved. And then all of a sudden, the dam broke with the adoption of immuno-oncology drugs and MAP kinase pathway inhibitors, so melanoma went from one of the least interesting diseases in terms of therapeutic agents to one of the most exciting areas of therapeutic development in oncology. Currently, most melanoma, even metastatic melanoma, is cured, which is a tremendous therapeutic triumph. But for the first 45 years of that 50-year odyssey, it didn't look like much was happening. Similarly, pancreatic cancer is not an area where we're having tremendous success at the moment in terms of new therapeutic agents, but there are many good ideas being developed. It is possible that very soon one of them will start to pay the kind of dividends that we've seen in melanoma, but it's hard to say when that's going to happen. Trying to forecast the advent of cancer cures is a challenging endeavor.

What is different today from 50 years ago is that we have an understanding of cancer. Even for treatment-refractory cancers where we haven't made as much progress as we would like, we have a pretty good understanding of physiology, and cellular and molecular biology. We now have ideas about how to either prevent these cancers or diagnose them at an early stage when they might be curable, or if those two things fail, to treat them in the established disease setting. We've also learned that there is no cure-all for cancer. Instead, we need very tailored, personalized therapies and approaches to each cancer. That paradigm of breaking the heterogeneity of cancers has been very successful, and it means that we'll see significant progress in some diseases, like hyper-mutant colon cancer, but there might be no progress in other diseases for a while, until something good happens. When we talk about cancer writ large, that will translate into a steady decline in annual cancer mortality, which we're already seeing. The cancer death rate is down by approximately 30% from its peak incidence in 1991 in the United States, and the rate of decline of cancer mortality has been accelerating, particularly powered by progress in lung cancer, melanoma and a few other diseases.

We also have many great ideas and great momentum. If we invented no new therapies starting today, we would still have enough to keep us busy in clinical trials for 10 or 20 years, just by using known treatments and pairing them together in the proper sequence. We're going to see a lot more progress both through new discoveries and by learning to use existing therapies optimally.

I think President Biden was careful not to say "we will eradicate all cancer". I don't think having cancer never occur or ending all cancer death is biologically likely, given our understanding of the relationship between cancer and aging. Cancer is a fact of being a long-living mammal. Instead, I think the President was talking about trying to end the experience of cancer as a tragic, life-changing entity that affects otherwise healthy individuals, particularly younger people. That is an area where we can speak honestly about the path we need to take to achieve the President's goal, and I think that there is much we can do to end the tragedy of cancer.

I mentioned that the rate of cancer mortality is declining even faster, most recently averaging an approximate 2.2% reduction per year. If we could accelerate the rate of decline of cancer mortality, for example to 3–4% per year for a decade, it would lead to a significant reduction in cancer mortality — a laudable and realistic goal.

In addition, developing better prevention, diagnosis and screening approaches is a real opportunity to have a marked effect on cancer outcomes at the population level, without resorting to highly toxic or very challenging therapy regimens and surgery. We've had some success in these areas, but we can do a lot more. We also have a big focus on improving the survivorship experience for the over 20 million cancer survivors in the United States. That number is growing at a phenomenal rate because of our successes therapeutically. Currently many people with cancer are put into remission for very long periods of time, or are even cured, but the therapies that achieve that are quite toxic. So, improving quality of life after cancer treatment is becoming a big concern for the NCI and is an area where we could certainly do much better by using these therapies sooner, or making them less toxic.

I can't say what date cancer will no longer be a public health issue. I think we are making very good progress already and we'll get there, but it requires further biological mastery of cancer and the associated problems experienced by the individual patient.

As I have said many times, I think we'll look at this period of the past and upcoming decades as a golden age of cancer research, when we achieved as much for cancer as antibiotics did in the early part of the twentieth century, when they provided

successful treatment of many terrible infectious diseases. That's not to say that we've cured all infectious diseases and I don't think we'll cure all of cancer either. But we will render it into something very different from what we knew in the 1990s and the earlier part of the century. For instance, skin cancer used to be a terrible, life-ending entity, but therapeutic progress has made it much more tractable.

Thinking into the future, what are your predictions for the NCI, also considering new initiatives to accelerate research — for example, President Biden's proposal for a new organization within NIH, the Advanced Research Projects Agency for Health (ARPA-H)?

NS: Despite the great progress of the past 50 years, cancer is still a big problem in the United States. It is still a tragic, life-changing or life-ending diagnosis for many people — cancer still results in the death of 600,000 Americans per year — and is also phenomenally expensive given that it costs hundreds of billions of dollars to our society each year. The challenge for us now is to prioritize the many good ideas we receive, and synchronize these different efforts and approaches as quickly as possible to get to the President's goal. That will require several things, but it is important to mention that the NCI will continue to believe in the importance of investigator-initiated research. This means that rather than adopting a top-down approach through which a federal official or employee in the federal government is going to propose the solution, this will come from scientists working in a lab, who will have a great new idea for research that the NCI will support because we believe the collective body of science internationally is cleverer. We want to always maintain the flexibility to support basic and translational scientists who have great ideas and come to us with investigator-initiated proposals. This will continue to be the biggest part of our budget in the future, because we still need new ideas for so many types of cancer: pancreatic, brain cancer and ovarian cancer, to name a few. We still need new ways to approach cancer health disparities. We have made so many great advances in cancer and they typically work well in the tertiary 'cancer palace' — the academic hospital — but they are not disseminated well in the community, to underserved populations in particular. In some ways, we consider that to be a scientific problem, a challenge of disseminating new information for prevention, diagnosis and treatment, and therefore we want to identify the barriers that preclude the wider adoption of these new approaches. This is an area in which we still need to fund science and investigator-initiated proposals.

Nevertheless, I think there's certainly an important role for top-down science in the NCI portfolio. An example of a federal-government-driven program is the Cancer Moonshot, which is now in its fifth year and was championed by then Vice-President Biden. The Cancer Moonshot has been led by the NCI with a lot of input from the community through a Blue Ribbon Panel of external experts who helped to identify 10 areas in which we need to make progress. We then set up new networks and funded new initiatives to achieve this. There is something very compelling in this approach and whether the NCI or some other part of the government should drive more of this type of initiative its under discussion and is something that the White House will decide working with cancer advisors and Congress.

You mentioned ARPA-H, which is a very interesting idea. This is a proposal from the White House that is now being embraced by Congress in a bipartisan manner, to create a novel capability within the NIH that would be similar to the Defense Advanced Research Projects Agency (DARPA), which is a nimble, milestone-driven entity enabled to sunset funding very quickly for projects that aren't working. The NIH and the NCI fund science in a different way from the DARPA model, so this proposal is an effort to bring some of the DARPA capabilities into biomedical research. I think that's very exciting, as there are areas in cancer research where ARPA-H capabilities could be quite useful. However, we should manage expectations. For example, I don't think ARPA-H would be a good place to do investigator-initiated basic science — the NCI does that particularly well — but it might be a great place to address a specific need, such as a medical device of a certain functionality, or new technologies to diagnose cancer, for example through blood-based screening tests, or so-called multi-cancer early detection tests. There are many such technologies and they each analyze different molecules from a blood sample to diagnose cancer in otherwise healthy individuals. That's a clinical need that might be a good fit for an ARPA-H entity that could set up quickly, utilize flexible contracting and get the budget for such an endeavor. The challenge would be to use ARPA-H capabilities to fit with what the NCI is doing and to avoid redundant or overlapping initiatives. But it's encouraging to me that ARPA-H will be located within the NIH, because planning with another NIH partner is relatively straightforward for the NCI and this would enhance the coordination between the two entities.

A complicating factor in all these plans and progress is the ongoing COVID-19 pandemic that is now well into its second year. What have been the short- and long-term repercussions of the pandemic in cancer research and care and how are we mitigating them?

NS: First it is important to note that cancer research has proceeded quite well during the pandemic, despite the fact that we've all had workplace disruptions, intermittent closure of labs, and slowdowns in clinical trials and other kinds of translational research. I think the research productivity of those initiatives that we fund, and in general of scientists working in cancer, has been remarkable throughout the pandemic. I was initially very concerned that we wouldn't be able to do cancer research during a global shutdown, but it turns out cancer research can be conducted in a pandemic environment quite successfully. I would now argue that 2020–2021 have been great years in terms of scientific creativity. For example, 2021 has been very successful in terms of Food and Drug Administration (FDA) approvals of new therapeutic agents. During this time, many scientific publications have advanced the field and that has been paradigm-shifting. At the NCI, we are receiving a considerable number of new ideas and requests for funding, perhaps even slightly more than we would typically get. So I think that by whatever metric one would choose to measure scientific productivity, the pandemic has been quite productive and this is really a testament to the ingenuity and tenacity of cancer researchers.

Nevertheless, some parts of cancer research have been affected. From my vantage point the most affected area is clinical trials research. We saw a dramatic decline in clinical trials enrollment early in the pandemic that lasted for four to six months. Although accrual has largely recovered for most of the NCI clinical trials, there are still some areas where this is not the case. As a result, the clinical trials that reported reduced accruals over long periods are going to take longer to complete. Because that's how we make progress in cancer care, those advances are going to be delayed, unfortunately, and they will cost more when they finally materialize. So we're very concerned about the impact of the pandemic on clinical trials, even though we have seen a return to normalcy in most of our networks.

It's also important to mention that cancer care has been greatly disrupted. At one point we saw a ~95% decline in mammography

elective care screening for breast cancer and a decline in cancer diagnoses of >50% for some months. This was the case even for cancers that are not screen-detected, such as pancreatic cancer and most lung cancer cases, presumably because patients were not visiting their doctors for new symptoms or standard screening tests, such as mammograms, computerized tomography (CT) scans for lung cancer, Pap smears or colonoscopies. We think that in the United States, we missed something in the order of 10 million screening events, and we do not have the capacity to recover all these screening events. Therefore, we think that some of these delayed diagnoses are going to present as later-stage cancer with presumably worse prognoses. We also observed delays and deferrals of cancer treatment, with fewer cancer surgeries and fewer cancer treatment sessions. Earlier in the pandemic, we were very concerned that clinics were closed and treatment was being deferred. Although patients are now largely getting care on time, these interruptions in diagnosis, screening and treatment will have an effect on patients for years to come. On the basis of modeling we have done at the NCI, we think that the pandemic disruptions could cause as much as a 1% excess in cancer mortality over the next decade. A 1% excess, when we currently have 600,000 deaths per year, is significant. That is layered over the declining cancer mortality of ~2.2% per year that, as I mentioned, we have been seeing for the past few years. So the decline in cancer mortality may not be as pronounced as it could have been had the pandemic not occurred. We're still going to make progress in cancer, but this pandemic is definitely going to be a speed bump along the way.

At this stage, hospitals have largely resumed normal care for patients with cancer, and we need to get the word out so that people make up those missed screening appointments and do not ignore their new symptoms. We need patients to understand that even though the COVID-19 pandemic is starting to appear in our rear-view mirror, cancer is still very much with us, and we don't want to trade one public health emergency, which is the global pandemic, for another public health emergency, which is undiagnosed cancer. The NCI has been working aggressively on this front, together with other organizations that conduct education for patients, such as the American Cancer Society, the American Association for Cancer Research, the American Society of Clinical Oncology, and the American College of Surgeons, which provided good triage guidelines for surgery during the pandemic. Through our collective voice, we are working to make the cancer community aware of the need to minimize the impact of the pandemic on our patients. A particularly clarion voice, and someone who's been a really wonderful advocate on a national level, is the First Lady of the United States. Dr Jill Biden has talked about cancer screening very emphatically on several occasions, including through a recent Good Morning America segment about breast cancer screening.

You mentioned that cancer research has progressed very successfully during the pandemic. The response of scientists to COVID-19 in general has been quite remarkable, including with the development and rollout of vaccines. What are the positive lessons from this level of research response and the adaptations to healthcare that we can translate to cancer research and care?

NS: We've learned a lot from the scientific response to the pandemic. For example, I think we're all very excited about the mRNA vaccine platform. We've learned that mRNA therapeutic agents can be very useful and can shape the immune response. So mRNA is here to stay and there is no doubt that this is going to be important to cancer. There are several different groups already working on utilization of RNA therapeutic agents for cancer treatment.

The pandemic has also brought into sharp focus the need for integrated national clinical trials capabilities, even though we had that capability in cancer more than we did in infectious diseases when the pandemic started.

The fact that cancer is an incredibly heterogeneous collection of diseases, with each cancer subtype being relatively rare, also speaks further to the need for international collaboration, the ability to share data and collate trials done in other countries with those done in the United States. The need for clinical trial adaptability and data sharing is an important realization from the pandemic, and these are among the issues we will be discussing in the upcoming US–UK Cancer Summit.

Also, one of the things that was remarkable to me, was how effective some investigators were in using real-world evidence during the pandemic — data that were not gathered in the context of clinical trials, but through other approaches, such as registry and claims data. Some of these analyses were very important as they allowed us to discover how the pandemic was unfolding in the general population outside of the context of a clinical trial. That kind of aggregated, real-world data is something the NCI sees as a future opportunity. We've had the benefit of real world databases like SEER and Medicare-type databases for some time, but the pandemic has taught us that there's a lot more we can do in that area.

The last thing I think the pandemic has showed is the power of targeted funding. For example, about $17 billion was spent to support the development of COVID-19 vaccines through Operation Warp Speed. This type of approach would be valuable in other areas of biomedical research, including cancer and other diseases. We would not have that kind of expenditure every year of course — cancer is already well-funded in the United States with an NCI annual budget of about $6.5 billion. But I do think that if we really want to accelerate development in a specific area, the application of targeted federal resources can be very motivating, particularly if one can work with industry, which the NCI has a long history of doing.

Earlier you mentioned underserved populations in cancer care. The pandemic has certainly exacerbated societal and health inequalities. What has been the impact on cancer health disparities and the efforts to address them?

NS: We have clear evidence of health disparities in outcomes in the United States based on race, ethnicity, socio-economic status and access to healthcare. The pandemic and other recent events in the United States, such as the murder of George Floyd, have shone a very bright light on these inequities in American society, and as a result have motivated the entire research community to try and make further progress against disparities. Why these health disparities exist is a very interesting scientific question. At the NCI we have thought a lot about the particular areas where we have an obligation to support research and have funded research to identify the drivers of these disparities for many years. This is an important part of our portfolio that has grown steadily over the last decade. But having a very strong portfolio in cancer health disparities research doesn't mean it is perfect. We also have an obligation to continually reevaluate that portfolio and ask whether we are addressing the right questions, spending the right amount of money, doing the right trials in the right populations. We constantly get advice from our external advisors on these topics and although we have some very good examples of successful research, there is significantly more to do. As an example, a topic of some concern for the NCI right now, is the difference in outcomes between rural and urban patients. In the United States rural patients have a worse outcome than patients within urban areas, and that

disparity is increasing somewhat every year, which is troubling.

So the first part of our work is whether we are funding the right portfolio on disparities research. The second part is whether we are building the appropriate scientific workforce in cancer research and care that is representative of the populations they serve. We have conducted careful analyses of NCI grants and have found that the representation of scientists from certain racial and ethnic groups is significantly lower than the general population, and has been this way for more than a decade. The NCI is focusing on improving the diversity of our pool of trainees and grantees with regard to race, ethnicity, geography and research interests. We are governed by law as to how we can fund grants and we have to comply with certain rules, but this is an area where as a society we all want to see more progress and the NCI could do more.

The third area of focus is our internal culture. We have taken a long, hard look at the NCI itself and asked whether it provides a diverse, inclusive and supportive workplace environment for our employees. That analysis has shown that NCI is a great place to work — people like the mission of the NCI and our passion to end cancer suffering. But that doesn't mean that we don't have some challenges. For example, we found that there are disparities in promotion by race. Our goal is to end such disparities and to ensure that we have a workplace that values all of our employees, that promotes inclusivity and diversity, with hiring and retention policies that are fair, equitable, and of maximum benefit to the entire organization.

There are many other aspects of cancer disparities that are not in the NCI's remit. For instance, the cost of healthcare in the United States is not in our lane. So we have to be very precise about what we can focus on, and try to address issues that are outside our direct purview by working with other parts of the federal government. However, the three main areas I described are very important for us, because by continuing to work on these areas, the NCI can use its significant influence to promote social justice and health equity in the United States.

As our discussion comes to a close, what are your hopes for cancer research and patient care for 2022 and for the next 50 years?

NS: Cancer research is such a high priority for this Congress and this administration, and there are so many great ideas and such opportunity for progress right now, that my immediate hope, my Christmas wish if you will, is that we will receive a sufficient budget from Congress to fund all the great science we conduct through the NCI and realize all these great ideas. Over the last few years, we've been able to steadily increase one of the major pay lines that drives the success rate of our grantees and I hope we will be able to at least keep that pay line stable, if not increase it further, because it is still too hard to get a grant from the NCI, and we'd like to increase the success rates for funding.

My longer term hope is, as I described, to see more advances in prevention, treatment and diagnosis across the spectrum of cancer that will translate into is less cancer death and suffering every year, and a better quality of life for our patients. On the basis of the progress we've had over the past 50 years, I'm very confident and optimistic that we're going to see this, and that the President's goal of ending cancer as we know it, is not unrealistic. As I said, I think we'll come to look on this time as a "golden age", a brief period of a few decades during which we transformed the experience of cancer for our patients, and made it into a chronic disease, rather than the devastating illness that it has been up until now.

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Published online: 21 December 2021
https://doi.org/10.1038/s43018-021-00313-6