Dr. David Solit Discusses the Ethical Issues Surrounding Genomics and Precision Cancer Care

Jennifer Cohen

Welcome to the voices and bioethics podcast. I'm Jennifer Cohen and it's my pleasure today to welcome renowned physician scientist David Solit to the podcast. Thank you for joining us, Dr. Solit.

David Solit

It's nice to be here.

Jennifer Cohen

You are an oncologist at Memorial Sloan Kettering Cancer Center in New York City. And you have a number of roles there. I'd like to focus initially on your role as the director of the Marie Josée and Henry R. Kravis Center for Molecular oncology at MSK. I think that when most people think of oncologists, they think of a cancer doctor that specializes in one type of cancer affecting one organ of the body, breast cancer or colon cancer. Can you describe your team at the Center for Molecular oncology? How many people work there, how long you've been running it? And can you explain what the field of molecular oncology encompasses?

David Solit

Sure. So, molecular oncology is an effort to try to understand the underlying causes of a patient's cancer, and then try to use that information to guide their care. And that's often-called precision oncology, or personalized oncology. And it's an effort to try to, sort of, use molecular information to better sub-classify individual patients with cancer, their specific tumor types, into smaller groups, so that you can better customize their care. There's a couple hundred people who contribute to this effort at Sloan Kettering directly. These are folks who work in pathology, who helped run tests that help identify certain genetic alterations that contributed to cancer formation and maybe biomarkers of treatment response. We also integrate with a lot of the clinical teams, the surgeons, the medical oncologists, radiation oncologists, nursing staff, who I also consider to be part of the broader molecular oncology effort, but they're not directly part of our team.

Jennifer Cohen

Okay. Even someone unfamiliar with cancer might be aware that genetic mutations are the underlying cause of cancer, but genetic mutations and genetic expression have become key tools in diagnosing, treating, and providing

a prognosis for response to drugs as you've been describing. Can you give a brief overview of the genetic revolution that has taken place in detecting diagnosing and treating cancer over the past few decades?

David Solit

So, when people say that cancer is a genetic disease, what they mean is that there are certain changes in our DNA, that lead to dysregulated growth of cells and those cells that accumulate and cause a tumor in terms of a solid tumor cancer, or maybe a leukemia, in terms of a blood cancer. And there's really two major classes of these mutations. There are mutations, which we also call variants that people are born with, they inherit those alterations from one of their parents. And then there are other mutations that we call somatic mutations that accumulate over the course of somebody's life, either from just errors in DNA replication that just spontaneously occur, or due to toxin exposure from things like cigarette smoke, or other environmental toxins. And what we've learned is that these mutations, they dis-regulate the normal functioning of a cell, and they lead to the cell growing excessively or not dying the way it should, thus the cells accumulate and cause a tumor.

Jennifer Cohen

Okay, and Can you discuss now your role as a clinical physician, how your genomics lab works to treat individuals and how this understanding of genetic mutations in cancer can help you pair people with standards of care, regimens that might be already existing or put them in clinical trials? How does that work?

David Solit

So, there's three main reasons we want to do genetic testing to look for these mutations. The first of these is that it helps us actually figure out what subtype of cancer somebody has. And so, cancer is oftentimes considered this single disease, but it's not it's hundreds of different subtypes. And what we've learned is that there are certain mutations that are what are called pathognomonic. They're definitive for a diagnosis of a particular subtype. So, the way we've historically subtype cancers is that we've looked at the cancer cells under the microscope, and if they look one way and came from a certain organ, then we would classify them as say, breast cancer, adenocarcinoma, or a lung cancer, a small cell. But what we're now doing is we're adding molecular data to those classifications. And the reason we want to do that is by sub-classifying the tumors, we can better advise patients as to what their prognosis will be, whether they're going to be cured of their cancer. Whether there's a likelihood that it could come back, and whether they're going to respond to certain types of treatment, or whether it would be better to do surgery or radiation, you know, all this standard type of treatments can be guided by what molecular subtype of cancer a particular individual has. So that's one reason we do the genetic testing, it helps with the diagnostic part of a cancer workup. The second is, is that we've learned that some of these mutations that helped cause the cancer can be targets for therapy, so we can develop small molecule inhibitors or antibodies, that will inhibit these mutations. And thus, testing for these genetic alterations can be used as a guide to therapy selection for one drug versus another drug. And then finally, these mutations can be inherited, as I mentioned, and can lead to an increased risk of cancer if they're in all of the cells of your body, if they're called germline mutations. And we thus test patients with cancer for those germline mutations to determine whether they had an inherited cancer. And whether their family members, their children, their siblings, their parents, may also have the same cancer predisposition, and that should be monitored a bit more closely for developing cancer as well. So, this genetic

testing is now starting to touch on all aspects, you know, of cancer treatment, from diagnosis to treatment selection, to counseling of future risk of cancer.

Jennifer Cohen

Okay, fascinating. Let's focus now on this third aspect of genetic testing that you were just discussing inherited mutations, let's turn to an ethics issue that arises when that sort of genetic testing is done. As you say, the genetic information that a patient has does not necessarily apply just to that patient. It may be inherited from their parents, it may be shared with siblings, it may be passed on to children. What type of issues do you see surrounding privacy interests that patients may have in their genetic information? So, on the one hand, they might want to keep that information private. On the other hand, the dissemination of that information might represent significant health risks to people beyond the patient. How do you deal with those types of privacy issues?

David Solit

So, there's two main reasons why we're concerned about privacy related to germline mutations. And this privacy relates not just to the patient that might be sitting in front of us in the doctor's office, but also to their family members. So, the privacy concerns extend, again, away from just the index case, to also that patient's family. So why is this concern? The first is sort of financial risk for individuals. And some of that has to do with the uniqueness of our healthcare system, and that oftentimes, people don't have secure health insurance that is provided by the government. And there's always this concern that if somebody has a genetic mutation that predisposes them to a particular disease, such as cancer can be other diseases such as cardiovascular disease, or neurologic diseases like Parkinson's disease, that they may get discriminated against for harboring or being a carrier of that particular mutation, maybe some people are not going to want to provide them with health insurance, or maybe life insurance.

As another example, where knowing this information could lead to someone being denied of insurance coverage. And so, there's concern that if this data is not kept private, that people could suffer this sort of discrimination and be harmed by that. And so, there are some laws that are in place to sort of protect against that. But given the lack of a centralized universal health care system, that becomes a real burden on providers and a real concern for our patients, to ensure that patients who need to know this information to really optimize their care are not going to be discriminated against in the future. And it's why we're also very careful about it in terms of disseminating this information and keeping it private, because their children or their other family members are not making the decision to necessarily make it public. And they can be harmed by this information as well. The secondary risk of this really comes around to people worrying about getting a future cancer. So, if you are a carrier of one of these risk mutations, there are some instances where your risk of developing a future cancer is 90 or 100%. And what are you going to do with young people who might be carriers for this type of alteration? Do you want them to worry about these mutations all their life, have to deal with that anxiety? You know, is there a certain age that you would inform them of this risk? Would you want to tell children that they are carriers and have them deal with this worry and anxiety over this future cancer risk. So, this is debated pretty widely in the cancer community as the trying to balance knowing this information so we can best optimize somebody's care versus protecting them from these financial implications of knowing this information or the worry, and future anxiety of knowing that your risk for a particular disease?

Jennifer Cohen

Yeah, I can imagine there is enormous variation and how comfortable people are in knowing their own medical information. And there must be a constant balance between informed consent where you have a duty to give people as much information as they can, and then a duty not to harm, as you say, through psychological discomfort. Do you think there's a right not to know, your own genetic information?

David Solit

You know, I think we have patients who decline this kind of testing, because they simply don't want to know this information. But the reason that it's starting to become more difficult to do that is that there are certain drugs that have been shown to only work if you have a particular inherited genetic mutation. And so, patients who have a life-threatening cancer, if they were to not find out this information, they may be missing out on a potentially effective treatment. So, the risks of not knowing the information have gotten greater, as newer therapies have been developed that work only in a certain genetic subtype.

Jennifer Cohen

And you mentioned that there are some mutations where the corresponding risk of developing cancer is quite high. Can you be confident in tying in mutations to cancers in general, you know, other than the BRCA genes, or Huntington's or other examples that have been well documented?

David Solit

Well, there's major differences among these heritable cancer genes and what the risk of future cancer would be for some, as I mentioned, there's close to 100%, you know, like a, you know, BRCA mutation, there might be at 90% risk over someone's lifetime, that they may get cancer, there may be other genes where maybe the risk is doubled or tripled. But the overall risk is still very small, maybe it's 1% for the population, and maybe 3%, for a carrier, meaning that most patients are still not going to develop the cancer. And one could argue in some of those situations, the anxiety of worrying about that, maybe worse than the cancer itself for many years, especially for the people who never subsequently develop that cancer. Again, you have to sort of offset that with the fact that if you knew you had one of these risk alleles, maybe you would do certain screening tests that would help identify the cancers if it's going to occur at a much earlier stage, and thus, in a much more curable stage. So, this really becomes a real dilemma. There's sort of some cases where it's obvious, yes, you definitely want to know, if you have this really highly penetrant, we call it mutation, where you're almost very likely to get the cancer. But for more low penetrant genes, where even if you have this, it's only a small risk of getting the cancer, maybe the harm of the anxiety of knowing about this and worrying about it is greater than the clinical benefit. And for some neurologic cancers, you have certain neurologic diseases, not cancers, there's clearly situations where we might find out about a risk of a neurologic degenerative disease, like Huntington's, good example. But we don't have much we can do to fix it anyway. So, knowing this information, doesn't provide the patient with a lot of benefit, but does cause a lot of anxiety.

Jennifer Cohen

Do you find yourself as a clinical physician counseling patients? Or do they have genetic counselors at MSK, who perform that role? How do you speak to your patients about disclosure of this information to family members and children?

David Solit

Yes, so we do have a--, there's a whole field of what we call medical genetics, where there are both doctors who specialize in the issue surrounding this germline genetic testing and these inheritable not just cancer syndromes, but other types of medical illnesses. There're nurse counselors who spend a great deal of time talking about the risks and benefits of this type of testing. The dilemma that we're entering with oncology is that historically, when there was only a small number of genes that were relevant, and there weren't any therapies that were linked to these inherited predispositions, then it was reasonable to refer young cancer patients or those who are concerned about a family history of cancer because multiple members of the family had gotten the same cancer or multiple cancers, that you can refer these people to a medical geneticists or to a nurse counselor. The dilemma we have now is that there are many cancer types where every patient needs to have genetic testing, not to assess heritable cancer risk but to guide treatment. And we sometimes need to know that information immediately. So, we don't have time to spend months referring a patient to genetic counseling, to consider the risks and benefits. We need the treatment information now because the patient has a life-threatening illness, that if they don't get treated, they could die quickly. And so, we don't have time to sort of maybe debate with a specially trained nurse. All of these potential issues. And I think that this type of testing and counseling is now going to sort of fall to the point of care surgeons, medical oncologists, radiation oncologists to sort of talk to their patients about these issues, order the testing, interpret the testing, and many of these doctors only have limited experience with this type of genetic. So, we're gonna have to spend a lot of time educating this sort of point of care physicians to understand how to interpret this data and how to counsel their patients. And we're really gonna have to change the paradigm, it's not going to be possible for everyone to go talk to a specialist before they get tested in the future.

Jennifer Cohen

That's fascinating. How would you describe the current state of access to genetic testing with the issues you've just raised? Does that contribute to health inequities in this country that some people are not able to meet with doctors who are well versed in that aspect of cancer care,

David Solit

as with many things in our healthcare system, access to certain tests is almost defined by whether it's going to be paid for by an insurance company. And I would point out that increasingly, health insurance companies are paying for this germline genetic testing. So, while not everyone has access to this, potentially, or at least, is going to get reimbursed for the testing through their insurance, I would say increasingly, we are seeing for more and more cancer patients, this becoming a standard of care, that's part of their insurance coverage. But there are some patients who don't have as good insurance and their insurance is not willing to pay for it. And I do worry that this

type of genetic testing, both somatic testing, tumor testing, as well as germline genetic testing is going to become an increasing component of healthcare disparities. That's a concern I have, I don't necessarily really have any hard data that that's the case. But I worry that that's going to be an increasing issue going forward. But we are finding that as this is being viewed by expert panels, and consensus guidelines as part of how you routinely care for patients, that that's being reflected in sort of more universal reimbursement. But we still have patients where the insurance company denies this type of testing.

Jennifer Cohen

Okay, let's turn to your work. As a researcher, one of the most fascinating areas of focus in your research is your work on outliers or exceptional responders, people who've survived cancers against the odds or people who in a trial that otherwise fails for most participants, maybe there was one person who had a good response. Can you tell us about what made you interested in those cases and what you've learned?

David Solit

Yeah, so I think that as I said, before, every cancer is a bit different that the genetics of an individual patient's cancer, help define the biology of their tumor and whether they're going to respond to a particular drug. And the work you're referring to was part of our efforts to try to understand why does every individual get cancer? And can we identify a mutation in their particular tumor that is a target and makes them susceptible to a particular drug that we have. And so, the idea we had about a decade ago was, there were all these clinical trials that were disappointing, you know, maybe a couple dozen patients were treated with an experimental or standard cancer drug, and only a small percentage of them responded. But in some cases, the responses were very durable. They lasted for years. And we benefited from a real advance in sequencing technology that allowed us to look at not just one or two cancer genes at a time, but potentially the whole genome we could interrogate for mutations and all the cancer associated genes. And all the genes that we didn't even know were related to cancer. And we were able to, in many cases, discovered specific mutations that explained why these individuals were unique. Why did they respond where most of the other patients, if not all the other patients in the trial, failed to respond? And we've then been able to use those insights to then prospectively, look for patients just like those individuals who responded. And it's very attractive as a way to repurpose drugs because you already have the drug, the drugs already been developed, you just didn't know who to give it to. But this now, tumor genetic testing can help guide which patients are most likely to benefit and that's really the theme of cancer treatment. Going forward, you're gonna see increasing amounts of personalization, that not all patients would say breast cancer being treated the same, not all lung cancer patients are going to be treated the same. There's going to be dozens of different subtypes molecular subtypes of breast and lung cancer, colon cancer, bladder cancer, and there the treatment for those molecular subtypes are really going to be customized to really address the specific underlying causes of the individual patient's cancer.

Jennifer Cohen

You stated that one of your research goals is to accelerate drug discovery is the traditional gold standard model of a double blind, randomly controlled trial being overtaken by advances in clinical data sharing and a willingness by the FDA to be more flexible in their requirements?

David Solit

It's a great question. And I would say right off the bat, we're not going to replace completely randomized clinical trials with real world data. It's called when we sort of look at big data sets in a more uncontrolled way. But there's really a role for both. I would say that when there are two treatments that are both effective, but we're not sure which is better. A randomized clinical trial is a great way to show one treatment is better than another treatment. But there are many scenarios where there are no effective treatments, or the cancer is extremely rare, or the molecular subtype of the cancer is extremely rare, that doing a randomized clinical trial is either unethical or impossible. And in those situations, the best data we may have is in a small series of patients that is not randomized, that, that we only have the treatment arm, we don't have a control arm treated with, say, a placebo. And in some situations, it makes sense for regulators to look at the data and if it is overwhelmingly positive, approved drugs without randomized clinical trials. And we've started to see that from the FDA over the past decade, that there are some molecular subtypes of cancer where we know that a certain drug that targets the underlying molecular cause of the cancer can have a response rate in the 70, 80, 90% range. In a scenario where there is no effective treatment. And so, a randomized trial, there becomes to me a bit unethical because we know the treatments working very effectively in the patients who have received it, there is no effective alternative that you're really comparing against. And maybe again, the cancer is rare enough that maybe only dozens of patients get in the United States every year that doing a randomized study might take a decade or longer or may never be feasible to finish. And so, in those scenarios, these what we call basket studies, where the trials not really testing the drug and a particular cancer type, but in particular molecular scenario may be sufficient to lead to regulatory approval and a change in the standard of care.

Jennifer Cohen

So interesting. Okay, let's turn now to the issue of funding for research. I've heard you say that there are many good ideas that don't get pursued due to lack of money. Can you discuss the current state of funding for cancer research and rare cancer research, in particular, just remind our listeners, what constitutes a rare cancer?

David Solit

So, you know, I think there are a lot of great ideas out there. And I think there's always more ideas, and there is funding. And you know, as a cancer researcher, one thing we spend a lot of our time doing is piecing together funding from many different sources. Some funding might come from the federal government in the of course of competitive grants that we wrote, other funding might come from philanthropic organizations, or fundraisers, and other funding might be sort of subsidy we're receiving from the hospital from our employer. So, there's all kinds of funding, we need to try to piece together for a research program, both a clinical research program and a laboratory research program. And there's definitely ideas that I see every day that are good ideas that just have not been able to receive funding to be pursued, really, the most tragic to me sometimes is when you've got a really good idea. But maybe the number of patients that would benefit from that idea is very small. And that's what you deal with, with rare cancers that maybe a lot of the drug companies are not going to be particularly interested in that. And that's a source of funding for many clinical trials and for a lot of drug development. But maybe the potential market of the drug is going to be quite small, because the cancer is very rare. And, you know, that's where we really need philanthropic organizations or the government to really step in and help fund some of those

orphan indications, we call them where there's just not a lot of financial payoff to that drug development. But there are patients that would benefit and with cancer, what we find is that there's a many, many rare subtypes. And if you actually added them all up, it's about half of cancers are designated rare cancers, individually, there's not many patients in many of these rare cancer subgroups. But when you add them up, there's lots of rare cancers that combined together to represent a lot of patients. So, I think one of the challenges in the field is to find ways to perform trials and fun trials for rare diseases, like rare subtypes of cancer.

Jennifer Cohen

And as you say, pharma might not be too keen on investing in a lot of rare cancer research--

David Solit

while they're running a business, and if there's not going to be any return on that investment, then they might be more interested in the more common diseases.

Jennifer Cohen

Right. Do you feel that it behooves centers like Sloan to pursue industry relationships to fund research and if so, how do you manage conflicts of interest given the high cost of most cancer drugs?

David Solit

Well, I mean, I'm a big believer that we need to collaborate with industry to move the field Forward, I mean, I have patients who are dying of cancer every year. And we don't have adequate treatments for many types of cancer, too many of our patients still are suffering the consequences of cancer, some are being cured, but the treatments are too toxic, and they're having lots of side effects or they're losing their lives to cancer. So, we need to be doing better. And I think drug companies need to be partners for the development of new treatments. So, I've throughout my career, tried to collaborate with industry both to develop new, better diagnostic tests for cancer, these genomic tests we talked about, or to develop better drugs for both common and rare types of cancer. And, you know, in many ways, the trials, the definitive clinical trials are oftentimes funded by drug companies. And so that is a really important source of funding for many of our clinical studies. And I think we need to collaborate with drug companies, I think what we need to do is we just need to be transparent as to who's funding the study, and where that funding is coming from. And I think you've seen that over the last couple decades that there's been much more disclosure as to who is paying for a particular clinical trial, is that being paid for by the federal government from the NIH? Or is it being paid for by a particular pharmaceutical company that's developed the drug and thus could benefit from the drug getting FDA approval and being marketed? So again, there should be a collaborative effort with industry, because they have knowhow and expertise that complements what we do in academia. They're good at developing drugs. That's what they do. Yeah.

Jennifer Cohen

Yeah. You yourself have been a fundraiser for cancer, you've been involved in a Cycle for Survival, which since its inception, has raised I think, a staggering something over $200 million for rare cancer, 100% of the money then goes to research. What made you start a team with Cycle for Survival? And how has that affected your work?

David Solit

Yeah so, I, like many, almost everyone in the country or in the world know, someone who had a family member who had cancer. So, you know, my personal story is similar to lots of other personal stories. In that, you know, I've been directly affected by family members who have suffered from cancer, and some have had rare cancers. And that was one of our inspirations of getting involved in cycle for survival. And, you know, I think cycle for survival has been really a spectacular source of funding for rare cancers that are neglected, as we discussed by both NIH government funding mechanisms as well as by industry. And their impact has been tremendous. they've raised over $250 million, I would say our team has made a good contribution to that I, part of Team Hop, usually led by my wife, Barbara, and we've raised over $2 million, throughout the course of the last 10 years, is trying to fund certain cancers that were really not being researched, we really saw a need that there were some types of cancer that other groups were not focused on. But there were patients suffering from those cancers. And we felt the need to go out and try to raise money for research in those underserved areas. And, you know, I thank Cycle for Survival, there's many other philanthropic groups that do similar things and their impact is has been tremendous, but we still have a long way to go. We still have a lot of patients who need better treatments.

Jennifer Cohen

You mentioned that you have a lot of patients who suffer through their treatments and the toxic side effects. One of the many benefits of your work could be less toxic treatments. Do you think that an end to traditional surgery, chemotherapy, radiation is in sight?

David Solit

I don't think we're going to see the end of it. I think the newer treatments, what we've learned is that they're complementing in some cases replacing but, in many cases, simply complementing older treatments like surgery and radiation, and cytotoxic chemotherapy. But those older treatments are sometimes still the best treatment, there's still many cancers where the best thing to do is resect the tumor or to radiate the tumor or to treat with combination chemotherapy that is curative. But there were many other cancer types, one could say most of these common solid tumors like lung cancer, breast cancer, that we're not that sensitive to older types of chemotherapy. And what you've seen is these newer types of targeted therapies and immunotherapies have come along. And they've made a tremendous impact in some cancers. So, some cancers have really benefited from the newer treatments, but other cancers and I would use pancreas cancer as a good example. The improvements in outcomes have been pretty modest, so far in that specific cancer type. So almost sort of all of the above type of guy, I'm not wedded to any particular type of treatment. I just want treatments that are going to work and be less toxic. And sometimes the least toxic approach is just to cut out the lesion. Other times it's to use a novel immunotherapy or novel targeted therapy but there isn't one solution that's probably going to work for all cancers. Because cancer is a very different among patients, there's not one cancer, it's not one disease.

Jennifer Cohen

And my last question Dr. Solit, are oncologists becoming more comfortable speaking in terms of curing cancers, can patients realistically expect to be cured rather than being in a state of long-term remission?

David Solit

Absolutely, I mean, I do hear the talk of sometimes oncologist saying, you know, our goal is to turn this into a chronic disease. I disagree with that. Our goal is to cure the cancer so that you don't have to take any more treatment because even the least toxic therapies, if you take them for years or decades are going to have side effects, even things that are very safe and non-toxic compared to say older cytotoxic treatments, over time can accumulate chronic toxicities. And so, the best way to avoid side effects is to simply cure the cancer and then not need any more treatments. So, we do cure many cancers. I think if there's a belief out there that we don't cure a lot of cancers, that's untrue. Many patients are cured of their cancers. And I think you're seeing a very large increase in people who are cancer survivors out there. And in many cases, those patients have unique needs due to the prior effects of their treatment. But, you know, there's been a huge progress in curing childhood cancers. And for cancers like chronic myelogenous leukemia, the life expectancy is approaching that of an age matched control patient. So, in some cases, we're curing the patients. In some cases, they're living longer. But I still think the best way to ultimately treat cancers to cure it. Well, I take a new therapy that prolong someone's life many years. Yes, of course. But our goal is to cure people and we do cure many people. We just don't care enough people. And there's still too many people dying at too young an age or are suffering too many side effects from their treatment. At this point, we need to do better.

Jennifer Cohen

Dr. Solit,thank you for sharing your expertise and for your commitment to cancer, patient care and research. We are all so grateful to you and your team's dedication.

David Solit

Well, thanks for your interest in the topic and we need everyone in this effort. We'll take all the help we can get.

Jennifer Cohen

Thank you.

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