

**President's Council of Advisors on Science and Technology (PCAST)  
Public Meeting Transcript  
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**Welcome from PCAST Co-Chairs**

>> John Holdren: Good morning, everybody. Welcome to the members of PCAST to the OSTP PCAST Secretariat and to the members of the scientific community that joined us for this PCAST meeting. Thank you all for being here and thanks to those who are watching on the web. As usual, we have a full agenda this morning. We will be hearing about the National Science Foundation science and engineering indicators, the latest report, the 2016 report. We will be having a panel on One Health and we will be having a panel of cancer researchers talking about frontiers in cancer research, and then we will have public comment. So without any further ado, let me ask my co chair Eric Lander for words of welcome before we launch into the program.

>> Eric Lander: Let me add my welcome to everyone in the room, and watching on the web and in the archived version someday to come and PCAST itself who remains tremendously active. Many studies ongoing, studies under discussion it is fantastic to see the energy and commitment to the group and I want to express my thanks.

**NSF Indicators**

>> John Holdren: Without further ado, I want to welcome Beethika Kahn from the National Science Foundation. If you will take your place at the front, she is going to tell us about the science and engineering indicators heavily used by many of us to keep track of the science and engineering enterprise in the United States and around the world. Beethika, thank you very much for being with us and we look forward to your remarks. And her title is up on the screen, Director of the Science and Engineering indicators program at the NSF.

>> Beethika Khan: Thank you Dr. Holdren good morning everyone it is a pleasure to give you a briefing on the science and educators report that we just released two months ago in January of this year. Here is an outline of what I hope to cover today. I'll give you some brief background information on the indicators report, and I will then give you an in depth at some of the major data and trends from the 2016 report. I will focus on a number of indicators, math and science performance of U.S. 15 year olds, production, research and development, patents, publications and knowledge intensive production all within an international context. And I will wrap up by highlighting some coming attractions in our indicators related product lines. Science and engineer indicators or Indicators in short is a congressionally mandated biannual report on the U.S. and international science and engineering enterprise. The report provides Comprehensive data drawn from a high quality of wide variety of federal, non federal and

international data sources. The report provides the data in context in a policy neutral and policy relevant way and the report does not offer any policy options or policy recommendations. It is prepared by the NSSES under the guidance of the National Science Board. NCSES, one of the 13 principle statistical agencies in the U.S. and housed in NSF's social, behavioral and economic science directorate and has extensive review by experts, agencies including NSF internal reviewers and national science board members for accuracy, coverage and balance of the information presented. As I just mentioned, in January of this year we released the 22nd Edition of the Indicators report. And beginning with this edition, Indicators will be published as a web based digital report rather than a printed volume. We are very excited about our new digital format. We believe that the report's new digital format will improve access to and understanding of this statistical resource. The new website is responsive on multiple platforms, allows for a greater degree of interactivity and easier navigation across Chapters and topics. The complete content of the report is downloadable as a PDF. I wouldn't recommend it, the main report, just Chapters 1-7 without appendix is 900 plus pages, so you can customize and print part of the report as necessary. So because of the central nature of the topic, which is U.S. and global science engineering technology it has a wide and diverse audience, including but not limited to policymakers, researchers, journalists and academics. This is why we produce a suite of products which we sometimes refer to as the Indicators Ecosystem which utilizes a variety of presentation styles to make the content accessible to a wide and diverse audience. So the main report is organized around seven Chapters, the topics of which are K-12 science and math education, SNE higher education and work force, research and development, knowledge intensive industries, innovation and global landscapes and public attitudes and understanding in science and technology, information and landscape and public attitudes and understanding science and technology. In addition there is an overview Chapter and science and engineering indicators digest, both bringing together major stories and themes from across the volume and thus draw connections among the different topics. The overview has a policy neutral synthesis on the major themes, whereas the digest uses graphics and narrative text to provide a broad brush summary. In addition, we have a state indicators data tool providing detail state level data on many of the indicators. And what's interesting about the State Data Tool is that in addition to providing the data in tabular format the tool utilizes things like maps and histograms to easily and ready to demonstrate geographic trends. And the board on top of the main report and tool, the National Science Board has authors one or more companion reports which draw on the data indicators, but unlike Indicators offer policy recommendations on various issues related to science, engineering and R&D policy in keeping with the board's statutory responsibility to shed light on these issues. So with that background lets dive into the data to explore science and engineering. I will discuss trends in a number of areas, education, degree production, research and development patterns, SME publication and knowledge intensive industries. Let me start by giving you a brief context for the data that we will discuss. This is sort of the big picture tying all the indicators together. The international and domestic science and engineering trends that we discussed in the report can be understood in light of the world wide trend towards more knowledge intensive economies and increased competition in science and engineering. In science and engineering research, the commercial utilization and other intellectual work is of growing importance. Such economies rely increasingly on a skilled work force as well as sustained development in R&D to produce discoveries and knowledge

streams that form the core of knowledge intensive production. Whether in manufacturing industries that produce aerospace computers, pharmaceuticals, or in service industries that provide financial business R& D health and education services. So knowledge intensive production is growing worldwide and it's increasingly a key feature of both developing and developed economies. At the high level, education, R&D, and knowledge intensive industry are intimately linked allowing companies to participate and compete in the global marketplace as well as addressing challenges in the areas of energy, health, climate and other important domains. And we are in a global connected world, so international trade, supplier chains, internationally mobile students and workers and their exchange, and global collaboration and infrastructure tie and connect this very global landscape together. This graph shows average math scores for 15 year old students in 32 developed countries. And the main story here is that the average math scores of U.S. students are toward the bottom of this list. And students from 23 developed nations statistically scored higher than students in the United States. And this graph shows the average science scores. Tells a similar story. Students from about 16 OECD other countries statistically out performed our students, that's math and science assessment scores. This graph shows S&E bachelor's degree production in selected countries. The main story here is that developing countries, primarily China and India, China represented by the black line and India actually not on this graphic. We don't have as complete a time series for India. But China and India have seen a very steep increase in the bachelor's level degree production. This shows S&E, but they have shown a steep increase since the turn of the century. As of 2012, China and India together produced nearly half of the global total of S&E first level degrees which are bachelor. And the U.S. produced another 9%. While there are some challenges comparable the international data, particularly between U.S. and China, it is clear that China is putting great emphasis on building their S&E capabilities. Some brief context on rapid growth rates. Rapid growth rates frequently echo the early stages of economic development, so as developing countries devote a lot of resources in R&D, education and knowledge intensive production, the initial rapid growth rates can exceed those seen in developed countries. Allowing some of them to approach the capabilities of the developed world. Having said that though, the long and sustained increases we have seen in China in a number of areas are quite remarkable. This graph shows S&E doctoral production. Like bachelor degrees, China represented by the solid black and India not on the graphic, increased production. And the U.S. however the U.S. total represented by the solid red line. The U.S., however, produces more S&E doctoral degrees than China or India. Now understanding the relationship between the degree production in a country and capabilities of the work force is complicated by immigration. Particularly for countries like the United States, which is a popular destination for international students. In the U.S., a considerable proportion of S&E doctoral degrees nearly 40% go to temporary visa holders and this proportion is higher, about half or more, in computer science, engineering and economics. However, if the past trends continue, nearly 2/3 of the doctoral degrees recipients with the temporary visas will remain in the U.S. for subsequent employment and we call that stay rate. We will now look at data on R&D spending and this graph shows the concentration of global R&D in selected regions. So east, southeast and South Asia and the Asia Pacific region. And North America and Europe account for nearly 90% of global R&D. The graph shows concentration in 2000 and 2013. A notable trend so global R&D, similar to degree production. Global R&D, is highly concentrated geographically. A trend

over the last decade is the rapid increase in R&D spending in the Asia Pacific region primarily led by China relative to other R&D performance areas. As a result of this differential growth rate, the proportion of global R&D taking place in the Asia Pacific region has increased from about 25% in 2000 to nearly 40% in 2013.

>> John Holdren: Can I ask one question? Are those dollar figures corrected for inflation, or are those current dollars?

>> Beethika Khan: Current dollars. Yes. So the proportion between 2000 and 2013 Asia region has gone up 25% to 40% and you can see the corresponding shares in North America and Europe both declined. With that global snapshot in mind, let's look at R&D spending in selected countries and the European Union. And again these are in current dollars. The U.S. and both public and private are included in this graphic. The U.S. spends the most on R&D off any single country, accounted for about 27% of the estimated global total of \$1.7 trillion and China was second. So the U.S. was followed by China, who spent about 20% of the global total in 2013. And China's R&D total the upward sloping black line is approaching that of the European Union. And you can see the slope of the black line. China has seen a very steep growth in R&D spending in that time at about 20% annual rate between 2003 and 2013 compared to 5% average annual rate in the United States and E.U. Another country seeing quite an impressive growth is South Korea. It is hard to see the slope because of the scale, but South Korea has seen about an 11% average annual growth in the 10 year period between '03 and '13. And accounts for about 4% of global R&D. Now let me just focus on the U.S. data for just a moment. Looking at the red line, you can see the flattening in the U.S. growth rate beginning in 2008 during the great recession. And then after 2010, 2011 the uptick in growth returned. The story there is, during the great recession U.S. R&D was held up by federal R&D which got a boost from AARA, the American recovery and reinvestment act of 2009. After about 2010 2011 federal R&D has been on a declining trend. By then business R&D recovered getting an on upward trend, the uptick in growth that we have seen in the past was driven by the business sector. If you look at the last five year period between 2008 and 2013, overall we have seen a growth in U.S. R&D but R&D growth did not outpace the GDP growth in the most recent data and that's a departure from a long term historical trend. So just some context there. This graph shows R&D intensity, which is R&D as a proportion of GDP. South Korea and Israel, Israel is not on the graphic has the highest R&D intensity of about 4%. The R&D intensity of the big R&D spending countries, U.S., China and European Union between 2% and 3%. And China's R&D intensity represented by the black line has exceeded that of the European Union. Now some more context. R&D intensity is a convenient indicator for understanding countries priority to advancing science and technology, it is normalized for size. However, keep in mind that governments have only limited direct control over the size of their economy, as well as total R&D spending because businesses tend to be the leading source for funding R&D in many countries, right. This is why achieving the ratio may be a matter of some luck. Additionally countries have a tendency to specialize in different activities. For example, China does a lot of basic research than the U.S. spending about 5% of the total R&D spending on basic research compared to 17% in the U.S. Having said that though, 5% of a very large number means China does more basic research than France. But these are some important context for understanding

who has comparative advantage in what, and how the pieces of the global puzzle fit together. So some context behind the numbers. And really quickly, speaking of relative focus on research versus development, we see a similar phenomenon in global efforts to generate clean energy, okay. Commercial investment worldwide in clean energy is focused primarily on development of later stages of technology in relatively mature areas like wind and solar. If you look at total investment globally, China leads, and attracts the most, about nearly 1/3 followed by European Union and the U.S. By contrast, the U.S. leads in a very small segment of total commercial energy that focuses on venture capital and private equity investment, and that part focuses on emerging and future trends in clean energy technologies. Again, sort of similar phenomenon we see across the board. In addition to R&D spending, we also look at peer reviewed S&E output of countries and region. And consistent with the trends seen in R&D spending and doctoral degree production, China has seen a rapid increase in its S&E publication output, and the share of the worldwide S&E publication that China accounts for now is comparable to the U.S. in terms of the number, in terms of the number China's share of the global total is comparable to the U.S. In terms of the number, that is an important caveat because U.S. publications are more influential. U.S. publication receive the most citations adjusted, after we adjust for the size of the research pool of each country, and the U.S. shares the distinction with Canada, Switzerland, the Nordic countries and the United Kingdom. This graph shows data on patents. The share of U.S. PTO patent awarded to inventors in the United States, Japan, E.U. and other developed and developing countries. And patents are a broad, you know, but imperfect indicator of invention. The propensity to patent vary across technology areas, and many patents don't lead to commercial products or useful invention. But nonetheless, this is one area where we have international data. Unlike R&D spending data, unlike R&D spending and education data, the patent data shows a dominance of the developed world. US PTO awarded about 300,000 patents in 2014, and the largest share of which went to the U.S. followed by Japan and the European Union. China and India, which are included in the developing country total in that orange part of the vertical bar, the shares going to inventors in China and India are quite small, okay. Now, for any national patent office though, data on the number of patents don't tell us anything about the quality of those patents, right? Which is why we look at triadic patents. Triadic patents are patents where they seek patent protection in three of the world's largest markets: The U.S., Europe and Japan, and they indicate patents that are likely to have high commercial value. Like the USPTO patents, U.S. and Japan and the E.U., the developed part of the world account for the vast majority of triadic patents. The shares going to China and South Korea are increasing, so they accounted for about 10% of the triadic patents in 2012 but they still received far fewer triadic patents than the global leaders. I'll wrap up my presentation with showing you some data on knowledge and technology intensive industries or KTI industries. KTI industries include high tech manufacturing and knowledge intensive services. This graph shows high tech manufacturing which includes aerospace, computer and communication equipment, semi-conductors, pharmaceuticals, and scientific instruments. High tech manufacturing is an order of magnitude smaller than knowledge intensive services but they're a big lever of R&D and they account for almost half of business R&D in the U.S. And high tech manufacturing the U.S. retains a slim lead over China accounting for 29% and China accounting for about 27% of the global output. And again, by the steep slope of the black line, you can see that China has seen a dramatic increase over time, so output has risen by a factor of 10 between 2001 2014.

And again context, we see some curves are converging but the context that is helpful is that U.S. and China concentrate in somewhat different types of activities, the U.S. is particularly strong in aerospace and scientific instruments. The supply chain which is largely domestic, and China, the largest global producer of ICT, Information Communications Technology goods and pharmaceuticals. And ICD production is the most globalized among high tech industry and usually the supply chain span multiple countries. So the part of production in China is heavily reliant on final assembly of inputs and components that are either designed or produced in other countries. So the activity in China is particularly reliant on this final phase of the supply chain. And very quickly, you can see how countries have recovered from the great recession. If you look at the U.S. line, you sort of see the flattening around the great recession and the uptick in growth seems to be back. China just kept on going, was barely affected during the Great Recession. If you look at the green line for E.U., output largely stagnant due to weakness of member country economies. And Japan, the light blue line, the output declined since the Great Recession and it is quite interesting to see how the countries recovered from the Great Recession. And the last side shows commercial knowledge intensive services including business, financial and information services. Business services include computer programming, R&D services, those are some examples. Financial services include banking, insurance, securities, information includes traditional phone, wireless, communication, TV distribution, etc. Unlike high tech manufacturing, in commercial knowledge intensive services global output is concentrated in the developed world. The U.S. and E.U. together account for more than half of the global output. China remains weak and accounts for 10% of the global output, but again is making rapid progress. Other countries actually have seen quite an impressive growth, particularly Brazil, India and Russia. Brazil and the growth in Brazil was led by financial and information services, and India was led by business services, in particular computer programming. And Russia's growth led by business and financial services. And very similar trends here in terms of recovery of the recession. And, you know, when we talked about S&E publications, yes China seeing a growth nearing U.S. in terms of publications, but other developing countries, India and Brazil seeing democrat mate particular growth also. In summary how are we doing in the U.S.? The global landscape experienced quite dramatic shifts over time. Over time we have seen a catching up catching up in particular parts of the industry in the developing world. And special concentration for developed nations that have historically led the global efforts in S&E, right. So a multi polar world for S&E is emerging after many decades of leadership in the developing world. And the developments have taken place in context of an increasingly interconnected world. Capacity building around the world in R&D and human capital, improvements in communications technology and greater international collaboration in S&E. So the U.S. still leads in a number of areas S&E doctoral degree production, high impact S&E publication, intellectual property, knowledge and technology intensive production, but parts of the developing world, particularly the Asia Pacific region led by China, is working on improving their capabilities in these areas. So we see these hubs of growing importance globally, and we will continue to watch this fast changing global landscape. Very quickly I want to highlight some coming attractions in indicators related product lines. I mentioned that the national science board authors multiple companion briefs and plan to release them in 2016 and 2017, have been redesigned to be short, timely and digital, so stay tuned for those. The board is also in the final stages of producing an infographic which is a visual tool for understanding

trends I showed you. The board is also organizing a user workshop to rethink the future of indicators. How can we make the data more relevant? Do we have the right mix of products? How do we improve the balance of the high quality of our data and analysis in a world that expects shorter cycles for information turn around? The workshop will be the first step in addressing some of these questions. And speaking of data quality, I wanted to quickly highlight that we work with our international counterparts to develop internationally comparable data that are useful and relevant for policymakers. And a wide variety of data users. Every 10 years the OACD engages the policy holders and data users and providers into an open dialogue to review and develop its long term agenda on science, technology and innovation or STI data and indicators. This event is known as the OACD Blue Sky Forum was in 2006. And the upcoming 2016 forum will be in Belgium in September and we will carefully review the outcome of the forum to identify STI indicators for inclusion in future volumes of indicators. And WMPD, women, minorities and persons with disability in science and engineering is another congressionally mandated publication we produce which has detailed data on employment and occupation in S&E. Thank you, and I am happy to take any questions you may have.

>> John Holdren: Okay thank you very much. Our usually format of the PCAST members raising their flags and Craig Mundie is the first one up.

>> Craig Mundie: Thank you that was a good presentation. I was looking through the digest version you handed us, and one thing that strikes me both in your presentation and most of the graphs that are there, with the single exception of one, the B graph on page 7, U.S. R&D performance by type of R&D and performance in that performing sector. Historically all of this has said R&D, R&D, R&D, like that was one thing. And that one graph you break it down into basic, applied and development. I think the separation is absolutely crucial, particularly if you are trying to make policy decisions and predict the future. And I think the fact I mean many of the trends are troubling enough whether education, etc, and you look at China and recognize they are still sort of developing. They're four times our population. They have per capita GDP as a result and we measure even comparing against that. And not so good. So I am curious as you go forward you entertain the idea of very systematically reporting on basic science and applied research and development and really in a disciplined way keep them separate.

>> Beethika Khan: That is a great question. Basic, applied, development, although we get some criticism because R&D is not as linear as the trio would suggest, basic applied development, but it is an important distinction, and again, the digest presents a very small subset of indicators. If you look at Chapter 4 of the Indicators report, we have a lot more analysis by what we call type of work which is basic, applied and development. And you can see, you know, how the funding and performance looks likely sectors and some international trends, also.

>> Craig Mundie: Your remarks demonstrated that you have the data. What troubles me is when the digest version, which is largely what the policymakers are going to consume, is presented and it tends to re consolidate everything and I think it masks how bad our situation is on a projected basis and I am sure the data is there, it's all in how it comes out and I just offer that thought.

>> Beethika Khan: Thank you for the comment.

>> John Holdren: I am next on my list. And let me start by saying thank you not only for the presentation, but for the amazing work you and your team do on this document. I have often commented that I may be one of the few people around the country who has used the great fat now 900 page annual or every other year report as a textbook and course on introduction to science and technology policy. It is the best such introduction, I think, out there. The question I have though has to do with timeliness and updating. The principle short coming of the document is if you look at this one, for example, in most graphs the latest data are for 2013. A few you have 2014, particularly for the United States.

>> Beethika Khan: Yes.

>> John Holdren: Mostly it is 2013, Since it only comes out every other year, in 2017 we'll still be looking at a version of this that has 2013 data.

>> Beethika Khan: Yes.

>> John Holdren: The question is, in the electronic age when so many more of the relevant basic statistics are becoming available online, including in other countries, what would it take for you to sort of lift your game in terms of the timeliness of the data, including the possibility of issuing a sort of an interim report online with some of the most important data updated in between the every two year publication of the giant volume.

>> Beethika Khan: Yes, thanks for the comment, point well taken. Having worked at a policy shop before I joined NSF, I know how timeliness is at the heart of being relevant. And the board is this is very central to, you know, to the board. The board frequently engages in this conversation. And our hope is we are taking baby steps, right, this is the production process for indicators is about 18 months. And it is a biannual publication. A lot of coordination happens across federal agencies, contractors, data providers, data users. Our hope is the digital format is a first step. It's a baby step, but it's a first step in the right direction. And we are very much, you know, interested in looking into what kind of efficiency gains can be had in the production process from this digital version, and how can we build on that perhaps to provide interim data updates. Because again, we are in this world where policy makers and data users they expect timely, relevant data. So, you know, one avenue that we are exploring is, you know, perhaps some intermediate data, publishing the intermediate data via either science board companion or NCSIF publication vehicles. And I mentioned WMPD, some of the workforce and education data will be updated in WMPD. And some of the KTI production data and some of the R&D data we are looking into publishing some updated data at some point before 2018, and that's a great comment. We are also looking forward to this workshop which is again a first step in exploring some of these options of how do we become more relevant? What are the options and opportunities and how our data gets used, and how can we focus on the cycle. And the cycle is central to, you know, again sort of the board talks whenever the board talks about rethinking

indicators I see two main themes, which is data updates and outreach. So we will be working on this. It's very much central to what the board is thinking about.

>> John Holdren: Good thank you very much. Maxine Savitz is next.

>> Maxine Savitz: You will find it is very useful over the time. It is somewhat related to Craig's basic and applied, and it is the U.S. expenditures, the amount. In the 80's we crossed over where the Federal Government stopped being the major funder.

>> Beethika Khan: Right.

>> Maxine Savitz: And the industry business more, and business tends to be more applied. But do you break down in the other countries, when you give the total R&D, do we know the breakout like in China how much is business versus

>> Beethika Khan: For some of the major countries we have that data. For the U.S. we have very detailed data by the type of work. And you are absolutely right, you see that somewhere in the 1980s businesses sort of crossed the 50% line and became the major funder of R&D in the U.S. Actually, my PowerPoint presentation had a slide in the back where it shows how the R&D ecosystem in the U.S. has changed over time. So sort of federal share has been going down and business share has been going up. And yes, exactly. So the black line is the business. So somewhere in the 1980s the two crossed and businesses became the majority funder. And I believe funding source for U.S. basic research again sort of shows the proportion of basic research funded by Federal Government, business, Universities and colleges. And the same data, I have the same data for development. And development, you see that businesses do the majority, whereas this is basic research, Federal Government does it. And yeah, for some of the countries we do have that break down available, not for all countries. For China we have the break down available.

>> Maxine Savitz : And that will be, I can go online and get that data?

>> Beethika Khan: Yes, that data is in Chapter 4, national and international trends and research and development.

>> John Holdren: Good, thank you. The last question will be from Michael McQuade.

>> Michael McQuade: Thank you. I continue to echo my colleagues at the detail and macro level is a good report. The timeliness is something we all hope gets better. Technical questions. The graphs showing the geographic spin, sort of the central section, is that where they are actually spent or where the ownership of the dollars come from. So does US expenditures include what U.S. companies spend overseas?

>> Beethika Khan: U.S. expenditure includes that is it a good question. We do break the data down for multi-national enterprises. I believe it's expenditure in the U.S. actually.

>> Michael McQuade: So It is where the money is actually spent.

>> Beethika Khan: Yes, yes. And I kept referring to Chapter 4. Chapter 4 has a section on multinational corporations, and there you can look at U.S. M&E's, how much they are spending in the U.S. versus how much the foreign affiliates are spending abroad. And you can look at the opposite also. Foreign international enterprises, how much they spending in the U.S.

>> Michael McQuade: Off the top of your head do you recall comments or trends in that data?

>> Beethika Khan: Off the top of my head, I know that if you look at U.S. and the foreign affiliates and the R&D they do in I think the \$40 billion range that U.S. MNE's, the foreign affiliates and the R&D they do abroad. And an interesting trend there is this in terms of the country hosting the R&D, so foreign affiliates and where they are spending the R&D, the host countries are very much in the developed world. So I believe Europe and Japan. That's where most of this R&D is hosted. One exception is professional scientific and technical services. And there you see that in addition to these traditional centers, Europe and Japan, China and India are playing an increasingly important role. If you go to Chapter 4, you can find much more details than what I have just given you.

>> Michael McQuade: Okay, thank you.

>> John Holdren: Okay that takes us to the end of our allotted time for this topic. Beethika, thank you very much for that presentation.

>> Beethika Khan: Thank you.

>> John Holdren: And thank you for the work that you and your team on this most valuable compendium and we look forward to continue to draw on it as we contemplate the state of the US R&D enterprise and larger research and development enterprise, including in relation to the rest of the world.

## **One Health**

>>John Holdren: We are now going to make a transition to the next topic. The next topic is One Health. And the moderator for that discussion is my PCAST co chair, Eric Lander.

>> Eric Lander: Great. If I can get the panel to come to the front, I have got them here. So, One Health is a succinct description of the fact we can't just think about human health and animal health as separate matters. From the point of view, for example, infectious organisms, the development of antibiotic resistance, pathogens they don't have such a sharp line between humans and animals. They move back and forth between reservoirs and sometimes over the course of evolutionary time where the pathogens can be short, sometimes over decades. For all of those of those reasons, a number of agencies in the U.S. government are thinking of a more

integrative approach to health. And PCAST encountered this point of view at the squarely on the report on combatting antibiotic resistance but it is broader concept than that with One Health. We are joined by three speakers who can help us think broadly about this, we have Marguerite Pappaioanou from I guess the CDC liaison the FDA. So maybe from both CDC and FDA. And that is already a really important sign of the oneness of the One Health is that it stretches across CDC and FTA, and USDA. And we have Ellen Silbergeld from Johns Hopkins University professor in epidemiology and environmental health science and Health Policy and Health Management. And also joined by Keith Hamilton at Kansas State University the director of international programs and theof the college of veterinary medicine. We have not discussed the order, but I am guessing Dr. Pappaioanou will start and will move down the panel. So, welcome, thank you very much for coming and we be eager to hear from you.

>> Marguerite Pappaioanou: Is that on? Good morning and thank you for the invitation to share my thoughts and views on One Health with you today. How I view it the opportunities and benefit it is affords, current gaps and challenges, what's required to implement it most fully, and some positive examples of One Health today. A definition used for One Health very frequently is that which was developed by a task force at the American veterinary medical association and the American medical association. And it's on my title slide. The collaborative effort of multiple disciplines working locally, nationally, globally to attain optimal health for people, animals and our environment. My introduction to One Health concepts began in parasitology class in veterinary school in the early 1970s followed the study of epidemiology and graduate school learning about webs of causation and interconnectedness between human, animal and environmental health under the mentorship of doctor Calvin Schwaby who wrote the book veterinary medical in human health. I went on to work as an epidemiologist at the CDC for 24 1/2 years. And I also have worked as a professor of infectious diseases in the school of public health at the University of Minnesota for three years. And as executive director for the Association of American Veterinary Medical Colleges for four years. At CDC I worked in a variety of position and programs, none which directly involved animal clinical care. But in which I applied my comparative medical education and training to bring a different perspective to the table in solving global public health problems, such as malaria, H.I.V. aides, evidence based public health and surveillance of infectious diseases. Over the years I came to understand a One Health approach was important to most effectively address the full spectrum of challenges confronting the health of people, animals in our environment. For many years, I used this very graphic to convey the broad spectrum of One Health going beyond infectious diseases, which many do connote most closely with the topic. Largely following increasing urbanization of our human population, people began to lose awareness and understanding of our fundamental connections and reliance on nature, biodiversity and ecosystem health until a continuing series of highly communicable infectious disease outbreaks began to occur globally, west Nile, highly pathogenic avian influenza, H1N1, SARS, Ebola, MERS and it goes on. Transmission of pathogen from animals to people led an institute of national resource council committee in 2009, on sustaining global surveillance and response to emerging zoonotic diseases of which I was a co-chair to include this diagram in our report. Emphasizing the pathogens and disease pathways in animals before transmission into the human population. And then major, highlighting major drivers, human population and environmental drivers,

creating the environment for disease emergence, transmission and spread. The small squares located on the bottom of the X axis in the report actually refer to a series of interventions that can be applied to intervene, and prevent and control the disease transmission pathways. The drivers include human population factors, food and energy, production and consumption factors, climate change, globalization and others. So another way I have in my own evolution of One Health have come to look at the full spectrum of One Health is shown on this slide where individual clinical and population disease challenges are represented in the top and the middle tiers, but with this graphic there is a much better reflection that these two top tiers are a consequence of the bottom tier, which is an unbalanced what we're seeing now comes from an unbalanced ecosystem that is being impacted on by food and energy, population and consumption for our rapidly growing human population on our way to eight billion people and growing. To date, the majority of efforts in One Health have been aimed at the middle and the top tiers. With the critical importance of One Health to ensuring sustainable healthy ecosystems upon which all species depend is, in my view, the most important gap and has been largely overlooked as an opportunity to apply the One Health approach. And environmental expertise, for the most part, has not come in fully as a full partner in our One Health triad. Addressing the bottom tier again, in my opinion, is the most important One Health challenge and gap and opportunity of our time. Related gaps and areas of concern include failure to adopt a comprehensive whole systems framework to identifying and addressing our complex health problems of the day, with multiple disciplines and sectors participating. Moving away from single sectors and disciplines attempting to solve single problems, single species issues, an approach invariably results in unanticipated other problems. Those problems unanticipated by a single discipline trying to solve a single problem. Other important gaps include a lack of appropriate metrics and a lack of One Health competencies and disciplines among the professions. Putting One Health into action then requires policies and funding that enable and reward collaboration of cross sectors. Teamwork in the field working at the front lines, multidisciplinary integrated research, cross departmental integrated education and training and continued evaluation and improvement. Challenges to implementing One Health therefore follows, including leadership, failing to frame our complex health problems in a comprehensive framework, and then not bringing different disciplines to the table to work together to solve those problems. Siloed funding, and I use the term jurisdictional in the sense of government departments, and missions which that prevent agency and departmental funds coming together to help fund the work, this collaborative work that's needed, and also the lack therefore of awards and incentives. Confusion over what One Health is. And I listed a couple of different terms used, so again it is confusing to a lot of people and then there are some basic work force issues which I would be happy to comment if there is further questions. At this stage, however, and all this said, I will close my remarks with several positive examples of One Health applications. First, there's a growing awareness of the importance of the approach by public and private sectors to solve a variety of health problems. And the leadership by PCAST in application to the antibiotic resistance is but one example. International recognition upon which you will hear more shortly. The report on planetary health by the Lancet planetary health commission and new sources of funding for One Health approaches to complex problem solving and I have listed a variety of examined there on some of the funds, more are needed. Successful community programs have been initiated. Re establishing human connections to

nature, ecosystems and all other species that we share the Earth with. Work force studies that highlight the need to support assurance of a One Health work force. There's a growing number of One Health academic educational and research programs and centers in our universities, and most recently, and I will close with this, is a recent legislation introduced by senator Al Franken from Minnesota, just introduced, the One Health Act of 2016. Although it is still focused on the middle tier for the most part of the pyramid that I have used, if passed, it would be an important step forward to building that enabling environment to which I referred to previously. Thank you very much.

>> John Holdren: That's great, thank you for that big framing of One Health, that's very good to see the whole frame there. We'll turn next to Dr. Silbergeld and hear from each of our speakers, and then turning to PCAST for general discussion. Dr. Silbergeld?

>> Ellen Silbergeld: Thank you very much and for the ability to participate. And I am going to focus much more narrowly, taking advantage of the fact that I knew we would present the overview, and talk about one issue in which the One Health perspective is absolutely critical, and it is a bridging point between ecosystems and nonhuman and human populations, and that has to do with agriculture, which takes place in the environment, involves on human species and eventually involves ourselves as persons who interact with agriculture as well as assume its products. And I also want to pay a great deal of homage to the many DVM's who are my students at Johns Hopkins and really educating me on cross talk between our disciplines. My outline here really is to talk about how the One Health perspective is, from my experience of over 15 years of doing this kind of research, moving from a really deep geeky mechanistic involvement in toxicology to understanding much more broad perspectives as best I can in the domain of intensive animal food production. This is not working okay I am sorry, I guess this is not going to work. I will talk about ecological impacts briefly. Health impacts a great deal, and how thinking ecologically, which is something I had some earlier training in in terms of applying spatial temporal analyses and engineering background in understanding flow of materials, quite literally when I talk about resistance Genes, and the interactions of what we look at as microbiomes and macrobiomes, by which we might talk about populations of organisms, and finally critical questions and research. There are extraordinary ecological impacts the way in the which we produce animals and this is an outbreak of harmful blooms in Maryland in the heart of the chicken industry, which was a driving factor through eutrophication of surface waters and the over production of algae including harmful species that can generate neurotoxins. And this is the Pocomoke River, and which you see in the long white buildings are chicken growing houses and my state is actually a part of the fourth most dense, most productive region of the country in producing broiler chickens, a fact that was little known. The fact it affected the nonhuman species is also evident in the insert picture in the upper left hand corner, which was this characteristic kind of scarring of fish and fish kills that occurred punitively in association with *Pfiesteria* although we have never really been able to pin it down. But ecologically there is sort of this doomsday we've developed in terms of agriculture, much of it in many countries of the world takes place in highly sensitive coastal ecosystems, in the top is North Carolina, the second or first, there is a war with Iowa over this in hog production in the United States. And it is right in the tide water zone which was heavily impacted by hurricane Floyd as you may recall

leading to the destruction of the industry, which was rebuilt with no change in practice. And the lower area the Pearl River Aqua system that actually takes place in the Pearl River delta in China. And I mean by saying agriculture is embedded in the ecosystems. Now, animals, humans and food are extensively connected. As my colleague just said, most emerging infectious diseases that have been recorded over the past 30 years are zoonotic in origin, which is not where people traditionally look, but nonetheless it is an important flow of pathogens as we have seen most recently. I want to make the point, because many of my colleagues in one medicine like to go out and look at monkeys in the rain forest and that is much more fun than going to chicken houses on the eastern shore, but I want to state very clearly that the most intensive and extensive animal human context involve agriculture and human interactions with domesticated animals, not wildlife. If we're really trying to make a big impact on this Nexus in order to prevent damage and disease in all species, I think we have to give considerably more attention than what we have to agriculture. Our production methods disrupt shared ecosystems, as I have told you, and of course the great focus of my work coming admittedly from a human health background has been the use of antimicrobials in the food animal production which drives antimicrobial resistance, emergence and dissemination through microbiomes of animals, humans and ecosystems, which is what I mean by materials flow. This is one of the most recent, although now quite old, analyses of emerging infectious diseases and what these data show is that most of these diseases that have been charted over the past 16 years or so are actually drug resistant and that's what makes them novel. Many cases they are the same old pathogens that we knew quite well like staphylococcus but are now requiring highly dangerous treatments of single or even multi drug resistance, phenotypes, they are also largely zoonotic in origin as shown on the right hand side of the slide so I think we see here the opportunity to pose the question as to whether our interactions with animals, which include the administration of sub therapeutic zoonosis to antibiotics are doses to antibiotics are linking these two prevalence's as shown in the graphs. I do want to say from the human health point of view the burden of antibiotic resistance is enormous. This is from the U.K. review on antimicrobial resistance conducted by the Ministry of Health. And it just shows the burden of deaths attributable to antimicrobial resistance every year. This is the projection to 2050. Many of you know with the discovery of resistance genes in pigs last disease, many have said that we may really have now crossed over the threshold to the end of the antibiotic era not to be a doomsday sayer. The drivers of antimicrobial resistance which we've known forever, and Fleming predicted them and Lederberg gave us some of the mechanisms it indicates that all use inevitably contributes to selection for resistance, and now we know also starting with Lederberg's work that it drives the remarkable ability for pathogens and commensals to exchange resistance genes without cell division. Therefore speaking as a simple engineer, the intensity of the antibiotic use has got to have something to do with the intensity of the emergence and perhaps the comprehensiveness of the poly-resistant phenotypes. Inappropriate antibiotic use is particularly dangerous in the setting of kind of inevitable forces between us and the microbial world. And this is my definition of inappropriate use I'm sorry to say this, and that is the antimicrobial use in animal feeds. Despite various hand waving by the Food and Drug Administration nothing is really happening here. I just went and looked last night at the most recent report for FDA and actually uses of the antimicrobial drugs in animal feeds has increased since the FDA began issuing its totally infective statements about what

industries should or should not do. And it is a major component of total antibiotic production in this country and in many other countries. Now we have adopted a kind of ecologic perspective in trying to figure out how this operates in ecosystems and among and within various populations in which we are now really not focusing so much on specific pathogens or even specific drugs, but the movement of Genes and gene flow within micro biomes in animals, within soils and ecosystems, and finally within the food supply and even within us. Some of these webs of transfer are quite literal and this is one of my students, one of my very good DVM students at CDC who did her thesis looking at resistance at pig farms in Peru. And while she was there, this is what is known as a lagoon where the waste is stored and what I call an open cesspit and it is drained largely now. And what you see are migratory birds hanging out in this lagoon because there is a lot of spilled feeds and other nutrients for the picking, and they will go up and down the western Pacific flyway carrying these resistant genes to a variety of other wildlife species, as well as human populations. This also contributes very directly in a molecular sense to building the capacity of the microbiomes in terms of the genetic tools at their call for resisting novel or continued antibiotic use. This is a study by NANDI into which they looked at the resistance genes that moved from poultry litter into soils. We have a study going on the eastern shore of Maryland looking at historical patterns of the enrichment of soils that have been receiving animal waste over the period of intensive food animal production and antibiotic use. By the way the use of antibiotics in animal feeds began two years after the production of streptomycin so it was very early and has continued unabated until this time. Gordon Wright and others have said a good way to look at it is look at the resistome, which exists within microbiomes and it is the antibiotic resistance genes and other mechanisms that can be transmissible genetic elements, which provide the communities for the resources both natural and anthropogenically applied to microbial stress. And this can be very complex and this is a very nice story showing the communities are highly organized and we need to understand this organization so we can figure out how these genes flow within and between microbial communities. I really thought of this as a kind of, excuse me for this cloud computing aspect of the way that bacteria behave, they really tap into this resistome which can be external to that bacteria, and can be genes in soil as Jose Martinez has pointed out. And through quorum sensing and signaling it can call upon that resource and incorporation when a population or subpopulation is under threat. And, of course, the information that's encoded within the resistome is genetic. And this is Jose Martinez kind of riff on this concept of antibiotics and the antibiotic resistance genes in the environment and his suggestion we should think of them as environmental pollutants. And in areas of intensive use and disposal of waste containing animal waste, even human waste, this could in fact are domain in which we really need to enlarge our focus on what antibiotic environmental pollutants mean. It is not just food, of course, because the operations take place within human communities, as well as ecosystems and therefore a variety of populations of animals and humans can be exposed. We ultimately may all be exposed through the consumption of livestock and poultry products, even through vegetables that are grown in soils where animal waste is used as fertilizer. And it's really our feeling now that it's the story of many microbiomes and the best way to understand it really does obliterate as the previous speaker said any boundaries in various host species. Thank you for your attention.

>> John Holdren: That's great and thank you and we in particular appreciate your very frank comments about some of the issues there. Issues that PCAST is indeed engaged with in the past. And we will turn to Dr. Keith Hamilton

>> Keith Hamilton: So, thank you for the opportunity of being here – before I started at K State, I used to work for an organization called the OIE that is the World Organization for Animal Health and worked on a number of OneHealth projects on them and my perspective is it an international policy perspective so that's what I will talk about today and focus on emerging infectious diseases. As our other speakers pointed out, diseases like Ebola, MERS, H1N1, SARS, bird flu, and NIPA Virus; all emerged over the last ten years causing widespread international concern. Several events declared by WHO to be public health emergencies of international concern which has a legal basis. All of the diseases have an animal origin. They don't come from outer space, they come from animals. There is an absolute certainty that in the future infectious diseases will continue to emerge and have an impact on humans, and they will continue to emerge from animals. And as Marguerite and Ellen pointed out the drivers for disease emergence are climate change, land use and population growth. As a result, we're going to see greater opportunities for diseases to emerge, and for them to spread rapidly around the world. Although it's not possible to predict when and where the next disease will emerge, it is possible to be prepared and put systems in place to respond to these diseases quickly and minimize the impact. We need no reminding in addition to the terrible human and societal costs of emerging infectious diseases, they also have a very significant economic cost. And it's well acknowledged in many reports, and some published by World Bank and other organizations, demonstrating that the costs of dealing with biological disasters are far greater than the relatively modest costs of investing in health systems globally and in preparedness. In very over simplified terms, when it comes to infectious diseases, the animal and human health sectors collaborate in three broad areas. The first area is really what experiences of human health sector dealing with purely human infectious diseases, can help the animal health sector fight the diseases with comparable approaches and vice versa. And a good example of this is two diseases, smallpox, a human disease, and rinderpest an animal disease, and the two sectors shared their experiences for the betterment of each eradication campaign and then going forward to Polio eradication and other looking ahead to measles. Other infectious diseases that cause significant problems for animals and humans, For example, bird flu, H5N1, antimicrobial resistance and for these diseases it is in the mutual interest of the animal health sector and the public health sector to do something because there will be positive impacts for agriculture, as well as human health. There are impacts for both. And just to point out that antimicrobial resistance is a big deal for food and animal health as well as public health because if you run out ever are antibiotics it will have a big impact on animal health, welfare and food production. And the third category really infectious agents shared by human and animal populations which have a very serious impact on human health but don't really have an impact on the agriculture or the animal health sector. And examples of these types of diseases would be MERS which has a very mild clinical disease in camels getting a runny nose, but causing serious problems with human health in the Middle East and led to hundreds of deaths in people. And rabies doesn't have a very significant effect on agricultural animal health but kills up to 60,000 people a year in the most horrible way, mainly children in Asia and Africa. For this third category, the animal

health sector is playing an increasing role in taking action to protect human health when there are little immediate benefits in animal productivity or agriculture but it needs more resources to do it, because traditionally it is focused on controlling diseases of an agricultural impact. And for the diseases and events like antimicrobial resistance have less of an impact on the agricultural productivity but impact on human health and may not receive the immediate benefit when the farmers and producer take action, but the intervention should still be applied because it is for the good of the public and humanity. So in such cases financial behavior and social incentives are needed to get producers and industries to take action, and economic investments are also required when there is no immediate return for producer or industry when they take action. And a fairly simple message, but the best way to reduce the impact from the zoonotic diseases those spread from animals to human is to tackle it in the animal source and prevent the spillover to the human population at an early stage, this is true of many endemic and exotic animals similar to Asian flu, rabies and others. And the detection and control in the animal source is much cheaper and more effective than trying to deal with the disease once it has spilled over into the human population. Zoonotic diseases can be detected and controlled in animal populations before humans are infected when you have strong and very well governed and resourced veterinary services. Unfortunately in many parts of the world due to underinvestment in veterinary surveillance, many of the diseases sufficient as Rift Valley fever, Ebola, and Avian flu only detected in humans even when they have been circulating in animals weeks and months before. If action were taken earlier it would have prevented a significant human health problem. On the global level, the inability and the weakness of one country's health system to detect and respond to disease event is a threat to all other countries. If they don't detect the disease and contain it quickly, the disease spread rapidly across borders showing little respect for national borders and controls. Likewise, if one country doesn't take action on an issue such as antimicrobial resistance that is also detrimental to the whole international community. Conversely investments in one country's health system, investments in making that health system better also protect all other countries in a positive investment for the international community. So when diseases do emerge, as we have seen over the last ten years, it's very important that research and development into that new disease starts immediately so that scientists can work out what they are dealing with, how best to control it and what the likely impact is. This requires a rapid mobilization of resources and streamlined regulatory processes to get the products onto the market quickly. We also need to incentivize research and development, because for many of these OneHealth interventions there isn't necessarily a large market for the products in farmer and industry, and the private sector can't see an immediate return on their investments so there does need to be investments from philanthropists and government to stimulate this research. And WHO is currently working on a research and development blueprint action to prevent epidemics, which is aiming to coordinate research globally to work towards agreed priorities. If research is coordinated there can be a much more efficient use of the limited resources to achieve useful and worthwhile goals that have an impact. The blueprint also aims to develop mechanisms for incentivizing research, which is for the public good, but may not necessarily be commercially attractive. And also looking at developing mechanisms for creating mechanisms so research and development can be set into action as soon as a disease emerges. Now this is sort of a 10-12 month process and they're engaging policymakers from the human and animal sectors at the

moment and engaging scientists as well to come up with a plan and hopefully that will be rolled out in one to two years. And WHO and others are discussing implication of the health on the 11th of April, so next month. Because it is widely accepted that the health of humans, animal and the ecosystem are inextricably linked there is interest in supporting One Health. And this has started to reap rewards at the international level. WHO, OIE, and the FAO are now working much more closely together and have formalized their working relationship to reach priorities in the agreement. And they also developed common strategies to tackle One Health problems. Thanks to the new intergovernmental One Health mechanisms, data about influenza virus is circulating in animals, and they are being shared rapidly with the human health sector to help with the preparation of human vaccines, and action is being taken to eliminate rabies from street dogs, the human and animal health sectors are working jointly to promote the prudent use of antimicrobials and other models in other countries where it worked well like the Netherlands and U.K. The health and security sectors are working more closely together to reduce the threats from bioterrorism. Things are working well at the international level, but at the national level implementation of the One Health approach is very patchy. Some countries embrace One Health, other countries don't. Assorted barriers include politics and funding, and some countries the public health sector sees it as more to lose from One Health and the veterinary has more to gain. And status, some countries veterinarians have a low status and other countries they have high. And also in the historical context, in some countries like in my own country, the U.K., we had to deal with One Health crises like BSE, so the public health and animal health sectors have been forced together. But OIE, WHO and FAO they are focusing their efforts now on helping the countries strengthen the health systems and strengthen governance of the health systems to respond to all events rather than respond react to one crises after another. And WHO and OIE developed a framework to assist member countries to strengthen their abilities to meet competencies shared by the national, human and animal health services which are required to tackle One Health threats. And they do this by helping their country to assess its ability to tackle One Health threats on a number of core competencies, and then this reveals the gaps and they work with the country to fill the gaps. It is a harmonized approach which has been developed within consultation with the member countries themselves and policy experts. And the framework helps countries better comply with legally binding international standards, that's the IHR set by the WHO and OIE's international standards. They are finding on a global level the strength of governance of health services is still woefully inadequate, and as I mentioned earlier, one country's weak health system is a threat to all other countries including the U.S.A. In conclusion the key messages are the global public health security is not possible without animal health security. It is much more cost effective to invest in preparedness not just in the U.S. but in other countries because a problem in other country is it a threat to the U.S., then react to disasters. Further investments needed to advance One Health, and that means building capacities in other countries, and also incentivizing action from producers and incentivizing research where there is not necessarily a commercial benefit. And another plea from my experience is really for people, for countries to use the existing capacity building frameworks which have already been agreed by member countries, such as ones set by WHO and OIE, rather than countries developing their own frameworks. A lot of countries are inundated with different agencies and countries approaching them to assess their health systems when it would be much more efficient to use a system that

has been agreed to internationally already. This is just a reminder this is taken at the time of the last U.S. election. But just a reminder that all of these countries are looking to the U.S. and what happens in the U.S. does have an impact on countries in all corners of the world, as I am sure you know. Thank you.

>> John Holdren: That's great. What a wonderful set of presentations and you covered this landscape very beautifully. It is an area of great interest. And the pattern is to put up our flags and I did not note the exact order, I am just going around the room here with Rosina first and then Chris and Barbara and then Susan and then Dan I did note just came in last there. And I will at least put Susan ahead of Dan.

>> Rosina Bierbaum: Thank you all that's incredibly sobering, so I thought maybe I would give two points of light. I wanted to come back to the first speaker and the challenges to health at different levels and that pyramid that you showed us, and how the attention is focused mostly on species and populations and I think most of the talks focused on the important middle tier. I wanted to come back to that large bottom about ecosystems and environment and how very important that understanding needs to be integrated back up into those two tiers. To that end I wanted to remind us all that PCAST actually did an earlier report on sustaining environmental capital five years ago. But I think in what is exciting progress, two executive orders are kind of moving that bottom pyramid up into the middle. Most recently President Obama issued an executive order that all of the federal agencies have to figure out how to value ecosystem services in their normal course of actions. And how all agencies or another have to think of climate change and build that thinking into their contributing missions and mandates going forward. So I think that's, you know, very interesting pushing at that large bottom into the very important middle area that you focused on today. And a second point of good news as an educator at now two great public universities, the system's approach that you all call for is just so much more natural to the students of today than it was to us. And I'm seeing an incredible profusion of dual degrees between students in natural resources and then public health or engineering, or public policy or urban planning and business. And I think those are really the great hope that we can get this entire pyramid built together much more quickly than the way we were trained historically. I just wanted to offer two points of good news.

>> Ellen Silbergeld: Thanks, I would like to however cast a sobering note that you already raised and that is that unfortunately the funding agencies have not adopted this kind of approach. If I told you the various parts of agencies for which funding has come from our research you would be astounded. There's no conversation, if I may be frank, at the NIH between the environmental health institute and the institute that is concerned with infectious diseases. If you send in a grant to one they say we don't do pathogens, and you send to the other and they say we don't do environment. We got funding from some of our research from of all places NIOCH, because workers were involved. That's not all we were studying, but the students are hungry, policymakers are hungry for this kind of thing but it is a devil to get funding for it. A lot of funding came from foundations. And NSF, usually when they see John Hopkins school of public health they say oh, no, go to NIH.

>> Eric Lander: Have you had a conversation with NIH leadership with that?

>>Ellen Silbergeld: I have spoken to the director of NIEHS.

>> Eric Lander: How about the director of NIH?

>>Ellen Silbergeld: Since it doesn't seem to involve Genes, Dr. Lander with all due respect he doesn't seem to be interested.

>> Eric Lander: With due respect I would actually ask before concluding such things. I think it is probably worth investigating. I think it is a good thing to ask about, because, you know, the idea of inter-institute discussions at the NIH is a very important one. We have many institutes and you raise a valid point and I would press it, it is a good point.

>>Marguerite Pappaioanou: And to the point, there is only there's a set of priorities that NIAD has so if it involves anything from outside of animal models, of human disease, they're just is no, no interest.

>> Eric Lander: Nonetheless, I don't want to conclude it without the experimental evidence of raising the conversation, that's all.

>> Marguerite Pappaioanou: I would like to stay on the bottom tier, too I think it was a gap in One Health coming out of the gate where the focus was on the top two tiers. That environment health scientists went elsewhere. And that was where I believe the planetary health effort and report thing came from. But as you read that report and their work, that is One Health. That goes back to the opening definition. But now you have the problem of disciplines talking and collaborating with each other. And people have commented you can't get environmental health specialists and health specialists in the same room to talk to each other.

>> Ellen Silbergeld: I might just suggest that your committee open this conversation with the director of NIH. I am just a lowly worm, you have influence.

>> Eric Lander: [Laughing] Yeah I think there are opportunities to convene that get people in the staple room, and I would not be shocked if there was receptivity at least to convening to discuss these discussion. The One Health concept brought people's attention to this idea much more. Who knows, you might find the receptivity at least for a meeting to talk about how those kind of connections could be built more. I am an optimist about such things, oh, well. Chris.

>> Christopher Chyba: I want to thank the panel for a set of interesting presentations. My question is really almost kind of a footnote and back to Silbergeld. You commented that the use of antimicrobial drugs in animal feeds has increased since the FDA statements, and I assume you mean the voluntary guidances. Could you break that down for us a little bit. In particular has the use of human medical use of antibiotic increased?

>> Ellen Silbergeld: Yes, there are reports issued episodically by FDA under ADUFA which was legislation requiring them to report on uses of animals. And the two most recent, one in 2011 and the other one just issued in 2015. There is an increase. If I may, and they do break this down in convenient so called medically important and not. If I may, and they do break this down between medically important and not, if I may speak from the perspective of my friends in the microbial world they could care less. We know exposure to a medically unimportant drug can drive a multi drug resistance set among bacteria and I think we have to get over this. Therefore, if we continue, almost all meth resistant staphylococci arising from animal populations contains a tetracycline gene. And who cares about tetracycline, but if you expose the bacteria in an in vitro situation which we have done you can drive horizontal gene transfer of a multi drug set among staphylococci populations with tetracycline.

>> Christopher Chyba: So I think we've talked in this group about just that issue before. But even if one just focuses on human medical use relevant, that is also increased, thank you.

>> Eric Lander: I will ask, do we have experimental evidence of that in animals? That use will drive

>> Ellen Silbergeld: Yes. Very elegant studies done by USDA, as well as at Iowa and other institutions which show that if you look at the gut microbiome of animals you can see the phenomena going on.

>> Eric Lander: Great, thank you. Barbara?

>> Barbara Schaal: Thank you all very much this is interesting and I want to continue in the line we just were talking about. The concept of a resistome is really interesting. And the fact that horizontal gene transfer really between microbiomes changes the way we look at how agriculture works. And I can see this as a plant biologist, plants share the soil microbiome with animals, so there are some really interesting possibilities. And your conclusion that the lines between microbiomes are blurred, this is really a different way of looking at things. So antibiotic resistance is really daunting, and now it is really exceptionally daunting with the new way of looking at it. So what do we do? What are the new practices that need to be implemented? What aren't we doing to address this way of looking at the microbiomes and sharing of genes in a very different agricultural way?

>> Ellen Silbergeld: Thank you very much that's at the heart of the research in my laboratory right now. In fact, by the way the same phenomena can be observed in soils that is the spreading of the resistance genes from microbes that have been added in animal feces to the soils, as well as resident bacteria in the soils. A study done by one of my graduate students. I think we need to stop focusing on good and bad bacteria and good and bad drugs. We need though have a policy that looks at and focuses on controlling gene flow. And the way in which we do, for example, narms is still embedded in the very 1950's definition of bacteria. And our relationship and animal's relationship with bacteria. Unless it is really a bad bacteria and a vital

drug that's involved, it's not really a problem. And that does not really reflect what goes on in the microbial world, thank you.

>> Marguerite Pappaioanou: And I would just add, however, that going back to drivers that antibiotic use came into food animal production because of the more efficient production of meat. And so as our human population grows, and as we get older, and as we get wealthier and our diet preferences tend to ask for meat, trying to find a sustainable food production system on this planet that would not right now we're looking at a serious reduction in rain forest, so land use and water use and what is happening around the whole area of food production is an incredibly missed One Health opportunity to really look at it in a comprehensive framework, and it's critical. What we're looking at in the next 10, 20, 30, 40 years is really critical. So it's you know, the focus even now to the genes, but let's look at the driver. Where is this coming from? How can we change how we get our food, and it's only going to get more severe as the number of us continues to increase.

>> Ellen Silbergeld: Well actually we looked into that, and I got all the registrations for all the drugs used in animal feeds from the FDA with the assistance of my senator. And in fact, the evidence that there really is a growth promoted effect is highly dubious. And the one major study we wrote a review with this done by Purdue that was a double blind clinical trial saw no effect on growth no effect on feed consumption and no effect on diseases. So I am operating right now that it's a rebuttable presumption that we need antibiotics at this time.

>> Marguerite Pappaioanou: Even more how important to look at how we are producing our food.

>> Keith Hamilton: Can I just mention a couple of initiatives that are in progress at national and international level. OIA Producing guidelines on the use of antimicrobials that will be kind of reiterated each year from feedback from their member countries, and action being taken; the Netherlands have taken a lot of action to reduce the use of antimicrobials in their agricultural system without impact on productivity. And talking about livestock and farming in general there is this progression of One Health that has been towards this sustainable crop and livestock system which takes and really looks at minimizing the impact of all systems including climate, antimicrobial systems, animal welfare, local kind of waste and environment. That's a pretty positive thing and that's been launched—people do acknowledge that livestock do have a role to play in food, we're not going to stop farming livestock, but what we can do is more efficient and in more ways with less impact. And on the research side, there's evidence providing recommendations on vaccines for animals that can lead to further reductions in the use of antimicrobials. So some of these productions could be tackled with vaccines rather than having to use antimicrobials.

>> Susan Graham: In this discussion I see One Health as an umbrella program in some respect. And you've talked about animals without ever saying what is meant by animals. And so I am inferring that that's the animals that are of interest to the veterinary medicine community. Maybe it's broader than that, that's part of my question. But the rest of my question is where

are insects in this whole story? Because, for example, we talked about mosquito as lot yesterday in connection with it, and there are parasitic insects, and insects that live in soil, insects that live in water. And it would seem to me that they're part of this science picture, and yet I didn't hear them mentioned at all.

>> Marguerite Pappaioanou: When I often speak of One Health and the 10 minutes didn't allow it, I have a slide of all of the disciplines that are needed to work together on these issues. And there is no single discipline that has it all. And that's why the One Health approach and a comprehensive framework and the organizer and a convener to bring all of the different disciplines to the table that are needed. So whether insects fall in the environmental world or environmental piece they are there. And that expertise is it needed for a variety of problems that we face. So animals are quite broad. And on the clinical side can include companion animals. On the food production side we talked about that, there's wildlife. But it is one of the challenges on work force, any discipline actually is very fragmented. So, you know, as people frame complex problems broadly, it is somewhat of a challenge, but it's a surmountable challenge to actually bring the right groups and the right, you know, the needed people to the table. But thank you for raising that. They are often overlooked. I was speaking to someone with Zika Virus and I said I hope have you some of those people in animal control in the discussion because they are often forget. Thank you for the question.

>> Eric Lander: And the last question is Dan and only a minute or two left.

>> Daniel Schrag: I appreciate all of your perspectives is sympathetic for what you do. And I am involved with Harvard and what is aligned with the One Health concept. It is a research grant, a capacity building grant to create a community on planet health, almost the same thing as One Health. And I will tell you two problems we are having and I would love your perspective on them. One is a problem of actually getting health scientists really interested in engaging with there is lot of entomologists, and the other is a bias. Most of the people in this field, a small number, focus on examples where destruction of wildlife or habitat has negative health consequences. And there's a concern expressed by some people in the health community that what they are overlooking is all of the ways that, in fact, destruction of wildlife can have very positive health consequences, also. For example we know emerging diseases like Zika come from the interface. There are lots of examples where it actually can work both ways and there is this kind of bias and it makes some scientists afraid to be associated with this because it feels like a crusade, and doesn't feel like science. So I would love your perspective how to handle that, because it is something I am struggling with right now.

>> Marguerite Pappaioanou: This is where I made the comment that sometimes where this has gone to environmental health scientists and human health experts, it's hard to get them in the same room to talk to one another. Recently there is an upcoming meeting, the Consortium University of Global Health and this year focusing on the planetary health report and we convened a panel outside of the plenary, but a panel that is bringing the human global health so people traditionally working upon malaria, T.B., H.I.V., AIDS, but a speaker is speaking at the planetary boundaries work and where we are on that. We have a speaker who's going to be

speak being women's reproductive health. And one of our moderators is Dr. Sam Meyers, on the Rockefeller planetary health work. And we are getting them together, but it has taken extra work and effort and nurturing to bring them together. So I think you have underscored the gap which I was trying to allude to in a challenge, but I firmly believe that if we can keep putting the focus on the bottom tier and what is needed together to come up with sustainable solutions, we can overcome the biases and some of the other things that keep these folks apart. It's absolutely critical. Funding is a part of it. If you can get some of this joint funding, or funding that doesn't pit mission against mission, or you can't spend we have money but we can't give it to you. Or you have money, but we can't get it over here. And therefore, the silos continue. That leads to it. But it's a serious problem, but I am optimistic, like many of you here, that it is a challenge that can be overcome with appropriate attention and nurturing and support.

>> Eric Lander: We must end a few minutes over our time but I thank the panel for coming and informing us about this and doing so in a very frank manner, so thank you. [Applause]

>> Eric Lander: We are going to take a break about 12 minutes and resume and discuss research and cancer.

### **Cancer Research Frontiers**

>> Eric Lander: Okay. Welcome back. We're now going to turn to a discussion of frontiers of cancer research. There are a lot of motivations for having this conversation today. First, there's just been extraordinary progress in cancer research and the understanding of the underlying genetic and epigenetic changes that cause cancers, and thereby identifying targets, great progress in immunotherapies in particular, other modalities for treating cancers that are complementary to targeting particular processes that go awry in cancer. And an increasing influx of people from chemistry and engineering and other disciplines that are coming in with various different approaches. And we're really lucky today to have three speakers who can talk to us about this. And, of course, it's especially relevant because the President has declared a real focus on cancer research with his remarks in the State of the Union declaring a cancer moonshot that the Vice-president has taking leadership of. And so we're eager to here today from Charles Sawyers, from Carl June and from Tom O'Halloran. Charles Sawyers is the Chair of Human Oncology and Pathogenesis at Memorial Sloan Kettering Cancer Center, and a tremendous expert in the development of cancer drugs. We have Carl June, who's a professor in Immunotherapy in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania. And he is a tremendous leader in the field of immunotherapies in cancer. And we have Thomas O'Halloran, the founding director of the Chemistry of Life Processes Institute at Northwestern University. He's also the Director of the NCI Chicago Regional Physical Science Oncology Center. And he's really in a great position to talk to us about the roles of chemistry and physics and engineering coming together in new methodologies so we couldn't have imagined a better panel. Each of the speakers is going to take no more than 10 minutes, and perhaps less, and then we're going to get into general discussion. We'll start with Charles.

>> Charles Sawyers: Thank you, Eric, and the committee for inviting me. So I've had the occasion to meet with the Vice president or his team three times since the beginning of the year, so I titled this Reflections on Moonshots. I want to start with this slide, which is a concept you're all familiar with. It's driven by genomics as having the ability to add precision of diagnosis of cancer and to guide treatment decisions. And I won't go through the flow chart, but this is something that, I think, has been adopted by most cancer centers in the academic world and is rapidly becoming the way clinical treatment outside of clinical trials is starting to go. So let me just at a very high level remind you that cancer is a disease of mutations. You get a mutation every cell division results in mutations. These are due to the error rates in D.N.A. polymerase if that mutation is in the wrong location, meaning the wrong base pair in a cancer gene, or in the -- and in the wrong cell, it has to be in a cell that has the potential to expand rather than just terminally differentiate and die. And there's this concept of timing. It turns out, the incidents of cancer we all think goes up with age, but there's a certain point when you're at a certain age your risk of cancer is actually going down because you've sort of made it through the critical period. So we also have this concept of bad luck. Some of you may recall a lot of attention in the press about a little over a year ago when Bert Vogelstein and colleagues published a really very compelling mathematical analysis of those first three bullets. But this was the press, and then there was another. Those were two "New York Times" articles, then there was actually a quite nice piece in the cancer letter about the press misinterpreting things. So what do we know about these mutations? As I think probably everyone is aware, both at a national and international level, the cancer research community made investments in deploying sequencing technologies to complete sequencing of thousands of cancers. So there's concepts like exomes, that's all of the coding regions, and just six, seven years that was a very big idea and now it's routine. And there's, of course, whole genome sequencing. Roughly 10,000 cancers have been sequenced through these efforts and are all publicly available exomes which have formed the basis for a lot of calculations of how many cancer genes there are. The second point here is that with those numbers we can, with confidence, say that we've defined all of the common cancer drivers. And "common" in this case means within a tumor type, and a "tumor type" means lung cancer or colon cancer or melanoma, if it's present at greater than 5% or more present in that cancer, we know about it already. So what does that really mean? Well, it means that there is a list of cancer genes across tumor types, in the -- depending on what you want to call -- it's in the 200, 300 range of genes. Which you also find out is there are -- those same genes are mutated at a much lower frequency in other cancers, and this is this concept called the "long tail." It's a very important concept in the clinical management of patients that's being exploited now through the clinical sequencing efforts. And let me give you a cartoon, sort of, to make this point. There's a concept that you may have heard of called in clinical trial lingo called "basket studies." And these are trials in which patients are enrolled based on the presence of a mutation regardless of the histology or the site of origin of that cancer. Patients are treated in the same protocol in this basket approach, and as a result we learn -- we can accrue these trials much faster and we learn that the drug works extremely well when the mutation's a certain context, but less well in another context. It was very difficult to accrue patients to such trials if you don't have mutation profiling happening in patient populations. And just as an example of how recent this is, at Sloan Kettering where I work, we really invested

in this heavily just beginning two years ago and you can see the rate at which we're sequencing. I want to point out the number at the bottom is 8400 cases. I want you to contrast that with the 10,000 across an international consortium that took several years to develop. This is how fast this is moving. Now these aren't whole exomes, these are panels, which is a detail. Now this slide shows the impact of that test which is called Impact. And that big, dark gray line is the accrual to these trials and that dotted line sort of between November and March of 2013 is when we launched this assay. And you can see the rate at which patients are accrued on these trials. It's a very positive outcome for enrolling patients and getting effective drugs more efficiency and precisely delivered to patients. What I want to finish with though, is that's a really great story, lots of excitement, it's the whole rationale behind precision medicine in cancer. But how many patients, of all cancer patients, are really benefitting from this? So I have a couple of pie charts that I want to walk you through. So we call these mutations when we sort of lock it down and say this is a cancer gene, we call it a driver. So how many cancers have known drivers? And it's about 2/3. About 1/3 we sequence an exome and we still don't really know what's causing that cancer. That's – there's a project out there we call the cancer of unknown driver. We need to figure that out. Then of the ones that have a known driver, one the right I've split that roughly in half and these numbers are approximates. Those are the -- and of those, how many do we have a treatment that we can offer that we believe is rational? About half. We call that druggable versus undruggable. So for the first pie chart, how do we get – how do we improve on the unknown driver problem? Well, we need to do more exome sequencing because then we will have mutations – we'll discover mutations that are present at an even rarer frequency. And we need to do, I think, whole genome sequencing on some subset of these to find out if there are mutations outside of the coding region to explain these cancers. And there are enough examples, precedent for that being an explanation. What do I think will happen? We'll never get rid of completely this blue slice, but it will get smaller. And how do we address the problem of the undruggable drivers? This is a very large challenge. I think we need new chemistry and pharmacology and we can go through some of these details in the questions if you want, but there are very clear steps forward. Another strategy is to generate a map, what I call a map of cancer vulnerability. So if you have a driver and you can't make a direct drug against it, perhaps you can take advantage of a dependency that the presence of that driver creates on another gene or pathway. That's known as synthetic lethality. And then the third point, is that the perfect drug actually is nucleic acid-based drugs because of the perfect match with the driver, but the problem has been delivery, and I think this is a potentially solvable problem. Though note at the bottom, is that I also want to, you know, I'm enthusiastic about this. Druggable does not mean cure. And we need combination therapies to overcome resistance. Essentially it is an exact parallel argument as we heard with the antibiotic resistance. So I want to conclude with four sort of thoughts. We really have to leverage this explosive growth in clinical sequencing. This fits into the data sharing mantra that the Vice President has been talking about and I'm involved very intimately in one such data sharing effort called Genie. I believe we should do a large scale project, it has the sort of feel of a moon shot engineering style to define all cancer vulnerabilities. We need to invest in this new chemistry. And we'll hear from Carl, but this explosion of immunoncology, including huge commercial investments by biotech and pharma, it's happening, I think, on a background where we don't have a fundamental understanding of the basic cancer immunology underlying all of this and there's a

lot of challenges in the models to make those conclusions. And so I will stop there. And there's two of my photo opps with the Vice President. [Laughter]

>> Eric Lander: Where's the third? That was one of the most coherent tours of the horizon that I've heard. Thank you so much, Charles, for coming down and distilling it in that fashion. So let's turn to Dr. June who's going to talk to us, I presume, indeed about cancer immunotherapy, an old idea that finally has its day.

>> Carl June: Well thank you, Dr. Holdren and Dr. Lander for the -- and members of the Commission for the opportunity to participate in this. I think everyone here has been challenged or touched by cancer in some way. My head actually was touched last week, and that's the reason for the patch on the top. What I would like to do over this next few minutes is go over some of the excitement in cancer immunotherapy, and you'll see how it dove tails in with the precision medicine that Charles has just outlined. So cancer immunotherapy had a quite disappointing history for over a century. It's not a new idea, but finally some major advances occurred beginning and around 2010. And that was recognized by science in 2013 as the number one breakthrough in all of science and engineering. So it's now a field that's recognized, after some time, and making rapid progress. When you look at the cancer epidemic, for many years heart disease over -- was over represented as a cause of death, and it was only about 10 years ago when cancer actually became the number one cause of death for those under age 85. So we faced this as a challenge in the United States and worldwide it's an epidemic that we need to solve. So cancer therapies traditionally have been looked at as a way to treat patients and the end points of those trials that led to FDA approval was pushing out the median survival curve. Often as few as six weeks of lifetime extension could enable commercialization of a drug. What is unique about cancer immunotherapy is that it has pushed the survival, long term survival out so that people live decades and maybe are cured. And that's the appeal of immunotherapy is it's long lasting effects. And where we're at now in the field is how do we combine therapy so that we can basically have everyone have long term remission and cures. We're not there yet. So what is the case for immunotherapy? The immune system is a living drug, if you will. The immune system, a vaccine at age 5 can protect you at age 60 against chickenpox. So the immune system is a living drug. The cells that we give last. They only need to be given once in many cases. And another advantage, is that the immune system can evolve as a tumor may evolve so that it can respond to escape mechanisms, whereas single drugs given cannot do that. And the data so far is that immunotherapy can, in fact, cure some subsets of cancer. I think the data is best at this point in melanoma and Leukemia. So one of the hallmarks of cancer, other than the mutations that lead to the growth abnormalities that you just heard about from Charles, are that the cancer, to become metastatic, needs to escape the immune system and that, in immunologic terms, is called tolerance. There are two mechanisms and approaches now in the field to overcome this, one being so-called checkpoint therapies. Antibodies that are antagonists of the systems, immune systems that normally shut things off. So these are ways, if you will, to take the brakes off. These first became FDA approved in 2011 and have now been extended too many kinds of cancers. The particular area that I have been interested in are the area of cell therapies which can be given to patients as a form of transfusion. A number of these are being developed for many kinds of cancer. And I would

make a point that these should be synergistic based on the modeling data that we have at this point. So, so-called CAR T cell, that many of you have heard about is a synthetic module that creates a T cell that does not exist in the natural immune system and that's one point that really differentiates the engineered cell therapies from standard vaccines. One can create an immune system that is more potent or has properties that didn't exist in nature. And in particular the goal that we have is to make an immune system that will be resistant to the tumor microenvironment. For instance, the tumor microenvironment may have poor vascularization, might be hypoxic and have a number of immunotoxic aspects there, so the field is rapidly evolving in this area to overcome some of the subversion from the cancer system. So the first patients treated with CAR T cells were in 2010. Initially adults with refractory Leukemias and then pediatric cases. Now hundreds of patients in our most recent assessment more than 500 patients have been treated with various forms of CAR T-cells and so we've gone from small numbers of patients in 2010 to now at least three companies have registration trials in place for various types of CAR therapies. We know now the initial responses have been durable. They've been durable in both Leukemia, lymphomas, myeloma, and melanoma. What we don't know and where their future lies is what their role will be in solid cancers like lung cancer. These are the first examples of synthetic immunity, using the principles of gene transfer to improve the immune response. They're living drugs, the first patients that we infused back in 2010 continue to have these CAR t cells in the body and we can show that they are functional. And, as I mentioned, the immune system can evolve with the tumor. If you will, it can encode a counter punch to help prevent relapses. The data so far with 5 year follow up indicates in some cases patients are cured. One of our first patients with acute Leukemia was with President Obama at the launching of the Precision Medicine Initiative last January and remains in remission now nearly four years after therapy. So there is a deep pipeline of cancer immunotherapies shown in the review. Many different antibodies engineered drugs, vaccines and subtherapies are being developed. The first T cell therapies are anticipated to have FDA approval in the next year or so, so there will be both many new therapies come on the market and the real issue is going to be figuring out where the resistance mechanisms are and how to efficiently overcome those. So we're at a point now in medical delivery where healthcare system consists really of three pillars, one being the pharmaceutical industry, the other biotechnology industry that delivers recombinant proteins and medical devices that form the basis of our system. Where we're headed now is the new pillar being added, which will be cell therapies. And that's a new one. There are a number of issues specific to this, one being that at this point the cell therapies are personalized coming from the patient's own cells. And so they're no called N-of-One therapies from the regulatory point of view. One major effort is to develop universal cells so they would be off the shelf. At this point red blood cells are transfused from universal donors and to engineer T cells that way is a realistic goal. Another issue is what the reimbursement models will be for these kinds of more expensive cell therapies. Another point I would like to bring up is that this is highlighting, in my view, meetings with the Vice President. We found there is a shortage of trained scientists and clinicians in this area. For many years the field was not viewed as one having a future. So translational research in cancer immunotherapy was ignored. It's not different from other areas where we have a very strong pipeline in basic sciences. What we need to enhance, I think, is the intersection of clinical sciences. And that is there is an evolving new specialty in how to efficiently conduct the first human trials with these kinds of

therapies and how to work with what may seem to be orthogonal therapies with precision medicines that may target basic molecular pathways. So in summing up, synthetic biology is adding to the tool box of cancer therapies. The first engineered herpes virus was approved by Amgen this year for metastatic melanoma, and CAR T cells have pivotal trials on the way for Leukemias and lymphomas. There are combinational trials with many other agents where these appear to be synergistic. So that means there were thousands of potential combinations and we need to understand how to efficiently conduct those trials. The Moon Shot Initiative may accelerate the cure for cancer and I thank you for your attention.

>> Eric Lander: Wow, another extremely helpful and coherent presentation, thank you, this is really great. I hope that the people watching it on the web will come to the site and listen to the talks, because I think they do a beautiful job of summarizing the state of the whole field. Thank you. No pressure there, Dr. O'Halloran, but let's see if we can let a hat trick here.

>> Tom O'Halloran: Well, I have to say the last slide that Carl presented, maybe the second to last is a perfect segue. My simple thesis for you in these slides, going to take a very high level view is that we can really accelerate the rate at which we make these kind of innovative discoveries to the rate at which I think society expects of the scientific community. We all are having friends dying of cancer regularly in spite of the phenomenal progress in breast cancer and prostate cancer and therapeutics and early diagnostics in those areas, but we are not going fast enough. My talk is about how to do that. It really involves around how to stimulate translation, and that's my thesis, that we bring in outsiders into the mainstream of cancer biology and oncology and put the teams together in innovative ways with short term goals and expect the best out of it, so why should we expect that and how will we do it. Well, the NCI is one of the most successful organizations in the world in stimulating advances in human understanding of cancer and the treatment of it. It is, by nature, a silo driven process. The expertise to reach a cure or an application of immunotherapy takes 20 years of training and of investment and cross checking and developing an understanding of the molecular pathways. The molecular pathways is generally one of the hearts and focuses of the basic science research at NCI, and the silo structure creates a set of incumbents, using two types of terms. Incumbents are people that are experts in the field with great depth and knowledge in the field and knowledge in training in particular subsets of cancer biology. The outsiders are people who have interests and ideas often orthogonal to what the normal approaches are and when they come into the field they bring revolutions, sometimes, and other times they bring nonsense. So the question is how do you optimize that process? So how do you do that? This kind of Silo structure gives rise to really excellent communications between oncologists, molecular biologists, cancer biologists, immunologists, but all of these other parts of the structure, there's not nearly enough communication and transfer of knowledge and rapid insights. We're now looking at single molecules within cells; we're watching where they go. This is something we couldn't imagine 5 years ago. How can that help a cancer biologist think about a pathway or help a drug discoverer optimize thinking about a target? I would argue the way that we're going to do that is by having a much more extensive communication network. This is easy to draw, the kind of thickness of these lines would often represent the number of publications that have a joint co-authorship between people from two different fields, and this is kind of an idealized

version of the system in the future. All sorts of hurdles and buried and sunken costs in given technologies, language differences and culture differences. Even how to do a simple control is so different between these fields so is it building a tower of babble? I would say historically oncology has been dependent on the physical sciences and the breakthroughs that have come from them. From using x-rays, using radio activity within 20 years of Marie's first Nobel Prize, we see these applications in cancer in radio-immunoacid – I just picked some Nobel Prizes here—I think you can see how they each transformed the current practice of oncology, the problem is these types of translational events are incredibly slow. Much more than 20 years, sometimes between when that fundamental discovery gets established and when it works. So what's different over that kind of 110 year period is that science is evolving culturally, and the highest impact papers, and this is a beautiful study from my colleagues at Northwestern in the Kellogg School of Management; they analyzed over 20 million publications and looked at them over the function of time over 60 years and that we are absolutely moving towards team based science and that team based science gives rise to the highest number of highly cited papers, over 100 citations, these teams dominate 6 to 1 over a single investigator or a very singular discipline approach. So that's the future, but how do you build these teams and how do you catalyze this and I would argue the moon shot is a phenomenal opportunity for the administration to come in and say "Look, what we're doing now is the best that each of us and our groups can do but we are going to now put a connectivity layer over and we're gonna start catalyzing the cross fertilization of ideas and focus those cross fertilized ideas on to immediate goals in cancer. In another Brian Ouzi publication. He wonders where does creativity come from? And he asked a very simple question and he analyzed the analytically prior relationships between collaborators. If they published a bunch of papers before they are going to have a high value on the lower access. A lot of prior relationships. And he plotted that against the experience of the team when it came into a project. They had very little experience, like a graduate student. They would be low on the other axis. What he found, is what did he take? He took Broadway musicals. Going back 70 years for Broadway musicals. These are the same types of problems we face in science. You have a librettos, you have a book, a composer, and you have all of these creative people that had to work together. He said how often did they highly the team that had worked together on dozens of musicals, come together to produce something and how often did they have a lot of experience. He took this kind of matrix and then asked well what is the criteria of success and looked at the box office revenues and he saw that there was a sweet spot between having a bunch of prior relationships and having very few. And that sweet spot is there, is in the blue. So those were the most successful musicals. The critical reviews also had a sweet spot in this type of analysis and in the end one of the favorite examples is "West Side Story" where a phenomenal team came together but needed fresh blood when they were composing and went to an unproven guy who was 25 years old, Stephen Sondheim. And this is an exact example of incumbents mixing with outsiders that we want to achieve in science. This is not a brand new idea. If we go around the room, I bet half of the panel was an outsider whether they started in the community where they made a significant scientific impact. The national cancer institute and NSF, and other agencies experimented with these. I think we have phenomenal success stories with the Cancer Centers for Nanotechnology Excellent, and the Physical Science Oncology Centers that the NCI has said but these are always fighting a head wind of funding of silos. When the silos, which are very important farms for

cancer research are only funded at the 7% level the outsiders are the first to take a hit. This is where the opportunity comes, that if through the process of the moon shot, that a real plan for sustainable breakthroughs could be built. And here now is the big issue: The moon shot I did not warm up to this analogy, it took me a long time. But within the period of eight years from Kennedy's announcement from Cape Canaveral that he was going to put a man on the moon to Apollo 11 in 1969, what was spent was about \$152 billion in today's dollars, all right. And that was a multiyear investment over time to get there. All right, \$1 billion is a good start, but it has to be part of a vision. And what should that vision do? I would argue we create centers to begin training people to speak multiple languages across the disciplines. To think across physical science and quantitative biology and systems biology and synthetic biology, and bringing all of these types of players together. How do you do that? It has to be a multiyear program. I think the national nanotechnology initiative NITRD are examples of this that this group knows much better than I do. I would argue you have to integrate the incumbents and the outsiders as you do this. We can talk about themes in the discussion. I think immunotherapy, biology, early detection is so critical. And it is also right in the sweet spot of the materials and engineer communities that we're talking about as outsiders. Mining health data, etc., new materials to deliver drugs, right, to deliver the nucleic acids that we talked about and that the previous speakers have talked about. And I will not go through the National Nanotechnology Initiative but it was started under the Clinton administration at about \$1 billion a year and it's still going and it had a profound and continuing to have a profound influence on interagency research across the fields where nanotechnology can have a stunning impact on our national well being. And my last slide and what I would recommend. And it is kind of from my experiences in leading interdisciplinary teams. This is not only doable, but we have a lot of assets and a lot of templates. We know what works and what doesn't. We need teams of five and ten people that integrate these outsiders and incumbents. And I would argue if we want to do the moon shot, we take that same period of time, about that same amount of money, and we can transform the practice and treatment of oncology treatment of cancer and its early diagnosis and I'll stop there.

>> Eric Lander: Great. Thank you. We have time for a few questions. I think we have 10 or 15 minutes or so. Chad Mirkin and Dan Schrag have flags up. Dan Schrag just had a leftover flag, so Chad Mirkin.

>> Chad Mirkin: I want to start by thanking all three of you, I thought it was fantastic and what an incredible diversity of ideas and I think spot on from starting with Charles in terms of I believe nucleic acids will be the next and I believe that the terms of what we do and in terms what we are trying to accomplish on the cancer research side of things. I also believe what you said, that there are major hurdles. Understanding pathways, it's critical. It's the bread and butter of what we do in biology and medicine. But if you don't have in parallel, efforts aimed at developing the right materials and the right ways of getting drugs where you need them to go, a lot of that's wasted. And I didn't hear from both Charles and Carl, maybe by design the way you guys set this all up, what you thought the path forward was in terms of really capitalizing on this. I look at things like antisense, siRNA, antisense has been around for 30 plus years. And siRNA now 20 plus years. We're just beginning to see drugs come online and the sad part is all

of them are for diseases of the liver. Because that's where these things get dumped, it's the lowest bar. And we are missing this incredible opportunity. How do we use the moon shot to capitalize an effort that does not just move the needle, but create a (for lack of a better term) a quantum leap in how we develop therapeutics for cancer.

>>Charles Sawyers: Chad, I think you are more qualified to answer than I am. But I will just make a couple of points. The antisense got a bad rap for quite a while but my understanding is that maybe liver is the only indication. And I know eye is another one. And I am hearing that the chemistry is much better. It just took, you know, time. And there's this - maybe this is the incumbent problem - Incumbents have trouble forgetting about the failures of the past. And so then readopting once the kinks have been worked out. I actually saw a presentation on antisense recently in a research context, very detailed. And everyone is like rolling their eyes, we heard this 30 years. But instead of saying wow, it looks like it is finally working, so maybe it is a cultural aspect. I didn't know what Tom was going to say and it resonated very much with me to bring in newbies and people in the material sciences because I believe in this nanotechnology concept and the nano initiative is 8 to 10 years old, maybe that's not enough time. Maybe there's just a few centers, I think there is clearly more there.

>> Eric Lander: Carl, do you want to respond at all?

>> Carl June: I think it is a very similar analogy to what we had in immunotherapy. And I think for instance the delivery of nucleic acids is at a tipping point and it will happen with the liver deliveries, and I think it was just more complex than anyone assumed. I think the great thing is that now the momentum will happen. The mixture of incumbents and outsiders will occur. And I think we will see rapid after maybe more than 30 years of stagnation and it is a wonderful time to see that happen.

>> Eric Lander: Bill Press and then Craig Mundie.

>> Bill Press: One of the biggest incumbents of all is the FDA. And I guess I've heard at least two of you suggest that there's going to be a need for different kinds of clinical trials, different kinds of regulatory apparatus generally. Between combination therapies, personalized therapies, cellular therapies. So really a question to all three of you, if you were going to give the new director of the FDA advice on how does FDA have to change to support this moon shot, what would your advice be?

>> Charles Sawyers: I've met with the new FDA director actually and I am very excited that he's finally approved. Honestly I think the FDA is not a right limiting step at all here. They very much understand a lot of what we talked about today. They need and they're interacting with the academic community for advice on how to set up the guidances. For sort of telegraphing to the commercial world what they will set as bars for approvals. There are also new incentives to push companies to start combination trials earlier, which we all need. They include things as simple as instead of if it is a two drug combination, the old way was a 4-arm study, the standard of care, A, B, A plus B. Now you can do standard of care, A plus B. You can count A + B as a

single drug. You have to do a little safety on each one. There are also incentives to extend patent life for certain orphan or pediatric indications. So I guess my main point is the FDA is not really the problem in my view, but let's see what Carl says.

>> Carl June: I deal with the side of the FDA called CDER and also the Office of Cellular Tissue and Gene Therapies, and I can tell you they are widely regarded as leaders around the world in the development of new technologies. The critical issues are acceptance of basket, trial designs that Charles mentioned and the other issue is surrogate in points and when they can be accepted for rapid trial completion. The FDA has been a leader in how cell therapies can be done. I think their next challenge is with genetic engineering, issues such as crisper and so on. But I think they have a very good relationship with science balance and the regulatory parts with the science, which is so rapidly changing. So I would agree, they are not the problem. And our issue is learning how to work together with different siloed data sets.

>> Eric Lander: Did you want to add something Tom on that?

>> Tom O'Halloran: Briefly, I think the issue is speed and innovation. And we have to adapt more quickly to the novel materials and the novel biological tools that allow us to interrogate where they are now that they are working and I think it is one of the critical things that the FDA can do better, is to innovate more quickly.

>>Eric Lander: Great, Craig Mundie.

>>Craig Mundie: As I listen to all three talks, there is certainly an undercurrent of the role of computing related to the genomics itself. But it seems like there is a lot more computing and modeling may be able to do than was implied in the discussion. And even Tom, I think made mention to systems biology once. But it seems a lot of these questions, the pathways, interactions and rather than the ad hoc, they have two things and maybe they interfere with each other. That whole thing seems to be underrepresented to me in the moon shot and even this discussion. So I was curious if you think that's true or not. There was a lot of talk about the physical sciences, etc., but computer science seems broadly underrepresented in the way you described at least bringing these together.

>> Tom O'Halloran: Craig, I think you hit on a critical part of this the type of outside communities that need to get for fully integrated. I think these types of people come from applied math, from systems analysis, complexity analysis, looking at flow of airlines and clients through airports on a minute-to-minute basis looking at patterns. It takes large computational capacity and we keep every year getting more of it. So we're actually able to do more modeling now than we actually know how to design the right questions to make sense out of the complexity of all the patient data we are getting. I think it is a critical part of it. There is a fellow at Northwestern I know in applied math and physics and basically is redoing the way we understand the Warberg effect by looking at it as a massive protein production opposed to net energetic calculation. So it is a really important need.

>>Eric Lander: Any other

>>Charles Sawyers: I'll just I take your point, but I don't want you to think the biomedical research community has ignored this. At our center, we have computational biology, systems biology, most others have. Whether or not it is resourced at the level it should be, I can't really say. I don't have a good sense for that. What has happened though, is that the genomics, the clinical sequencing genomal efforts created a demand for a certain type of computational person which is not necessarily what you are getting at, it's also an incredibly safe career path for a young mathematician. We may be unfortunately sort of skewing people down more that applied pipeline when we can leverage them for larger questions.

>>Craig Mundie: Even in your comment, computation biology, that's all basically people who are using computers in the biology, you know, as they understand it. And I was suggesting, you know, that people who are trained as computer scientists, not the people who use the computers, the people who design the computers, who design the networks, figure out how all that stuff works, they actually also bring some skills to these things that you don't have. And you won't discover it, you know, just coming at it from the application. And so I am just saying getting computer science people coming in and thinking about these networks, the way that they think about computer networks might actually inform these things in a way you might not otherwise find.

>>Tom O'Halloran: Craig, amplifying on that, I think the key is you have to train them in the language and some of philosophy of cancer. That is a little bit of a road ho right? There is some investment in that. But, you look at the moonshot, you look at the Kennedy's initiative, the average age of the person on the entire Apollo mission platform, average age 28 years old. So it was new thinkers. It was equivalent of our post-docs, coming in, being the nuts-and-bolts, inventing stuff and accelerating the rate of micronization of electronics transistor, printed circuits, creating drive and a demand, they had no training in it, they had to invent the languages as they go and I think that's the kind of spirit that we want to kind of inculcate with this opportunity. Very unusual to have this kind of money sitting in between normal age.

>>Craig Mundie: But it has to go both ways. You can't just teach those guys about cancer, you better take some cancer guys and teach them computing.

>>Tom O'Halloran: That's right. That's what the centers do, the physical science oncology centers are able to do.

>>Eric Lander: And we are officially at the end of the period but I think we are okay, public comments are just two today. And Charles, tell us a bit more about the Genie program that you and your colleagues have launched. I think it is something that folks on PCAST would be interested about.

>>Charles Sawyers: This addresses the silo question. And basically these institutions, a lot of cancer centers have used their own funds, philanthropic funds, etc., to build out this clinical

sequencing infrastructure which we have done, because we believe it is good for patients and faculty, and interests an incredible database of what I almost would call maybe a little bit of a misnomer, but kind of a population science experiment in a way. And this is, you know, on a background of electronic medical record tracking of clinical phenotypes. So, you know, a couple of years ago it dawned on many of the people who were first doing this that once you have done a couple of thousand and realized you haven't really cracked the problem, you need bigger numbers. So to cut to the chase, seven centers agreed to participate in a pilot to pool their data. It required an unbiased sort of neutral Switzerland to become the broker. That is the American Association for Cancer Research which for many reasons was a good idea, including the fact that I served as its president a couple of years ago so I knew how much money was in the treasury and could afford at least to get it started. But going through this, there's been a lot of learnings about what are hospital systems willing to share from the general council's point of view for legal risk and what are the faculty members willing to share for all of the reasons we hate about not wanting to give up the low-hanging fruit before they had a chance to pluck it. But we came to a pretty good understanding, and I mean for the nitty-gritty, all the genomic data from the seven institutions is pooled into a central database including a little bit of clinical annotation of the sample. So it's now 17,000 patients' genomes in in data set. Now an investigator or clinical group from any of the sites can say we have seen 10 people with this mutation, that's it here. Has anyone else seen it? You can instantly find it out. If it is a compelling enough question, you can ask headquarters to do a query out to each of the centers to collect more phenotyping data and so forth. So those kind of projects are now happening. And we have bigger visions as well, and part of this was to sort of build the model for the ecological mix to happen at a comfort level that everyone was familiar with.

>>Eric Lander: That's fantastic, and I think moving slowly but carefully to work out the issues is really important there. So well done. I know we have come to the end of our time. It really was a great panel. The three of you just fulfilled the assignment in just a spectacular way. I will reiterate that I hope people will navigate to the PCAST website and listen to these talks, as many young people in particular are thinking about the cancer moon shot. The educational value of each of the talks, plus the vision was really a great combination. So let's thank our speakers. [Applause]

### **Public Comment**

>> Eric Lander: And the last order of business is public comment at this meeting, for which I am going to turn to Bill Press to share that session.

>> Bill Press: Thanks. We have two public comments today, if they are present. There is Ernesto Perez-Chanona why don't you go to the front. And you'll have 2:00 and I will give you a 30 second warning.

>> John Holdren: Press the speaker button.

>> Bill Press: And his topic is the post-doctoral community of the biomedical research sciences.

>> Ernesto Perez-Chanona : Thank you so much. Before joining the CNI as a post-doctoral fellow I work at Johns Hopkins University, University of Florida recently graduated from the University of North Carolina chapel Hill. And I come to you as a private citizen today because I am interested in the question, are American taxpayers getting enough bang for their buck from the current research communities. While I do not know the answer to this question, I do believe that the efficient City of our laboratories to finish and publish products in decline. One thing I found striking from my graduating class is the very few Americans who obtain their Ph.D.s in bio medical science interested in pursuing a career in research. Most people went on to consulting, public policy and a lot of private sector jobs, leaving a vast number of foreigners in our research labs who are also not necessarily interested in pursuing tenured track positions due to their struggles with the English language, or sometimes the assimilation of the American culture. And so what it has culminated to is it the vast wealth of data in our labs that goes unpublished sometimes. And I think that this level of this discontinuity has made an expensive, glitchy machine in which should be a 21st century efficient engine and I urge you to take up this matter and discuss. Thank you very much for your time.

>>Bill Press: Thank you very much. Our second public comment from Andrew Maccabe, is he present? Good. He is the executive director of the Association ever American Veterinary Medical Colleges and his topic today is One Health.

>> Andrew **Maccabe**: Thank you. The AAVMC represents colleges and faculties of veterinary medicine throughout North America, Europe and Austrail-Asia. And One Health has been a long priority of ours and specifically with interest in inter-professional education in the health professions and transdisciplinary research approaches. AAVMC has participated with the office of the director the NIH over the past two years to host a series of interagency meetings on One Health. We have been very pleased to have the participation of nearly a dozen NIAH centers and institutes and representatives from CDC, FDA and USDA at the meetings and have been very gratified by the willingness to collaborate among those members and use the One Health approach to their issues. We're also very excited about the recent introduction of the One Health Act of 2016 by Senator Al Franken which would charge the nation's agencies to work together on identifying specific goals and priorities to help prevent and respond to animal disease outbreaks that threaten human health and well-being. Using the One Health approach requires that partners with different mandates collaborate and communicate effectively. And since federal agencies have different mandates, different cultures, and even different values, a One Health approach will help bring them together to address some of our most challenging health threats. And as PCAST recognized in the 2014 report to the President on combating antibiotic resistance there is a need for a One Health approach to that. And the animal and health facility accepted the responsibility and challenge to be an integral part in the reduction and the mitigation of antibiotic resistance.

>> Bill Press: 30 seconds.

>> Andrew **Maccabe**: It limits it and the result is that those working on the animal and environmental related goals which significantly lower funding are struggling. While those in human health are making more progress. In addition, we would advocate for public private partnerships including human health, animal health and environmental health partners. Which are necessary for the One Health approach that's recommended by PCAST. Thank you for your time and I appreciate your leadership and interest in this One Health issue.

>> Bill Press: Thank you very much. Mr. Chair.

>> John Holdren: Well that brings us both to the end of our agenda and the end of our time. So again, my thanks to the PCAST members, to all of the presenters including the public commenter, to the wider audience both in the room and on the web. We look forward to seeing you next time.