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Modernizing Drug Evaluation To Bring Faster Translation

ReachMD would like to wish you a happy and healthy New Year and with each New Year comes a fresh start. As we look ahead, ReachMD is proud to present this month's special series, Focus on Future Medicine.

We spend tens of billions of dollars each year on medical research. What do we need to do differently to make sure this research better treatments and cures for patients. Welcome to this special report on future medicine on ReachMD.com on XM160, The Channel For Medical Professionals. I am your host, Dr. Bruce Bloom and joining us to discuss the need to overhaul the way we undertake medical research, to drive better treatments and cures to patients is Mr. Scott Riccio, Founder and Director of Accelerate Progress, a not-for-profit organization dedicated to increasing the speed and efficiency of the systems that directly impact patients fighting cancer and other life-threatening diseases and Dr. Scott Gottlieb, Resident Fellow, The American Enterprise Institute and Former Deputy Commissioner for Medical and Scientific Affairs at the US Food and Drug Administration. For purposes of full disclosure I am a recent addition to the policy advisors for Accelerate Progress.

DR. BRUCE BLOOM:

Mr. Riccio and Dr. Gottlieb welcome to ReachMD.

MR. SCOTT RICCIO:

Thanks for having us.

DR. SCOTT GOTTLIEB:

Thanks a lot.

DR. BRUCE BLOOM:

So Mr. Riccio when was Accelerate Progress founded and what are its aims?

MR. SCOTT RICCIO:

Accelerate Progress was founded little over a year ago. I was sitting at the dinner table with my wife and said you know there is clearly a need to focus on **(01:30)** what we thought of as better policy and better science, that the system that we use to translate benefits in clinical progress, these new therapies for patients fighting life-threatening diseases, the system we used to translate that progress in the clinic into patient benefits is in dire need of overhaul and modernization and so that is really what formed the background for Accelerate Progress.

DR. BRUCE BLOOM:

Dr. Gottlieb what got you to be involved in this. What new background led you to have those same kinds of conclusions?

DR. SCOTT GOTTLIEB:

Well when I was at The Food and Drug Administration we were trying to work hard on incorporating what we felt was better scientific principles into the development process for drugs. When you look at the way drugs are developed today, there is a lot of very new, very interesting science going into the development of actual molecules, but even the molecules reach the development stage and reach the regulatory process, the scientific principles that we are using to evaluate those molecules are very old. In some cases, they are decades old, in some cases you will get certain therapeutic spaces they are 50 years old and so we are not leveraging a lot of what we are learning about the science of genomic and prodromics and better statistical techniques, better clinical trial methodology into the way that we develop medical products and this has been a better particular obstacle in the cancer product space, and I think we really reached a point where the science that is coming into the pipeline is so advanced and is bumping up against a process that is so outdated that the process itself has become an impediment to getting products to patients and this is one vehicle, very important vehicle, I think, for trying to address some of these problems. (**03:00**)

DR. BRUCE BLOOM:

So Dr. Gottlieb give us a specific example of what you are talking about where the system evaluating the drug or the molecule or the concept isn't as advanced as the molecule itself?

DR. SCOTT GOTTLIEB:

Well, I will give you one example. We don't have a good process for doing what I would called enriched clinical trials inside the US Food and Drug Administration for allowing sponsors to over represent patient populations in clinical trials for markers that might predict their propensity to response to certain treatment. so a lot of the drugs that are going into development right now are very targeted therapeutic, targeted against specific markers, specific aspects of tumors. So lets focus on cancer, and yet when they reach the development process, we as regulators still say, well you have to study the drug in all patients with breast cancer or all patients with colon cancer, rather than saying you should study the drug in patients who over-express a certain marker or certain characteristic that you are trying to target with the drug, and that would be called an enriched clinical trial. We haven't really articulated how we would enable sponsors to do that. So the science is there for enriching clinical trials on the basis of markers that could help predict response to a treatment, yet the regulatory process hasn't been set up to do that. So the science hasn't been translated into policy, if you will. That is one example where I think that the process itself, the rules that we've set up, the policy that we have established hasn't really caught up with the science.

DR. BRUCE BLOOM:

So you are saying for example, we test a drug on a thousand general breast cancer patients and it has a 12% efficacy in helping and we say 88% of the patients aren't getting better, this drug is a failure and what you are saying is we have to find **(04:30)** a way of finding the 12% or 20% that this looks like it is going to help and get a 50%, 60%, 70% success rate and know the drug is going to work.

DR. SCOTT GOTTLIEB:

That is exactly right. I mean, there is many of them just trying to pursue this approach. First of all, you are not exposing people to a drug that they are unlikely to get a benefit from. So if you can find the patients who are more likely to benefit or at least set up in the clinical trial a set of tests to try to determine what characteristics can predict who is likely to benefit, by the time you are done developing the drug, you will have more information about how to prescribe the drug more appropriately, so you are not giving it to a lot of patients who aren't going to benefit. When you look at a lot of the targeted therapies that have been put into development in recent years, when you look at traditional chemotherapy where a traditional chemotherapeutic agent is after all is a poison. You get a variable response, some people respond a lot, some people respond less and it forms sort of a bell-shaped curve because different people have a different level of response to an agent that you know is generally targeting the cancer cells, but in the case of targeted therapy, you see much more of a binary response in the clinical trial where it is all or nothing and so in some cases where drugs have been put into development, you see exactly that. You see a 10% response where 10% of the patients do very well and the other 90% get almost no response at all and so the trick is to find the characteristics that can help determine who the 10% are going to be. There have been examples where we have studied broad populations of patients and we see a very small cohort having a very robust clinical response, but then when you look at the averages under the old frequentist model **(06:00)** for doing clinical trials, it doesn't reach statistical significant, because 90% of the patients don't respond, 10% of the patients respond a lot. When you average that out, you don't reach your threshold for getting the drug through development. We need to find ways to allow a flexible framework for doing more enriched adaptive approaches to clinical trials where you can test a thesis about who is likely to respond in the context of the clinical trial itself. These models for doing clinical trials exist. There has been a lot of science developed over the last 5 to 10 years about how to incorporate different methodology to clinical trial design, but the models that we still use as a regulatory matter are still the models that were used lets say 40 years ago even though the science of statistics itself has undergone a lot of advance.

DR. BRUCE BLOOM:

So Mr. Riccio is the government one of your targets of policy change and how will you go about taking this information that we have gathered over the last 5 to 10 years and moving it from concept to practice?

MR. SCOTT RICCIO:

Absolutely Bruce, certainly the government is a focus of ours in the sense that you are looking at federal policy makers and trying to help inform policy, you know, I think part of the issue that we faced over the last few years is that, you know there are a lot of different constituencies involved in this system. Dr. Gottlieb touched on the different folks both on the regulatory side of the equation and also in industry and there are folks in academia doing research and there are folks who have an expertise in biostatistics and there are folks, in fact, you know to do the sorts of equations that we need to do and the computational power, I mean there are a whole, you know, computer technology folks that we need to bring to the table. So there are many constituencies that we need to bring together (**07:30**) and that is really what Accelerate Progress is focused on and saying that we are going to reach out to those constituencies, we are going to bring expertise from all of the different folks, you know, whether the regulators or industry or academia or patients treating patients, physicians who treat patients, physicians who do research, all of those constituencies and we are going to be the independent body that brings them together beholden to none, and I think that is important, that we can maintain the independent expert credibility to helping inform policy makers because you know, one of the challenges they face is they hear a lot from specific constituent groups about how the policy might affect them or how changing the status quo might affect them and these policy makers clearly are looking for someone to provide an independent expertise to say, you know, help me understand, help me think about a policy that could bring everybody, lets say a half step closer to a solution.

DR. BRUCE BLOOM:

So what are some of the things that Accelerate Progress has accomplished since its inception a year ago?

MR. SCOTT RICCIO:

I think that really one of our greatest accomplishments has been bringing together a truly world class advisory board, people who are essentially, we went out and thought about, if we are going to try to inform policy and also bring some leadership to what I call better science and Dr. Gottlieb talked a little bit about that, whether that is enriched trial design and that enriched trial design is informed by Bayesian analysis or if its work in biomarker identification and validation and other sorts of modern science pieces, if we are going to do those things, **(09:00)** we really need to bring together the best people across the whole variety of disciplines and so we went out and have looked for and brought together I think just a tremendous group, people who in many cases literally have written the book in their particular area of specialty, but beyond that and I think this is important, they have gone from thinking about something, writing about something, lets says biostatistics, Bayesian analysis, and they built a lifetime of practice of knowledge in the system, what's it like in the real world, and that's really important I think to informed policy because at Accelerate Progress we said we want to go beyond the traditional policy organization that puts together a thoughtful white paper and puts it out there and that's it. We want to make sure that that policy is thoughtful, defensible, but also actionable and implementable that this is something that could inform policy makers where they could take this and say, here is something that we understand could be realistically implemented and would benefit the system.

DR. BRUCE BLOOM:

So Dr. Gottlieb Mr. Riccio just described Bayesian analysis, could you tell us what it is and you said as an example of how me might go from thought to implementation to actually effect what is going on for patients and for the clinicians.

DR. SCOTT GOTTLIEB:

When you look at the way we design clinical trials, we use what I would refer as the old frequentist model which the idea was to try to hold as many variables unchanged as possible, so you have 2 groups of patients, you try to make those 2 groups of patients look exactly alike and the only variable that changes between 2 groups, is whether or not they get the active treatment, that is the old frequentist model. **(10:30)** That works very well, it is a very pure statistical way of trying to evaluate 2 different approaches to care and one of the reasons why historically that model developed was because we didn't have the quantitative tools to measure multiple variables changing across populations at 1 time. So we had to hold as many variables as constant as possible, age of patients, other comorbidities that might have been affected by other treatments they were on. We wanted the only variable that changed to be whether or not they got the active treatment that we were investigating. Well Bayesian types of approaches allow and Bayesian statistical approaches is a school of statistical thought, it is in wide use in sort of, in financial services for example, what it allows you to do is look at multiple variables changing simultaneously across the population. So rather than holding everything constant and only changing one thing between 2 groups, you can change multiple things and by using Bayesian types of approaches, one thing that enables you do is to look at retrospective data, look at historical data and make better use of it, to try to draw firmer conclusions from retrospective data rather than only looking perspectively and it also statistical approaches, Bayesian types of statistical approaches allow you to look perspectively in data sets that aren't held in a sort of rigorous fashion. Well you don't have a randomized population where you are controlling the 2 groups very actively as you do in the traditional clinical trials. So what this enables you to do, is use things like perspective registries or databases of patients in a large payer system where you can look perspectively at a large database. You don't have to randomize patients to different treatments, you can just look at the entire patient population and try to draw **(12:00)** conclusions about a new medical treatment based on what you are observing over a broad population.

DR. BRUCE BLOOM:

I would like to thank our guests, Mr. Scott Riccio and Dr. Scott Gottlieb, for joining us to discuss the need to overhaul the way we undertake medical research. I am your host, Dr. Bruce Bloom, and you have been listening to a special report on Future Medicine from ReachMD.com on XM160, The Channel For Medical Professionals. Please visit our web site at ReachMD.com which features our entire interview library available through on-demand podcasts or call us toll-free with your comments and suggestions at 888-639-6157 and thank you for listening.

Thank you for listening to ReachMD on XM160 and this month's special series, Focus on Future Medicine.

You are listening to ReachMD, The Channel For Medical Professionals. Welcome to the CDC Flu View Update provided by the Influenza Division of the Centers for Disease Control and Prevention. This week's featured speaker is Dr. Anthony Fiore, CDC liaison to the ACIP Influenza Vaccine Working Group.

CDC recently released 3 articles on vaccine coverage. The survey results showed that coverage remains below targets in all of the adult age groups that were measured. Among 18 to 49-year-olds at high risk for flu complications, coverage was just 35%. Among 50 to 64-year-old all of whom are recommended for annual vaccination, coverage was 42% and among persons 65 and older coverage was 72%. The second of these articles looked at coverage among 6 to 23-month-olds in the 2006-2007 season as measured by the National Immunization Survey. This survey showed that 32% of children 6 to 23 months old during the 2006-07 season had received one or more doses of influenza vaccine and 21% had been fully covered. The reason this second number is lower is because most children in this age group are going to require 2 doses of vaccine because it is their first year of being given. These results were somewhat disappointing in that, this represents no change from the previous influenza season. The third report described information from the immunization registries. This systems allows us to look at coverage from this past influenza season. In this season, 41% of 6 to 23 month olds who received at least one dose, 22% had been fully vaccinated and among 24 to 59 month olds, 22% had had one dose and 17% had been fully vaccinated. Influenza vaccination remains the best way to be protected against influenza.

You have been listening to CDC Flu View Update provided by the Influenza Division of the Centers for Disease Control and Prevention. For more details on this week's show or to download the segment, visit us at ReachMD.com and tour the CDC's flu view web site at CDC.gov/flu.

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