E06-pbb The-biology-of-it-all

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SPEAKERS
Madge Kaplan, Paul Batalden, Bruce Marshall

Madge Kaplan 00:00
Welcome to The Power of Coproduction, a podcast series that explores the lived experiences of patients and professionals who are redesigning healthcare service to achieve better health through mutual respect, collaboration and science informed practices. Your host and guide is Paul Batalden,Professor Emeritus of the Dartmouth Institute for Health Policy and Clinical Practice and a Guest Professor at Jönköping Academy. The Power of Coproduction is produced in partnership with the International Coproduction of Health Network (ICoHN), the Dartmouth Institute, Jönköping Academy and the Health Assessment Lab. On Episode Six, “The Biology of it all,” Paul is joined by Bruce Marshall who works on the biologic knowledge of cystic fibrosis, which is helping to shape the coproduction of treatment and the design of services for persons who are patients with CF. Here's Paul.

Paul Batalden 00:59
Today we begin our consideration of the ways in which science informs the practice of coproduction. Our guest today is Dr. Bruce Marshall. Dr. Marshall has been a doctor for people with cystic fibrosis for many years. Now, he serves as the Senior Vice President of Clinical Affairs for the United States National Cystic Fibrosis Foundation. Many years ago, Bruce, you started the program for adult patients with cystic fibrosis when you were at the University of Utah. And now for the past 20 years or so, you've also had a ringside seat at the Foundation, where you've had a chance to witness the ways in which biologic knowledge the knowledge of the way the condition of cystic fibrosis works in somebody's body, and the way that knowledge has informed and changed how we can help people, deal with the burdens of cystic fibrosis. We're so happy to have you with us today. Bruce, welcome.

Bruce Marshall 02:05
Thank you, Paul. It's a pleasure to be with you.

Paul Batalden 02:06
At the beginning here, help me understand Bruce, what is cystic fibrosis? And how did we come to understand that?

Bruce Marshall 02:15
Cystic fibrosis (CF) is an inherited disorder that leads to thickening of mucus secretions, and that blocks the lungs and it blocks the pancreatic ducts. (And) Many of the manifestations of the disease track back to this very thing, the thickening of the secretions. And we've learned about this disease…(Actually recently) within the last 100 years, some diseases go much further back. But cystic fibrosis was really first described by a pathologist, a woman physician by the name of Dorothy Anderson, and she did autopsies of children that died before they reached school-age years. (And) She found that CF was a distinct disease from celiac disease and she went on and described so much about the disease, and then later contributed to a finding of sweat test abnormalities.

Paul Batalden 03:11
Someone said that what's been going on here, in a condition like cystic fibrosis, has been a construction of something like a tapestry with many threads of understanding and knowledge. And so she contributed some really important understandings to this condition of cystic fibrosis. And my sense is that, as you said, this is an inherited condition. So that opens up this question about how it is inherited and how genetics works in the creation of this condition. How did that knowledge come about?

Bruce Marshall 03:48
Yes, it is, as mentioned, an inherited disease. It's an autosomal recessive disorder; it affects about 100,000 people worldwide. The discovery of the gene was the final piece that put it all together to pick up on that thread from Dorothy Anderson in the late 40s. There was a heatwave in New York City, and they found that children that came into the emergency room, they had cystic fibrosis, and they were dehydrated, and follow up studies showed that there was a sweat test abnormality, and this actually turned into the way we make the diagnosis of CF and then looking at airways, colleagues at UNC showed the same sort of defects in ion permeability across epithelial membranes in the airways. And then ultimately, there wasn't a unifying way to put it all together until we got to the gene discovery. (And) This was a multi-year effort. TheCF foundation where I currently work contributed to this, but many scientists around the world were after the CF gene. Then finally in 1989, colleagues from Canada–Toronto-and UNC and Michigan found the gene. This is Laci Choi, Jack Reardon, Francis Collins, now the director of the NIH, they were the leads on this. I remember this vividly. This was published in *Science* in 1989. It was right around the time when I joined the CF community and took up CF care and research. It's the first time I went to the North American CF conference. Francis Collins gave the speech and described the gene. This is a complex gene and complex protein that's formed from that gene. He went over all the particulars of this gene and the major defect, which is just a three base pair deletion at the 508 position in this gene. And everyone was just spellbound. It was just an incredible, incredible experience. At the end of his speech, he went backstage, and he came out with a guitar, and he sang a song, “Dare to Dream.” And everybody joined in, it was amazing. It was just an amazing, amazing event. I realized at that time that I was in a very special community.

Paul Batalden 06:11
This experience must have been so electric for the group of people.

06:14
Bruce Marshall

It was amazing.

Paul Batalden 06:18
But you said you've worked for the Cystic Fibrosis Foundation now since almost 20 years ago. The director of that foundation for many years was a man by the name of Bob Bell. Now he wasn't a clinical doctor or a nurse. He was a chemist wasn't he?

Bruce Marshall 06:36
Yes, he was PhD trained. He was not, he was not a clinician.

Paul Batalden 06:41
He started a process to try to discover some chemicals that would interrupt the way in which this condition causes this problem. How did that screening or that discovery process work?

Bruce Marshall 06:55
Just a general comment about Bob Bell. He was driven by the science. He knew the clinical description of the disease and the clinical approach to the disease. (He) was very familiar with that. But he realized the scientific underpinnings were relatively weak. So he was very science focused. And along the way, there had been therapies developed for the various symptoms of the disease downstream symptoms, but he wanted to get at the root cause.

After the gene was discovered, there was a sense that, oh, there's gene therapy (that?) will cure this disease within a matter of a few years. In fact, there's a story that the (CF) Foundation wouldn't sign a long term lease for office space, because people thought we would be out of business. Well, that proved to be wrong. But Bob Bell was laser focused on the basic defect, and how could we address that basic defect? (And) He was always poking around looking for innovations.

He came across this idea of high-throughput screening for drugs that might impact the basic defect. And he reached out to several companies, because he felt like the academics, they didn't have the experience in developing drugs and that's what he wanted. He wanted drugs to treat the basic defect. So he reached out to several companies and finally got a bite from a small company in Southern California called Aurora Biosciences. He engaged them in a contract and they developed an assay that they could screen 1000s and 1000s of chemicals. That was the basic idea, but what Bob did was, (he was very familiar with academic grants, the Foundation had issued so many awards to academics), he took a different approach in this arrangement, this contract that we signed with Aurora biosciences. (They were subsequently acquired by another company called Vertex pharmaceuticals.) So what Bob did has been referred to as venture philanthropy. And what that means is the Foundation put money into the company, Aurora Biosciences, to do this high-throughput screening, and there were milestones in that contract. So if they hit a milestone, there would be a release of funding to them; if they hit the second milestone, an additional release of funding. And all eventually tied to reaching an FDA-approved drug so that if and when this company achieved that final milestone, the FDA approval of a drug, it would trigger a payback to the Foundation. So for example, if the Foundation invested a million dollars and we got to an FDA approved drug, there would be a multiple or a royalty stake in the

sales of that drug. And that was so that the Foundation could invest in the next great idea that's been termed, venture philanthropy. And it's worked, it really worked for cystic fibrosis.

Paul Batalden 10:10
That's just an amazing story and his focus is legendary. You have some options now, for treating this condition, cystic fibrosis. Once you have options, you have to find a way to make sure that the person that you're going to give the drug to is the right fit for the option that you've got. And that matching of the treatment and the person is another quite fundamental source of biologic understanding, if we're going to progress from just knowledge to better health.

Bruce Marshall 11:04
Absolutely. And (that,) to go back to the Vertex story, they capitalized on all the academic research around the CFTR gene and the CFTR protein. What was discovered is (a) complex gene, complex protein. There's so many mutations (that) are what are referred to now, as variants. There is that one major mutation that I mentioned that accounts for about 85% of individuals in the US. (They) have either one or two copies of this three base pair deletion at 508 Dell. But there are now over 2000 described variants in this gene, some cause the disease and some do not. There's hundreds, hundreds that cause the disease; they can be put in different buckets. And in one bucket the full length protein is actually made, and it makes it to the cell membrane where its function is very important. But the gating of anions, it's chloride and bicarbonate that flow through this gate, and that gate doesn't open properly. That affects about four or five percent of CF patients in the US. (And) that is the easiest defect to fix. You just need something to open that gate.

And back to the Vertex story, they found a drug that would open that gate, and it's called Ivacaftor. And so that played out over many years. That project started with Aurora biosciences in 1999, (and) then Vertex acquired Aurora. (And) that played out to discover that drug, Ivacaftor, that works on just those gating mutations, and then ultimately went through all the clinical trials. It was amazing. I remember when the results of the phase two trial came out, there were a number of us, the leaders there at the Foundation, and many others. It was a big group in our largest conference room, and the results were displayed. And I still remember to this day, the findings on sweat chloride, because it brought the sweat chloride levels down to a normal level. And people realized, “Oh, my God, this drug is going to work!”

So it's back to your point, Paul, where there's so many mutations that affect the protein in different ways. I mentioned this one class of gating mutations, but onto that major mutation, that f508, that three base pair deletion: the science to unravel that was absolutely incredible. It relates to the folding of the protein. (And) there were two defects in the folding of the protein. So as it turned out, two distinct drugs were needed to help that protein fold properly, make it to the cell membrane, and then that drug that I mentioned earlier, the Ivacaftor, to open the gate. So there were two drugs that we call correctors. Correcting the folding and a gating drug, the Ivacaftor, you put those all together in a triple combination. That's been a major breakthrough, you know, within the last couple of years, I think it was October 2019, that three drug combination was approved. And now 90%, or a little more, (CF) people in the US will be eligible for one of these drugs that are called CFTR modulators. So, an amazing story, and it's played out: the first drug came out, then Ivacaftor in 2012, and that triple combination drug approved by the FDA in 2019, 20 years later.

Paul Batalden 14:38
So this story about the chemistry and the genetics of cystic fibrosis is a fascinating science story. But these are people and you have to measure the effectiveness of all of this, not just in the laboratory and not just at the bench, but in the lives of people. So you've created systems of measurement that help you understand the successes of various therapeutic efforts. This process of measurement development, and what happens when you have good measures, is a fascinating part of this story because the CF community has used measures for a long time…(but) help me understand this idea of measuring clinical success.

Bruce Marshall 15:26
Absolutely. Measurement has been key. I think about the care for a complex chronic disease, and I've sometimes described it as the Yin and the Yang. There's an evidence driven data driven part to it, but the Yang is the relationships center, trusting relationship between the care team and these folks with a complex chronic disease. So the evidence and data side of that has been a strong focus of the CF community for many years. And there's a measure of pulmonary function, there's a measure of nutritional status, there's a measure around flare ups of the disease or what are called pulmonary exacerbations. And we track this in a patient registry that's been in place for decades, and we've refined it over the years. And we look in the registry following the FDA approval of that drug in 2019. We just finished a complete analysis of the 2020 data and shared it with our community at our recent North American CF conference. And the data in that report was absolutely stunning. Remember, 2019, October 2019, that triple combination drug was approved. And the data for 2020 showed the stunning impact of that drug, it was just every clinical metric, markedly improved, everything from pulmonary function to the number of flare ups of the disease, these pulmonary exacerbations to weight gain and on and on and on. But in addition to that, we heard so many stories from the community. I'm reflecting on a woman with CF that met her husband in college, but she knew about the expected lifespan for CF; at the time she heard it when she was a teenager. And she thought that she might live into her late 30s. She had wanted to be a mother, but never felt like she could have that experience. But she met her husband-to-be in college, they went on to get married. And she went on to this triple combination therapy. And sure enough, she became pregnant, and she's delivered twins. And it's just been an incredible story, anecdote after anecdote from people with CF living with this disease, not everyone, but the majority have had a tremendous impact from this disease. And back to the registry. Typically, we were tracking the number of pregnancies every year… was about 200-250 per year. In 2020, there were over 600 pregnancies! So that's just one one of many metrics that we looked at.

Paul Batalden 18:15
Amazing story as you go through what you've just gone through. And this amazing narrative of the sort of the building of knowledge and the using of this knowledge. With that comes this challenge, because along the way, people who are treating these conditions, develop habits, they develop usual ways of doing stuff. And now some of those usual ways effectively have to be unlearned. Is that true in cystic fibrosis?

Bruce Marshall 18:48

Absolutely, Paul. I mean, when we think about the people that have gone on this triple combination, the tremendous impact I've described, even their sweat chlorides, they come down into the high normal range. I think everything we've learned about cystic fibrosis over the last several decades, it may no longer apply. We have to start over. I talked about the flare ups of the disease earlier. You know, we expect there still will be flare ups to the disease for those that have advanced lung disease, but we think they may look very differently, they may present differently. The community has always tracked the sputum cultures and what are the microbes that are growing in the lung. Now all of a sudden many of these people aren't producing sputum. So the community has to be comfortable with, you know, a metric that they've tracked over the years that might not be relevant. (And) we don't know, there's so many unknowns, so unlearning is one way to describe it. I just think of it as starting over again, learning a new disease and that disease is "Effectively-treated-CF."

Paul Batalden 20:01
Wow! So you've had a couple of decades or a little more time working in this space. Have you ever thought about what things would be like a couple of decades from now?

Bruce Marshall 20:12
Yeah, we have thought about that, Paul. We've done some projections using the registry data, and we anticipate that by 2040, 70% of the (CF) population will be adults, that's completely flipped. When I started in the late 1980s 30% of the patient population were adults, so by 2040 70% of the CF population will be adults! We expect that the population is going to be aging, that they're going to be healthier, that hopefully they're leading long and fulfilling lives. But there still will be people that have mutations that don't respond to these drugs. And we're committed to try to get treatments for everyone. And that will likely be different sorts of approaches. These are mutations that result in no protein production. So this is gene therapy and gene editing. And that's the next horizon for us, there is going to be that minority, maybe seven to 10% of the population, that are going to need a different therapeutic approach. But I think the landscape is going to be very different.

We're going to need to deliver care in different ways. You know, we've experienced telehealth through the pandemic. And I think a lot of these healthier adults who are busy with their lives are going to appreciate the convenience of at least intermittent telehealth visits. But you know, still, the face to face visits and developing the trust and relationship with the team will be there.

So Paul, I think the disease is… it's mind boggling when you think about it. And I'll close with one final thought about going forward. Once we get these effective modulators down to younger and younger ages, because they (now) start in adolescence, and then younger children, and younger and younger children down to infants…once we get them to that point and show that they're safe, we might be able to prevent all the manifestations of the disease from A to Z. And if these people take what might be referred to as the daily cure, they may lead a normal life and a life expectancy that matches the general population!

Paul Batalden 22:20
What an amazing story. Thank you so much for being willing to share what you've seen as you've been a part of this marvelous process.

Bruce Marshall 22:32
My pleasure, Paul, I enjoyed speaking with you.

Paul Batalden 22:40
Building an understanding of the disease or condition that's changing someone's body or mind often involves many scientific disciplines that are generally grouped under the category of biology. These include genetics, biochemistry, anatomy, physiology, pathology, microbiology, virology, immunology, and many others. These disciplines can help identify the problem or condition and help predict its natural course and what to expect.

We can also garner clues for limiting the impact and burden of the condition and get insight into associated risks and safety. Science sheds light on what to look for, and what to pay attention to. Bruce Marshall has told us how this knowledge can be of concrete practical help in understanding cystic fibrosis.

Genetics helps understand what causes cystic fibrosis, biochemistry helps understand what chemical or chemicals might prevent the effects of the inherited condition, physiology helps anticipate what to monitor or measure. Bruce has also shared some of the challenges associated with new knowledge. We have to unlearn the habits that are associated with our older understanding of the way that CF works in the body. Jerry O'Connor, a wonderful former professor and colleague at Dartmouth, used to remind people that the tragedy of science is “hypotheses killed by data.” What he so succinctly described is the ever changing character and usefulness of scientific knowledge. Theories can last only for as long as the latest information and data support them. New information requires reassessment of basic assumptions and practices.

A good science informed practitioner is a good observer, a good describer, a good documenter, always looking for unanticipated signals and information. As human scientists, we must appreciate the importance of curiosity, discipline, imagination, gratitude, humor, community, humility, truth telling, and so much more. We should be driven by a deep respect for how we may be like and/or different as kin to each other.

Because there is always so much to know. And yet to discover, we can appreciate the counsel of Sir Ernest Rutherford, formerly of the Cavendish laboratories at Cambridge University. He was always interested in fostering conversation about what people were trying to figure out more than simply rehearsing what they thought they already knew to one another. All of these are good lessons for the coproduction of healthcare service, because it involves two parties who are kin to one another, each of whom is trying to figure out what's happening, how to make sense of it, and what to do as a result, that helps the person with the condition. We thank Bruce for introducing the biology of the disease known as cystic fibrosis, and contributing to our discussion of science informed coproduction. Thank you. I'm Paul Batalden.

Madge Kaplan 26:27

Thank you for listening to Episode Six of the podcast series, The Power of Coproduction, with Paul Batalden. On Episode Seven, “The Web I Tend,” Cristin Lind joins Paul to discuss the interconnected daily experiences of long term conditions that coproduction must address and help. All podcasts in this series, including an overview of coproduction are available at ICoHN, that’s ICoHN.org/podcasts. The website is where you'll find supplementary materials, guest bios and brief profiles of the production team. You can subscribe to the podcast series wherever you get your podcasts. Thanks for listening.