

### **Disruptive: Accelerating Diagnostics**

Host Terrence McNally interviews Wyss Core Faculty member, David Walt, Ph.D.

McNally:

Hello, I'm Terrence McNally, you're listening to Disruptive, the podcast from Harvard's Wyss Institute for Biologically Inspired Engineering. Today's guest, David Walt, makes the point that we usually measure the achievements of a research scientist by things like publications, grant funding, students trained and patents. He terms these outputs.

To gauge the real world impact of a scientist's work, he argues, we should instead measure outcomes. For example, how many patents have been translated into commercially viable products? And how many lives have been improved or saved as a result? From that perspective, David Walt has had significant impact, working with investors and business partners to take technologies developed in his lab and turn them into companies.

The most successful, Illumina, manufactures the technology behind the majority of gene sequencing systems, and has reduced the cost of sequencing exponentially. The company currently has a market capitalization of over \$40 billion. [1:01]

The mission of the Wyss Institute is to transform healthcare, industry and the environment by emulating the way nature builds. Our bodies and all living systems accomplish tasks far more sophisticated and dynamic than any entity yet designed by humans. And by emulating nature's principles for self-organizing and self-regulating, these researchers develop innovative engineering solutions for health care, energy, architecture, robotics and manufacturing. [1:27]

In addition to being a member of the Wyss core faculty, David Walt is a professor at the Brigham and Women's Hospital and the Harvard Medical School, and a Howard Hughes Medical Institute Professor. He's the scientific founder of Illumina Inc. and Quanterix Corporation, and has co-founded several other life science startups.

Previously, he was a University Professor, Professor of Neuroscience, Professor of Oral Medicine at Tufts University. David received a B.S. in chemistry from the University of Michigan, a PhD in Chemical Biology from SUNY at Stony Brook, and did postdoctoral studies at MIT. He's a member of the National Academy of Engineering, the National Academy of Medicine, a fellow of the American Academy of Arts and Sciences, and a fellow of the National Academy of Inventors.

David Walt, welcome to Disruptive. [2:11]

Walt:  
Great to be with you, Terrence.

McNally:  
Thank you. [2:15] I mentioned some highlights, both in terms of academia and entrepreneurship. But, could you tell us your own story, your path to the work you do today?

Walt:  
Sure, I'd be happy to. I was born and raised in Detroit, Michigan. I moved across the North border of the city to a place that was made famous in a movie a few years ago, called Eight Mile Road. And I moved between Eight and Nine Mile Road, which, in those days was the hinterlands of Detroit. It was the nascent suburbs that were about to sprout up.

[2:48] When I was six years old, I began to just go out the back door of my house or take my bike down the street - they were dirt roads - and go into these areas that were completely unexplored. This was new territory. It was filled with frogs and turtles and ponds and insects, and, I just would spend pretty much all day out there exploring.

And really being immersed in a natural environment gave me the opportunity to connect with nature, to realize, really, the wonder of nature, and inspired me to be curious about how things worked. [3:30]

That's really kind of the early days and sparked my interest in science. I proceeded to be interested in science throughout middle school and high school. I took the usual courses...

[3:44] I went to University of Michigan, I was actually a pre-medical student, that was my interest. My parents having been working parents...My father, having achieved only a two-year college education at a community college, was a furniture salesman, and education was the opportunity to move up in the professional world, and medicine was perceived as being the top of the opportunity chain.

And so, even within my first semester in college, I started doing research in a laboratory of one of the faculty. I became interested in research and fairly soon thereafter realized that the opportunity to contribute to the world and to contribute to medicine was more likely to be something enabled by discoveries, by inventions; and doing this on a global scale, as opposed to an individual patient-to-doctor scale.

And so, that's why I took the path of going into life sciences research, and Chemical Biology, which was a combination of chemistry and biology, and really was where I began to develop the research tools to begin to explore those areas that could have the greatest impact in medicine. [5:18]

McNally:

You were actually looking at, "How can I have the greatest impact?" I'm not saying that that's remarkable, but I think, a lot of kids probably aren't yet. But you actually had that perspective...?

Walt: [5:30]

I would say, as I pursued my research path in the university, I definitely saw that the kinds of questions that could be asked were of the nature that you really could begin to see how doing something, developing a new drug, uncovering a new pathway in biology, would lead to something that could, in fact, have an effect on many thousands, if not millions of individuals. Yes. [6:00]

McNally:

So then you do postgraduate studies at MIT. And you have said that, it was in George Whitesides lab, he was then at MIT, that you grew from being a chemist, to being a scientist. What do you mean? And how did that happen? [6:17]

Walt:

Yeah, it's interesting. I once made that comment at a public event and it garnered a lot of chuckles, because, I think, folks were misinterpreting my statement to mean that I didn't think that chemists were scientists, which was not the case.

What I meant was that, from the perspective of - at the time I was an organic chemist, which is a very interesting, important area of pursuit, but, it's narrow. You think about molecules, you make molecules. You study the transformation of one molecule into another, from a mechanistic perspective.

[7:00] But, as I began to go to seminars at MIT, which was really this incredibly rich experience... This is back in the late 70s, early 80s. This was the time when DNA sequencing was being invented by Maxam and Gilbert, and Fred Sanger. Recombinant DNA and the whole genetic engineering field was beginning to develop.

I would go to these seminars in these other departments, and, realized that here's an opportunity for a chemist to contribute in ways that others were not thinking at the time because most of those fields were dominated by biologists.

And so, as I began to explore these various new fields, I began to read a journal such as *Science* and *Nature*, instead of *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, and expanded my horizons from chemistry to thinking about problems on a larger scale that chemists could begin to think about and solve. [8:07]

McNally:

The point that I raised in the introduction, that you've made about the difference between outputs and outcomes, could you talk just a bit about that and the role that that has played and plays in your approach to your work?

Walt:

Sure. [8:22] I usually qualify my comments about outputs - things such as publications, grant funding, the number of students that you've trained. These are what I refer to as the coin of the realm in academics. And they're important things, don't get me wrong. It's important to publish high quality papers and journals.

[8:48] The problem with that is that if that's as far as things go, and, the only thing that people measure themselves by are the number of citations that those papers garner, and again, the number of students and grant funding that they have, then, it's a dead end, because, what you're really trying to do in research is you're trying to ultimately improve the world.

[9:12] And that does not speak against fundamental science. It's a critical, important part of the scientific enterprise. It's the seed corn that provides the inspiration for the next technologies and the next discoveries that are made.

[9:32] But, from my perspective, if a laboratory just publishes a paper and there's a technology that is coming out of that laboratory, then I feel it's beholden upon the inventors, the scientists, to take the next step if they think that technology is genuinely going to have an impact on the world.  
[9:54]

And so, that's the perspective that I'm coming from. It's something that I think, is not for everyone. It's not necessarily the best thing to do as a junior faculty member or a young graduate student or postdoc. You need to finish your training, you need to establish the credentials of publications, so that you can put yourself in a position where you can get the job that allows you to have that impact.

[10:25] But, nonetheless, I think that ultimately the long-term goal for all scientists should be, as you look back on your career, have you made an impact? Have you changed the way people think about things? -- do things? Have you made a better world out of what you've done in your research career? [10:44]

McNally:

Illumina is your most successful company, as I said. The current market capitalization is over \$40 billion, which is, for scope, "larger than the Marriott hotel chain, for instance."

Could you share the Illumina story? What was the problem that it solved? What was the breakthrough that allowed you to come up with that

technology? [11:06]

Walt:

Well, it's a very interesting story and is not necessarily a linear one, in the sense that, we didn't set out to accomplish what we ended up doing, that led to the technology that was the basis for Illumina. [11:22]

Sometime, perhaps three or four years after I left MIT, working with George Whitesides as a postdoc, I began to work in the field of sensors, and one of the new opportunities back in the mid-1980s was this field of fiber optic sensors.

This was a technology that was developed for the telecommunications industry to send light signals. And we began to do some interesting things, where we would attach materials to the ends of these optical fibers and you could put them into the body, you could put them underground to measure environmental contamination. And these were measuring typically one or two things at a time. Things like pH and oxygen or carbon dioxide.

And what we learned over a period of time is that measuring just one or two things at a time turned out to not be what people wanted, because they began to want to measure multiple things, something called multiplexing. And so, we started to bundle these things together, but that began to get very complex with the instrumentation and the keeping track of signals in these days was not easy.

What we learned is that there were these new kinds of optical fibers called imaging fibers. These were very high-density bundles of optical fibers. They were melted and fused together and they were being used to carry images. And one of the applications that people were pursuing, and still use to this day, are using these optical fibers as endoscopes to be able to go into the body.

So, we got our hands on some of these and began to create these fibers that had many different sensors on them. We published a paper in *Nature* on this, and one day we decided to pursue the possibility that we could create a very high-throughput type of nano-probe. This is a probe that allows you to detect things below the diffraction limit of light.

And what people were doing at the time, were taking single optical fibers and pulling them to a very tiny tip. Kind of melting the glass and pulling it very quickly, and you could get a nano-tip at the end of the fiber, and you'd coat it with gold, and you'd be able to scan that over a surface and get a sub-diffraction limit. Meaning, something on the order of about a 50 nanometer resolution image by scanning this thing over a particular surface area. [14:18]

But, it required something called raster scanning, meaning taking kind of a pencil tip and scanning it over a piece of paper in order to detect an image.

It took quite a while to even assemble an image that was just a couple of microns in diameter.

So, we realized that, with these imaging fiber bundles, we could potentially etch these things to the same kind of tips, but we could make these things on the order of 50 or 60,000 of these at a time, so that you could speed up the process by 50,000 fold because you had 50,000 tips doing the scanning. [14:57]

And so, we decided that we would begin to etch these glass fibers with something called hydrofluoric acid. And every time that we tried to etch these things, such that we got these tips, we got these little microwells instead. That is, each of the fibers, instead of etching back to a point, actually, etched to a kind of a little well, similar to maybe an egg carton, if that might be a decent analogy for the listeners. [15:31]

And so we eventually accomplished what we wanted to accomplish, which was making these tips. But this is in the late 1990s, we were working on creating these micro arrays, these DNA arrays that were able to detect multiple DNA sequences at a time. And we published a paper in *Nature Biotechnology*, where we were able to measure six different sequences in a sample. So, this was dipping the sample into a solution, we could measure six of these DNA sequences. [16:09]

This was the early days of gene expression, and everybody was excited about that, but, as I was talking to one of my collaborators, he said, "David, as I talk to more and more biologists and geneticists, they're talking about potentially wanting to measure a hundred sequences at a time, and potentially one day in the far future, there may be a possibility of needing to measure thousands of sequences at a time." [16:40]

Well, at that instant that that person mentioned this - and this was in the privacy of my office - I realized that we had a very interesting solution to this problem, because just a few months before, one of my students, Kerry Michael, who was a PhD student at the time...She had done an experiment where she took these little beads, these tiny microspheres of plastic, just latex beads, and she took a droplet of suspension of these beads and put it on one of these optical fibers with these little divots on them, and, lo and behold, when she looked under the microscope, every well was occupied by a bead. [17:25]

We thought that was an interesting thing but we didn't know what the heck it was good for, but when this person said, "David, we may need to measure a few hundred or a few thousand of these sequences at a time," I had - the best way to describe it is - an epiphany.

That happens a few times in your career, where all of a sudden...for those folks who are fans of the original movie, *The Matrix*, where, at the end of the movie, Neo, all of a sudden is able to read the binary code.

All of the pieces fell into place, and we realized that we could attach DNA sequences to these beads, we could encode these beads, and we could then put these beads into wells and make what is now called random arrays. You would make these arrays in a random way, and figure out which bead went into which location after you made it. And that really revolutionized the way people thought about making arrays. [18:25]

A few months later I found myself giving a talk at Scripps Institute in La Jolla, and, unbeknownst to me, in the audience were a couple of venture capitalists, one of whom, Larry Bach, came up to me after the seminar and asked me if we could meet for breakfast the next day. And at breakfast that day, he proposed that we start a company that would potentially pursue this random array technology for a variety of potential applications. [19:00]

McNally:

What I love was that, there was... call it an accidental discovery of these wells, that was not what you intended and that was set aside for a while. Discovered, noted - the researcher working on that didn't just go, "Oh damn," but he noted that that happened, but there was no use for it. Then a random conversation points out a need that you hadn't thought about, and in that moment the set aside discovery and the random comment came together for you. [19:35]

Walt:

I would say that's exactly correct, but with one small correction. The postdoc who was doing the etching, Paul Pantano, who's now on the faculty at University of Texas at Dallas. Paul did say, "Oh, damn," every time. He said it daily, because pretty much every time he tried this experiment, he got the opposite result to what he expected. But, yes, in the end, we made lemonade out of lemons. [20:03]

I knew exactly what needed to be done. It's a little bit of a challenge as a faculty mentor to go into a laboratory and ask students to abandon what they're doing, in favor of something that, at least to them, may sound like the research advisor's idea of the day. But this was an idea that I felt was important. I recognized it - even before we had reduced it to practice - as something that had the potential to be incredibly important.

I literally pointed to four students who I knew were stuck on their projects at the moment and may have been looking for a break. Three of them ended up agreeing to work on this, and a few months later we had a paper on this. [20:53]

McNally:

And then, it's after that paper that you speak in San Diego?

Walt:

Yes, that's correct.

McNally:

And so, as you point out, Larry Bach says, "Let's have breakfast." At breakfast, he proposes there's a company to be made based around this. What happens next? You're a scientist, he's a V.C., what happens next...when the two of you sit there at breakfast and say, "Let's do this"? [21:13]

Walt:

Well, I think I was a little bit reluctant to embrace this right away. I wanted to make sure that this was going to be done in a way that was going to enable the technology to be successful. But by the end of three or four weeks, I was pretty comfortable that this was a legitimate team. I did my homework on them, talked to some friends who had been involved with them previously.

[21:40] The next step was for them to get a license to the technology or an option to a license to the technology, followed by coming to the lab and kicking the tires. They sent folks to the lab, who were there really to see - did the technology work?

One person came to my lab, Mark Chee, who had recently left what ended up being a fairly substantial competitor to Illumina in the early days. And Mark had a hotel reservation, I think, for three weeks. After four days, he left and said, "Definitely this works. It's easier than I thought. And, by the way, is there any way I could join the company."

McNally: [22:28]

One of the things that I've heard you say is that, if you've got a good idea, you're thinking about starting a company, the money will find you. What's more important is finding the right people. Can you speak to that?

Walt:

[22:40] Yeah. That's exactly right. What I try to convey to people is, good ideas can attract money. You need to get money that comes with something more than just the cash, with people who have a network, who are able to have the vision, have the connections to be able to find the right initial hires, the right business people to run the company, and have a reputation that will attract other high quality investors to also participate.

And it's the high quality investors who really help bring people to the table that can help you execute in a way that jump-starts the company and gets it off on the right foot. [23:23]

McNally:

What happened next?

Walt:

The microwell array with beads developed and became Illumina's signature product for many years, [23:35] it does genetic analysis. It's what's used for things like 23andMe, for ancestry.com, for all the very high throughput, what

are called genome-wide association studies - called GWAS - that are carried out on tens of thousands, hundreds of thousands of individuals because it's very cheap, very high throughput. You can measure millions of things at a time. [24:05]

McNally:

You're working with the structure of DNA, which is relatively simple compared with that of proteins...

Walt:

[24:13] While Illumina was focused on the DNA technology for genetic analysis, the technology that we developed for proteins became another company called Quanterix.

McNally:

[24:22] How much have your technologies increased the speed and precision and reduced the cost of sequencing?

Walt:

Let me give you some numbers. The human genome project cost north of \$3 billion to get a single sequence, and that sequence was done eight times. The reason for that, is that, when you do a single sequence run, you get errors; when you do the sequence multiple times, the errors go away.

So, that's what was called an eight-X sequence, and that was about \$3.2 billion. By the time the human genome project was completed, roughly in 2002, 2003, the estimate was, if they had started it over again, it would cost 100 million dollars.

So, the technology had improved by a factor of about, tenfold - 20 fold in that intervening time in terms of, the instruments that were being developed and the processes for doing it. But, it was highly labor-intensive, it required 40 institutions contributing over a period of 13 years, at \$3.2 billion. [25:41]

Today, on one of the high-throughput Illumina sequencers, you can obtain - and these are just rough numbers - approximately 30 human genomes that have all been done at about 30X. And each one of those genomes costs about \$1,000. So, you're taking lots of zeros off of it. About 3 million fold, or, if you take the hundred million, you're now down a factor of 100,000. So, you've taken a lot of zeros off the sequencing cost. [26:19]

McNally:

Right, which changes the whole ball game, of course.

Walt:

It does.

McNally:

It's not an exceptional achievement, it's something which happens over and

over again, all over the country, every day.

Walt:

That's exactly right. And it's at the point where, it's now something that people can do. There's lots of compelling reasons in the medical field, clinical field for having a sequence done, particularly, for folks who have been diagnosed with cancers. I just saw the other day that something like 60% of all cancer patients have their sequence done, because it helps guide therapy and predict outcomes. So it is having an incredible impact already even though it has a long way to go before it's achieved its full potential. [27:07]

McNally:

How did you choose what role you wanted to play? And, what advice would you give others in that position?

Walt:

[27:16] The good investors value the inventors. And the reason for that is that they bring with them very deep knowledge and understanding of the technology, and that really helps catalyze the foundation of the company. It helps get the company going much quicker than if it's simply taking the license and forgetting about the inventors.

The inventors had thought about the technology a long time, and most of the time, as with any researcher, experiments fail, technology fails. And when it works, it works because people are clever, they've created something, they've avoided all the pitfalls, and you want to take advantage of all that knowledge base so that you don't repeat the same mistakes if you go forward. And I think that the good investors recognize that having those individuals involved at the beginning of a company really brings tremendous value. If you're ever in a position where you have the opportunity to start a company based on technology that's come out of your lab or that you've invented, my advice is that you're in a good position to control the conversation and control how much or little you want to be involved. [28:42]

If you really want to see the technology end up working as best as it can, then, you as an inventor are obligated to ensure that you provide the best advice to the company, at least for a period of time before you can efficiently transfer your knowledge to the people who are then going to run with the company.

If you decide that joining the company is something that's of interest, go for it. I think, it's a great opportunity, there's tremendous excitement in working at a startup, and in some cases, some of the best science, some of the best technologies are being pursued in some of these well funded high profile biotech companies. [29:32]

McNally:

But, you also make the point, that, don't think, because you're a great

scientist, you're going to have the best ideas about the business. You said that the business folks may not focus on the coolest science, they may focus on the first product they can get out the door, but there's reasons for that. [29:53]

Walt:

Scientists and engineers are great at what they do, but they also have to be humble about what they don't know. And, I think one of the biggest mistakes of certainly folks who are interested in biotech and life science tools, is joining a company and thinking that you can be the CEO.

Bring in the best business talent. These people have experience, they know how to run companies, they know about finance, they've got relationships with investors, they have marketing and sales skills, they know how to build organizations. As a scientist, we may be good at running an academic lab, but running a business is a whole different ballgame, and use the talents of people that will bring the same level of creativity and vision to the business as you bring to the science and to the technology. [30:54]

McNally:

If you are doing world class science, you want to be partnered with people who are doing world class business.

Walt:

That's exactly right. What I always tell people about the success of Illumina, is that the technology and the science are only a piece of it. Yeah, it might be an important piece and I'm not going to put a percentage on it, but without those individuals who had the vision for what products to introduce, how to build the sales and marketing force, how to finance the company in a way that did not give away too much of the company to investors, and retained enough to give incentives to the employees - that's what requires an equal if not greater degree of talent than just coming up with the original technology. [31:46]

McNally:

Right. What advice do you give scientists interested in moving into entrepreneurship?

Walt:

[31:52] Becoming an entrepreneur enables you to see technologies develop in ways that simply publishing papers does not. And so, it's an incredibly rewarding experience, it allows you to have the impact, if that's your goal.

When I started Quanterix with this new single molecule technology, people said to me, "David, are you crazy? Why would you want to start another company?" I had been successful with Illumina, both financially and from a career perspective, and it's a lot of work. And so, that's something that I would tell a young entrepreneur, it's an incredible amount of work. And so, people ask me that question, "Why would you want to start another

company?"

And I said, "Well, if I don't do it, if I don't take this technology from my laboratory and translate it into the private sector, then nobody is going to do it. I'll publish a nice paper, but that's going to probably be the end of the story. Other people may pursue it, but it won't have the intellectual property protection, it won't have the investment. Because, it'll just be out in the public domain." [33:06]

I felt compelled to do it, because, in order to make an impact in the field of clinical diagnostics for proteins, the only person who was going to take that path, was going to be the inventor or inventors of the technology. And so, that's why we started Quanterix. So, what I would say to entrepreneurs is, lot of hard work, a lot of fun. You'll learn a lot, and, if you don't do it, nobody else will. [33:37]

McNally:

What advice would you give entrepreneurs or V.C. types interested in working with scientists? [33:42]

Walt:

That's a great question. I don't think I've ever received that before.

I think, there's a number of things I would tell investors working with scientists. And I think that, the best investors approach scientists in this way. The first is to treat the scientists with respect.

The second is - particularly for young scientists, first time entrepreneurs - serve as a mentor for that individual or individuals, because this is a learning experience for them and they need to be mentored throughout the process.

The third is to make sure that you sufficiently incentivize them and to understand what their motivation is, in terms of incentives. Whether it's consulting fees or equity, depending on the stage of their career that they're at.

And then, fourth, to keep them in the loop and keep them involved, so that they feel that they're part of the decision-making process. [34:44]

McNally:

David, you recently, after a long and very successful career at Tufts, decided to move to the Wyss Institute. What went into that decision? How and why did you do that?

Walt:

[34:56] I was very happy at Tufts, I was planning to serve my entire career there. But this is one of those opportunities that comes your way, and it's one of those opportunities that you can't refuse.

The Wyss is an extraordinary place. It's incredibly collaborative. Its mission is to translate these technologies, and so it meshes well with my personal goals and values. The quality of the people, from the core faculty, the staff, the students, just an incredible compilation of expertise and facilities.

[35:50] But I think the most compelling aspect of it is that it's located, really, in the heart of one of, if not the greatest concentration of high quality hospitals in the world, which allows the technologies that are being developed to be tested directly in a clinical environment and to work with clinicians right at the outset in helping identify what the unmet needs in clinical medicine are.

To me, that was really the driving force for my moving, was just being embedded in that incredibly rich environment that combines both technology and a very rich clinical ecosystem, that allows you to literally walk across the street to three different hospitals and find experts in whatever disease or whatever clinical area you need to talk to, to understand what the problem is, so that, you can optimally design your technology to meet that need. [37:04]

McNally:

One of the things that's come across to me in previous interviews with folks at the Wyss, is that from bedside to lab is just so rapid and fluid. [37:20]

Walt:

That's correct. MDs walk in the hall, but there's PhDs who could walk across the street and talk to world experts., I think one of my goals at the Wyss, at least in this area of diagnostics that I'm so passionate about, is to try to turn the approach from one where it's a technology push to a clinical need pull. And I think that dynamic is developing in ways that I think is going to be incredibly transformative for the mission of the Wyss. [37:58]

McNally:

What you just said from a technology push to a clinical pull, it seems to me, that's almost, the next level of translation. Where, it's not, "How do we translate this?" It's, "What do you need translated?" [38:12]

Walt:

Yeah, that's exactly right. It's really about finding the right technology to fit the problem, rather than trying to fit a technology to meet a particular problem.

I think that's been the traditional way: folks come up with the technology and then say, what's it good for? And I think now the conversation is very different. What is the clinical need? And, can we find a technology at the Wyss? And, invariably the answer is yes, because, it's so rich with technology, that there's probably three or four technologies for any problem that could potentially be purposed to solve a particular critical problem.

[38:53]

McNally:

So, we go from discoveries that never get out of the lab because they're stuck in academia, to translation. And now, the next generation of translation. You've actually started a lecture series at the Wyss, Diagnostics Grand Rounds. What is that? How does it work? And, why did you feel the need to create it?

Walt:

Well, it speaks directly to what we've just been talking about, and that's bringing clinicians to the Wyss to talk about unmet needs in their field. So whether it's cardiology, infectious disease, pulmonology, orthopedics, emergency room medicine... What we're trying to do is bring people who live and breathe in those clinical environments to the Wyss to articulate, what are the unmet needs in those fields that technology potentially could solve? [39:45]

And so when I give speakers instructions, I say, "Look, it's great to talk about what you do, but we also want to hear what you can't do, because there will be people in the audience who probably will be able to help you figure out how to do what you can't do." [40:04]

Invariably after the speakers finish their formal presentations, even during the presentations, there's lots of questions. But we have ample time afterwards for informal discussion with speakers, and there's always six or seven people who end up approaching the speaker to find out if there's an opportunity for collaboration. And I think we're going to see the results of that over the next few years as these conversations and collaborations get going in full force. [40:40]

McNally:

And you're working on something else at the Wyss called the Diagnostics Accelerator. What is that? And where's that going? [40:47]

Walt:

The diagnostics accelerator is a way in which we can take technologies that can make a difference in clinical diagnostics, and really help do exactly what the name says, accelerate the translation of those technologies into the clinic. [41:06]

I hearken back to my experience with Illumina, where the company is 20 years old. Really, the first clinical applications did not get introduced, until, somewhere in the 15 or 16 year timeframe of the company, where they began to be used for non-invasive prenatal testing. They are now being used in the clinic for cancer.

These technologies took a long time to get into the clinic. And so the accelerator is aimed at identifying the unmet needs and really, helping the

technologists work with the clinicians in a very direct way to accelerate the translation from that discovery phase right into the clinic, to help make the impact on patients' lives happen in a much more compressed timeframe. [42:05]

McNally:

And what do you see, say, five years down the road with this diagnostics accelerator? [42:10]

Walt:

I think it's going to be an incredibly rich environment for researchers, which will include scientists and engineers, clinicians, and also the people who deliver care, nurses, EMTs, to really work in proximity to create what I would say is a machine that's able to translate these things in a very efficient way.

As we learn what the barriers are in the regulatory system, we learn the barriers to translating technologies into the clinic, that is the behavioral issues, the social issues, the reimbursement issues.

Just as we were talking about building a business, it's not only about the science and technology, it takes talented people on the business side as well. I think in the clinical realm, there are a lots of issues with just entrenched technologies, the way that people are trained, that they don't want to change.

These kinds of psychological barriers and, for lack of a better term, some of the political barriers that exist in getting new technologies into the clinic. I think we need to understand those so that we can really help accelerate these technologies, because I think in many cases those kinds of barriers are of equal magnitude to the technological ones. [43:43]

McNally:

Sure. A few minutes ago, one thing you said really surprised me, and I don't suppose it should have. Which was that you said, Illumina becomes successful, becomes, in some ways, phenomenally successful, is having a big impact, and yet, it took 15 years before it moved into diagnostics applications. And what you're hoping here is that a technology that might be useful for diagnostics will get there quicker. [44:08]

Walt:

That's correct. I think that there's a real opportunity to compress the timeframes from technology development to the clinic, to something more on the four to five year timeframe, than the 15 to 20 year timeframe, which is traditional.

And the reason for that is that companies that introduce these new technologies, like sequencing, for example, or an ultra sensitive protein measurement, oftentimes the first and easiest path to commercialization is

as a research tool. They build an instrument, they get them into the lab, and, if that's successful, if the uptake of those instruments and the consumable pull-through that results from selling those instruments, and then selling reagents to support them, build up the revenue base of the company, it's very difficult for the company to switch from being a life science tools research community company to one that now transitions to a clinical company. The incentives are different, the markets are different.

And so, I think, what's going to be critical is to show the clinical utility of some of these technologies early so that the clinical applications can be pursued at least in concert with the research applications. [45:40]

McNally:

So, as you're developing your culture, as you're developing your incentives, as you're developing your focus... Does that go again back to your original thing about impact? That having impact and making research better is great, but let's get it into the clinic... [45:53]

Walt:

Yes, that's exactly right, because in the end, while it's wonderful to provide new research tools to the research community, to enable new discoveries to be made - it's equally if not more impactful to see these technologies translate into the clinical environment where they begin to have an effect on patients' lives. [46:20]

McNally:

How long have you been at the Wyss at this point, David?

Walt:

I arrived at the Wyss in July of 2017.

McNally:

Year and a half.

Walt:

Year and a half.

McNally: [46:32]

Yeah. Anything you want to say about your experience? Something that surprised you? Something you hadn't thought about that has shown up for you? [46:38]

Walt:

I think that for me the biggest surprise is that... When I spoke with Don Ingber, the founding director of the Wyss, Don said, "Look, we're going to give you some space, but, the way that you can increase your profile and the space that you have at the Wyss, is by engaging in collaboration. That's what we're all about."

I was thinking that, "Boy, I'm going to have to spend a lot of time talking to a lot of people." But the way that the Wyss is set up, is such that the six people that I first put at the Wyss all talk to other people at the Wyss, and it's just this organic development of collaborations and ideas that occurs.

Every week now people come and say, "I was talking to so and so, and, they're interested in doing something with us, and we've been talking about a way to do something together." And so these collaborations just occur, as I say, organically. They're part of the fabric of the institution. And so, it's very low barriers to working with people and coming up with really interesting new ideas. To me, that's the biggest and most pleasant surprise I've had. [48:00]

McNally:

What's interesting is, in their very definition I think, which I read at the start, they talk about self-organization and self-assembly. And I think most people probably assume they're talking about within their experiments, within their research, but, what you're saying is self-organization and self-assembly take place within the culture. [48:19]

Walt:

That's exactly right

McNally:

[48:20] What are you working on now - both in terms of science, translation, taking advantage of the situation, what are the questions driving you these days?

Walt:

How do we take technologies and accelerate their impact in the most pressing health care problems of our day - cancer, neurodegenerative disease, infectious disease for the developing world?

These are all problems that I think are really things that people have been working on a long time, and we need to begin to come up with the tools to, one, understand those diseases; two, diagnose them early; and three, come up with therapies that can either delay the onset of symptoms or cure the diseases entirely.

Those are the things that I'm laser focused on and the specifics of how we're going to solve those problems, get into the nitty-gritty details of the technologies that we're bringing to bear to solve each of those problems. But, that's the way I organize my lab and try to drive the efforts that we undertake. [49:41]

McNally:

It's interesting going back to the start of the conversation, where your parents hoped you would become a doctor. As you describe what drives you at this point, it's everything that would drive a doctor with an individual

patient, is the same thing that's driving you with the whole field. [49:58]

Walt:

That exactly right. I've set very high goals and aspirations. If I am able to check the box on one of those three areas, I'll consider it a success, but I'm hoping to have an impact on all three. [50:14]

McNally:

Thank you, David Walt, for your time and for your work.

Walt:

Thank you, Terrence. It has been a pleasure. [50:20]

McNally:

You've been listening to DISRUPTIVE: ACCELERATING DIAGNOSTICS.

I'm Terrence McNally and my guest has been David Walt.

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