“Remote Monitoring and Deep Data” (Mike Snyder) [#52]

Brad Power
April 12, 2023

“We try to actually follow people's baseline and look for these shifts.” – Mike Snyder

“The goal is to try and understand what a healthy profile looks like. How does it change over time? How does it compare between different people? What happens when people first get ill? And importantly, for trying to transform the healthcare system, can these advanced technologies, like genome sequencing and wearables, be better used to manage people's health?” – Mike Snyder

Meeting Summary

Advanced cancer patients are interested in monitoring their health, and there are a growing number of tools to help them.

Mike Snyder, PhD, is uniquely qualified to talk about disease monitoring technologies and the data that they generate. He is the Chair of the Department of Genetics, and Director, Center for Genomics and Personalized Medicine at Stanford University School of Medicine. He is an expert on everything related to the "digital self" in healthcare: on the state of developments in remote monitoring, sequencing and other “omics”, and novel medical devices, such as wearables. These technologies and the big data they generate hold the promise to transform healthcare and detect health problems early. His major research involves collecting and analyzing data on people's DNA, activity levels, diet, stress, and other environmental factors longitudinally and looking for any shifts that may indicate health issues before they become serious.

What can you measure to monitor your health?

Your goal should be to try to understand what your healthy profile looks like. How does it change over time? How does it compare with other people? What happens when you first get ill?

Your health is influenced by your DNA, your genome, and lots of other things: your activity, the food you eat, stress, and environmental responses. You can quantify a lot of this easily, like your genome and your activity. Some of the measurement systems are clunky, but it's quantifiable. You can also quantify the effects of these things by taking deep data measurements.

- From your blood, using mass spectrometry and other methods, you can profile proteins, metabolites (substances made or used when the body breaks down food, drugs, or chemicals, or its own tissue), and lipids (the breakdown and storage of fats).
- From tissue or blood, you can sequence your genome, transcriptome, and proteome.

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- From peripheral blood (blood circulating through your body), you can isolate mononuclear cells (PBMCs, blood cells with round nuclei), allowing you to measure your immune system cells (monocytes, lymphocytes, and macrophages).
- From blood plasma (the part without the cells), you can measure proteins and cytokines, which are small proteins that are important to the immune system and blood cell controllers.
- From fecal, urine, gut, nasal, tongue, and skin samples, you can follow your microbiome.
- From questionnaires, you can track your feelings, pain, nutrition, exercise, and symptoms.
- From advanced tests, such as stress echocardiograms and glucose control measures, you can track deeper clinical status.
- From wearables, you can track heart rate and rhythm, blood pressure, oxygen saturation, skin temperature, quality of sleep, total steps in a day, amount of exercise, and exercise response. With a continuous glucose monitor, you can track your glycemic response to what you eat.

How often should you be taking these health measures?

You should track your data longitudinally. Wearables can track you all the time. Metabolic tests can be run every month. Otherwise every six months may be enough while you’re healthy. Then if an adverse event comes along, like a viral infection, you should take more samples. (This is what the Snyder Lab does, though they do not know the real answer.)

How can you use your health data?

Increasing the data you gather from health monitoring tools can help you:

- **Diagnose**: For example, Mike Snyder is type two diabetic, which was predicted from a genome sequence and then got picked up through profiling. Mike also detected when he had Lyme disease pre-symptomatically, because his heart rate went up, and his blood oxygen dropped. This was picked up with a pulse oximeter, although you can now get it from a watch.
- **Provide an early warning**: Seeing things are off before people have symptoms. For example, early lymphoma, pre-cancers that can convert to aggressive cancers, and heart issues have been detected. Mike’s lab developed a COVID predictor based on raised heart rate.
- **Monitor**: For example, through longitudinal profiling, a case of early pancreatic cancer was detected. Other cancers can be monitored for recurrence.
- **Personalize treatment**: For example, your normal temperature is probably higher or lower than 98.6, which has been the generally accepted normal temperature. Everybody reacted differently to an Ensure shake.

How could microsampling be used to monitor a particular disease, like prostate cancer?

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Microsampling is a fantastic opportunity for semi-continuous monitoring and could give you useful surrogate indicators. For example, one of the challenges metastatic prostate cancer patients face is getting tissue to support diagnostics because their lesions are typically in their bones. Today, they rely on cfDNA tests to identify oncogenic and resistant mutations that characterize their solid tumors. This is a huge step forward, but we would want to explore whether or not blood-based proteomic microsampling could detect solid tumor protein expressions that are currently limited to tissue samples.

However, there are challenges to designing a microsampling and monitoring protocol for a particular disease. What to measure is as important as how often to measure it, as well as how to look for fluctuations in whatever is monitored that may be meaningful. Some commercial vendors provide monitoring, but for specific analytes or measures that may or not be the most informative. For example, there is no obvious answer to the obvious biomarker(s) for prostate cancer. To find them, we would look for the most homogeneous patient population and treatment pattern with distinct outcomes of response versus non-response. Then we would develop an observational study to see what kind of data would separate the two. The key is a simple clinical trial design to keep the study fairly small and reasonably easy to recruit patients.

We are exploring convening a group to discuss this possible trial design. The study would need prostate oncologists and clinical trial statisticians.

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Meeting Notes

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Discussion Outline

SUMMARY KEYWORDS

people, called, question, heart rate, blood, data, brian, measure, sampling, monocytes, markers, measurements, health, smartwatch, micro, cells, genome, run, important, meaning

SPEAKERS

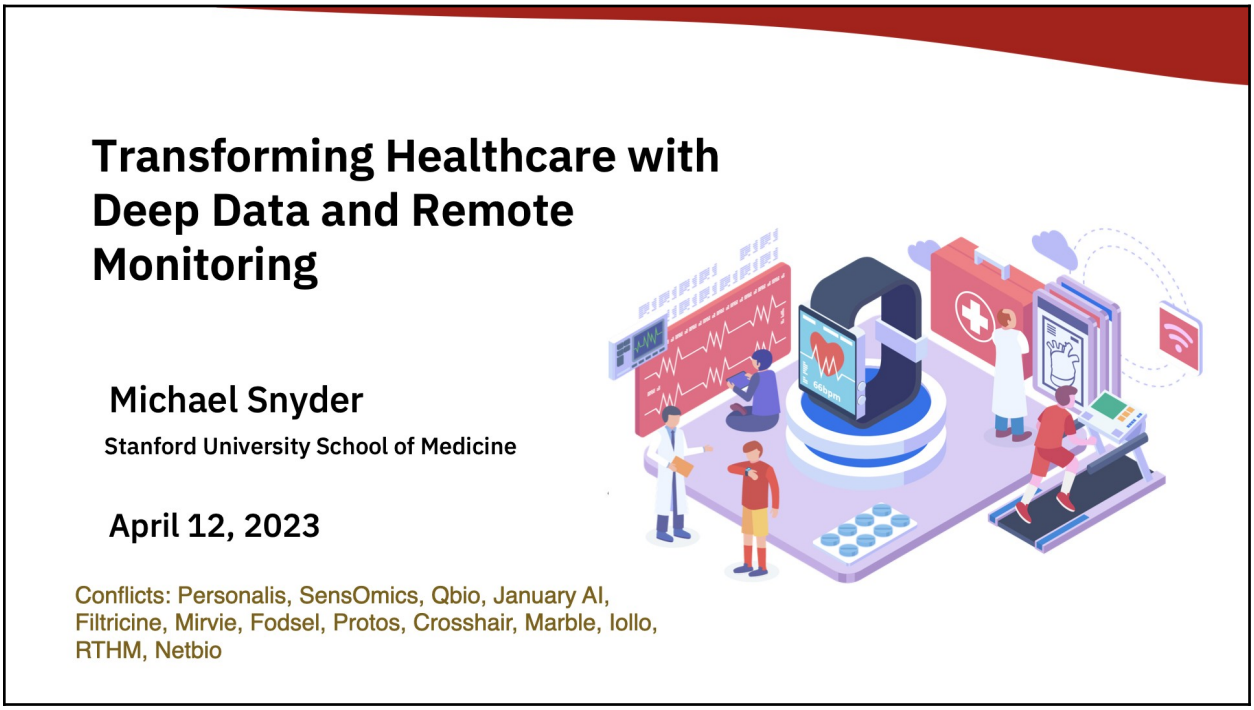
Mike Snyder (77%), Brian McCloskey (12%), Gitte Pedersen (4%), Jason Crites (2%), Richard Anders (2%), Russ Holyer (1%), Eric Hall (1%), Amit Gattani (1%), Rick Stanton (1%)

Brian McCloskey

Welcome, everybody to the Prostate Cancer Lab. We're very excited to have Dr. Michael Snyder with us. He is the chair of the Department of Genetics at Stanford. He is also a very well published author, most notably the genomics of personalized medicine, which everyone needs to know. His research has spanned many different areas. He was the first to perform large scale functional genomics in any organism, and has developed many technologies in genomics and proteomics. These developed the proteome chip, high resolution tiling arrays for the entire human genome, methods for global mapping of transcription factor binding sites, de novo genome sequencing of genomes using high throughput technologies and RNA seek. And these technologies have been used for characterizing genomes, proteomes, and regulatory works. And so, Mike, that's coming directly from your, from your biography on your site. Some of it, I know, tell them but I don't know. But I mentioned that just because you have some patients

here, and researchers, etc, that are bioinformaticians. And that's going to mean something to them. Your research has also gotten into HIIT training, and we have talked a lot about it, relative to other training. Rick Stanton, who's on the call here, the cofounder of the Prostate Cancer Lab, bioinformatician from Amgen, three years at human longevity. And he's sporting his guitar there. He's really interested in HIIT versus LDT, long distance training. Oh, anyway. So you've got a lot of really interested people.

Mike Snyder
3:02



I'm not an MD. I'm 100% conflicted and everything I'm gonna tell you in terms of startups that have spun off from some of the work that we're doing here. So I will tell you a lot about 20 minutes of slides, and they give you a flavor for the kinds of work we do. And it's all revolving around big data, trying to use big data to solve biological problems. And probably our flagship work is the one I'll tell you about which is really using big data to try to transform healthcare and monitor health. And we're trying to be a bit upstream, I think of where this focus group is. But we do do some work on taking on certain cases that we do try to solve I suppose.

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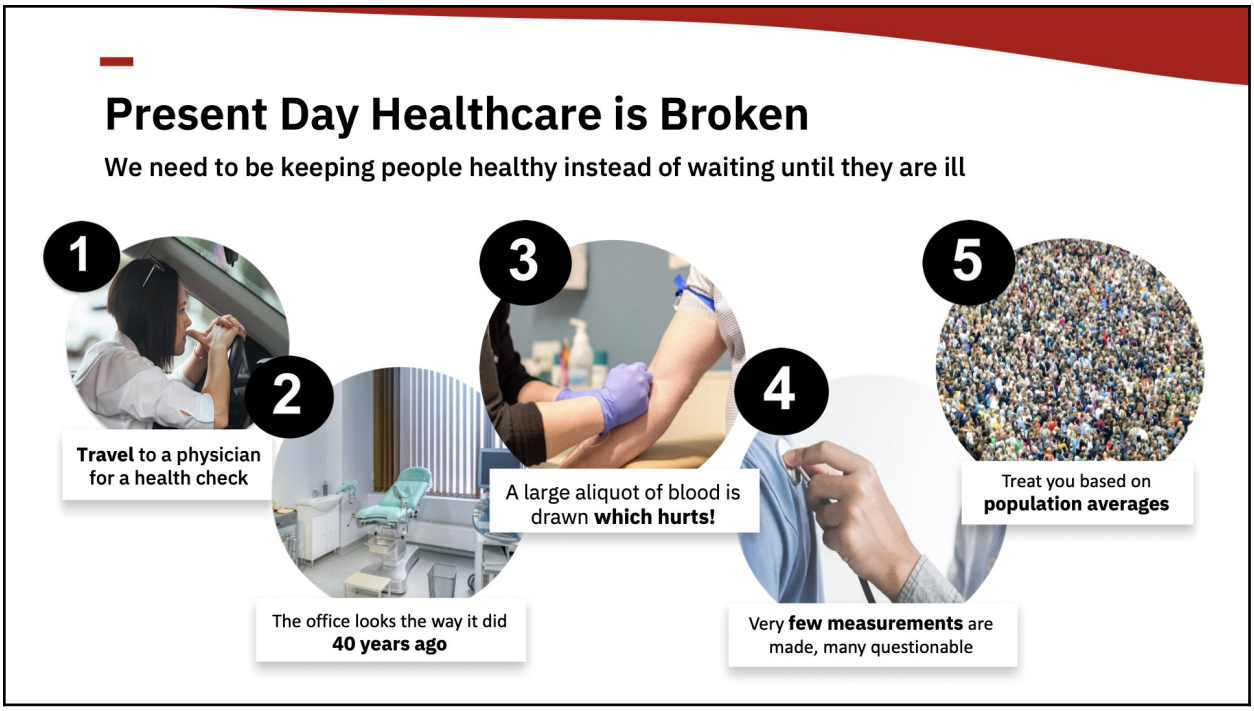

So anyway, we think the healthcare system is broken as it currently works, it's really more sick care rather than health care. And even when you practice health care, if you think about it's kind of archaic, the way we do it. You typically get in a car to travel to a physician to show up at the doctor's office, which pretty much looks the same as it did 40 years ago, with a few new gizmos. They'll draw a very large aliquot of blood using a needle that typically hurts. From all that blood they usually don't make very many measurements, and then they'll make decisions about your health based on population averages.

We think all of these steps can be dramatically improved. And so that's really been a focus of our work. And I'll tell you about some of the latest stuff, which I think you could see how it might apply to this particular group should lead to a fun discussion with regards to this last point about population health.

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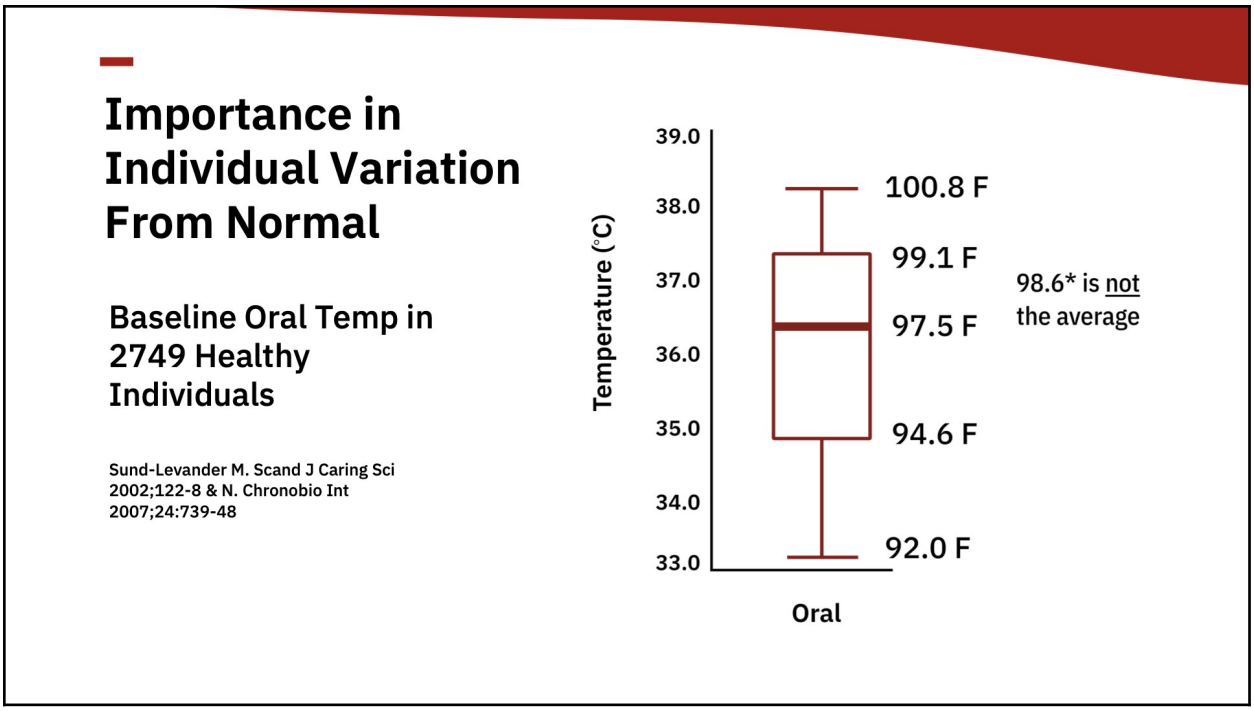

You've probably been told since you're little that your normal temperature when you put a thermometer in your mouth is 98.6. But if you actually read the data It's out there, it's more like 97.5. But the more important point is there's a spread, this is the 25th, quartile 94.6. And this is the 75th, quartile 99.1. So that means if your normal baseline is here, 94.6, and you go to the physician's office today, and they measure 98.6, they will tell you are healthy or normal. But if you're up four degrees over your baseline, we would argue you're not healthy, something's probably off. And so that's sort of a big part of what we do, we try to actually follow people's baseline and look for these shifts.

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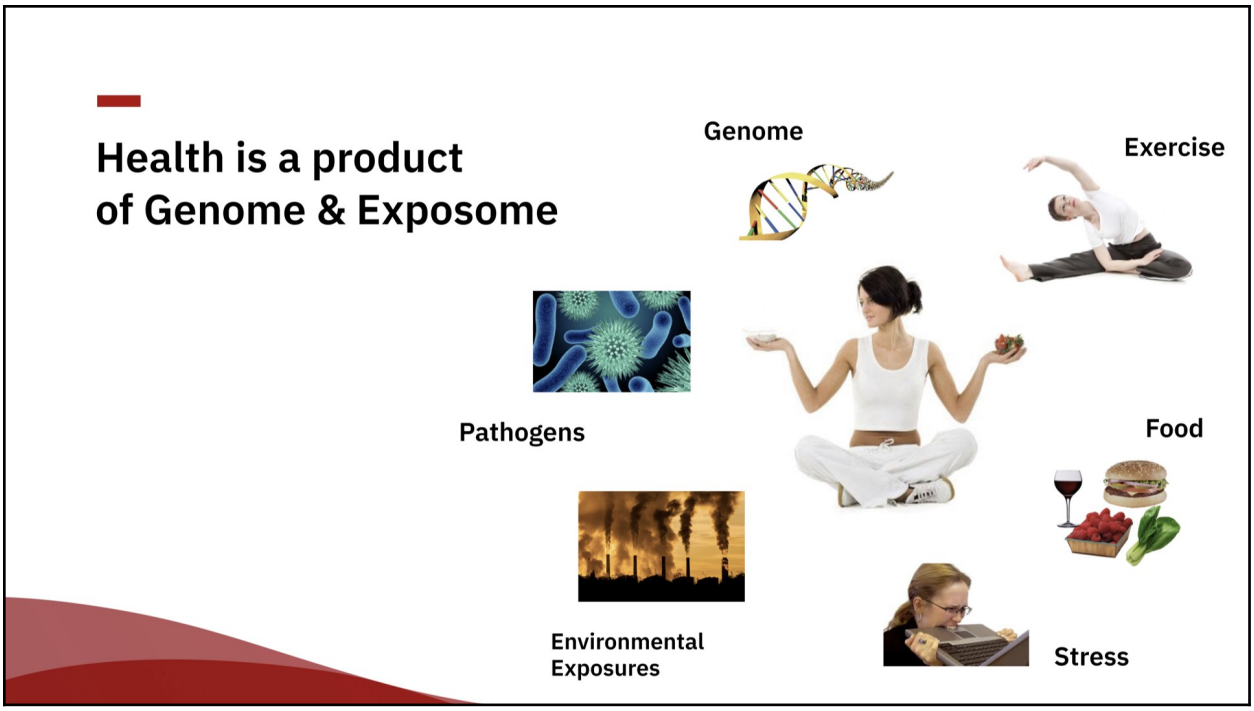

And so a number of years ago, actually 13 Little over 13 on me, and now 10 for the cohort, we got involved in the idea of trying to use big data to see if we can probe people's health. And basically, your health is influenced by your DNA, your genome, then lots of other things, your activity, the food you eat, stress, all these environmental responses, all of these impact your health, and we're in a world where we can quantify a lot of the some easily, like your genome and your activity, some is clunky, but it's quantifiable, but probably equally important, we can quantify the effects of these things by doing these deep data measurements on people.

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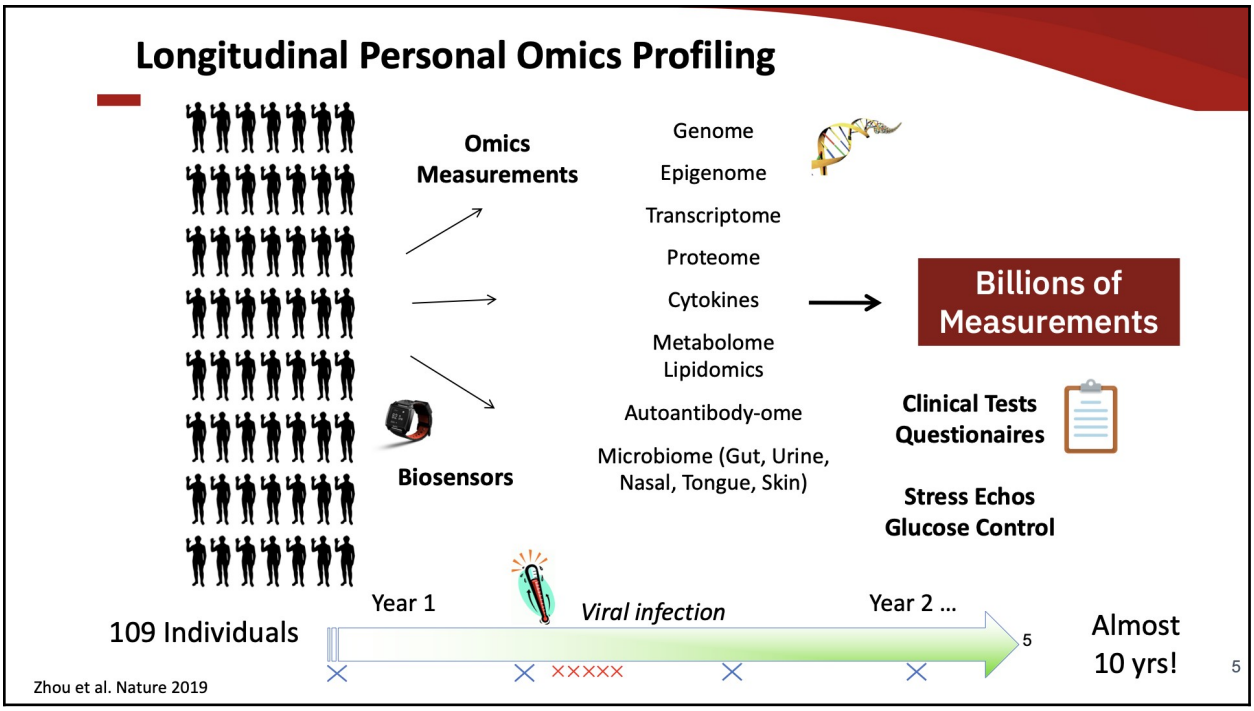

There's been a revolution in DNA sequencing and proteomics that was mentioned earlier. We are using mass spectrometry and other methods to be able to profile proteins and metabolites and lipids out of your blood. Starting about, as I say, 13 years ago, and then 10 for most of the cohort – It’s a smallish group of about 109 people – we've sequenced their genome once, but then we will basically out of their immune cells, called peripheral blood monocyte cells, measure their epigenome, transcriptome, proteome, and then out of the blood plasma, so that's the part without the cells, we will measure proteins and cytokines, which are important immune molecules. I'm sure this group knows about metabolites and lipids. On top of that we follow the microbiome. We do deep clinical testing as well in questionnaires. And then we have a number of advanced tests, stress echocardiograms and a variety of glucose control measurements.

I'm actually type two diabetic myself, that was predicted from a genome sequence and then got picked up through the profiling.

Anyway, we do a lot here.

We do a lot with wearables, which is what I think Brian asked me to talk about, and that's what will be the emphasis of this.

So we do these deep data collections on people.

We also do it longitudinally. That's the second aspect. We sample people every three months while they're healthy. Then if an adverse event comes along, like a viral infection, and there have been other things as well, we'll take more samples.

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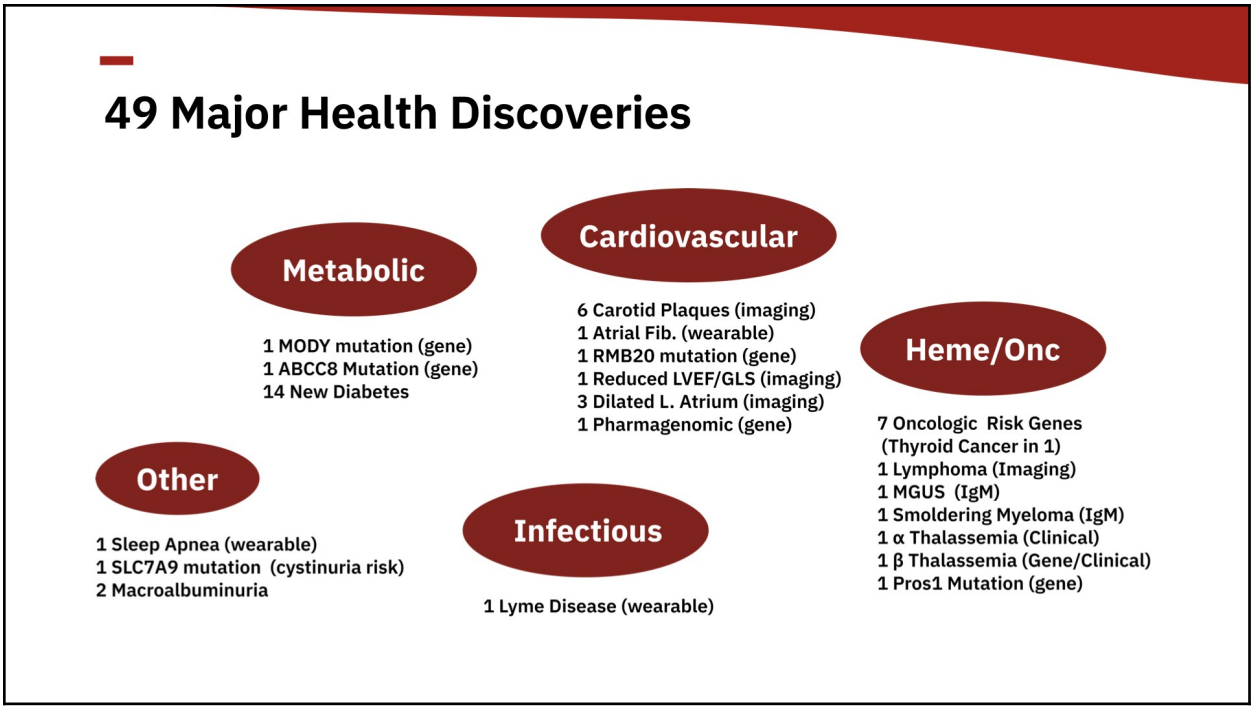
The goal is to try and understand what a healthy profile looks like. How does it change over time? How does it compare between different people? What happens when people first get ill? And importantly, for trying to transform the healthcare system, can these advanced technologies like genome sequencing and wearables, be better used to manage people's health?



With regards to this last point, basically, just in the first three and a half years, we had 49 major health discoveries, meaning we caught some of the early lymphoma that spanned a wide range of area hematology, cardiovascular, metabolic, so on and so forth.

So we caught some early lymphoma to people with these pre-cancers that can convert to aggressive cancers, to people with serious heart issues, one was picked up by genome sequencing and other by wearables, and so on, and so forth. These are all found pre-symptomatically, meaning we could see things are off before they had symptoms. And again, with the way we like to think about this is that if the way we follow people's health now is like a five piece jigsaw puzzle, by pieces out of 1000 piece jigsaw puzzle, we're trying to take more like five or 600 pieces, so we get a clearer picture of their health. And so that's what we're up to. And, again, these are all found pre-symptomatically. No one technology found it. It's just often the combination of genome sequencing plus blood markers, especially lymphoma that was by both imaging and seeing several markers off. So this is what we've been running for a while.

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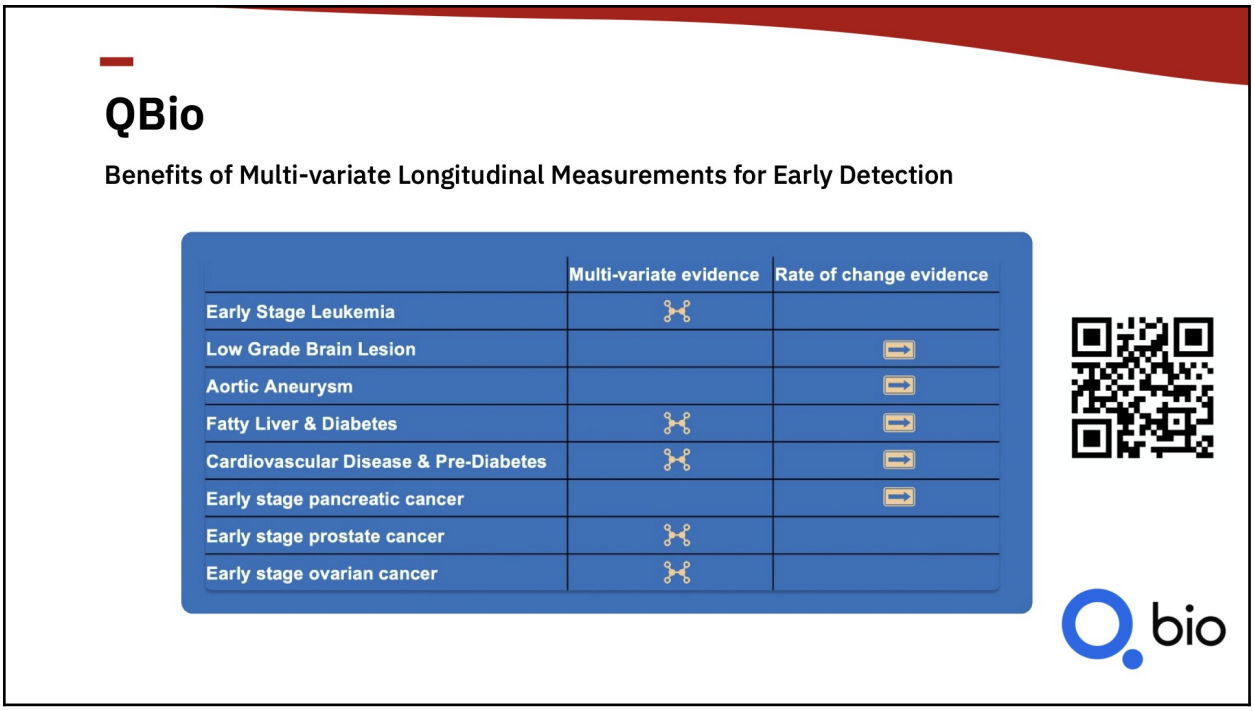

We did spin off a company to do a medical version, what I showed you was a research version. And a number of years ago, we have this company called Qbio. So you may have heard of it, and they're doing a medical version, but they're also adding in whole body MRI. And this we think is pretty important. The medical establishment these days will tell you if you ask any physician to do a whole body MRI? Pretty sure Brian can comment on this 100%? And we'll say no, absolutely not. And the reason is because everybody has nodules, women have them in their ovaries, men in their prostate as this crowd probably knows. And if you ask me, I'll tell you, you absolutely should do a whole body MRI, the key isn't whether you have nodules, the key is whether you have any growing nodules. And the way, you know, that is by the longitudinal profiling. So we actually caught all these are found pre-symptomatically, early ovarian cancer, prostate cancer, cardiovascular disease, and through the longitudinal profile, we've been picked up a case of early pancreatic cancers from the first 100 plus people, and so on, and so forth. Again, all found pre-symptomatically. So we think these big data dives can better find what's going on.

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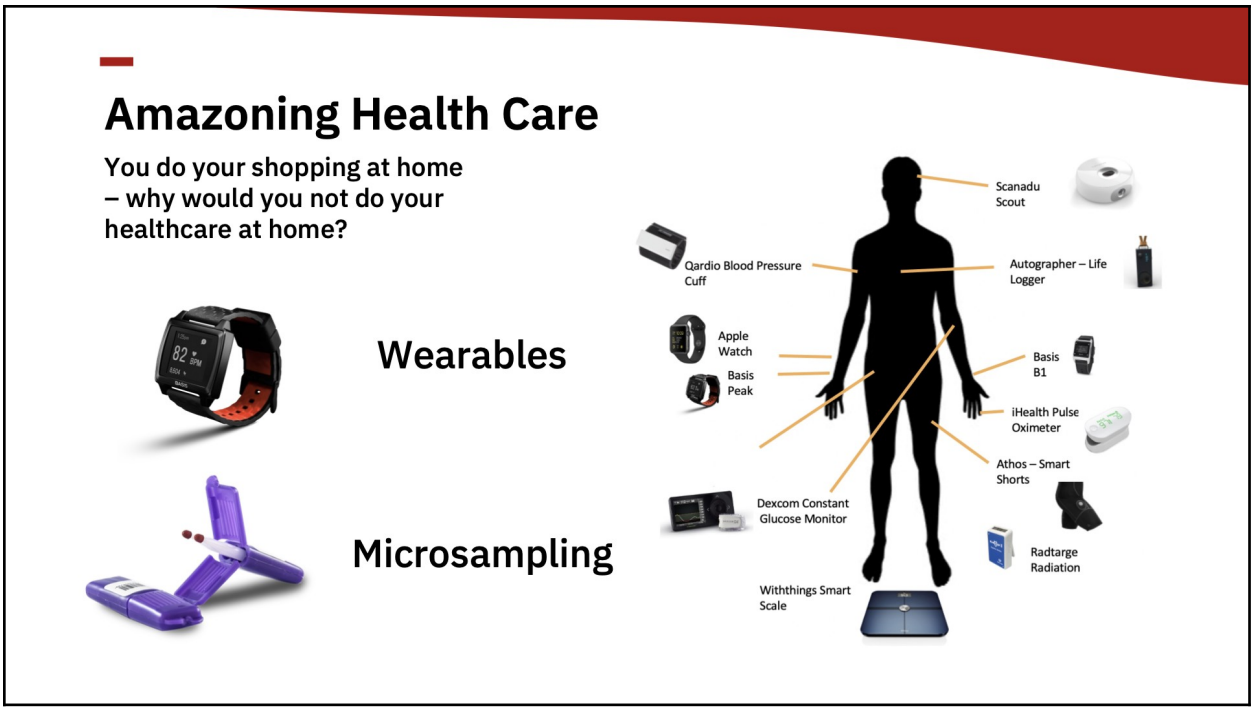

So we've been doing to the main point of that, I think, me being here, we're doing a lot with this sort of remote monitoring. And this could also fit into lifestyle things that you were interested in talking about, like, exercise, the effects of exercise, so we got involved as a number of years ago, before the Apple Watch was housed about, I think, eight years ago, now. We got involved with wearables, but when they're mostly just fitness trackers, we thought, well, these are probably pretty powerful health monitoring monitors. So we've actually worked with the watch code bases that don't even exist now. We put these on people to follow them.

I'll talk about microsampling, which I think this group may find interesting as well.

On wearables, you may know there's tons of them out there. They're mostly in the form of smartwatches, or rings. And they're powerful, because they measure all kinds of important physiology like heart resting heart rate, heart rate, variability, skin temperature, blood oxygen. Some of them are accurate, some of them less accurate. Some of them aren't accurate at all, like blood oxygen, and blood pressure. Some devices do that, they're generally not that accurate, but they're fine for picking up changes in the Delta we'd like to say. So anyway, these devices are powerful, because they'll measure you 24/7 365 days a year. And so as long as you keep them charged, and so we put these on our cohort right away, and discovered that you can tell when people are getting infectious disease. This might interest this group.

Mike Snyder
12:33

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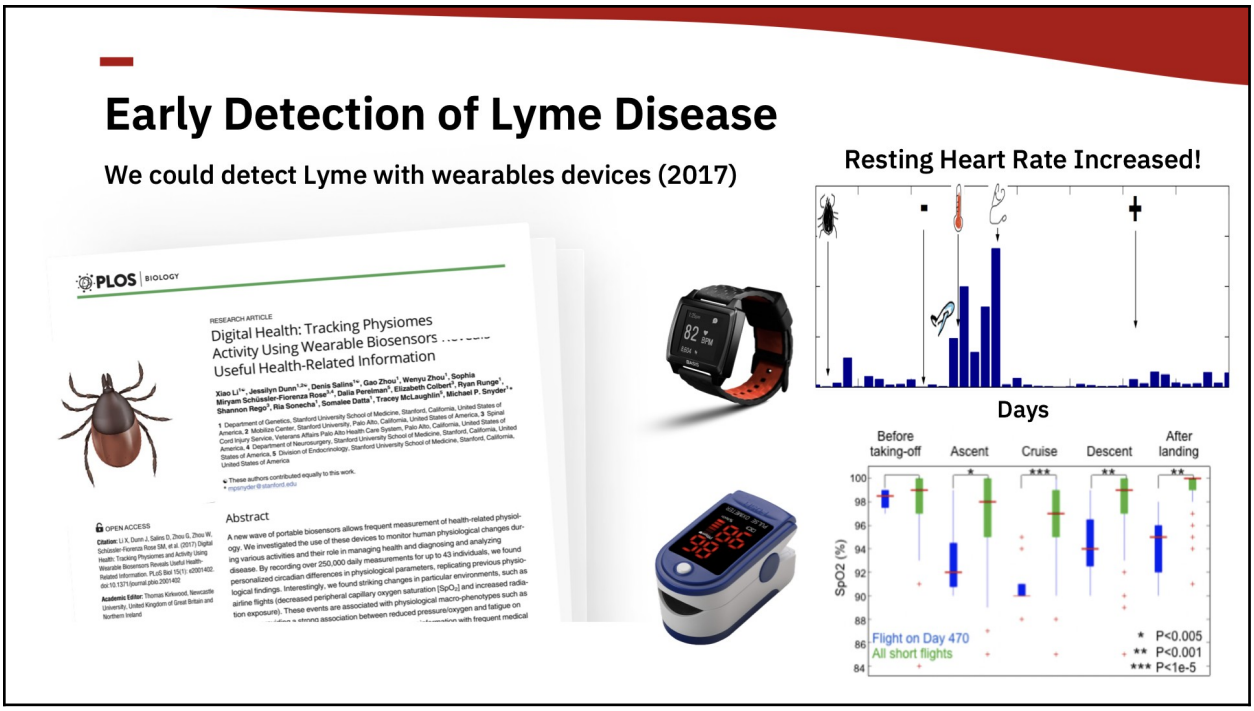

And we figured it out, because actually, I've detected my Lyme disease pre-symptomatically, because my heart rate went up, and my blood oxygen dropped. This is picked up with a pulse oximeter, although you can now get it from a watch. Again, pre symptomatically. We saw these shifts. I knew something was up two weeks earlier, I'd been in an area where pretty Lyme infested. And I later did get symptoms. Often I went to a physician who saw my immune cells called monocytes rapidly and recommended penicillin. I said no, I need doxycycline and got a little tense, but he didn't give in and cleared it right up. And then when he got back, I tested as Lyme positive. Yeah, go ahead. That's funny. Yeah, so no, most physicians are a little resistant to hearing from their patients. You know, here, I was telling No, I need doxycycline. I was in Norway as well. Anyway, it was awkward, but it worked out just fine. But it's well controlled, I gave blood just before I left, you can tell I measured myself, I forgot to say if you look up, I'm wearing these four smartwatches. And these hearing aids I have are for hearing but they actually have sensors as well, they can follow my interactions, my lever, not my physiology as well. So again, these are powerful. And then we I won't show you the data for this, but we went on to show that you could tell when you're getting a respiratory viral infection in advance of symptoms, because your resting heart rate jumped up. And that turns out to be generally true. That yeah, we can see your heart rate will jump up in advance of symptoms, your resting heart rate. And we showed that I had for even an asymptomatic case four times as infected every single time that popped up. Same with other members of the cohort.

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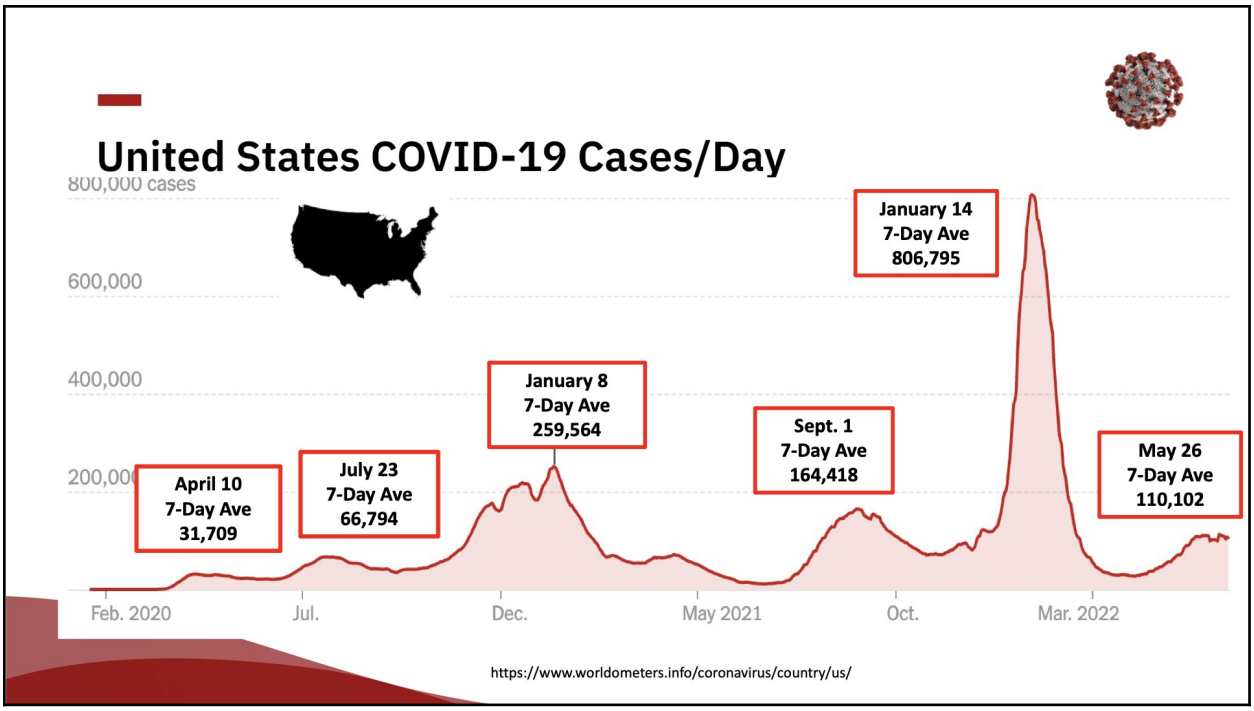
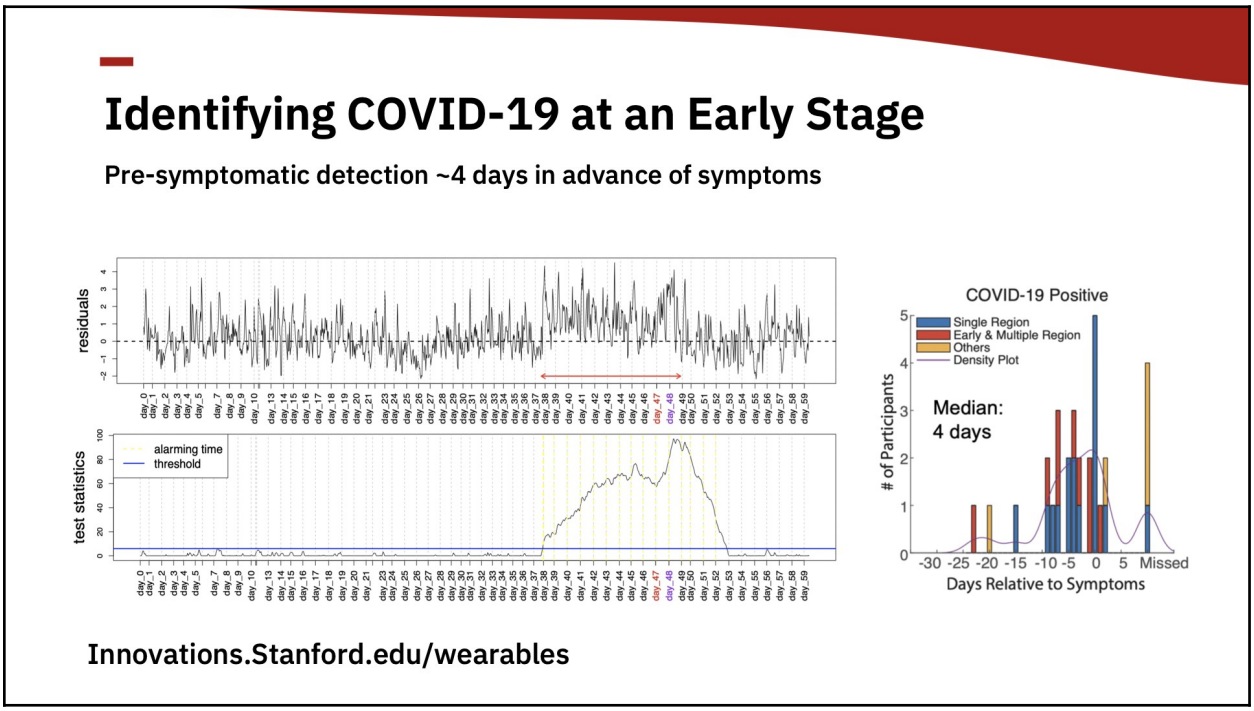


And so as you know, COVID has come along. We have all these waves. This is a year old now. But we're still running around 45,000 cases a day, which is an underestimate. Since people stopped reporting and, you know, we want to see if we could detect COVID with a smartwatch. You'll see where this is going and why it's relevant, I think to this group.



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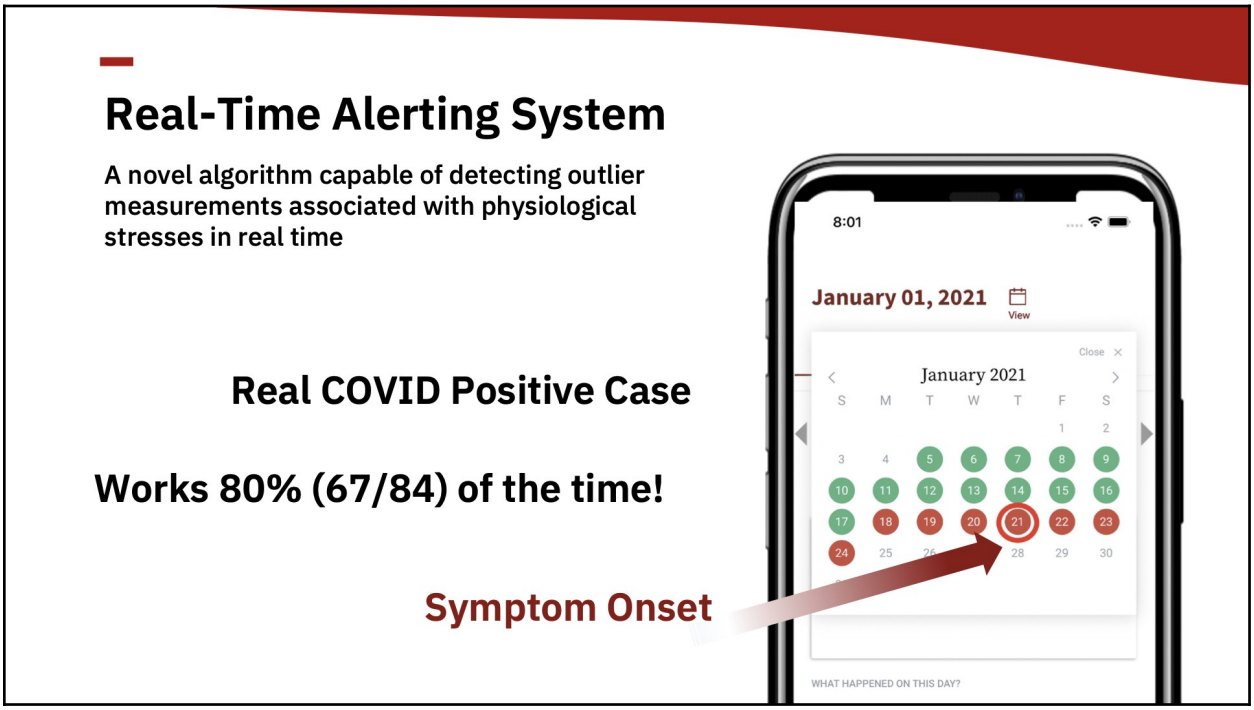
But when COVID hit, we quickly partnered with Fitbit and enrolled 5300 people and it turns out 32 of them had had COVID, while wearing their fit that they had a diagnosis day and a symptom day. This is our very first case. So this is resting heart rate. And here's the diagnosis day. Here's the symptom day. And you can see their resting heart rate jumped up nine and a half days prior to symptom onset. We have a real time detection system, I'll show you in a minute, that can track your baseline looks for this jump up the resting heart rate.

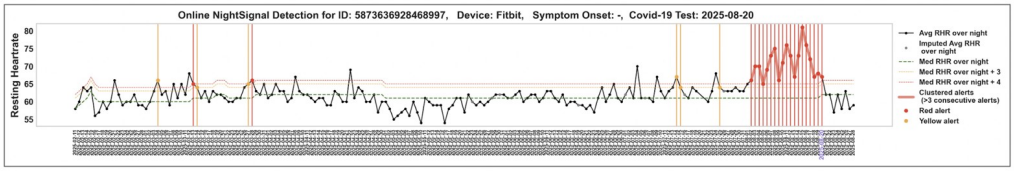


And it works, it turns out 80% of time, we can pick up this jump in heart rate. And the median is four days in advance of symptoms.

Asymptomatic Detection Examples

Fitbit

NightSignal



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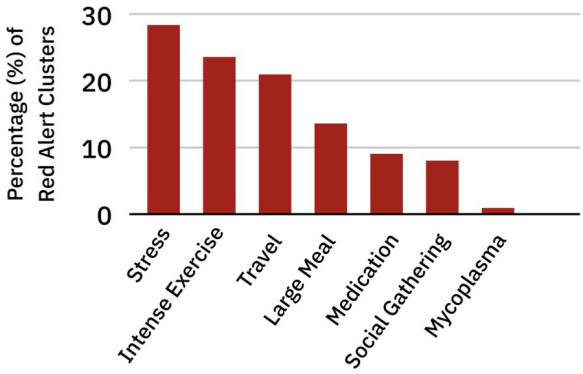
And it works because COVID has a long pre symptomatic period. So we can tell you when you're getting COVID by this and then to implement it. So this is four days prior to symptom onset. So we now have this real time alerting system. You're welcome to sign up. Let's see There's the well, maybe Brian, you can send around the group, I'll send you an email signup for the study if you're interested in. Yeah, a lot of folks probably well, yeah, we're trying to improve this algorithm.

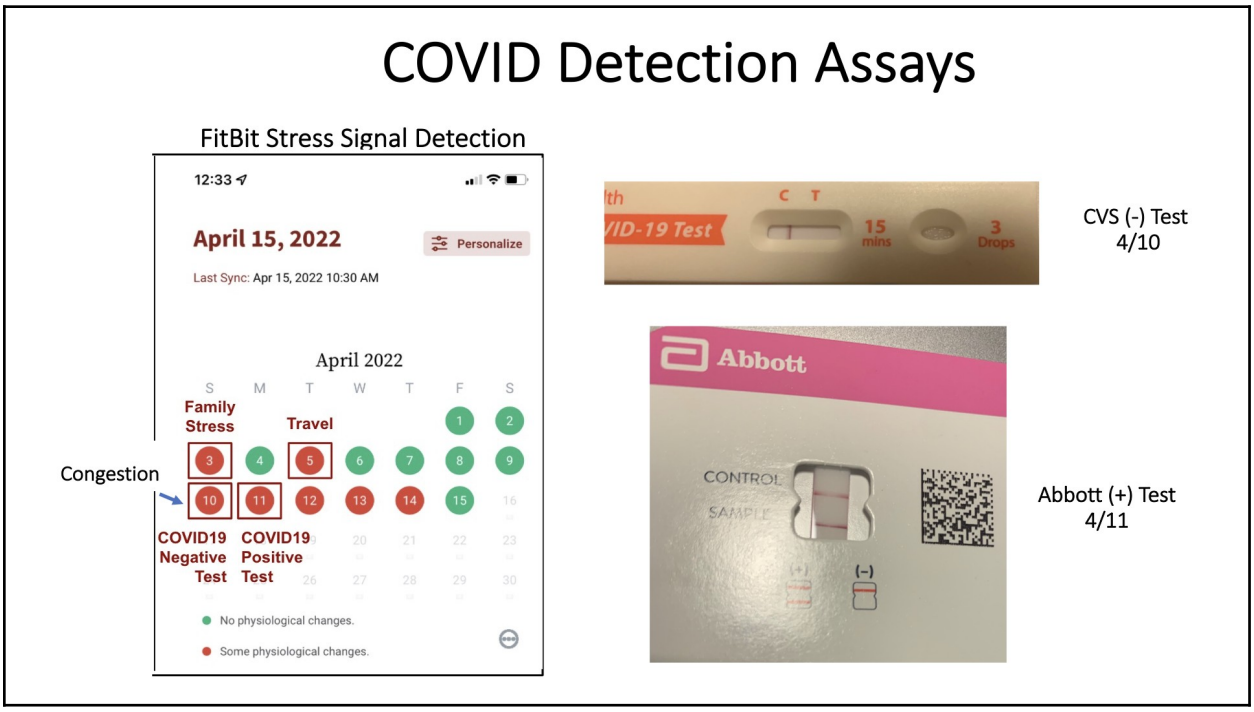
Other Stress Triggers

Wearable devices pick up changes in physiology brought upon by various stress triggers other than COVID-19

Activity Alerts COVID-19 Negative

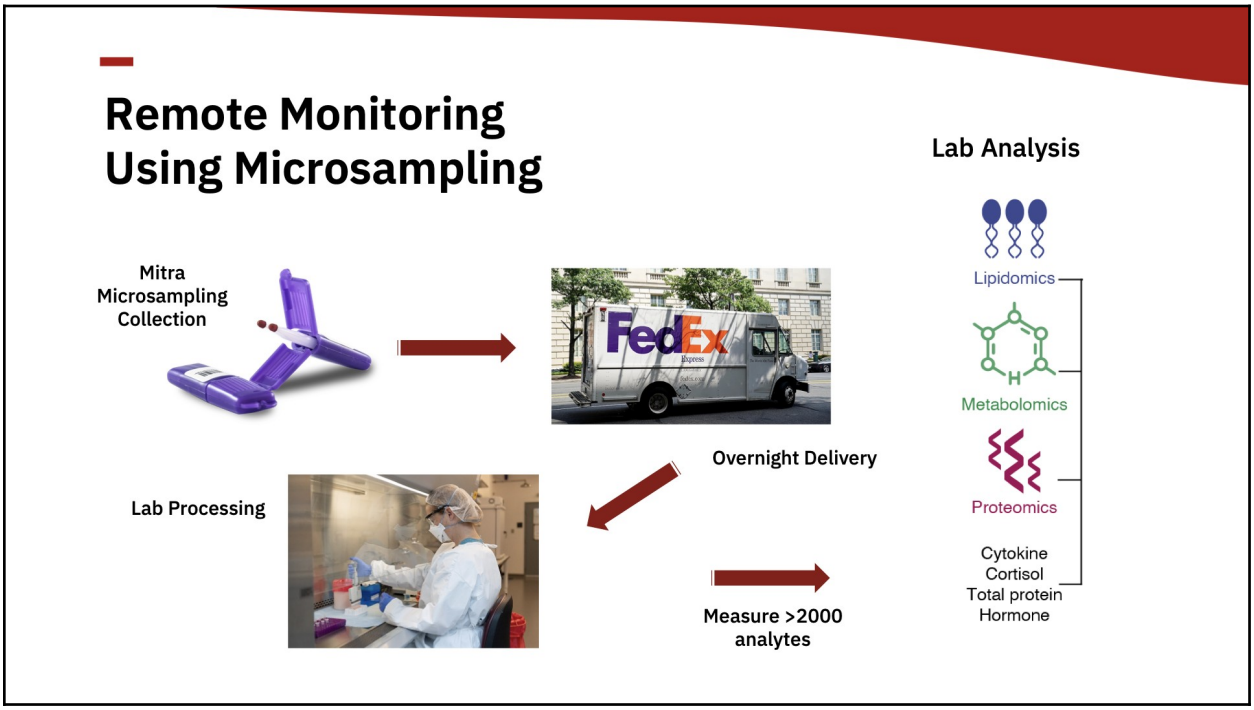


And so we what this does is it follows you on a circadian pattern, meaning, you know, time a day, we'll see if you have an abnormally high heart rate, it also integrates a little bit of sleep and other information and want to bring in heart rate variability that's been tricky to get data from the companies. But basically, it works the same number 80% of the time, it'll give a red alert now you have to click on it soon, you won't have to click on it. But right now you have to click on the app every day to see if your Green Day or Red Day.



And this is in fact, one of our first cases with this individual. And we ship time shift dates, not real dates, but they it's real red alerts and stuff. Here's their symptom day: they were diagnosed the next day, but they were getting red alerts for three days of prayers, symptom onset. It works on Apple, works on Fitbit, that will work on all the devices. Again, it's following your general circadian pattern looking for this. If you have a signal that's unusually high, for an unusually long period of time, it will get triggered by these red alerts and it even works on asymptomatic cases. So here's an individual. We think the same number 80% of the time they were this individual was diagnosed here, but they were getting red alerts for two weeks prior to symptom onset. And same for Apple, I can show you one of those two. Now I want to emphasize that it's not specific for COVID. Okay, so this is a jump up. And it's mostly built around resting heart rate. And the number one trigger of these signals is actually workplace stress. intense exercise, not your usual jog, because we build this around normal things. But if you run a marathon, your heart rate will be up for several days afterwards. And that'll trigger. I'll be honest, I don't know how I'll do with a lot of folks who have trouble with a stable baseline, that's why it fails 20% of the time, but these stressors can all trigger other infections too. Of course, even mycoplasma picks this up. So we're still that's why we want to bring in more data to get it more and more specific. It did work on me, I had a particular family stress event that led to these two red alerts. And then

when I was getting ready to go to New York City for a trip I woke up that morning, as a little bit congested. I wasn't sure if it was allergies, I'm coming down with something you know, that twilight zone this time of year, probably I'll go through this. I've been going through it every April, I'm that a little congested isn't allergies, I'm getting something. So I did a COVID antigen test as negative. I looked at my smartwatch and I was positive. So what did I do, I went ahead and went on the trip, I went to New York City. Before I can go to the meeting, I have to get tested and sure enough, a bright positive. So I actually wasn't able to go to the meeting, I spent a whole week in a tiny little hotel room in New York, all because I listened to my antigen tests and not my smartwatch. So it's more sensitive than an antigen test, you only need two beats per minute increase over your baseline to pick up the signal. But it's not as specific obviously didn't know as COVID I knew something was up but I didn't know as COVID. Now I know allergies don't trigger this. So if I see a red alert, I don't worry about it.



Here's this microsampling. I'll just spend a few minutes on this. This is super cool. You guys might like this. So basically, I know what this is gonna sound like but this actually does work. But the idea is that you would take little droplets of blood, mail them in, and we would run deep tests on them. So we've done that. We spent six years developing this that really requires getting the right matrix and defining fixed volumes. And so in the end, we settled on two kinds of devices. Mitra is another one called Tasso where he absorbed very fixed volumes. You then at AXA to our lab. And we'll do these deep profiles, we're looking at all your lipids, metabolites, proteins, I won't share the data, the proteins are quite stable with the format we've set. Same with the metabolites, there's a few that are off lipids a little less so. But in the end, we can measure over 2200 molecules in people's blood. And some of these are big deal. Like we can measure, we do targeted assays for cortisol. And these are immune markers, these cytokines and various important hormones. And so we can actually do, if you will, this remote sampling, we're trying to

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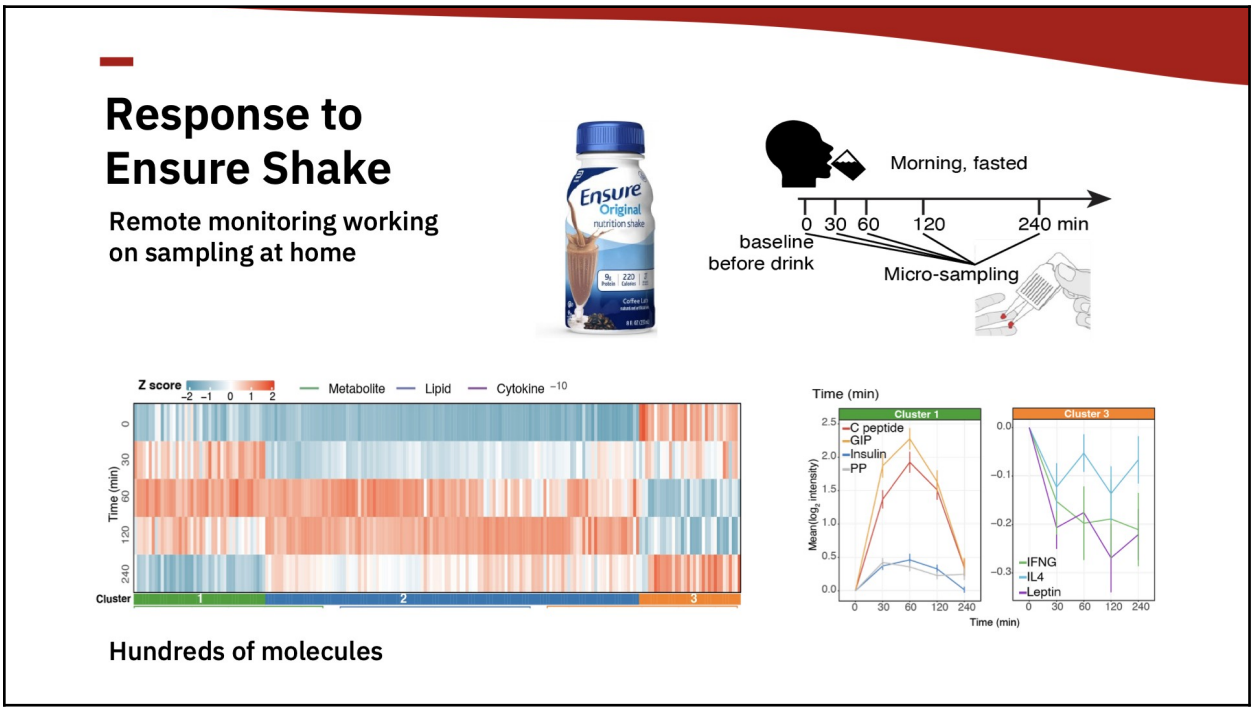
Amazonize, if you will, healthcare where you would mail us in. And I'm not saying all healthcare will be done at home. But there's a certain amount that could be like the monitoring and this microsampling.

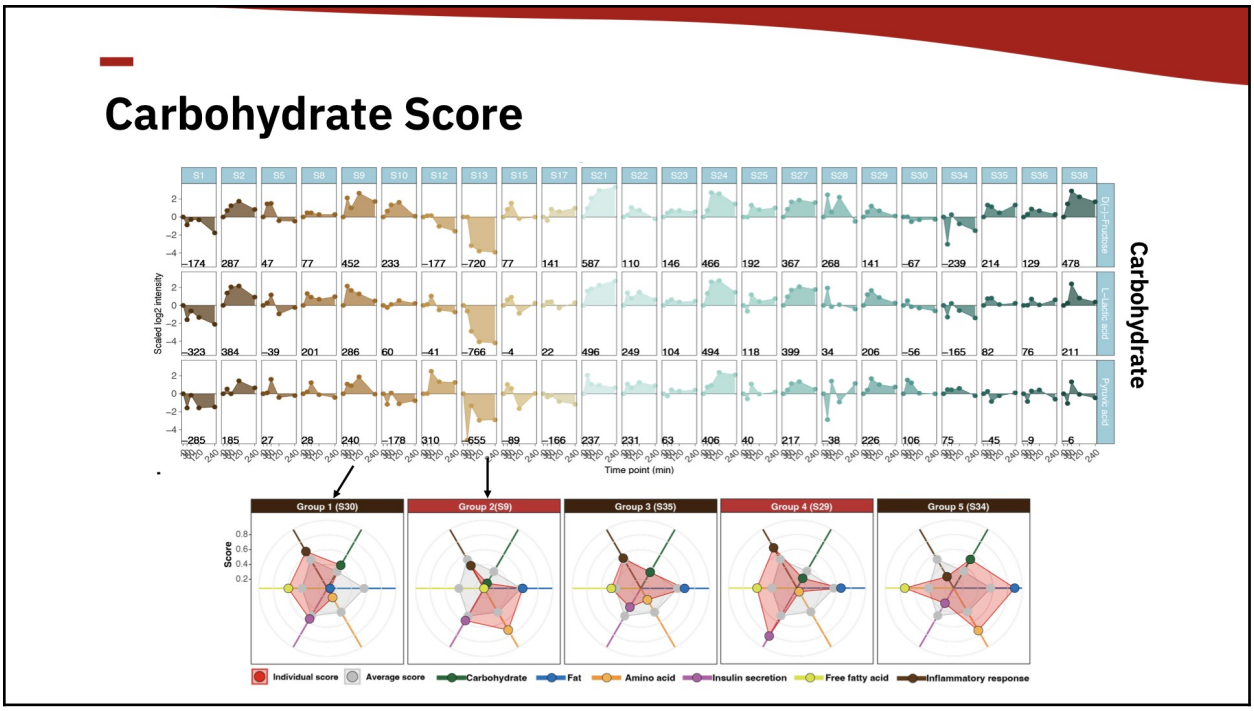
Mike Snyder
20:49

And secondary place physicians, by the way, it's only going to help them with these kinds of activities. Anyway, we did some fun studies, I think the group might like this, and you'll see where this is going.



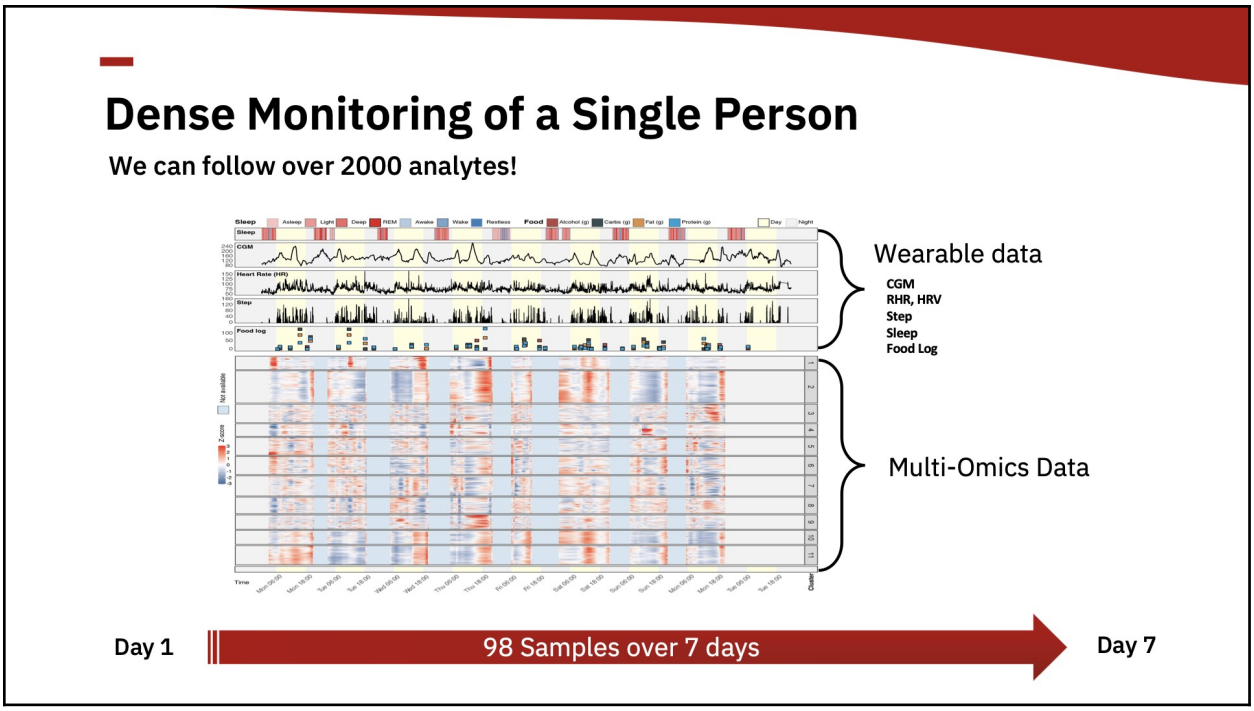
We have 32 people drink the shake that you can buy at CVS and most grocery stores called Ensure. Doesn't taste very good, in my opinion. But you basically take a sampling, you know, we hadn't sample do the microsampling before they drank it in 30 minutes, 60 minutes, two hours, four hours after drinking this thing. And then we say we're doing the micro sampling. And they did this in the morning, what before well fasted. And this is not surprising; hundreds of molecules shifted. Okay, that's what you would expect. But we can track it, we can follow pretty important glucose regulatory molecules, other inflammatory markers, things like this in response to the shake.

“Remote Monitoring and Deep Data” (Mike Snyder) [#52]



And the cool result is shown here. Everybody reacted differently to the shake. And I think this could be pretty relevant for this audience. So each box is a different person. This is just showing carbs. I could show you amino acids free fatty acids. These are three carbohydrates. Look at this person here, this, their carbs plummet, they really go down after drinking the shake. This person's carbs, skyrockets, skyrockets up, as another person goes down. Let's see here, this person hasn't changed too much at all. Here's a person who goes down. So everybody's behaving differently. And in the end, we could classify people into five categories. And it's pretty cool. So Gray is the average gray ball here. And elite, this category over here, in this group here, this, this group, their inflammatory markers go down after drinking the shake. So that shake actually reduces inflammation in this group. But for these groups, this one over here, and this one here, their inflammatory markers go up, meaning the shake is pro inflammatory. So it's having very different effects on different people. And that makes sense, right? We all react to food differently. But here's a pretty simple mixture, I have to confess, I didn't expect it to be this different for something as simple as us. And so we think that's powerful.

“Remote Monitoring and Deep Data” (Mike Snyder) [#52]

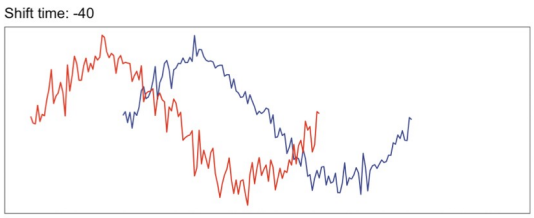


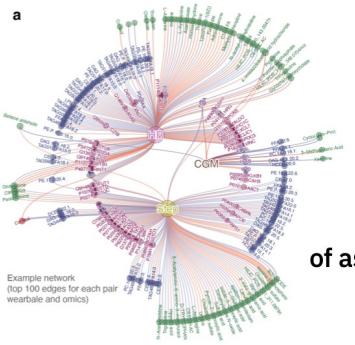
And then we can combine all this stuff. This is the ultimate. So we took one person, they sampled themselves every hour for seven days, every waking hour. And basically, we could track their cortisol, all the stuff. And they were wearing a smartwatch for all this, they were doing food logging, and something called a continuous glucose monitor. We do a lot with continuous glucose monitoring, it turns out your glucose can shift quite a bit and people spike to different foods. So we can follow all the molecules that were changing correlated with their activity, their glucose, the cortisol, all this stuff. And it turns out, it's really super cool.

“Remote Monitoring and Deep Data” (Mike Snyder) [#52]

Potential Causal Associations

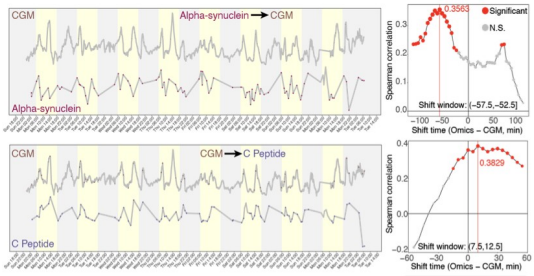
between wearables and molecules?





1000s of associations

Microsampling make the lagged correlation possible

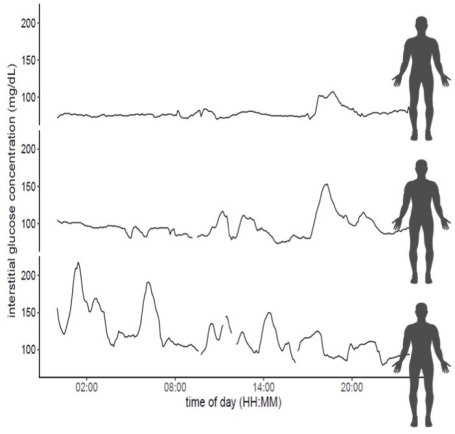


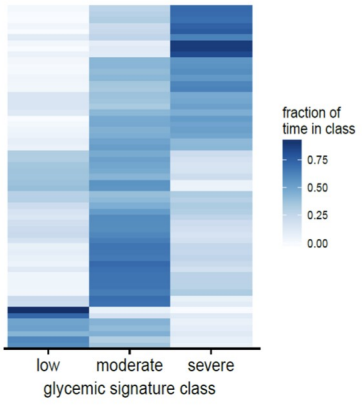
You can do these timeline correlations. So you can see what events are associated with what other events and build a timeline. And the idea is that early events are more likely to be causative of later events. So for example, steps always precede your heart rate going up by one minute, it turns out, we can quantify that. So it's kind of cool. So we can follow.

Continuous Glucose Monitoring

Different people spike to different foods

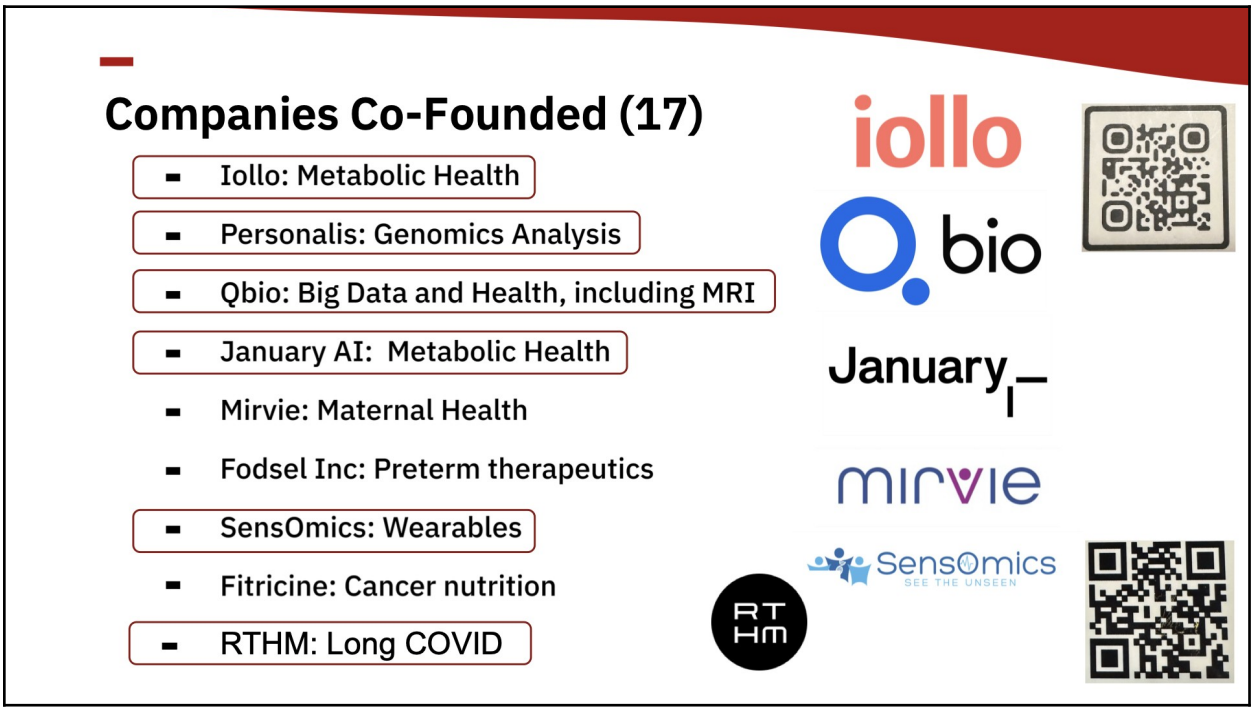
Dexcom





“Remote Monitoring and Deep Data” (Mike Snyder) [#52]

Here's a good example: your glucose goes up. Before you make this insulin C peptide. This is kind of obvious. But you can quantify this person and see exactly what that number is. But you can follow all kinds of things like cortisol and this might be relevant to this Rubini file people's medications and see how they're metabolizing. and such. If you look at this, this one's quite interesting. This is a marker involved in a ton of markets and protein involved in Parkinson's is called Alpha synuclein. And we can follow its pattern, which does correlate with glucose. We actually can correlate it with what we're trying to correlate with stresses and personalized things. So imagine if you're at risk for Parkinson's, we think it's pretty powerful to be tracking this because then you might want to reduce those activities that stimulate those from happening. So I know this may not be so relevant for prostate cancer, but you can see how I think these technologies can be adapted for this group for, for tracking, you know, drugs and other things. And we've gone on to build these, this, this platform for pulling in the data, the wearable clinical whatever, so you can display it back to the user. We think it's pretty powerful.



So I have spun off companies on this, I can tell you more about that later. So this is from another presentation, little accident there. One study we're doing it's kind of cool as we are to something mentioned earlier. We are running a study to compare high intensity training versus endurance training from people who start out sedentary to see which one leads the better, you know, health outcomes vo two Max and these these molecular profiles. And we're also doing another study this group that we're just waiting for approval on, we're actually trying to see if we can tell when people are getting cancer and how things are happening with a smartwatch. We think we're just trying to watch that one. So Brian, maybe you and I can talk more about that offline, that might interest you, might interest this group in general, who are very concerned about cancer recurrence. That's the group to start with. To be honest, we're setting it up around lung cancer, but I'm open to other possibilities as well. So those are the sorts of things we do.

Minimally, I think you folks can participate in the wearable study. It was mentioned earlier. We do try and follow the effects of exercise on people, we see their inflammatory response and other things after an acute bout. So yeah, we're trying to understand basic human physiology and human health using a big data approach. So that should give you a little flair of what we're up to.

Brian McCloskey
27:11

Rick Stanton wants to know a little bit about how you're monitoring monocytes. You also saw some correlations between I think it was the MRI, technology and human longevity, which I know that they do. But anyway, Rick, you want to talk to your questions?

Rick Stanton
27:55

Did I get that right with monocytes?

Mike Snyder
27:58

I mentioned that when I was in Norway for lyme disease, they measured my monocytes. To be honest, we normally just follow the CBC panel that you probably see for our routine stuff. So it's a more standard sort of thing. I know neutrophils and some of the other things are in there. So we get you know, something of a spectrum. Now with the RNA seq, we can get pretty detailed, something called convolute deconvolution analysis for exactly what immune cells you have in there for the bioinformaticians in the crowd, though.

Rick Stanton
28:32

I know the package for immune DICOM.

Mike Snyder
28:37

Yeah, okay, good. Yeah. Yeah, so we can follow this stuff pretty deeply if we want.

Rick Stanton
28:43

Then I'm very curious, because I only know how to do that from tissue. So I get the transcripts per million or counts from Tempus, but that's from tissue.

You're saying you can get it from blood?

Mike Snyder
29:02

Oh, for sure. Yeah. Because, in fact, that's where it started. So we normally start with the peripheral blood monocyte cells we already see. And then you can see the proportion of the different, you know, immune cells in there based on, you know, the presence of certain markers. It's a well, it's what you were just saying the deconvolution now, so that's actually where it started, started out on PBMCs and blood and has since moved into solid tissue.

Brian McCloskey
29:30

Well, that's one of the challenges that metastatic prostate cancer patients face is that most of the metastases happen in bone, which makes it very, very difficult to get. You can't get tissue, it's hard to get tissue. Yeah, and so many of the prostate cancer patients on this call are in that situation. And so just to be clear, you're saying that you have a way to use blood to actually Do RNA seq analysis? And I think you also said proteomic analysis as well. Is that correct?

Mike Snyder
30:05

That's right.
We do mass spectrometry, but we do a link as well. Now, this is a different form of sorry, proteomics. So you can follow these markers. So I guess the question is what metastatic markers would show up in blood? Right? And probably in this case, I think the key would be to do cell free, I would assume, does that right? Or do you think there are certain cells that are likely to be circulating?

Brian McCloskey
30:30

So Well, I wish that we had a representative from mProbe on - Sheeno. I don't think that Sheeno is on,

Mike Snyder
30:38

I'm happy to pursue this further offline, if you want about what kinds of markers might show up, we might set up assays for, again, I'm not a proxy, I guess that's why you have me on here to see how we might, you know, interface and see if something good can come out of those happy, happy to pursue if there's certain markers we should be specifically targeting in the

blood, you know, happy to consider that and see how we might adapt what we're doing for that sort of thing.

Brian McCloskey
31:05

Yeah, I think that they look at about 350 genes. So for example, I know for me, they picked up HER2, they're picking up AR, they're picking up various other gene expressions.

Mike Snyder
31:15

From cell free RNA, do you know, or is it from total?

Brian McCloskey
31:18

It's from tissue.

Mike Snyder
31:22

I’m a little bit familiar with it. What was it though now part of exact sciences, but the gene genome test set was out there initially for prostate cancer, the 21 marker panel. Anyway, they're there. We could dig into that more offline. If you want to hook me up with the experts. That's probably a gene expression signature like to say add a tissue, but have to see what part so those markers might show up in blood if you wanted to. Okay,

Brian McCloskey
31:56

Well, if you could do that, you would really solve a huge problem for advanced metastatic prostate cancer patients. The other thing that's also interesting is that the advantage of prostate cancer is that we have PSA so we can track our PSA. Over time, everybody, every cancer patient on this call is tracking through Excel.

Mike Snyder
32:20

all mine track to totally got it.

Brian McCloskey
32:24

like all the other data that you're getting correlates to that. So you can look at progression regression of what answered the proxy, but it's a pretty good proxy,

Mike Snyder
32:32

I bet we should be able to do that with microsampling, too. I'd be surprised if we could. Now we haven't tried. That's not one things we're asking in that microsampling, but I'll bet our test can be adapted for that. Okay, but there's gonna be a lot of I would say, why don't you hook me up with some of the relevant folks for what kinds of markers we might track that'd be relevant to your group. If you wanted to hook me up with the experts there, Brian, that would be great. Or anyone else to call my upper my email in the chat. I don't mind people reaching out, I do get a little busy, but usually can catch up. So okay, cool.

Gitte Pedersen
33:10

We are interested in moving into health monitoring. and we have taken the first step into blood Basically asking the question, what is normal? That's our first question. You can help me answer that question, too. Because of all the data you got. So I will definitely love to follow up. Sure.

Mike Snyder
33:54

Are you doing free RNA then?

Gitte Pedersen
33:58

We have to make decisions in terms of what we're going after. You want to do whole blood and RNA sequencing. This is my question to you: what kind of sequencing are you doing? Because we can also analyze your data.

Mike Snyder
34:31

So we've been doing mostly out of the peripheral blood monocyte cells, just sequencing everything there. Now we do save an aliquot of blood to be able to do cell free RNA. We have some other diabetes-related projects for that. We're trying to look for kidney failure, things like that. So like you say, it can be adapted right now just the way we're structured because we're mostly doing health profiling by looking at PBMC. Now when we do the micro scene sampling. That's whole blood. That's the nature of the way you collect the sample. I predict that the sensitivity with that assay from microsampling might be too low for RNA.

Gitte Pedersen
35:14

Is it 250 microliters?

Mike Snyder
35:21

Now it's only 10 microliters will take two spots. So 20 microliters. I think it's probably too low to look specifically for, like RNA cancer samples. So you may need regular blood draws. There are other devices though. tassa devices that will draw maybe up to mil and explore whether that's good. This is obviously very researchy.

Somebody asked about Human Longevity, I think McHugh bio does is where the Human Longevity is very focused on the genome just because Craig Venter is kind of what he did. We actually, even I'm chair of genetics, believe it or not, I actually think these other things metabolomics and such are just as important in their own right, you don't have to interpret, like, we can see a mitochondrial defect from a metabolomics profile without being able to figure out what's wrong with the genome, if you know what I mean. So we're trying to understand health in its if so each piece of data we call it features is contributing to a picture of that without trying to pitch in a pigeonhole ourselves into one, like the genomic space. So when human longevity does it, they'll look at a met metabolomics profile, and then they'll try and interpret it in light of the genome. And sometimes that works, but just as often as not, it fails miserably, but we think, again, just doing it on its own can be very powerful.

Russ Holyer
37:07

The heart rate increase predicts COVID, or can predict COVID. In some cases, does it predict colds? Does it increase before if you have sleep deprivation or poor sleep because heart rates increase and show you that? Or stress from exercising too much?

Mike Snyder
37:32

Yeah, no. So tell other colds mean respiratory viruses, things like Rhino viruses, influenza, it'll pick up that in advanced symptoms as well. Now, the Early Warning is probably about 12 hours, sometimes 24. And that's because they the pre symptomatic period for most respiratory viruses is not very long. It just so happens for COVID. It's quite long, which is, you know, useful for us to detect. But the smartwatch is bad for people because of spreading it around without knowing it, when they're running around pre symptomatic they so the answer is it does become rather cold. And I mentioned workplace stress, it does follow it indentifies that too, without people often realizing they have that they kind of they see the red alert, they kind of say, oh, yeah, I had been

stressed today. So it's, these are real signals, these jump up in heart rates, they're real. And I mentioned the exercise. So again, just doing your morning run or whatever won't trigger it, typically. But if you run a marathon, your heart rate will be up for several days. So something in excess over what you'd normally do by a fair amount is what it'll take to trigger these alarms. Because we build the baseline around your personal habits.

Russ Holyer
39:01

About microsampling: I'm wondering how often you can do it. Realistically, the cost of it. The turnaround time isn't available. Could it be done in Phoenix? I have questions about the parameters. Maybe I should address those offline with you.

Mike Snyder
39:20

Obviously, we're doing this as a research study here. One of the companies we spun off is called Iollo. They do basically a targeted quantitative assay that measures over 500 metabolites and I can send a sign up link to Brian and you guys can go visit it. And that 's interesting. A lot of these actually will give you back a readout now. It's about 30 different things that are read out like depression. There are markers for a lot of these things. It's not a medical test. It goes back to Brian's introduction here. It's a wellness task that sees the levels of these metabolites, mainly, which are correlated with some sort of immune and metabolic health and things like that. And actually, to some extent, mental health, so, so you Yeah, so feel free to take a look at the cost of that. Don't quote me, but it's around $290. As I recall something in that range for one of these tests, and you sample at home, you mail it in, they give you back the results. So yeah, so that's how we're trying to get. So I'm a believer, academics are really great at research, we're really great at proof of principle, we're absolutely no good at scaling. And this is what companies are for. And so given where I am in Silicon Valley, it's not that hard to start a company to try to get the stuff out. And that's how we're approaching it. And same thing to microsampling. We also were using a company spun off around long COVID trying to manage, diagnose and manage long COVID, which is very complicated if any of you have ever had, you know, experience with this or have family members who have it is very, very complicated. And so we were using a decision support structure along with the microsampling to better train and manage these patients. That's our goal.

Richard Anders
41:29

For clarity, this is a fingerstick capillary blood draw system that people can use at home, and it has a fixative to preserve the sample and then send it to you. How many analytes can you do simultaneously?

Mike Snyder

41:56

(NOT SURE OF ANSWER BUT I THINK:) 2200 simultaneous. We run four assays on 20, these 220 microliters of blood, basically. Yeah, so it's deep. It's mass spectrometry. So we can do this. I mean, it's, say the bad word here, it's Theranos that works. We're using a very sophisticated large instrument. We're not trying to squeeze this thing into some small box. And so we can measure many, many analytes. Now we don't measure everything. So for example, we don't measure LDL and HDL, you'll have to get that through your normal checkup. But we do measure a lot of stuff that we think is valuable. So for example, we can measure cortisol and all these cytokines, these are important immune molecules that most people don't measure. So we pick up a lot of stuff we think is valuable. And that's going to be particularly useful for just general wellness monitoring, hence Iollo, and then also for this long, COVID. Company. So I'll just put these in. If it interests me, or Brian can send around a little, I'll send a little thing. I'm totally conflicted. So don't feel like you have to do any of this stuff. But it's just something people often ask me about.

Richard Anders
43:13

You're measuring all of these analytes from one fingerstick, not even a blood draw, it's a capillary blood draw, and you can get 2200 analytes? I don't suppose you can do a CBC.

Mike Snyder
43:26

Not really, because the cells are lysed because of the way we collect the blood. You'd have to do a CBC separately. There probably is a way to do it but that hasn't been a priority for us. I should point out though, that that's what we do in the lab. We're profiling very deeply, over 500 metabolites, not the whole 2200. But now the 500 is pretty good. So yeah, and rhythms doing there's copper, they're doing cytokines plus.

Richard Anders
43:58

When you do all of these measurements, do you have validation about how well capillary blood, which has all that cell debris and other stuff in it, can reflect what you would measure in a standard blood draw?

Mike Snyder
44:12

I can send a paper we published on this in January, I'm happy to send it to you. And of course, feel free to tweet it out and advertise our stuff. But just kidding. Now, the same thing, maybe I can send that to you as well, Brian, the paper to circulate. So it actually describes the difference

between whole blood from these finger pricks versus plasma like you would do in a doctor's office. And most things correlate, but there's some things that are off and we know which ones aren't the same. Now, just because it's capillary blood doesn't mean it’s a bad measurement. It's just a different measurement. And so you would have to recalibrate against levels in normal blood.But a lot of the measurements are spot-on meaning that what you see in the sample is the same as whole blood. We have a correlation curve in the paper that you can take a look at if, again, if you're a scientist, you know how to interpret that. And the data are all available. One thing I'd like to point out, we always make your data available so that people can work with it. And, you know, well, that's really useful. And all that sort of stuff.

Richard Anders
45:24

Thank you very much. That's really impressive. And I will tweet it out. To both of my followers.

Mike Snyder
45:31

Oh, fantastic. I really was kidding.

Jason Crites
45:37

I can do my best to increase that by 33%?

Amit Gattani
45:56

Following up on Ross's question on the heart rate monitoring issue, right me, low hemoglobin leads to your resting heart rate to move up. And in a sustained manner, just like you're what you're showing with COVID. So this seemed like there are multiple things that can lead to the resting heart rate, you know, uptick in resting heart rate. Does the app have the ability to actually do precision pointing? Or it is, hey, the resting heart rate is up, and you know, talk to your doctor, because something else is going on here?

Mike Snyder
46:29

Yeah, no, great question. I think you're spot on. It's kind of like a check engine light in a car. You're not 100% sure what's off. But much of it, you can contextualize. Like if you're traveling, you go up in the mountains, your blood oxygen is lower, and your heart rate won't go up to compensate. So you can contextualize, you know, right away, you just say, All right, I just hiking in the mountains, of course, my heart rate is up, but I just ran a marathon. So a lot of it, you can just subtract out. But if you're just sitting around listening to boring Mike Snyder and your heart

rates are running high, something's off. You're either coming down with something or you're stressed. Something's not right. It's a very sensitive marker. And I like to point out that this is another one of my, if you will, digs at Madison, I'm going to insult some people here, I'm sure. But we've been using temperature as a measure for whether people are ill or not. That's a 300-year-old concept. But it's actually not a great one. Because for COVID, half the people don't get a fever. Yet, we still use it right? And you walk up to a place they shine the infrared light on. First of all, if it's cold outside, the measurements are worthless. It just always comes out too low. And they are wavy anyway. And then if they see a thermometer in your mouth, well, you may not get a fever anyway from COVID. But your heart rate I guarantee nearly always goes up. So we think resting heart rate, it's not as specific. There's no question. But it's like temperature. Temperature doesn't always tell you as well. But I know we can improve that in the future. Meaning I know with as we're measuring respiration from these devices, so I'm wearing my forest smartwatches. Here. As you measure as we pull more data, I'm pretty confident we'll be able to tell the difference between workplace stress and respiratory viral factor right? There are going to be very different signals already knowing till during contain a bacterial, like the lime signal and a respiratory virus, because the features are very, very different.

Amit Gattani
48:31

So is that just a quick thing? Is this available for us to try it out?

Mike Snyder
48:39

Yeah. So sign up for a study. It's a research study. So you sign up, we have 10s of 1000s of people signed up. So I'll put that in the chat too. But you can also give it to Brian to send around as well. And I'm taping and now I can answer questions while we're still going here.

Brian McCloskey
49:02

I'm just going to add a little bit of context to the importance of heart rate monitoring. I'll make this brief. I had surgery in November to remove a lesion from my bladder. Everything was going fine. Then about a month and a half later, I was sitting resting, and I noticed that my heart rate was just elevated. You know, normally my heart rate is below 60 And it was approaching 70 Just sitting doing nothing. And then I thought you know I better take my blood pressure. I took my blood pressure. My blood pressure was through the roof. It was like 180 over 110 Wow. Yeah. So went to the ER, long story short, what happened was the lesion that they removed that didn't get everything turned to grow back was compressing my ureter, creating a blockage in my kidney, my My kidney was beginning to fail, creating, you know, the full issue related to So anyway, the point is that heart rate monitoring if had I been more attuned to it, I might have been able to address it faster.

“Remote Monitoring and Deep Data” (Mike Snyder) [#52]

Mike Snyder
50:14

Yeah. And did you see it pre symptomatically? Even when you first went up or not really? Are you getting to know I wasn't? I wasn't really a bad person. Yeah, I've had people come up to me who have said, because I'm a big believer in this. Mike, I listened to your talk. And you know, I was one day I saw my heart rate jumping, just abnormally high, just like you described, Brian. And so they went to a physician, who said, Oh, well, there's nothing wrong with you, but wouldn't go down my back. And sure enough I had a strep infection, that the physician just didn't catch. And again, this is a very sensitive measure, if you know, your baseline and something's shifting like that dramatically. Something's wrong. Yep. Yep. Yep. We have other examples from other people in our cohort, that's Hunter nine, I can't give you a whole bunch of examples for this longitudinal, measuring the shift up is a big deal. Even if you're in the normal range, you'll see this big shift up here. So normal, something may be off now happened with one of our cohort members. Tell them better keep moving here. Yeah, we want to pick next Brian. Yep.

Jason Crites
51:23

So two things. One is I was one of the first folks in Chicago to come down with COVID. I went to the ER and ended up being in bed for a couple months, but I never had a temperature. I was actually my temperature was a degree lower than the normal anyway, so that's not the question. So you know, listen to the, to the talk, and some of the things that you're measuring and, and whatnot, are you familiar with the Wim Hof Method with deep breathing and cold exposure? I'm curious what your thoughts are based upon, you know, all the work that you're doing.

Mike Snyder
52:00

I'm just learning about that stuff. It's an area that's a bit of a hole in our studies, the whole mental health, we're just kind of adding that now. So I've been reading a lot about these breathing techniques. There's one out of Stanford, that might be the one you're talking about where you go.

Jason Crites
52:18

This is different from the gentleman guy out of Holland.

Mike Snyder
52:23

Yeah, I'm a believer in this stuff, because apparently it's affecting your parasympathetic neurons, and it really has a very positive impact on your mental health. And so from what I've

been reading, it does look right to me. I don't think it's bullshit. I've seen other stuff out there, I can tell you, that I think is bullshit. That one, it really there is some logic to and I've also, you know, again, I, I think what we want to see are these large, proper trials, and that would really make things a lot more convincing. And but I think we're in this early phase, and as those trials happen, then hopefully they'll get incorporated. Now, the cold stuff, I honestly don't know, people talk about some of this as being anti-inflammatory, like the, you know, when he called the hyperbaric chambers and things I get at once, just for fun. And it's supposed to help with your inflammation of the I have no idea, you know, psychologically, I guess I said, Wow, that was quite something. I don't know. But, again, we need to see proper trials right around us. And I've seen it for other hyperbaric oxygen stuff, too, about being very useful for people so we'll have to press one in here about that, I guess. Anyway, we'll, I'd love to see proper trials run around this. I suspect there's something to all these and I think the breathing one, by the way, it really does help people with stress is my understanding.

Jason Crites
53:52

Yeah, they're thinking, I guess there's been some not the best scientific study but uh, you know, around some of the antibody levels increase after some of these, like 2040 minutes worth of deep breathing. But anyway, I'll just drop a plug that I had, some of my friends are in that area. So if you actually want to do a public trial, you can reach out to him.

Mike Snyder
54:12

Yeah, they want to run a big enough trial. They're often run with like 10 people or something. So that in the end, nobody gets convinced by it. So you really need and I think combining it with the micro sampling. So we're running some depression studies that are really powerful. We think we're having people do an intervention and then doing micro sampling are following their inflammation markers, changing that sort of and metabolic change. It's pretty cool. So I think that's what's going to lead to, you know, people believing this stuff when we could show biochemical and other sorts of changes with enough people in it that convinces folks so

Jason Crites
54:47

I believe the right answer is to figure out whether or not it doesn't work.

Mike Snyder
54:50

Yeah, that's correct. Yeah. Better phrasing. Thanks, Jason.

Eric Hall

55:10

Let me follow up on the heart rate we were talking about before. So number one, I have a pacemaker for bradycardia. It keeps my resting heart rate from going below 60. Would this app work with that?

Mike Snyder
55:27

I don't think so. Because I think you're fixed. Is that right? Your heart rate is fixed?

Eric Hall
55:35

The lower end is fixed.

Mike Snyder
55:38

But yeah, maybe it would work. Yeah. I don't know.

Eric Hall
55:42

Bradycardia means slow heart rate, my heart rate used to get down into the 20s.

Mike Snyder
55:45

Yeah, it has a bottom limit. It has a bottom. I won't let it go below 60. Okay, well, then if it Yeah, we could see, you could try and see what you think. Okay, you'd be an interesting case for us. Second question around that.

Eric Hall
56:02

Does it work with an Oura ring? That's what I'm wearing.

Mike Snyder
56:05

Right now. Okay. Other people are using that. The Oura ring samples a little bit lower frequency than in, but we like to integrate data from all. Some people only wear their ring at night. So try to wear it all the time. Yeah, I wear my like to capture as much data as well. So we'll give it a shot.

We don't have as much data on or a ring. But there. Now other groups have published about aura ring detecting COVID. respectively.

Eric Hall
56:35

I think I heard you mentioned something about using a wearable to potentially detect cancer recurrence. Did I hear that right?

Mike Snyder
56:47

Yeah, you did. We're trying to launch a study where we're just waiting for the IRB. You know, it's kind of interesting IRB is for those who have to deal with the stuff, it has been gone on for nine months to get approval. But there are reasons why we think we've actually believe or not tried it out on a mouse. And now we want to try it on people to see if we can pick up the cancer, that early detection or Endor recurrence through a wearable because same thing, your heart rate may shift, and something called heart rate variability, which by the way, that's the deviation between heartbeats, you're healthy if you have deviation,

Eric Hall
57:25

Mine is low because the pacemaker doesn't let it go.

Mike Snyder
57:29

I don't know if it's kept that way. But once you go above that ceiling, ami, heart rate variability is another good measure of health. So we're pulling in all that data. And I don't know if it's going to work, but I think it'll work at some level. The question is, will it work early? Right? Can we do early detection? I don't know. And that's why we're rolling a study out. But you never know. Right? Who knew you could detect infection pre-symptomatically with a smartwatch. And I didn't show you but we actually, through machine learning some other advanced methods, we can tell people's red blood cell count, not a clinical rate measurement. But their hemoglobin or hematocrit. They're the red blood cell count from a smartwatch. Because of the kinds of measurements it's taking, even to some extent fasting glucose we can get from a smartwatch on a wrist. It's, again, it's not a clinical grade measurement, but it's good enough to detect shifts. And it's because you're collecting very interesting data. And you think about your watch, it's actually zooming in on your blood. Actually, it's doing spectroscopic measurements on your blood so they can measure these things. So I think these are going to get more and more powerful in the future. And we did that from 2015. Watch. So eight years ago, now I'm sure we can do better. Today's watches.

Gitte Pedersen
58:46

Quick last comment. I love what you're doing, by the way. And the more data the better. But I'm also a scientist, so I can't get enough. So one thing that I think could be really cool would be temperature, like continuous temperature monitoring, not just because it's important in order to be able to catch early infections, but also cancer.

Mike Snyder
59:19

That's on the watch is blue at skin temperature, which is some reflection of your internal temperature. It’s not exactly the same as I'm sure you know, but it's not bad. And some of my company's devices are actually quite accurate on skin temperature, which is nice. So we are bringing that in. And that's actually one of the features we build into our models for both infectious disease and cancer detection. So that's the hope and we think it's a big deal for diabetes to has to do with how you burn your energy.

Gitte Pedersen
59:54

Right. A metabolism in general.

Mike Snyder
1:00:03

We got it from the watch. As I said, we don't do it at all. I believe there'll be implantables and then we'll get it a different way. Everything's on the wrist or fingers.