**Human Skin Microflora: DNA Sequence-Based Approach to Examining Hand Disease**

**A National Human Genome Research Institute (NHGRI) Webinar Series**

**Moderator: Sarah Harding**
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Coordinator: This phone call is being recorded. If you have any objections please disconnect at this time.

I would now like to turn the call over to Sarah Harding. Ma'am you may begin.

Sarah Harding: Hi. Thank you very much. Good afternoon everyone or good morning depending on where you are calling from. I wanted to welcome you to the latest webinar and in fact the first in this year's series.

We are going to be talking today with Dr. Julie Segre who is going to be speaking about some of her research here at the National Human Genome Research Institute. We are very pleased to have you all on the call.

Just a couple of technical notes - if you have any technical problems at all during the call, like if you are having any problems accessing the Web portion or just hearing, dial star 0 and you will talk to an operator.

We are going to start with our presentation from Dr. Segre and we will be taking questions then over the phone after she is finished. If you want to ask your question, just dial - and there will be instructions for this - you can dial star 1 to speak to the operator and you will be put in a queue to ask your question.

Again, if you have any technical difficulties you can also email me at sharding@mail.nih.gov. If you would, just to make sure this goes smoothly, if you could just move any Blackberries or cell phones away from your telephone just so that there is no interference.

And then as the operator said, we are going to be recording these presentations as well as the question and answer session that follows. So, please just keep that in mind, but we definitely look forward to your questions and discussions shortly after Dr. Segre's talk.

So without further adieu, I would like to introduce Dr. Julie Segre who is a Senior Investigator here at the National Human Genome Research Institute. Dr. Segre I will let you take it away.

Julie Segre: Hi. This is Julie Segre. So today I am going to talk about my own research project specifically examining the microflora, which are the bacteria, the fungi, the viruses so on that live on your skin and also give an overview of the larger projects.

So what is really important to remember about this, and on slide 2 I do not seem to have control over the slides Sarah. On the next slide of this presentation, I wanted to - okay. I wanted to introduce some of the goals of the larger NIH Roadmap for Medical Research Human Microbiome Project.

And what is really important to realize here is that we tend to think of ourselves as humans, that we are these human cells. But in fact we are really made up of human cells that are living together with bacteria, fungi and other small microscopic organisms.

And it is really remarkable because in and on our bodies, these microbial cells actually outnumber the human cells by about tenfold. So for every human cell that there - you have in your body, you actually have ten more microbial cells.

But it actually - it is not that they outnumber us but they do not actually outweigh us because each human cells has about 1000 times more DNA and is about 1000 times bigger or - than - or at least 100 times bigger than a microbial cell. So we actually outweigh them even though they outnumber us.

Now as an example, the bacteria that live in the gut, in the intestine, we think that because of this microbial diversity and these large number of bacteria, that the bacteria and the other fungi and the other small organisms, they probably have 100 times more genes than our own human genome.

So there is a tremendous amount of diversity. And this microbiome is really the - microbiome means the total microbial DNA - is really an important part of our genetic landscape and also of our bodies.

So for example, when you take a drug, you probably think that it is your human cells that are metabolizing the drugs. But in fact, the bacteria that live in your gut are part of what metabolizes this drug.

And so it is really important for us to understand the complexity of our human DNA, but also to understand the complexity of our microbial DNA. So the overall goals of this project are really - the Human Microbiome Project - are

really to understand how the microbiode of the small organisms interact with our human cells and how that maintains health and disease.

So I just talked about drug metabolism via bacteria, but of course these bacteria also break down food and aid in digestion and on our skin, they can break down the proteins that are made by the human cells of the skin and create sort of a, you know, contribute to creating natural moisturizing factor that keeps your skin supple and smooth.

It is true on the skin they also have waste products that create part of what we think of as body odor. So, you know, we have to think about the full range of how the bacteria contribute to our health and to disease states.

And that really is the goal of the larger Human Microbiome Project written here. We are bringing in 250 normal individuals and sampling them at five different body sites - the gut, the nose, the oral cavity, the vagina for women and the skin.

And this giving us a baseline so that other investigators including myself are then doing clinical trials, we are examining the skin microbiota in people with common and rare skin disorders.

But in order to know what the differences are in a disease state, we have to first know what is normal - how much variation there is between people and how much variation there is between different sites of our body. So in order to do this, we are assessing the microbial diversity of 250 individuals.

And then skipping ahead to the third point here, our ultimate goal is metagenomics. Let’s say that I could just scrape the, you know, the dead layers of my skin off that sort of white flaky stuff that makes those dust

bunnies in your house. If I could scrape off those dead cells or could take, you know, a swab inside your nose, I would like to just directly sequence them.

But the bacterial diversity is so complex that we need to take some baby steps to get there. And that is why point number two is that we are sequencing bacterial reference genomes. So that means that we are determining the entire bacterial sequence for different isolates.

And using that to then form a springboard for future microbial studies because with metagenomics where we analyze the combined coating potential of a complex mixed environment that is what we would ultimately like to achieve. And we would like to achieve that, as stated in point number four to correlate the changes in the microbial community with disease states.

And the - another arm of the study is really to explore the (ethical), legal and social implications of this new field of research because every human genome project that we embark on, we devote a cert - you know, we devote time and energy to understanding how this information is going to be communicated to the public and how this is going to be absorbed by people in understanding that there may be a contribution of their microbial communities to their health or to their disease.

And as such I will get to, at the end, what are really the questions that we would like the - we would like people to think about in terms of how this research is impacting their own lives.

So let me now take you into my laboratory's specific research project which is to really understand that the skin is a barrier to infection of pathogenic organisms, but the skin is also an intricate home for microbes.

And those are what I will call the commensal microbes, where the healthy microbes, the good microbes, the ones that just normally live on your skin and serve the role of breaking down human proteins and keeping your skin moist and also serve the role of keeping pathogenic organisms from being able to adhere to or attach to your skin.

So when people think about the skin, they, you know, it is actually - I show you here a cross section of it. And underneath your skin are these blood vessels which are the red and the blue. And you know that because if you scratch yourself you can bleed from your skin.

Overlying that are these orange cells which are really the stratified epidermis, the top layer of your skin. And these go through a process where they lose their nuclei and they become dead cells on the top of your skin that provide the skin barrier. That is what you see on the upper layer of your skin.

Well, this is really - we think that there is a relationship between the skin cells, the immune cells that can sense if there has been like a wound or an abrasion because as you think about it from an evolutionary perspective, of course it is very dangerous to have an open wound.

You could have a bacteria get in and your body could, you know, develop sepsis. Well now of course we have antibiotics to treat that. So, it is less of a risk but antibiotics have only been around since the 1940s so the body still responds as if this is a tremendous risk.

And so the third type of cells that we will be talking about today are really the microbes, these small microscopic organisms. Well, we asked the question about how do you know what microbes live on your skin. And the way we

traditionally do this is by looking on Petri dishes and seeing what we can culture.

Well there has been a new method that has been developed, but this is new and old and just being altered so that it has greater specificity. What we do is that every bacterium has a 16S rRNA gene. Now the 16S - r stands for ribosomal. It is a ribosomal RNA gene.

It does not get made into a protein. What it does is it stays as an RNA and it helps guide other RNAs through the ribosome. The ribosome is where proteins are made. So mRNAs are translated into protein. This stays as just an RNA and is a guide.

But if you examine the sequence of the 16S rRNA, the ribosomal RNA which is shown on the left here, what you see is that it actually has these stem regions which form a lot of double stranded basic base pairing. And from those, that actually puts a fair amount of conservation constraint on those base pairs. And then there are the (loop) regions which are more variable.

Now, when we look at the sequence of the stem regions, those are conserved. And that serves as what we consider an evolutionary clock. So if we looked at the conserve regions we can say well there is some change in them, but that allows us to say this is a staphylococcus, this is a streptococcus and assign what type of bacteria it is.

The sequences in the loop region will change even faster than that. But these sequences of the 16S gene allow us to identify what type of bacteria it is. So the orange highlighted sequences are how we amplify this gene out of a bacterial genome and also we use the purple sequences. Those are highly

conserved and then we examine the intervening sequences. And that allows us to identify what type of bacteria this is.

Now here I show you an example of how we compare the data that we obtained with our DNA survey sequence identification with our culture methods. So what we did here was he had healthy volunteers come in. And we looked at two different sites of them. And actually we did 20 different sites of them as you will see. But I am just showing you the examples of two different sites here - from the face and from the belly button.

Now, on the right side of each bar graph, you see what we found when we brought these swabs down to the (microbiology lev) and tried to culture everything that we could.

Well the dark blue is called propriona bacteria from the face. And that is an oily loving bacterium. And so the skin is a little bit oily and that would make sense that those are the types of bacteria that live there. As well as the orange is the staphylococcus. That is like staphylococcus epidermidis which is one of the most common healthy bacteria that we can grow.

And if you compare what we found on the face from culturing versus survey, you can see that we did a pretty good job, but we completely lack the cornflower blue and the lighter blue. Those are actinobacteria and you can see the chart on the right hand side. We failed to culture them.

These bacteria are actually the (carinobacterium) and other actinobacteria are very hard to culture because they take - they are very slow growing. Sometimes we grow them after about six days. But by six days, the staff and the propriona bacterium grow so well that they have almost overgrown the culture plate.

And you see this even more when you look at the samples that we collected from the belly button of this person. Well culturing it seems like the orange and the red are the firmicutes. Those are the staph and the strep and other bacteria that fall under the greater taxonomic name of firmicutes.

And, so that is what we can culture from this person. But when we look at the survey, what we see is that really 50% of the bacteria are the (carinobacterium). And as I said, we just had a very hard time culturing them.

So the take home message from this is that we can get greater information and different information if we use this DNA based surveys that are less - that are - that have less of an ambiguity to them and there is less of a bottleneck that the strains go through. So the information is more precise.

Now, let's talk about how we would use this type of information. Well I am just going to show you one example of an animal model that we made and then I will get into our studies with human subjects.

So as you can see from this mouse, this mouse has scale skin. And you can best see it on their ears. In the bottom corner of the picture of the mouse, I show you what a wild type or what a normal litter mate would look like. And you can see there is smooth skin on the ear.

When you look at the histology of this mouse, you can see that the dark purple and pink layer on the top is thicker in the mutant mice. And then it has where the arrow is pointing is that sort of thick basket weave, and that is the scale.

So the question is, is this related to, you know, how does this then contribute - how does the bacterial community contribute to this because we were using

this as an animal model of the very common eczema which has that sort of scaly rash-like skin.

So now here I show you what is the bacterial survey that we find by sequencing. Well if we consider this an animal model for eczema, one of the things that we know is that in eczema patients, there is a large amount of colonization by the staphylococcus. And now the staph is the firmicute, so that is the third over.

And what you can see is that the mutants, this is - the mutants have about 11% firmicutes. So they do have an increase in firmicutes over what one bar over you see is the wild type litter mates.

So that is what we pick up when we culture. These mice have an increased amount of these straph - staph and strep and other types of firmicutes. But in fact, even though that is what we pick up on the culturing, that is not the whole story because if you move over to the actinobacteria, what you see with these mice is that they have a huge increase in the (carinobacterium) which are shown as the green bacteria.

Well I just told you, those are really hard for us to culture. So if I did not know to look for them, which my survey data tells me that there is an increase in (carinobacterium), I would think that there is an increase in the firmicutes and I would miss the fact that there was an increase in the actinobacterium.

And perhaps when you give antimicrobial treatment, you know, antibiotics, you decrease the amount of staph and you think you have cured, you know, the person’s microbial disorder.

But in fact, maybe it is really acting on the (carinobacterium). And so that is an equally plausible hypothesis. From this data, I cannot tell which is more likely to be causative - the increase in firmicutes or the increase in (carinobacterium), but I now have two hypotheses to test.

And in fact I have a third hypothesis to test because if you look at the first set of bars, the proteobacterium, when you see is that we have had an increase in firmicutes and an increase in actinobacterium. But they have come in and they have selectively pushed out the pink bacteria, the pseudomonas.

If you look at the bright blue bacteria, that (genthina) bacterium, that is about 35% in the normal litter mates and about 32% or 31% in the mutants. So those levels have stayed the same as have the other components of that bar, the dark blue, the orange and the yellow.

What has changed is that the pink, the pseudomonas have been pushed out. Well what about if those pseudomonas provide some beneficial effect to this skin. Then that is a third hypothesis to test.

So it is really about generating more ideas to test. So now let’s look in human skin. And as I have shown you before, there are different levels to the human skin as there are to mouse skin. And this is the histology.

So to assess things from the human skin, we took a swab which goes up to the very superficial bacteria. Then we scraped off - without drawing blood, we just scraped off the dead cells from the top of the skin. And those (pellets) what live inside that scrape.

And then we took a punch biopsy from a few sites to look at the full thickness because there are bacteria that live all the way down in the hair follicle that dwells - goes all the way down into your thick into the dermis.

And what we found is that if we used a swab, we could recover 10,000 bacteria per square centimeter. If we used a scrape, we could recover 50,000 bacteria per square centimeter. And if we use a biopsy, that yields 1 million bacteria per square centimeter.

So that means that when you are washing your hands, you know, like a swab would be, you are really only removing 1 in 100 bacteria. When you are scraping, which I promise you is, you know, less - I mean it is less harsh than even washing your hands, you can remove about 1 in 20 bacteria. But it is these bacteria that live down in the hair follicles that can then come back and repopulate and those are the healthy bacteria.

So we looked at the 20 different sites on the human skin to say - and now this is all done with scrapes because we decided that scrapes were as effective as punch biopsy and certainly less invasive.

So when we look at the scrape, what we see is that there is a great variety of bacteria. But in fact, the bacteria are determined by where you are on the skin.

So the blue sites are what we consider oily sites. And those are very similar to each other. They share a lot of the dark blue and light blue bacteria called the propriona bacterium, but can live on the lipids.

But then what you can see is in the middle of the body, there is a lot of moist sites that are more sweaty. And in those sites, those are - have a lot of the green bacteria, the proteobacteria.

And then you can see the cornflower blue which is the (carinobacterium) more at the base. There also are sites that have a lot of the orange bacteria, the staphylococcus.

And what we found was that the human body is really an ecosystem. So imagine it like a dry desert, but then there are sites that are streams. Those are the moist sites, the creases. And then there are the oases. Those are places like inside your nose or inside your umbilicus that really just harbor a huge amount of diversity.

And what we found is that the site like the left arm and the right arm are most similar to each other on the same person. But then my left arm is most similar to your - or my arm is most similar to your arm.

And my arm is more similar to your arm than my arm is to my chest region. And I have given all the anatomical correct terms, so I - instead of saying chest, we call it manubrium. But you can see here that the manubrium, which is five sites down on the left, is more similar to the side of my nose because those are both oily sites than either one is to the axilla - the axillary vault, the underarm which is considered a moist site and not an oily site.

So this is - another example of this is - of the data is just shown here on the next slide where what you see is that the back of every person is very similar. Retroauricular crease is behind the ear. It is very similar to each person although you can convert.

So you can see that healthy volunteer number 4, that site has been converted to being really staph colonized and that is a term that you sometimes will hear from your physician if you have a sort of what we call really below threshold

infection where this is, you know, it is not causing you any problems but that site has become overgrown with staph.

(Cansia) the antecubital crease which is the bend of the elbow is really a lot of the proteobacteria. And then actually what you can begin to see here with the nares which is inside the nose and the umbilicus which is the belly button, these are really diverse complex sites.

And that is shown actually in the next chart where you can see that there is a range now here where I show you these different anatomical sites and then they match up with a two letter code.

There are sites that are really very complex like the volar forearm which is the - the forearm has about 44 species on - each person has about 44 species living there. The site right before that is the umbilicus, the belly button. That has about 40 sites on every - 40 species for every individual.

Where some of the sites, like all the way over on the left behind the ear, the retroauricular is actually kind of simple. And the back is the next site. So those have about 15 species. And so there is a variation of the complexity of these different sites.

So I would like to just give as a summary how we think about the microbiome project and how we hope that this can serve as an educational tool.

First of all we would like this to really put forth the idea that as I showed you on slide number six, if you compare the survey and the culture data, they are both accurate.

When we culture, we culture (multuly) staphylococcus. And that is true. But that is based on culturing. When we survey, we can find that there is an increase in the amount of (carinobacteria). So that - what we understand about scientific facts is really relative to the methodology that we employed or how we determined that information.

And as science evolves and we find better tools, we can also find out new things. This is a real process of exploration for us. So we can learn new things about our microbial contribution when we have new tools to examine them. And that is really the process of science, understanding what is known and what is unknown.

We hope to use this project as a way to educate consumers about what is health. And in that regard, I think we need to lose the language of warfare with pathogenic microbes.

We need to not just think about all bacteria as bad, but remember that bacteria also do contribute to our health and that our goal should be to promote the growth of the healthy bacterium while maintaining, you know, low levels of exposure to any pathogenic microbe.

And of course our goal is also to educate physicians about how to make better diagnosis and treatment decisions. And so I will ask you, you know, really, why is - I mean this is sort of at the crux of it is we have to have this relationship between health and disease.

And I see in the culture right now that (Ubberland) wants to sterilize their exterior with using these hand sanitizers but then eat probiotic yogurt or take probiotic pills. And I think we need to really balance this and to understand that our goal is to balance the healthy bacteria and the pathogenic bacteria.

But it is not really just to sterilize our exterior because the bacteria will come back. And it is really about promoting the growth of healthy bacterium while maintaining the pathogenic bacteria.

And so finally in conclusion, I want to emphasize that this study is a very thorough relationship and trans-disciplinary investigation that is being led by the Human Microbiome Project, so HMP. But it is a scientific endeavor pursued by physicians in clinical medicine and in infectious disease combined with colleagues in microbiology and colleagues who have an expertise in sequencing DNA and analyzing that information.

So these are all the groups who are involved in the study, but it is really a three legged stool between DNA sequencing, microbiology and clinical medicine. And it is the strength of that three legged stool and the scientific disciplines that really is powering this project. So thank you very much.

Sarah Harding: All right. Well thank you Julie. That was excellent. And I definitely learned a lot about things I never knew. So I want to open the call to any questions that we might have from the group. And I need to just let our hosts know that that is what we are doing. So if you would just hold one minute.

Can everybody hear me? No.

Julie Segre: Well I could.

Sarah Harding: Oh you could?

Julie Segre: Yes.

Sarah Harding: Well potentially they can hear me but we cannot hear them yet. We are just waiting to open the lines to be able to ask questions. And so what we will do is we will have an open session. People can ask questions to Dr. Segre and we will just ask that you obviously go one at a time.

One question that was emailed to me Julie that we can probably talk about before we get everybody else on the line is just whether there is - you - I think you did this to a certain extent but whether there is more - can you translate.

The question is could you translate some of the bacteria speak into more of the diseases that we typically hear of in a...

Julie Segre: Right.

Sarah Harding: ...every day, public health kind of...

Julie Segre: Right.

Sarah Harding: ...the laundry list of terms...

Julie Segre: Right.

Sarah Harding: ...that was a...

Julie Segre: Yes. So there are several projects that are being investigated. Here we are looking at common eczema and what is the contribution of bacteria to eczema.

And we are also looking at patients who have recurrent infections of MRSA, the methicillin-resistant staph aureus. And we are looking at whether there are some people who are exposed to MRSA but never develop an infection and

other people who would develop an infection, and is that related to the MRSA that they are exposed to or is that related to something else in their micrbiome.

If you get exposed to MRSA but you have a (carinobacterium) that the (carinobacterium) can actually keep the MRSA in check because actually bacteria have a lot of ways that they have figured out to control the growth of other bacteria. So that is an interesting question for us.

Now other projects in skin are exploring acne, psoriasis. And then in the gut there are projects about inflammatory bowel disease, Crohn's disease, a lot of these diseases that are being treated with antibiotics but we do not really see a clear infectious agent.

So we do not really understand but we know that if we treat with antibiotics that the disorder, you know, can get better. So, that is what we are really trying to understand a lot of is what are the infections really - what are the antibacterials really treating.

So we are looking at projects that have to do really with all of the systems. The, you know, the gut, the esophagus, the - all of the digestive system, the oral cavity and trying to understand really a wide variety of diseases.

Sarah Harding: Excellent. Okay. Now I was told that the lines should have opened. So if somebody has a question and they want to try asking it, hopefully we can all hear you.

Okay. Well we actually - I have gotten a number of questions over email. And if that is something that anybody would rather do that is fine. So I will just ask a couple more questions.

And so one of them has to do with the slide that - one of the last slides that you put up, and that is that there has definitely been a - it has to do with the picture of the Activia yogurt that you have and why that of all kind of yogurts of all, you know, what has made that special in terms of having a pretty big campaign and you kind of see it. I think everybody knows the jingle. And, you know, why has that necessarily been any more special than any of the yogurt we have had before?

Julie Segre: So, I think here we really need to get into what is science based. And that is what we are trying to create the foundation for is to understand really who would, you know, who would respond to these probiotic yogurts and who is this really benefitting?

And in the same way that we do double blind studies, placebo studies and, you know, to try to test most drugs, we would like to, you know, we would to have that same kind of science based, evidence based approach to other things that we, you know, we consider that we are taking to increase our health.

And I think that there is a great potential for understanding probiotics from many systems of our body and to really understand what on an individual level is making each of us healthy.

But I just think that this is something which we really want to understand not as marketing strategy but as a scientific endeavor. And in that same way, what we have - I mean Activia is just adding, you know, a probiotic to a yogurt.

But the Purell, the hand sanitizer, has really substituted now for soap and water and washing your hands. And so it is, you know, it is great in that we often have access to having clean hands when we might not otherwise, you know, if you are traveling or something in the airport or something like that.

But we just need to, I mean we just need to understand what these products are really doing and how they are affecting our health and how they are preventing us from getting sick.

Sarah Harding: Great. Thank you. Are there any other questions from participants? Okay. Then I have one other question that has come in.

Jay Gee: ...hear me?

Sarah Harding: Oh. Yes. Hi.

Jay Gee: Oh, okay. This is Jay Gee and the CDC, just a simple question. Have you all gotten to the point where you can see if natural microbiota, the composition is preventing certain infections such as MRSA, I mean the ideal being the bacteria, the natural ones would occupy a niche preventing colonization? Have you gotten that far yet?

Julie Segre: So we have not gotten to the point where we know which bacteria are really having an effect of keeping others out. We recruit those patients to use the NIH Clinical Center. And patients we recruit are at an increased risk for developing staph aureus infections in some cases because they have eczema. And we recruit the entire family, you know, in to try to see if anyone else who has been exposed to MRSA is also a carrier for MRSA.

And so that is really the goal of our study is to do an in-depth analysis of exactly that type of question - how do we control the transmission of MRSA and can that be controlled by other microbes and promoting the growth of other microbes because you can imagine that it could be very effective to try

to over grow the MRSA rather than trying to wipe out the entire bacterial colony.

And so those are the goals and even ones that - harder than that is going to be to figure out what is causing these diseases.

But if we could even just figure out what is correlated with a protective effect, we could start to target that.

So no, this project - I should have said that - this project was launched just one year ago with the goal of trying to develop the basic understanding that would enable us to treat disease and also to control infection.

Jay Gee: Okay. Thank you.

Sarah Harding: Great. Any other questions from our audience?

So I did just receive one question from (Tim Burke) at Access Genetics. And he had a question about - he mentioned you had three hypotheses about skin flora and their cause for skin disorders, which is assuming that eczema is caused by a lack of some bacteria or an overload of others.

And so he poses the question of what if it is because - what if it is the other way around, if the skin disorder is causing a certain variety of bacteria?

Julie Segre: And so I completely agree with that. And that actually takes us back to the first slide that I used to launch into the question about what are the types of cells that inhabit the skin. And there are the human cells and, you know, the skin cells, the immune cells and the microbes.

And that it may very well be that the skin disease, which is caused by a defect in the human cells are then causing this scaly skin and that causes the microbes to be different.

And the - if it is only the skin cells, then affecting the microbial flora would not change that. But we know that in the case of eczema, what are the most common treatments for eczema are steroids, corticosteroids, antibiotics, sometimes even giving the kids bleach baths so that we can just reduce the microbial load. And that seems to make the kids look and feel a lot better.

So it is true that the root cause may be something in the human cells that maybe makes them make a less good barrier. But we already know that the treatments that we use are more likely affecting the microbial than they are the human cells.

So, it may be that the primary cause is something in the change in the human DNA. But what I am looking for here is how to really affect the greatest health for people with skin disorders or other disorders.

And so if I can intervene and give them a, you know, a topical therapy that increases their health even if it is not getting at the root cause, even if it is just getting at some other part of the pathway, I still think that that is our goal is to really be promoting health.

And so it will be very difficult to untangle what is causing the disease but really the outcome that we are looking for is to improve the health.

Sarah Harding: Excellent. So I appreciate this. There are a number of you asking questions over the Web portion of this webinar which I think is excellent. And I will just bring it to your attention to those of you who maybe haven't seen it.

But we did get a question from Ke Chen at Boston University. The question is, are you considering the impact of environmental factors such as the level of sun exposure or living in an area of more damp or dry area in to the relationship of human cells and microbial cells, sorry, in your study population? If so how, and what type of impact would these environmental factors have?

Julie Segre: So sounds another - and these have all been just great questions. And that is another thing that just makes this so complex. When we are trying to capture what is normal, of course we are finding individuals who live in a dry community, people who, I mean, even a dry environment like, you know, living in Arizona and people who live in a moister community.

And even that can change between if it is the winter time and you are spending your days inside, you know, a heated environment which dries out your, you know, is a dry environment.

So there are many variables here. It may be important, you know, just the sun exposure, all those things may really be important. And we are actually trying to capture as many of those variables as we can.

And we are asking people, you know, who they live with. We are asking them do they have a pet. It turns out people have a lot of contact with their pets. And so we are asking them all those questions.

I am not sure that we will have a great enough population that we can determine if there is statistical significance to any one of those factors. And it may be that what we find out is that the variance is just so great that you really cannot tell a difference.

But we are capturing all of that information in our questionnaires to see if there is a correlation between where someone lives and who they live with and, you know, what they eat and what allergies they have and those, you know, those types of questions to try to get to see if those are affecting their microbiota.

Sarah Harding: Great. So are there any other questions from the audience? All right. Well I want to thank Dr. Segre for speaking today. I think this was very interesting and certainly added some insight into one of the many programs that are going on here at the NHGRI.

This is a series of talks that we will be holding pretty much every other month for the next - for the significant future. And so we will be announcing more of these webinars as time goes on. So we hope to see you again.

There is a Web site that I believe went out with some of the emails that you would have received from me that would have information on our other webinars that happened last year.

So again we look forward to seeing you in future webinars and if in fact you would have other ideas of other topics that you would like to hear from, I would be very excited to hear about those as well.

So you will receive more information from me. But again, thank you very much for participating and I hope you all have an excellent afternoon. Thanks very much. Bye-bye.

END