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Prof. dr. Alexandra Zhernakova

The Gut Microbiome: A universe inside us

Inaugural lecture

10 March 2023

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Dear Rector,
dear Colleagues,
dear Friends,

Thank you all for attending my inaugural lecture. It is an enormous honor for me to talk to you in this aula. In this lecture, I will focus on the fascinating world of the gut microbiome.

For me personally, the topic of the gut microbiome represents one of my most long-standing scientific interests. In September 1992, I joined the junior scientific research community in the Department of Infectious Diseases at St. Petersburg Pediatric Medical University. The first presentation I made in this community was on the link of gut dysbiosis with diseases in children. The level of dysbiosis was determined in an old-fashioned way: as the ratio between beneficial and pathogenic bacteria, based on the number of colonies that were grown from 1 gram of feces. Analysis of dysbiosis was already very popular at that time, and it was a routine protocol for children with gastrointestinal complaints. Our analysis concluded that gut dysbiosis is a signature of allergies, colic and other infant diseases. Since then, I have considered the gut microbiome an important component of health.

In this lecture, I hope to share with you my excitement about the universe of gut microbes. I will first talk about our current understanding of the role of the microbiome in health and then discuss how we will follow-up this knowledge in the future.

The human body as a holobiont

First, let me briefly introduce you to the microbiome. We are not living alone. There is a vast community of microorganisms living on our body and inside us (Figure 1). The largest community lives in the gut and is called the gut microbiome. This ecosystem is very complex and diverse. It includes bacteria, viruses, fungi and other microbes. The total number of gut microbes is difficult to estimate, but we can be sure that there are at least hundreds of different species, thousands of different strains and millions of microbial genes in every single individual. All together, the weight of the gut microbiome is about 250-300 grams, which makes it a large organ, larger than a kidney but a bit smaller than a heart. When talking about the microbiome, we often mainly consider bacteria, but the main reason for this focus is that other members of our gut community are less well-studied.

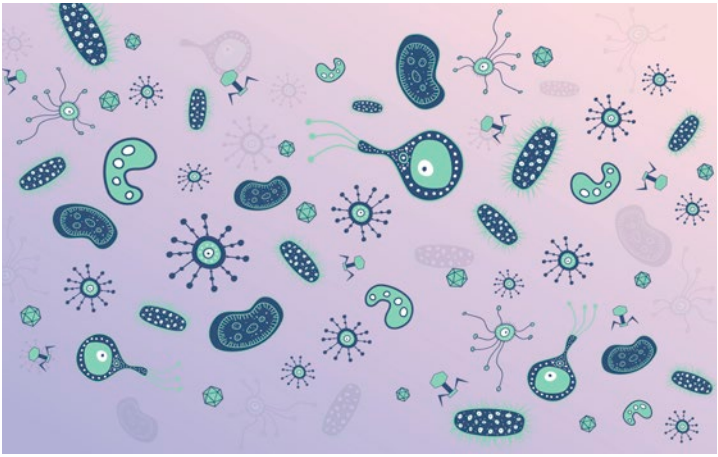


Figure 1

Researchers have been studying microbes for more than 300 years, since the discovery of bacteria by Dutch scientist and tradesman Antony van Leeuwenhoek. For many decades, bacteria were studied in relation to diseases and were seen as pathogens. It was only about 100 years ago that the idea of good bacteria appeared. One of the promoters of this idea was Ilja Metchnikov, who thought that bad bacteria cause aging, while good bacteria can protect people from diseases. He considered bacteria from sour milk to be good and thought that drinking it could help individuals stay healthy. This was the origin of the idea of probiotics – the idea that introduction of good bacteria can promote health.

Microbiome studies have become particularly popular and successful in the past 10 years. The main reason for this is progress in technology. At the beginning of this century, methods for massively parallel sequencing were developed. This made it possible to sequence the DNA from a community of many different organisms at the same time. This technological advantage boosted microbiome research enormously and enabled wide-scale studies in large numbers of individuals. Altogether, tens of thousands of participants were included in these studies, leading to the identification of thousands of microbes.

It was about 10 years ago that we started doing microbiome research in the Department of Genetics at the University Medical Center Groningen. Here, I would like to immediately acknowledge our Rector Magnificus Professor Cisca Wijmenga, who in 2012 initiated the first microbiome collection in 1500 participants from the cohort Lifelines-DEEP. In the same cohort, we also measured genetics, levels of proteins, levels of metabolites and other biological layers. The availability of this information allowed us to explore myriad relations between the gut microbiome and other biological outcomes.

In 2016, a larger collection, now called the Dutch Microbiome Project, was initiated by Professor Marten Hofker. It included 10,000 participants, which at the time made it the largest metagenomic study in the world. These were very timely initiatives, and they allowed us to perform pioneering studies in the human microbiome field. The very first Ph.D. students only started working on microbiome data in our department in 2012, whereas now more than 30 members of the Groningen Microbiome Team are using the data generated from these two cohorts. Moreover, we made the resulting microbiome data available for researchers worldwide; they have been downloaded more than 100 times and used in various research projects elsewhere.

The key factor in the success of these microbiome studies was the fact that they were done in collaboration with the cohort study Lifelines. For the tens of thousands of Lifelines participants, extensive health and environmental information is regularly collected. This allowed us to study the microbiome in combination with information on diet, lifestyle, environmental and many host factors. The deepness of this data is truly unique, and I am enormously thankful to all Lifelines colleagues and Lifelines participants, who provide Groningen researchers a solid foundation for studying the variations in human health on various levels, including the microbiome.

So, what did we learn from the past 10 years of microbiome research?

First, we learned that the individual microbiome is enormously variable. As humans, our genetic material is 99.9% alike. For gut bacteria, the overlap is much smaller, with only about 10% of bacterial composition shared across the people in this audience. When considering the gut virome, this situation becomes even more complicated. The virome is very individual-specific, with only a very small number of viruses shared across individuals. This high variability leads to the fact that the majority of microbes are rather rare and still not well characterized.

Second, the microbiome cannot be disconnected from its host, the human being. Almost everything that we, humans, do has

an effect on our gut microbiome. Food, sports, sleep, lifestyle, medications, diseases – everything matters. This includes not only obvious factors, such as diet and current lifestyle, but also family history and early life factors. For example, we see long-standing changes in the microbiome depending on the place where someone spent their childhood, whether it was in the city or on the farm. We also see an effect of our genetics on the abundance of some bacteria.

The **third** important observation is that, even with the extent of the individual variations, we do see common patterns of bacteria that are related to health. When analyzing the association of the microbiome with different diseases, we often see that the same bacteria are increased or decreased in unrelated conditions such as diseases of the gut, metabolic diseases, mental health and other diseases. This picture is, however, not black and white. It is important to consider that, for different individuals, the same microbe or pathway can be either beneficial or pathogenic, and this effect can also depend on dozens of factors. Still, the existence of disease-characteristic bacterial patterns is an important and positive observation. We can now focus on the community of bacteria that are generally beneficial for health and on the other set that we would prefer to eliminate from the gut.

Finally, the microbiome has not just been associated to disease; in several cases we can now also prove its causality. For example, fecal microbiota transplantation in mice is a common method for testing causality. In this practice, fecal material from individuals with certain conditions or diseases are given to germ-free mice, who do not have their own gut microbes. By comparing the outcome of fecal microbiota transplantation from different donors, healthy or diseased, we can see the effect of the individual's microbiome on such traits as metabolism, weight, behavioral traits (such as anxiety) or even response to treatment, for example the effectiveness of anti-cancer medications. Often, we do not understand exactly how changes in microbes affect health, but there are some examples where we can identify the mechanisms. We now know that many metabolites in our body are determined by gut bacteria. For example, some bacteria can produce short-chain fatty acids, which are considered good metabolites because they can improve glucose metabolism and regulate our immune system. In another example, a set of gut bacteria are involved in metabolism of tryptophan to serotonin. Tryptophan is an amino acid that we get from food, and serotonin is a molecule that is involved in learning, memory and happiness. This illustrates a direct link where the gut microbiome is a mediator between our food and our mood and brain function.

These are a few highlights from our current understanding of the microbiome. The next questions are: **Where do we want to go? What do we want to achieve? And how?**

It is my strong belief that we should aim at eventually using the microbiome as a target to prevent or treat diseases. In the next part of my talk, I would like to highlight a few research directions that we will follow to achieve this goal. It is good to realize that these directions will not always be straightforward but might instead look like the Strava running map images from the orienteering competitions that I use to run in with my husband Maxim (Figure 2).

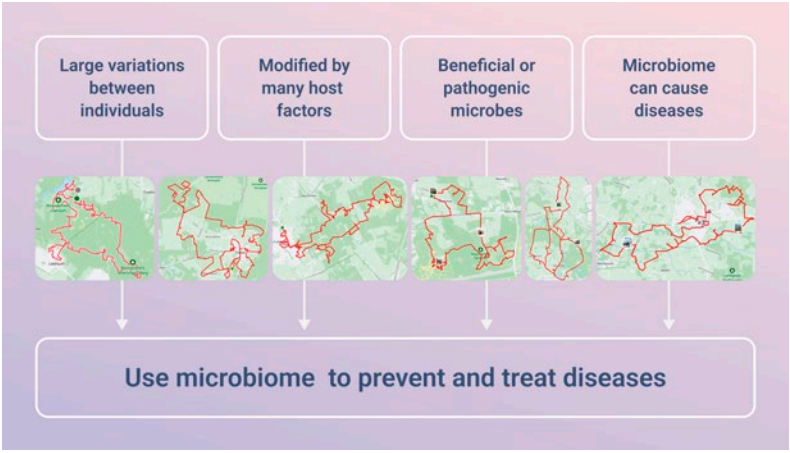


Figure 2

Characterization of the microbiome, in particular the virome

First, we do not yet understand the whole complexity of the gut ecosystem. Even after analyzing more than 10,000 Lifelines participants, we keep identifying novel bacterial species. Even more importantly, our current characterization of the gut virome is very poor. The research community has been constantly discussing viruses over the past three years, but our interest was mainly in human viruses – in relation to COVID-19. There are also millions of viruses in our gut, but most of them are viruses that infect bacteria, called bacteriophages.

Virome analysis faces enormous challenges. The viruses are, in general, much more diverse than any other kingdom of life. They have a high mutation rate, which means that they evolve quickly, and they do not have good marker or signature genes that can be used to characterize them. Viruses can also get in and out of bacteria, stay silent for a long time, transfer genes from one bacterium to another and even kill bacteria. The actions of bacteriophages, and the logic – what exactly dominates their behavior – is poorly understood.

On the other side, it is important to realize that bacteriophages have large therapeutic potential. Bacteriophage cocktails for treating bacterial infections were first proposed almost 100 years ago, before the discovery of antibiotics. A lot of work in this field has been initiated in Tbilisi, capital of Georgia, and I

was fortunate to study the opportunities of bacteriophage therapy during my medical education. Recently, a pioneering study by an international team of researchers used a cocktail of bacteriophages to eliminate pathogenic bacteria as a treatment for inflammatory bowel disease. We can expect that many more such studies will appear in coming years. So deep characterization of the microbiome, and in particular, the microvirome is one of the tasks for the future.

Analysis of the microbiome in relation to the host – the exposome

Second, it is important to realize that humans and microbes form one joint ecosystem, so the microbiome should be studied in combination with host factors. Host factors can be split in two. On one side, is our genetics, which is stable and never changes. On the other side, we experience a constantly changing environment: the hundreds of environmental factors around us, which together are called the exposome. If we want to determine if the microbiome can predict the development of diseases, we need to monitor the microbiome in pre-disease individuals. We should follow them longitudinally, simultaneously tracking other factors that contribute to wellbeing, including genetics, lifestyle, diet, diseases and many others. This all sounds like a huge and ambitious task, and it actually is. But we have already started making it a reality. In Groningen we are in a leading position for this research due to the unique opportunity to join forces with Lifelines. It means we can

sample stool from participants who will be followed for decades. This would allow us to later go back to samples from before the onset of a disease to investigate the microbial signatures of the future disease and explore it in combination with environmental factors and their changes. It is of ultimate importance that the Lifelines initiative continues for coming decades because it is essential for performing comprehensive studies on various aspects of health, including the microbiome.

I expect that within a few years, these longitudinal studies will have brought us to the point of being able to use microbes as biomarkers. This knowledge can be used in the same way as we now use other well-studied biomarkers. For example, we can now routinely measure blood lipids in combination with host genetics and lifestyle factors such as smoking. By putting all these factors together, we can accurately predict an individual's risk of developing cardiovascular diseases. In the same way, I expect that we will soon know which changes in specific gut bacteria or viruses, in combination with specific lifestyle, diet and genetic factors, can substantially increase or decrease the risk of a specific disease. This knowledge would be very practical because changing the gut microbiome – though not very easy – is still more realistic than changing other parameters such as genetics.

I also expect that in the future the methods for sample collection and analysis will be easier and more popular: collection of stool is non-invasive, and technological developments suggest that even home-devices, such as smart toilets or toothbrushes, will be able to sample and profile microbes. Collecting extensive environmental factors is much more challenging due to their high number and variations, but Lifelines has already created a globally unique exposome database. On top of that, information on the exposome can now be collected by various devices, such as smartphones for measuring physical activity, dust boxes for analysis of the local environment and wearable rings for collecting metabolite concentrations around us. Many corresponding methods are now being developed by members of the Gravitation consortium ExposomeNL. I would like to thank all the participants of the ExposomeNL consortium for their successful collaboration and joint projects.

Start early in life – Lifelines-NEXT

I hope I have convinced you that longitudinal collection of the microbiome, in particular in pre-disease individuals, is essential for understanding the individual-specific host–microbiome relations. But, of course, if we want to measure all the important environmental and microbial changes that can influence individual health later in life, we have to start early. It would be best to analyze microbiome samples from the pre-conception period, then follow parents during pregnancy and their

children from their first days of life. This is a dream project that brings together my background in pediatrics and my current interest in the microbiome and exposome, and I am very happy that I can focus my research on such a project, which is **Lifelines-NEXT**.

Lifelines-NEXT started as the 4th generation of Lifelines. In 1,500 families, microbiome, questionnaires and many other sample types are being collected from mothers during pregnancy and from babies and mothers at birth and regularly during the first year of life. The overall aim of Lifelines-NEXT is to explore the role of prenatal and early life factors on children's health.

There are many scientific questions that we aim to answer in the Lifelines-NEXT study. For example:

- Which pregnancy and delivery factors are crucial for long-term wellbeing?
- How exactly do maternal diet or parental smoking influence a baby's health?
- And, importantly, why do some babies cry all the time?

Of course, in my research team, our special focus is on the role of the microbiome and virome in developing and mediating

these conditions. We study not only the gut microbiome, but also oral, breast milk and other ecosystems.

The inclusion of mothers and babies into this cohort is still ongoing, but we are already making exciting observations. For example, we can now explore how exactly the gut ecosystem develops in babies, what are the origins of gut bacteria and viruses, which important bacteria and nutrients are coming from breast milk, and many other research questions. There is still a lot of work to do, so this is just the beginning of many exciting studies.

Lifelines-NEXT is a huge project initiated and supported by many people. I would like to give my deep thanks to the people who started this project in 2016: Cisca Wijmenga, Sicco Scherjon, Jan Sikkema, Folkert Kuipers, Jackie Dekens and the Lifelines team; to the UMCG for providing initial funds; to Nestlé for their collaboration on building this cohort; to the current core group and steering committee for their support; and to our nurses and our management team. I also want to thank the UMCG Cohort and Biobank Coordination Hub for recognizing Lifelines-NEXT as the priority cohort of the UMCG and providing funds for data and sample management support. But, most of all, I would like to thank my research team working on Lifelines-NEXT – our technicians, Ph.D. students and postdocs. It is your enthusiasm, curiosity, creativity, hard work and critical attitude

that makes Lifelines-NEXT research successful. It is my enormous pleasure to work with you.

Functional understanding and links with industry

I have been talking about comprehensive longitudinal studies, which are enormously important. But it is good to realize that even after completing them, we will still not be ready to use microbes to prevent and treat diseases. To make microbiome-based medication a reality, we need to understand the functional properties of each microbe and how exactly bacteria (and viruses) are linked to health. We also need to develop medications in the form of specific microbes or their communities, or metabolites, or prebiotics.

In the field of functional characterization of microbes, we can compare our current position with the early days of genetic studies. Genome-wide association studies in genetics became operational around 2006, and in just 10 years we identified hundreds of genes that are associated to common diseases. However, despite years of work, the process of characterizing the function of associated variants is still challenging.

Now we face a similar challenge in microbiome studies. Association analysis is rather straightforward, whereas functional implementation is slow and requires a lot of practical work. Here again, the UMCG provides an excellent research environ-

ment as several advanced methods for functional analyses are already operational here. One research line is bacterial culturomics – the method of culturing single bacteria and its further characterization. The group of Hermie Harmsen in the Department of Microbiology has huge experience in culturing both aerobic and anaerobic bacteria. By running culturomics in a collection of gut bacteria from patients and healthy individuals, we can further characterize bacterial strains to understand the mechanism of association of these bacteria with diseases.

Specific microbes can then be applied to model systems, such as the organ-on-a-chip model, which is another strength of the UMCG. Organs-on-a-chip (Figure 3), including gut- and liver-on-a-chip, have been successfully developed in our department by several scientists from the Netherlands Organ on a Chip Consortium. These model systems effectively mimic the human intestinal tract. Adding single microbes, a community of microbes or microbial metabolites to these systems will allow us to identify their effect on gut and liver tissues, intestinal permeability and the immune system, and will enable direct measurements of bacteria-bonded metabolites.

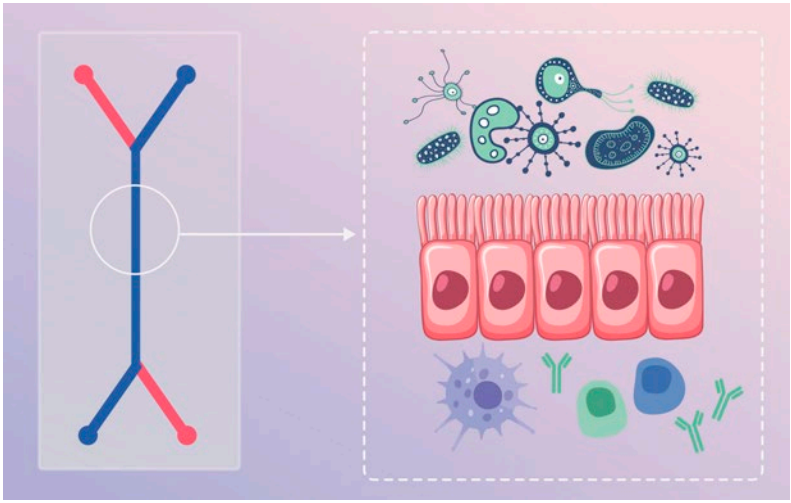


Figure 3

Culturomics, organ-on-a-chip and other functional methods will definitely be the follow-up of future microbiome work. It is clear that zoom-in studies into microbial functionality is a large task that requires scientists from different disciplines to join forces. It is therefore a great achievement of the whole microbiome team, and a big recognition of our success by the UMCG, that we were given the opportunity to create a new facility – the Groningen Microbiome Hub. The hub is still under construction but will become operational already in April 2023. The hub will combine work on large-scale metagenomics analysis with culturomics studies, organ-on-a-chip work and other functional studies. This is a big success of many researchers from the Departments of Genetics, Microbiology

and Gastroenterology. I would also like to acknowledge the UMCG board, who recognized the importance of microbiome research and supported this initiative. I am sure that opening the Groningen Microbiome Hub will bring our microbiome research to a new, deeper and functional level. It is also important to realize that this achievement is just the start of the new level of microbiome research. It will require a lot of clinical and research work, new investments and collaboration with other researchers and industry.

How not to be lost in translation: education and patient care

The final point that I want to discuss is how to bring the data to patients.

The Lifelines-NEXT and Dutch Microbiome projects have already generated a tremendous amount of data. The extension of these projects to larger sample sizes, more wearable devices and more phenotypes will bring the amount of data to a much higher level. The next challenge that we will face is interpreting this data and bringing it to patient care.

In fact, translation to patient care is already happening. A few years ago, I gave a lecture on the microbiome in a scientific forum in Tartu, Estonia. After the lecture, one participant came to me with a question. She said, “I have three kids, and I made a gut microbiome analysis for all of them. Two of them have high

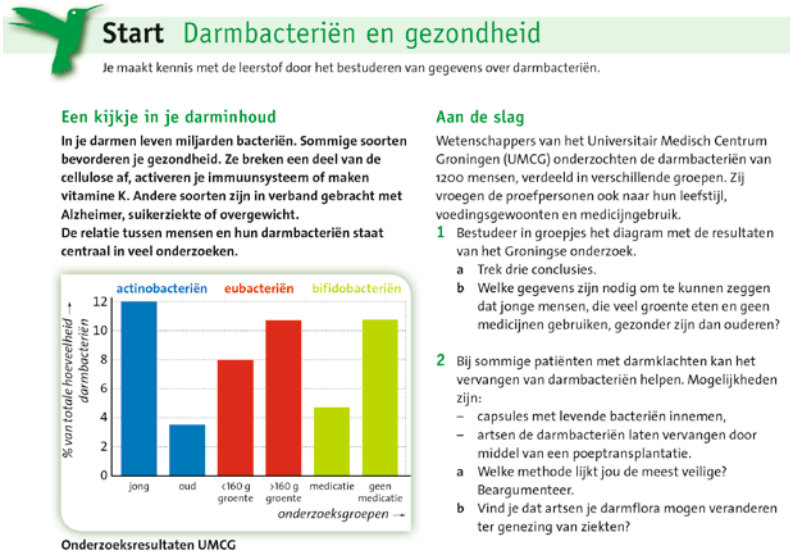
abundance of *Bacteroides* [which is a type of gut bacteria]. The third child, on the contrary, has little *Bacteroide*s but a lot of *Ruminococcus*. What can I do with these results to make sure my kids will grow up healthy? Should they eat a different diet? Which one?"

This is and will remain a difficult question for a while to come. Interpretation of an individual's microbiome in relation to health is a narrow path between Scylla and Charybdis. On one side, it is very easy to overinterpret the current knowledge without a clear understanding of the downstream effects of specific microbes. On the other side, it is probably unrealistic to wait until we get a full understanding of the microbial complexity. General advice based on current knowledge can, in principle, already be helpful. For example, we know that, on the population-level, a diet rich in vegetables, fruits and fermented products is, on average, associated with positive signatures of the gut microbiome. We can recommend this diet to almost everyone. Here again we are in a similar situation to the one genetics was in 10 years ago, where interpretation of the genetic risks of common diseases was constantly balancing valuable associations and low-confidence predictions. In genetics, we are now getting much better by applying polygenic risk scores based on the analysis of hundreds of thousands of participants. For the microbiome, I expect similar trends, and this process could now go faster due to technological and computational advantages.

On a positive side, there are already several examples of more personal implementation of microbiome analysis. One notable example is the personalized nutrition project from the Weizmann Institute, Israel. Researchers there first identified a link between an individual's microbiome and their sugar metabolism. Next, they used AI to develop an algorithm based on individual microbiome profile that allowed prediction of the reaction of blood sugar to various foods. Finally, they developed a service where participants can get recommendations about the optimal diet to maintain their blood sugar levels based on their gut microbiome. Application of this algorithm in pre-diabetic patients allowed participants to keep their blood sugar in a healthy range and worked remarkably better than just following the general recommendations of the American Diabetes Association. These and similar studies are current examples of using the microbiome in preventing diseases. This study is also a great example of using AI in the interpretation of microbiome results. This is a field that will be massively developing in the coming years (as we can already see in the examples of ChatGPT, DALL-E and other tools).

Introducing the microbiome into medical care will require training the new generation of researchers and medical doctors. For medical doctors in particular, knowledge about the microbiome is as important as understanding the function of any other human organ. The microbiome, its function and its

relations with immunity, metabolism, diseases and environment, and the interpretation of an individual's microbiome should be part of the basic medical curriculum. The Groningen Microbiome Hub can and should play a role in developing microbiome-focused courses for researchers and medical students. I am proud to say that our work has already made a notable contribution to education. Biology books for the 5th year of Dutch High School include chapters describing the basics of microbiome studies, with illustrations and text based on our results from the Dutch Microbiome Project performed in the Lifelines population (Figure 4). I believe that this is a true recognition of the success of our team.



Start Darmbacteriën en gezondheid

Je maakt kennis met de leerstof door het bestuderen van gegevens over darmbacteriën.

Een kijkje in je darminhoud

In je darmen leven miljarden bacteriën. Sommige soorten bevorderen je gezondheid. Ze breken een deel van de cellulose af, activeren je immuunsysteem of maken vitamine K. Andere soorten zijn in verband gebracht met Alzheimer, suikerziekte of overgewicht.
De relatie tussen mensen en hun darmbacteriën staat centraal in veel onderzoeken.

Onderzoeksresultaten UMCG

Aan de slag

Wetenschappers van het Universitair Medisch Centrum Groningen (UMCG) onderzochten de darmbacteriën van 1200 mensen, verdeeld in verschillende groepen. Zij vroegen de proefpersonen ook naar hun leefstijl, voedingsgewoonten en medicijngebruik.

1 Bestudeer in groepjes het diagram met de resultaten van het Groningse onderzoek.
   a Trek drie conclusies.
   b Welke gegevens zijn nodig om te kunnen zeggen dat jonge mensen, die veel groente eten en geen medicijnen gebruiken, gezonder zijn dan ouderen?

2 Bij sommige patiënten met darmklachten kan het vervangen van darmbacteriën helpen. Mogelijkheden zijn:
   – capsules met levende bacteriën innemen,
   – artsen de darmbacteriën laten vervangen door middel van een poeptransplantatie.
   a Welke methode lijkt jou de meest veilige? Beargumenteer.
   b Vind je dat artsen je darmflora mogen veranderen ter genezing van ziekten?

Figure 4 Nectar 5 vwo, 4e editie, Noordhoff, isbn 978-90-01-73601-9

In the last 30 minutes, I have discussed the enormous progress and success of the microbiome field, to which the researchers of the Groningen Microbiome Hub have made significant contributions. A lot of exciting work is ahead, and this work requires good planning, proper training, extensive collaboration and, most importantly, efficient teamwork.

I am enormously thankful to all my colleagues from the Groningen Microbiome Team for being active, creative and critical. You are a great inspiration to me, and I learn a lot from you. I also constantly feel that I am a very lucky person to be able to work with the best scientists ever. When we first came to the Netherlands, I did not have a work permit and was looking for a volunteer job. I went to a genetics seminar at the University Medical Center Utrecht and randomly approached one of the attendees. This person was Cisca Wijmenga (What luck!). I very much appreciate all of Cisca and Marten's support and trust since then. Also, enormous thanks go to Jingyuan Fu and Rinse Weersma for our pleasant, joyful and successful collaboration.

My path to this stage was not straightforward. Moving my career from clinical geneticist to volunteer and lab technician and then to researcher and group leader, a journey that took in three countries, with three children, would not have been possible without the enormous support of my family and friends. I would like to thank my children for their curiosity

and our scientific discussions, my partner Maxim for support and for bringing practical and realistic suggestions when I miss them, and most of all my mother and mother-in-law, who gave me a lot of support by taking care of the kids, sometimes literally passing them from one hand to another. Without you all, this achievement would never be possible. Thank you.

Ik heb gezegd.

Acknowledgements

I am fortunate to have had the opportunity to work with a diverse group of people who have provided invaluable insights, advice and encouragement throughout my academic journey. Without their contributions, this achievement would not have been possible.

I will start by thanking the enthusiastic docents and professors of St. Petersburg Pediatric Medical University, who spent their free time meeting with students and leading the student scientific communities, and my colleagues and supervisors at the Center of Medical Genetics in St. Petersburg, who paid personal attention to each patient case I discussed with them as an inexperienced junior clinical geneticist. I also extend my deep appreciation to Vladislav Baranov, the head of the Laboratory of Molecular Diagnostics, for providing an example of an open-minded scientist and for regularly greeting me with his genetics-focused poems.

Meeting Cisca Wijmenga at the beginning of my scientific career in the Netherlands was the best luck I could imagine in life. I am grateful to Cisca Wijmenga and Marten Hofker for their support, scientific vision, trust and critical discussions, and for the warm welcome of their home.

It was a great learning experience meeting a diverse team of researchers during my technician, Ph.D. and Postdoc time in Utrecht, Leiden, Boston and Groningen. An atmosphere of acceptance, valuing of each individual's strengths, teamwork, humor, peer support, critical thinking and high quality judicious science – these are the key qualities of the research teams where I had the privilege to work and were the result of the joint effort of researchers at various levels and their supervisors. I admire people who create this atmosphere in their research groups and who have provided me a role model for leading my research teams, in particular Cisca Wijmenga, Marten Hofker, Rene Toes, Tom Huizinga, Bobby Koeleman, Ramnik Xavier, Robert Plenge, Nine Knoers and many others.

The success of our microbiome research is made possible by the strong teamwork of many talented researchers. I am especially thankful to my Ph.D. and postdoc peers, former and current Ph.D. students and postdocs and to the extended team of people who have supported my research.

To my current and former Ph.D. students – Javier Gutierrez Achury, Ettje Tigchelaar-Feenstra, Marc Jan Bonder, Arnau Vich Vila, Sana Garmaeva, Trishla Sinha, Ailine Lopez Mazanova, Lianmin Chen, Esteban Lopera Maya, Siobhan Brushett, Johanne Spreckels, Marwah Doestzada, Sergio Andreu Sánchez, Renate Ruigrok, Asier Fernandez, Milla

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Rinse and Jing, it is not only successful science but also a great joy to run research projects together with you. I thank you for that.

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