

IMPROVING HEALTH

CIRCLE OF LIFE

AMSTERDAM REPRODUCTION AND DEVELOPMENT

ANNUAL REPORT

2022

REPRODUCTION

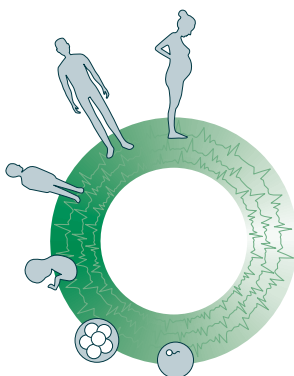
SOCIETAL IMPACT

DEVELOPMENT

RESEARCH



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Amsterdam Reproduction & Development
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A word from the directors

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As 2022, the European Year of the Youth, has come to an end, we proudly present the annual report of the Amsterdam Reproduction & Development research institute. Collectively, we have studied human reproduction from the very beginning of life, through its fascinating development into unique individuals. Our research has again led to breakthroughs into our understanding of the complex and fascinating process of human reproduction and development. In this annual report we show some of the highlights of our research and the societal impact we have created together to contribute to better healthcare and a healthier future for all.

As the world opened up again in 2022, after two challenging years that have been marked by the COVID-19 pandemic, an important aspect in this year was connection. Many new connections were formed in the year 2022. New researchers connected to the Amsterdam Reproduction and Development research institute, new connections were formed between researchers based in the laboratory with those based in the clinic. Connections were made between our researchers and policy makers as well as the public. Through travel grants, research grants and symposia connections could again be made with our national and international research partners. Moreover, by networking events and our retreat, organized by our enthusiastic retreat committee of young researchers, we have stimulated connections to form a fertile breeding ground for excellent science that ultimately serves society.

At Amsterdam Reproduction & Development we are dedicated to increase our knowledge of the process of human reproduction and development, as we believe understanding the origins of life contributes to a healthier future. Moreover, we focus on how to improve care for patients and their families. Many people together make the institute what it is today and are building the future. We present a selection of our research and events in this annual report, to give a glimpse of all the dedicated science that is done in the institute. We hope you will enjoy the read and feel some of the excitement of this amazing field of science. Feel free to join us on our discovery of the fascinating origins of human development, child development and the foundations of future health!

Lidewij Henneman & Tessa Roseboom
Directors Amsterdam Reproduction & Development



Starting the Circle of life



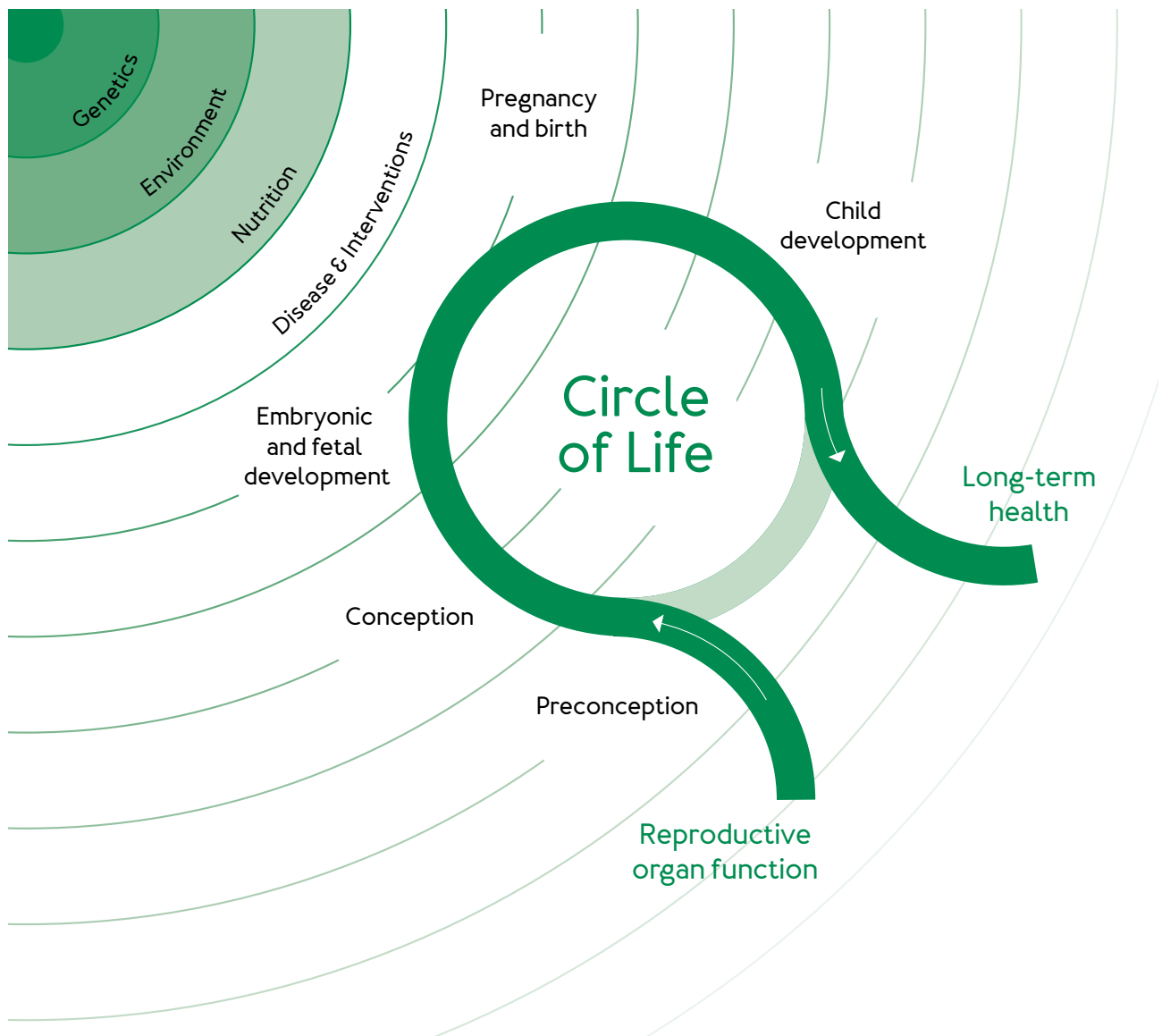
The Amsterdam Reproduction and Development (AR&D) research institute is unique in its goals and ambition, and Amsterdam UMC is the only academic medical center in the Netherlands with a research institute focusing on reproduction and development. Amsterdam Reproduction and Development is one of the eight research institutes of Amsterdam UMC, and as such related to both the University of Amsterdam (UvA) as well as the Vrije Universiteit (VU) Amsterdam. Amsterdam Reproduction & Development encompasses research themes that cover the Circle of Life: from before conception through pregnancy and child development to lifelong health. Our research focuses on all aspects of the process of human reproduction and development, spanning from preconception, conception, embryonic and fetal development, pregnancy and birth, to child development and reproductive organ function.

For more information please visit the website of AR&D:
www.amsterdamumc.org/ard.

MISSION AND VISION

The ambition of Amsterdam Reproduction & Development is the advancement of knowledge in all aspects of human reproduction and development through interdisciplinary team science aimed at improving health from preconception to adulthood of current and future generations.

We are inspired by a future of continuous and sustainable improvement in health for all. We aspire a role at the forefront of fundamental, translational, and clinical science and public health research in human reproduction and development, creating a knowledge hub to guide science that serves the wider society.



Research Areas

○○○ FROM PRECONCEPTION TO CHILD DEVELOPMENT



PRECONCEPTION AND CONCEPTION

The desire to have children is a fundamental driving force for all species. At AR&D we aim to support evidence-based care and information for people who wish to conceive, now or in the future. We study the spermatogenesis process, oogenesis and the earliest stages of embryo development from fertilization to implantation and translate this knowledge into new therapies. Our prediction models provide accurate and reliable prognoses for medical help to support optimal care for people who have difficulty conceiving. AR&D does not only offer develop medical treatments but we also evaluate whether they are truly of benefit for our patients. Thus, we stand for optimal evidence-based shared decision-making.

AR&D also investigates how to best counsel couples who are confronted with a high risk of severe genetic diseases in their future children, and to provide them with options for autonomous reproductive choice. We evaluate how novel genetic and reproductive techniques should be ethically weighed and whether they should be implemented.



EMBRYONIC AND FETAL DEVELOPMENT

Humans all originate from a single cell, the fertilized oocyte, and develop through a fascinating highly orchestrated process to become the individuals that we currently are. At AR&D we study how these processes are regulated, how perturbations can lead to congenital abnormalities or [late onset] diseases and how genetic and environmental factors affect development.

AR&D uses experimental model systems to study and simulate human development and use our unique twin register to disentangle environmental and genetic contributions to health and disease. By focusing on embryonic development, we provide the basis for understanding a huge variety of human diseases and disease susceptibility. We link these fundamental studies to clinical trials. We use highly sensitive ultrasound measurements and genetic tests to examine the developing fetus, and evaluate innovative implemented techniques. These are used for developing new tests to improve our clinical capacities.



PREGNANCY AND BIRTH

AR&D constantly strives to provide the best possible care for prospective parents and their children. Therefore, we routinely perform multi-center clinical trials to establish the benefit of specific interventions in obstetrics, midwifery and neonatology. The studies conducted by AR&D are in the context of national networks of collaborating hospitals, gynecologists, midwives, nurses, neonatologists, and other health care providers. Results of these trials are integrated into clinical protocols so that we can provide the best possible care and treatment for our patients and to support informed decision-making.

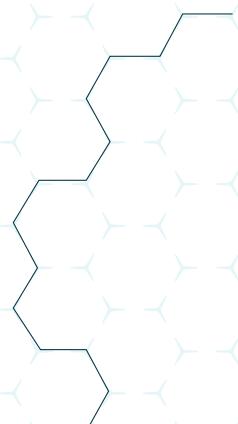
We also study the requirements for responsible implementation of advancements in prenatal screening and diagnostics. Another focus is to prevent morbidity of mother and child in high-risk pregnancies, to optimally treat pregnancy complications, and to reduce [the consequences of] preterm birth, as well as optimizing care for prematurely born infants. To learn more about how to give each child the best possible start, we investigate effects of environmental exposures during pregnancy on women's and offspring's health.



CHILD DEVELOPMENT

Healthy child development is essential for later health and wellbeing. AR&D follows children through their development, for example in cohort studies, after participation in intervention studies before or during pregnancy, or after they have spent part of their early life in the hospital, for instance because they were born prematurely. By doing so the behavior, growth and development can be monitored to gain insight in healthy child development, to better understand the long-term consequences of our treatments and to inform our patients more accurately.

AR&D develops online tools that help patients and their parents keep track of various aspects of child development. This covers the full range of psychosocial, mental as well as physical and behavioral aspects of life. We follow up children whose mothers participated in intervention trials. This provides insight into the underlying mechanisms of diseases before they become clinically overt. With the advancement of genetic sequencing technologies, we strive to optimize the genetic diagnosis in children with developmental disorders. We monitor development and follow individuals as they become the parents of the next generation and the circle of life begins again.



**“Improving
health across
the lifecycle”**

WOUTER HEHENKAMP AND
ANNE TIMMERMANS
Climate change - a role for healthcare

ANIKO KOROSI,
SUSANNE DE ROOIJ
AND AMBER BOOTS
Early life origins of dementia

RESEARCH AT AR&D

LAURENS EEF TINCK
SCHATTENKERK,
ADINDA PIJPERS AND
JOEP DERIKX
*Questioning surgical care
for young children*

ANNELIEKE MULLER AND
AGNIES VAN EEGHEN
*Personalized medicine for rare genetic
neurodevelopmental disorders*

JILLIS VAN MAAREN, CALLISTA
MULDER AND ANS VAN PELT
*Towards a fertile future for male
childhood cancer survivors*

A man with glasses and a beard, wearing a blue button-down shirt and black pants, sits on the left. A woman with long brown hair, wearing a bright blue dress and black boots, sits on the right. They are both smiling and looking towards the camera. The background features large green indoor plants and a modern office interior with concrete walls and railings.

“Healthcare
should be made
more sustainable”

Climate change, a role for healthcare



Climate change represents a great threat to human health and may be the biggest problem to solve in the 21st century. With their projects, AR&D researchers Wouter Hehenkamp and Anne Timmermans (both gynecologists), strive to involve all stakeholder groups in order to have the greatest possible impact on making healthcare more sustainable.



Wouter
Hehenkamp



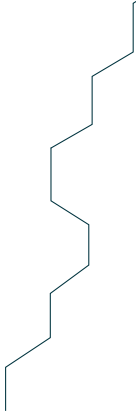
Anne
Timmermans

SUSTAINABLE HEALTHCARE

Climate change affects all generations, but children may be mostly impacted. Therefore climate change indirectly endangers the human circle of life. Healthcare is responsible for 7% of the carbon gas emissions in the Netherlands. Carbon gas reduction within healthcare is urgently needed in order to reach the target to become a 'net zero' healthcare in 2050. Health systems urgently need to transform and build resilience against the consequences of climate change. In order to make steps towards sustainable healthcare we need to gather information on sustainability parameters such as carbon footprints and waste production of different medical treatments. The future and the current health workforces have an essential role in this process. However, also the patients have an important role in this process. It is the responsibility of healthcare to engage patients. Hehenkamp and Timmermans both feel the responsibility to participate in the process towards a sustainable healthcare.

Both intrinsically motivated, they have been working to incorporate sustainability in their daily professional life, with a focus on research and education.

Through their research, Hehenkamp and Timmermans aim to ensure consideration of the different perspectives in sustainability in healthcare. In 2022, Hehenkamp and Timmermans have made steps towards building a sustainability research line in close collaboration with Amsterdam UMC Center for Sustainable Healthcare (CSH). Hehenkamp has formed the CSH research board together with Niek Sperna Weiland (anesthesiologist) and Dionne Kringos (Amsterdam Public Health). Their focus is on quantifying healthcare pathways, investigating patients literacy on climate change and interconnect these two through specific research projects. Since sustainability is a multi-disciplinary research field, they have built a consortium with the Faculty of Social and Behavioral Sciences, the School of Business and



“Healthcare providers, patients and (future) medical students can contribute to sustainable health care.”

Economics and the National Institute for Public Health and the Environment (RIVM). As an example for the research lines: AR&D awarded a grant to the research team ‘COmparative carbon Footprint assessment of trEatment options for utErine fibroids (COFFEE)’. In this project, the team aims to calculate the environmental footprint of different fibroid treatments by means of Life Cycle Assessment (LCA). Environmental impact categories are then incorporated into a decision aid for patients. The team will investigate whether patients are willing to incorporate sustainability variables in their decision which treatment they eventually choose. Also, the quantified environmental impact of treatments will guide the team towards ‘hotspots’ to act on as healthcare workers and policy makers. Eventually the team aims to share our methodology with the world in order to inspire other sustainability researchers to do the same, using our methodology (publishing the calculation tool that has been built in this project).

PLANETARY HEALTH IN THE MEDICAL CURRICULUM

Another perspective is the perspective of future healthcare workers. Researchers have called for the inclusion of planetary health in the medical curriculum. Heeding the need for change, a multidisciplinary team at the University of Amsterdam, came together to set up a module on planetary health with the aim of integrating this topic in everyday clinical practice. Besides Dr. Timmermans, this team included Dr. Ines Rupp [public health physician], Dr. Niek

Spurna Weiland [anesthesiologist], Dr. Berber Kapitein [pediatrician], and Iris Blom [at the time a final-year medical student]. Through a multidisciplinary and intergenerational approach, the team ensured consideration of diverse perspectives in the development process of the module. Teachers prompt students to think about their role in the context of planetary health, for three main reasons. First, the module aims to improve climate literacy and encourage students to share their innovative ideas, thoughts, insights, and solutions. Second, climate change poses an increasing mental health threat because of stress and anxiety, affecting young people most. In addition to knowledge of issues associated with climate change, tools that stimulate solution-based thinking and improve mental health are beneficial. Finally, this approach also aims to stimulate reflection on students’ role in building a climate-conscious, resilient, and environmentally sustainable health workforce, ultimately contributing to planetary health.

The module and its contents were developed in January 2021, and it started in January 2022. With the introduction of this planetary health and sustainability healthcare module in the medical curriculum, the team has started to empower future healthcare workers to take steps towards sustainable healthcare. Furthermore, it offers the possibility to bring research directly back into the classroom. Timmermans together with Marieke Sijm [medical informatician] has formed the education subdivision within Amsterdam UMC Center for Sustainable Healthcare. ●



“Patient-specific risk factors could aid in the decision making for surgical treatment”

Questioning surgical care for young children



AR&D researchers Laurens Eeftinck Schattenkerk (PhD candidate), Adinda Pijpers (PhD candidate) and Dr. Joep Derikx (pediatric surgeon) argue that challenging the status quo in practice is of utmost importance, as it feeds new research. With their research they focus on pediatric surgery for young children with intestinal atresia.

FIRST STEP IN RESOLVING A PROBLEM IS RECOGNIZING ITS EXISTENCE

One can hardly think of a more frightful situation for parents of a newborn child than to hear that their young infant needs an operation. In this case, the child is born with an atresia in the small intestine, specifically the ileum. This birth defect, which results in a full stop in the intestine, demands an operation within days. Luckily there is a pediatric surgeon to take them by the hand during this hard time. The pediatric surgeon walks the parents through the process step-by-step starting with the operation itself and the postoperative course. The clear explanation and determination of the surgeon puts the parents more at ease but when the surgeon has almost left the room the parents call the surgeon back with one last question: “Are you really sure this is the best treatment for our child?”. Although certain risks and benefits of the treatment will of course be discussed, undoubtedly this is not the time nor the place for our surgeon to answer with: “maybe, maybe not”.

STOMA VERSUS PRIMARY ANASTOMOSIS

In the case of a young patient with an intestinal atresia, there are generally speaking two options. One option is resection of the affected intestine followed by reconnecting the intestine, also called primary anastomosis. The other option is temporary stoma creation, where instead of an anastomosis, the proximal part of the intestine is fixated on the abdominal wall. Later in life, an anastomosis is created during a second operation. The choice between these two treatment strategies is influenced by, among other things, the clinical status of the patient and surgeons’ preference. A prime reason to develop an enterostomy instead of a primary anastomosis, is the fear of postoperative complications such as anastomotic leakage. Research has shown that anastomotic leakage occurs more often in patients receiving a primary anastomosis compared to solely stoma formation. However, by focusing on this sole complication, many other forms of stoma-related morbidity such as infections, depletion of fluids and minerals as a result of high-output stoma and later occurrence of incisional hernia are left out of the equation. Moreover, following stoma reversal, the patient is again exposed to the risk of developing postoperative complications. This leaves the question which treatment truly results in most post-operative complications.

A TRUE COMPARISON OF THE RISKS

Because of these questions, all children treated between 1998 and 2018 in both locations of Amsterdam UMC have retrospectively been evaluated. This cohort consists of more than 2000 children treated for different types of intestinal diseases. AR&D researchers Eeftinck Schattenkerk and Derikx showed that taking in account all patients who received a stoma, the incidence of major stoma morbidity (Clavien-Dindo grade \geq III, meaning resulting in re-operation, ICU admission or death) was 39% when taking into account the operation for both stoma formation and secondary anastomosis. Compared to jejunostomy or colostomies, children treated with an ileostomy were 2.5 times more at risk of these complications. This highlights the necessity of prevention of a stoma, when possible, in these patients.

“Comparing surgical treatments can provide the answer to the question which operation is best for children.”

The tendency to act like you are sure can, however, result in the creation of certain dogmas in surgical treatment based more on personal experience than on research. Questioning these dogmas might lead to resistance. In psychology this is called status quo bias; preferring to maintain the current situation and opposing actions that may lead to change. However, questioning the status quo is the corner stone of research and if a problem is not taken seriously then it will never be resolved.



Adinda Pijpers



Joep Derikx

When evaluating all patients who received a primary anastomosis, 5% developed an anastomotic leakage and 8% developed an anastomotic stenosis. An association was found between an increased pre-operative American Society of Anaesthesiology (ASA) score \geq III and male gender with anastomotic leakage. These patient-specific risk factors could aid in the decision making on which treatment to choose, thereby possibly lowering the risk of leakage.

It has to be taken into account that these results are based on all different types of intestinal diseases the team treated over the years. For this reason, the team also looked specifically at patients treated for jejunoileal atresias comparing those treated by stoma to those treated by primary anastomosis. The results showed that significantly more severe

postoperative complications occurred following treatment by enterostomy. Moreover, both short-term (surgical site infection, wound dehiscence) and long-term (short bowel syndrome, adhesive bowel obstruction) complications occurred significantly more in those treated by enterostomy. Lastly, no significant difference was found in occurrence of anastomotic leakage, stenosis and mortality rates between both treatment strategies.

FUTURE RESEARCH ON RISK FACTORS FOR COMPLICATIONS

Because of these risks of enterostomy creation and the relatively low incidence of anastomotic leakage the current preference of treatment is now primary anastomosis. Though perioperative factors might still demand stoma formation. In the future, the

team hopes to identify more patient-related risk factors for complications. These could aid surgeons in the decision when to perform a primary anastomosis. These factors can be based on clinical studies but also fundamental studies, evaluating both the biological process of intestinal anastomotic healing as well as the influence of the microbiome which is being researched in a joint effort between the Pediatric Surgery department and the Tytgat Institute (Prof. Wouter de Jonge). ●

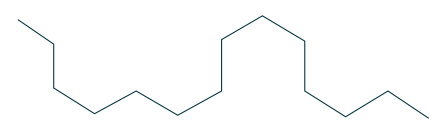


**“Interdisciplinary team science,
using human and animal models
to understand how early life
adversity affects brain aging”**

Early life origins of dementia



Early environmental exposures may have long lasting consequences. The group of researchers who have been studying the long term consequences of prenatal exposure to the Dutch famine are now exploring effects on aging.



It is increasingly being recognized that neurodegenerative diseases start many years before clinical symptoms become apparent. However, it is now emerging that the basis for risk of developing neurodegenerative diseases goes much further back and may be laid in the very earliest stages of life. This may seem like a long shot, literally, as the diagnosis of diseases like Alzheimer's disease usually occurs towards the end of life, and the factors playing 70 to 80 years before that may not seem significant. However, considering that the structural and functional organization of the adult brain is mostly laid down during pregnancy and the early postnatal years and we largely have to deal with these for the rest of our lives, it is plausible that aberrations in these early processes make the brain more vulnerable for disease in later life.

PRENATAL EXPOSURES AND BRAIN DEVELOPMENT

In a recently published systematic review, AR&D researchers Amber Boots, Susanne de Rooij and Aniko Korosi reported that factors related to a suboptimal prenatal environment, such as a low or high birth weight or being born in an area characterized by a high infant mortality rate, are associated with an increased dementia risk [Boots et al. *Neurosci Biobehav Rev*, 2023]. An additional systematic review by the team provided a convincing body of evidence showing that brain volumes in regions associated with Alzheimer Disease are often smaller after adverse prenatal exposures, including prenatal exposure to various harmful substances [e.g. alcohol and drugs], placental dysfunction and maternal anemia [Wieggersma et al. *Soc Psych* 2023]. With smaller brain volumes in these areas constituting a risk factor for the development of Alzheimer Disease, this suggests that the negative effect of adverse prenatal exposures on brain growth may be one of the ways that these factors increase the risk for Alzheimer Disease.

DUTCH FAMINE BIRTH COHORT STUDY

Studying the potential early life origins of dementia in humans is very challenging given the long time lag between exposure and

“The Dutch famine birth cohort offers a unique opportunity for research on aging.”

disease. Studies are usually dependent on retrospective reporting of early life adversity by older participants, which is hampered by difficulties memorizing this. The Dutch famine birth cohort investigates the long-term health consequences of prenatal exposure to undernutrition. With cohort members currently aging, this offers a unique opportunity to study potential associations with brain aging and cognitive decline and dementia. Using cognitive testing and MRI neuroimaging, De Rooij and Boots have so far demonstrated that especially undernutrition during early gestation seems to modulate the risk for dementia. Exposure to famine in early gestation was associated with decreased selective attention at age 58 and especially in men also with smaller brain volumes, worse brain perfusion, higher BrainAge and patterns of resting state functional connectivity network desegregation fitting with brain aging. Currently, they are studying longitudinal changes in brain structure and function in these individuals.

PRECLINICAL MODELS

The observational evidence in humans is corroborated by findings from preclinical models in which early life adversity has been shown to promote cognitive decline at a later age and to accelerate aging, both primary risk factors for Alzheimer Disease. Korosi and her group utilize exposure to an impoverished environment (limited nesting and bedding) during the first week of life in mice to investigate the effects early life stress in the offspring. When exposing



Amber
Boots



Susanne
de Rooij



Aniko
Korosi

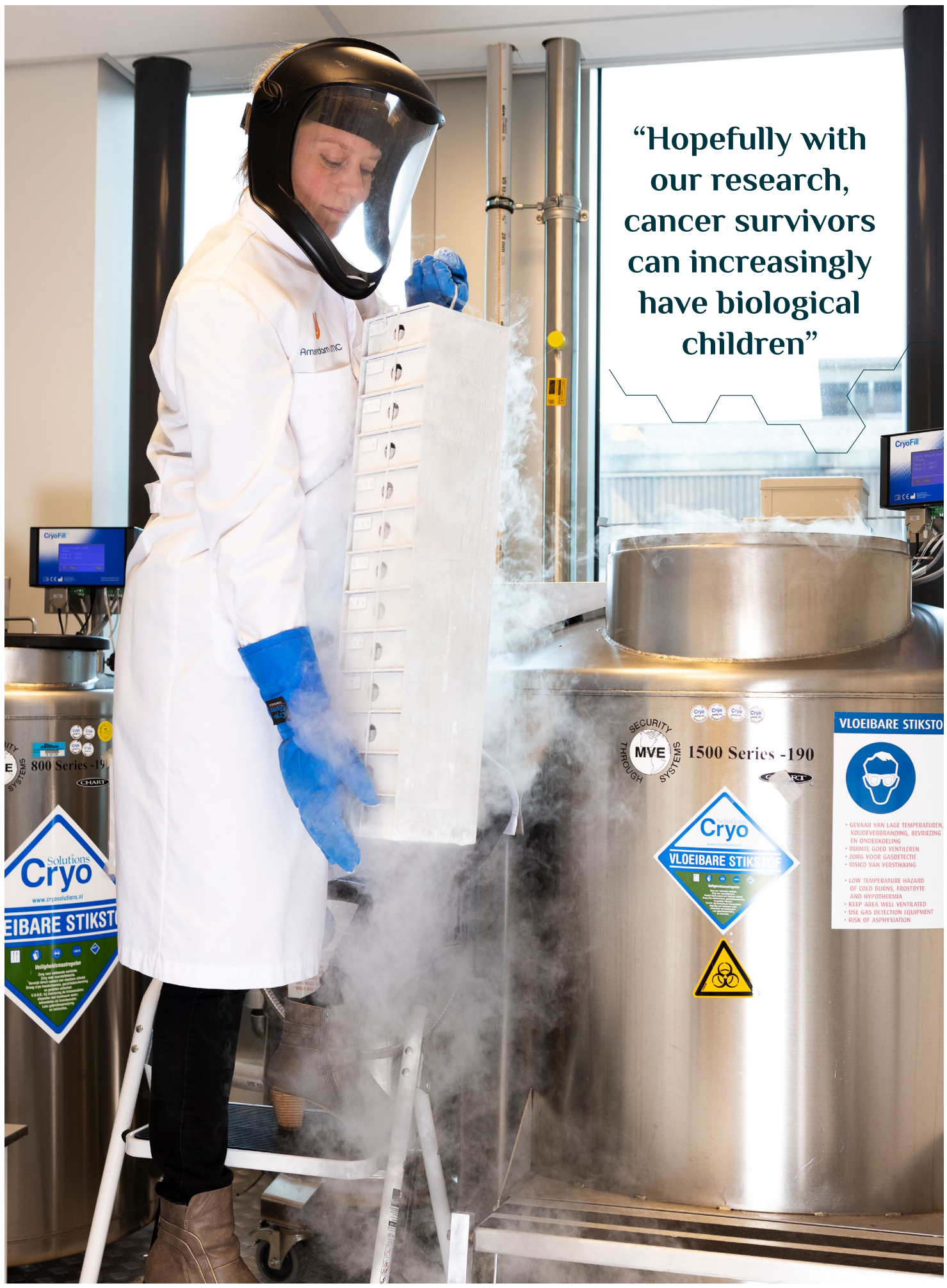
predictable transgenic Alzheimer Disease mouse models (APP/PS1) to early life stress, these exhibit further impairment in cognition, increased amyloid plaque deposition and excessive neuroinflammatory response. Korosi is currently exploring if these effects might be mitigated with an anti-inflammatory diet improved with fatty acids.

INTERDISCIPLINARY RESEARCH

Observing the complementarities between their lines of research, and with an eye for the importance of translation of preclinical models to humans, Korosi and De Rooij decided to join forces. With a grant from the UvA Amsterdam Brain and Cognition (ABC), they were able to set up a collaboration studying lipids and fatty acids as potential mediators in the relation between early life stress and cognitive decline later in life. Their collaborative work led to their mutual participation in a large international collaboration receiving a grant from the EU Joint Program for Neurodegenerative

Disease Research in 2022. The project is aimed at identifying early biomarkers of neurodegeneration and cognitive decline. In addition, the team also acquired funding from Alzheimer Nederland to investigate whether early life stress might increase Alzheimer Disease risk by instigating mitochondrial dysfunction and whether this can be targeted among others via dietary strategies. With these funds for research, the interdisciplinary team will now focus on early biomarkers predictive of cognitive dysfunction and neurodegeneration in the animal as well as human equivalent of their early life adversity studies and will employ the animal model to investigate the causal role of early life adversity in predisposition to Alzheimer Disease as well as diet-based strategies (early and later in life) for alleviating these effects. In the long-term, the team hopes to be able to contribute to a better understanding of the role of early life adversity in brain aging and neurodegenerative diseases and to find targets for prevention. ●

“Hopefully with our research, cancer survivors can increasingly have biological children”



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- Het is niet toegestaan om de tank te openen of te repareren.
- Het is niet toegestaan om de tank te gebruiken voor andere doeleinden.
- Het is niet toegestaan om de tank te gebruiken voor opslag van andere stoffen.

LET OP! De tank kan zeer koud zijn. Het is niet toegestaan om de tank te raken met de handen of andere lichaamsdelen.

SECURITY THROUGH SYSTEMS

MVE

1500 Series -190

Cryo Cryo Cryo Cryo

Cryo

VLOEIBARE STIKSTOF

BIOHAZARD

VLOEIBARE STIKSTOF



- GEVAAR VAN LAGE TEMPERATUREN, KOUDEVERBRANDING, BEVRIEZING EN ONDERKOELING
- RIJMEER GOED VENTILEREN
- ZORG VOOR GASDETECTIE
- RISICO VAN VERSTIKKING

- LOW TEMPERATURE HAZARD OF COLD BURNS, FROSTBITE AND HYPOTHERMIA
- KEEP AREA WELL VENTILATED
- USE GAS DETECTION EQUIPMENT
- RISK OF ASPHYXIATION

Towards a fertile future for male childhood cancer survivors



Although improved treatments have increased survival rates in childhood cancer patients, they are also increasingly confronted with late effects of treatment, including infertility. Research at the Reproductive Biology Laboratory brings hope.



Ans
van Pelt



Callista
Mulder



Jillis
van Maaren

CANCER-FREE, BUT CHILDLESS

Cured of their cancer, some cancer survivors are still held back by the chains of their disease. Life-saving treatments such as chemo- and radiotherapy can cause irreversible damage to the testicular spermatogonial stem cells (SSCs). These SSCs, which are present in the testes from birth onwards, are the precursors of sperm and therefore the key to male fertility. Once destroyed by gonadotoxic treatments, biological parenthood is out of question. The Reproductive Biology Laboratory, led by professor Ans van Pelt, aims to renew the hope, and ability, for these men to have children of their own.

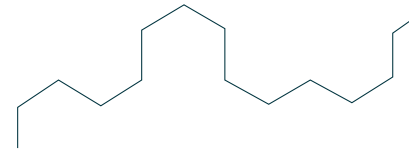
PRESERVATION AND POSSIBLE RESTORATION OF FERTILITY

Since 2009, Amsterdam UMC has offered fertility preservation to parents of boys at risk of becoming infertile, by cryopreserving a biopsy of the testis prior to treatment. As, worldwide, these boys are now reaching adult ages, the development of a fertility restoration treatment is an urgent topic in the field of male reproductive biology and medicine. In the Reproductive Biology

Laboratory, this is exactly what AR&D researchers Jillis van Maaren, Callista Mulder and Ans van Pelt are working on. Within five years, they hope to achieve clinical application of spermatogonial stem cell autotransplantation (SSCT). This potential treatment uses the patient's preserved testicular biopsy to isolate, propagate the SSCs and re-inject them into the testes. There, the SSCs can migrate to their natural niche and re-establish spermatogenesis within the tissue. Natural conception of children without additional reproductive techniques such as in vitro fertilization will then be possible.

SAFETY FIRST

Current research into SSCT is done within the ZonMw TAS project (in Dutch: Translationeel Adult Stamcelonderzoek). As safety is of course a major concern with any new therapy, studies have been performed in a mouse model to establish the safety of the procedure for both the cancer survivor and his future children. The procedure itself involves an injection of SSCs into the testes and mouse studies have shown that this is well tolerated without acute or chronic side



“Safety of Spermatogonial stem cell autotransplantation is of course of utmost importance.”

effects. Furthermore, within two generations of naturally conceived mice born from a SSC-transplanted male, no increase in congenital and developmental abnormalities was found. Throughout life, SSCT-derived mice showed no increased risk of cancer or metabolic diseases. These findings are crucial in working towards a potential therapy, which patients should feel secure to pursue.

CONCERNING SSCS – MORE IS BETTER

A crucial part of SSCT is the culture of SSCs to increase their number prior to transplantation, because the number of SSCs obtained from a pre-pubertal testicular biopsy is considered too small for effective restoration of spermatogenesis. Therefore, PhD candidate Van Maaren studies how various culture conditions might benefit the proliferation of the SSCs. Multiple factors, including the culture temperature and specific components of the culture medium appear to have a profound influence. In parallel, Van Maaren establishes methods to upscale the current lab-based culture to clinical volumes and methods consistent with Advanced Therapeutic Medicinal Product (ATMP) regulations. This research hinges on the availability of human testicular tissue, which is difficult to obtain. Therefore, the group is very grateful for previously donated testicular tissue from orchiectomies of prostate cancer patients from the Amsterdam UMC Urology Department. Additionally, through a recently established cooperation with the Center for

Gender Dysphoria, spare testicular tissue is donated by transwomen after gender-affirming surgery.

TOWARDS A CLINICAL TRIAL, AND HOPE

Van Pelt is enthusiastic about progressing to this pharmaceutical phase. Currently, a Central Committee on Research Involving Human Subjects (CCMO)-request is being prepared to ask permission for a first clinical trial. In support of this application, Mulder is leading a qualitative study to uncover the perspectives of childhood cancer survivors regarding their experiences with fertility preservation and wishes and concerns for possible future fertility restoration. The importance of this study has been recognized by ZonMw as well, who in December 2022 have allocated a VIMP (in Dutch: Verspreidings- en Implementatie-impuls) grant to the research group to execute this work. The study will be conducted in cooperation with a pediatric oncologist, psychologist and late-effect practitioners of the Prinses Máxima Centrum in Utrecht, a representative of the Vereniging Kinderkanker Nederland, and an ethicist of Leiden UMC.

Cancer can take away much from the life of survivors, including the ability to make certain choices to live it. Though a lot of work remains to be done, Van Pelt and her team are hopeful that for these patients hope may again be restored of having their biologically own children one day. ●



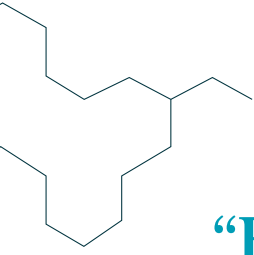
“We aim to provide a much needed bridge between practice and science for people with genetic disorders”



Personalized medicine for rare genetic neuro- developmental disorders



About one-third of the Emma Children's Hospital population, and up to 3% of the Dutch general population, consists of individuals with [rare] genetic neurodevelopmental disorders, such as Down Syndrome, 16p11.2 duplication syndrome, and Williams Syndrome. These disorders are accompanied by many complex physical and mental problems, and have a great impact on functioning and quality of life, for children as well as their families. Even though knowledge on these disorders is increasing, there is a currently lack of therapies. This calls for a framework of personalized medicine trial methodology for rare disorders.



“For rare diseases, a powerful alternative for RCTs are the N-of-1 designs.”

EVIDENCE-BASED CARE

AR&D researchers Annelieke Muller (PhD-candidate), and Dr. Agnies van Eeghen, intellectual disability physician (in Dutch: Arts voor Verstandelijk Gehandicapten), work both at the Emma Children’s Hospital and ‘s Heeren Loo, the largest Dutch care organization for individuals with an intellectual disability (ID). Within the research group of Van Eeghen, the main focus is on the development of therapies and outcome measures for individuals with rare genetic neurodevelopmental disorders (RGNDs) and/or ID. To identify targets for treatment and prevention, the group studies the natural history of several genetic syndromes, with a focus on neuropsychiatric manifestations. To get all this knowledge into care nationally and worldwide, they are improving guideline methodology with the European Reference Network for Rare Malformation Syndromes, Intellectual and Other Neurodevelopmental Disorders (ERN ITHACA). ERN ITHACA is a patient-centered network that meets the needs of those individuals for highly

specialized, multidisciplinary healthcare, providing an infrastructure for diagnosis, evidence-based management and collecting data.

TOWARDS PERSONALIZED TRIALS

The PhD project of Muller concerns interventions and outcome measures in genetic syndromes, focusing on alternative trial designs to enable personalized and evidence-based care. Interventional research in this population is quite challenging. Traditional randomized controlled trials are often not feasible, because of the rarity of the specific disorders, vulnerability of patients, and the heterogeneity between and within disorders. Powerful alternatives are single-case experimental designs (SCEDs), such as the N-of-1 design and the multiple baseline or stepped wedge design. In this type of study, the patient is his or her own control. Despite of its great potential to provide evidence of effectiveness for individuals as well as groups of patients, N-of-1 studies [randomized, placebo-controlled multiple crossover trials]

Agnies
van Eeghen



Annelieke
Muller

are sporadically performed in RGNDs. Based on a systematic review that was performed recently by the team, recommendations for future N-of-1 studies are provided. Also, several N-of-1 clinical trials were started to investigate the effectiveness of different interventions for genetic disorders. For example, the team is investigating the efficacy of novel treatments for shared comorbidity in these disorders.

They study the potential effects of cannabidiol (CBD) for severe behavioral manifestations in a proper scientific yet personalized way. An N-of-1 trial will start soon in 30 children and adults with Fragile X syndrome, Tuberous Sclerosis Complex and Sanfilippo, including various personalized

outcome measures. Furthermore, there are questions on the effectiveness and side effects of methylphenidate in patients with neurodevelopmental problems. To study this, an N-of-1 series of studies begins to investigate the effectiveness of methylphenidate for Attention Deficit Hyperactivity Disorder (ADHD) symptoms in Smith-Magenis syndrome, as this medication has been commonly used in clinical practice in this patient population.

In addition, the team is piloting different types of SCEDs in the clinic to gather evidence for treatments at the individual level, while hopefully also collecting cases for larger series. Different trial designs are proposed to the patient or family members and relevant



outcomes are discussed [see figure on page 31]. Based on the patient preference, such as whether placebo or withdrawal of the intervention could be introduced, trials were started.

MEASURING WHAT MATTERS

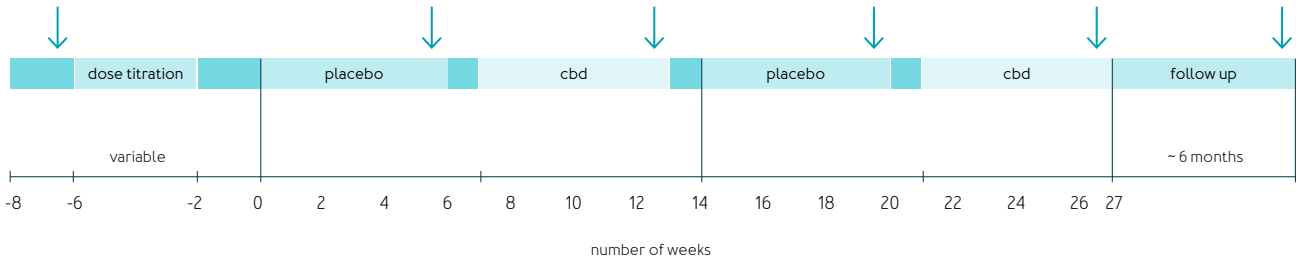
Only adjusting trial designs for patients is not enough. It is important to know what matters to them and incorporate these outcomes into trials, especially in such a heterogeneous population where health manifestations and treatment goals differ a lot. There is a great need for outcome measures that are relevant to patients, including patient-reported outcome measures (PROMs) and digital apps. As there are many available outcome measures, the team started a scoping review to provide an overview of which outcome measurement instruments have been used in clinical trials. Moreover, they developed and validated a disorder-specific PROM for Tuberous Sclerosis [the TSC-PROM] to assess health-related quality of life, which can be used in both clinical settings and research settings. Furthermore, the team is working on personalized outcome measures, such as experience sampling methodology (ESM), which includes real-time data collection on multiple occasions within the day and over time, and Goal Attainment Scaling (GAS). Prior to a treatment, goals are identified that are

relevant to the patient together with the patient and family or caregivers. Goals could be different for each patient, but it has to do with the construct that the treatment will target. In this way, outcome measures can be used that are specifically relevant to the patient, which eventually enhances treatment adherence as well. Also, policy makers such as the Medicines Evaluation Board, European Medicines Agency, and Food and Drug Administration are very interested in these types of outcome measures, with implications for registration or reimbursement.

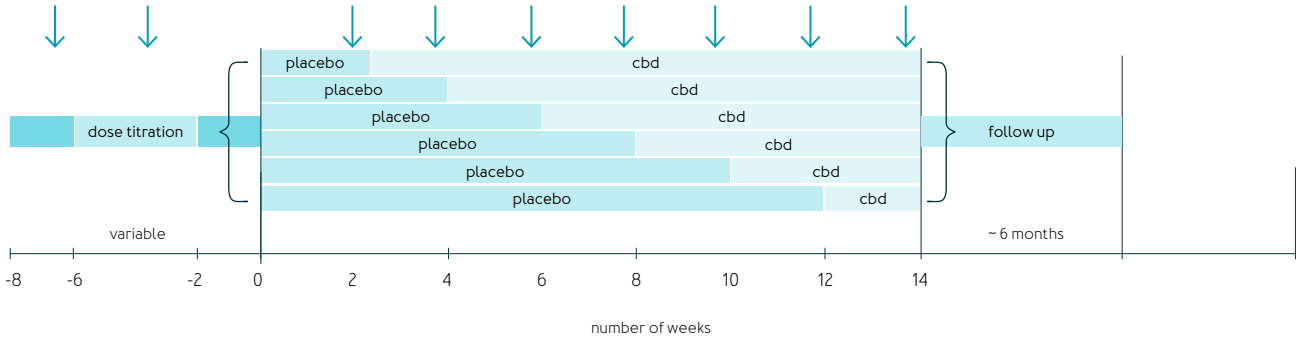
FROM INTELLECTUAL DISABILITY TO DISORDER-SPECIFIC CARE

Last but not least, the team wants to improve personalized care in the ID field. With advances in genetic technology they can increasingly identify a genetic diagnosis in individuals with an ID. Knowledge on the etiology of ID helps clinical management by involved medical doctors such as ID physicians, as well as other members of the multidisciplinary team such as psychologists, dieticians, and professional caregivers. They can use this information on the genetic etiology for education, [psychological] interventions (e.g. for anxiety or self-injurious behavior which is common in specific genetic syndromes), and understanding and treating disorder-specific manifestations (e.g. obesity

N-of-1-design



Multiple baseline design



↓ outcome measurements ■ no study medication

in 16p11.2 deletion syndrome, anxiety in Fragile X syndrome or epilepsy in Tuberous Sclerosis Complex). However, it is unclear to what extent information on genetic etiology has been implemented into multidisciplinary care. Therefore, the team started a cross-sectional study at 's Heeren Loo to examine the current clinical practice with regard to genetic diagnostics and multidisciplinary care. They aimed to study how often a genetic cause was reported, by whom (such as (ID) physicians, behavioral therapists or caregivers), and what clinical and demographical factors were associated with presence of the information on genetic etiology. Results will be published soon, but to get a first glimpse of the findings: a minority of individuals with an ID has received genetic testing. Results were mainly reported in the files by physicians and caregivers, and less frequently by behavioral

therapists. Level of ID, age, and who the legal representative was, were associated with initiating genetic testing. More research is necessary to identify facilitators and barriers for genetic testing, and to enable disorder-specific, holistic care.

For these projects, the team gets a help from colleagues, such as the pediatricians and colleagues from the Women and Child Center (VKC), Psyche and Departments of Psychiatry, Neurology, Community Genetics and Human Genetics, the Alzheimer Center; and many more. Together, they aim to provide evidence-based interventions and tailored care for the vulnerable and under-researched patient population, providing a much needed bridge between practice and science. This is also the aim of the Emma Center for Personalized Medicine [see page 53]. ●

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AR&D events 2022

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AR&D ANNUAL SYMPOSIUM

June 2nd, 2022

The annual AR&D symposium was held on 2 June 2022. The theme of the symposium organized by Prof. Dorret Boomsma and Prof. Tessa Roseboom was **Twinning and winning, just the beginning**. More than 50 participants were present online and heard the presentations of keynote speakers Dr. Jenny van Dongen and Prof. Eveline Crone.

Jenny van Dongen, assistant professor working at the Netherlands Twin Register at the VU, presented on the discovery of a unique epigenetic signature among monozygotic twins. Such identical twins arise from a single embryo that splits into two in the very early stages of pregnancy and retain the same base-pair sequence of their genes. To date, it is unknown why this happens. The groundbreaking discovery of a persistent epigenetic signature could lead to new insights into the blueprint of identical twins and is a huge step forward in understanding identical twins. Hopefully this work will also provide new insights into congenital disorders in which monozygotic twins are overrepresented. After the presentation, there was a discussion which included possibilities to collaborate with Dr. Bernadette de Bakker and colleagues to use material from The Fetal Biobank for further research.

The second keynote speaker was **Eveline Crone**, professor of Developmental Neuroscience in Society. Prof. Crone's research examines the psychological and neural processes involved in self-regulation and social development. All of her work employs a developmental cognitive neuroscience approach to examine the relation between brain development and changes in psychological processes from birth to adulthood, with a special focus on adolescence. Crone is the Vice President of the European Research Council (ERC), and based on her experience, she explained to the audience how to write a winning ERC grant application. She gave tips such as don't belittle on your resume, just let them see you can do the work (supported with preliminary data), and the added value of letting others read along when writing a research proposal. There was a discussion about the possibilities that Research Grant Support can offer within Amsterdam UMC in providing a range of support from pre- to post-acquisition.

The award ceremony of the **Travel grants** was also part of the symposium. A total of 37 applications were submitted, of which 13 grants were awarded. Two for a working visit and eleven for an international conference.

Netherlands Twin Register
<https://tweelingenregister.vu.nl>



Dept. Biological Psychology, Vrije Universiteit Amsterdam
Faculty of Behavioural and Movement Sciences (FGB)

Active members in March 2019	0-13 year	13-17 year	18+	Total
Twins	31,718	26,316	64,518	122,552
Non-twin siblings	1,136	963	11,751	13,850



The European Research Council

“
The ERC awards long-term grants to researchers of any nationality and age, from anywhere in the world, who wish to carry out their research projects in a host institution based in Europe. Scientific excellence is the sole evaluation criterion.
”



SYMPOSIUM 'LABORATORY ANIMAL (FREE) RESEARCH IN AMSTERDAM UMC - WHERE ARE WE NOW?'

June 8th, 2022

On Wednesday 8 June 2022, seven of the eight research institutes of Amsterdam UMC jointly organized a symposium on 'Animal (free) research in Amsterdam UMC - Where are we now?'. From each research institute, one researcher presented their research and indicated for which part no laboratory animals are necessary, and for which part they still are used/needed, and why.

From Amsterdam Reproduction and Development, Dr. Callista Mulder, presented animal-free research, such as testing the [epi] genomic stability of cultured human germ cells as part of the development of novel fertility treatments. However, pre-clinical investigation of the health risks for the generated offspring from these cultured germ cells can only be studied in vivo, as no animal-free alternatives exist. Careful consideration of both statistical and biological factors is cruci-

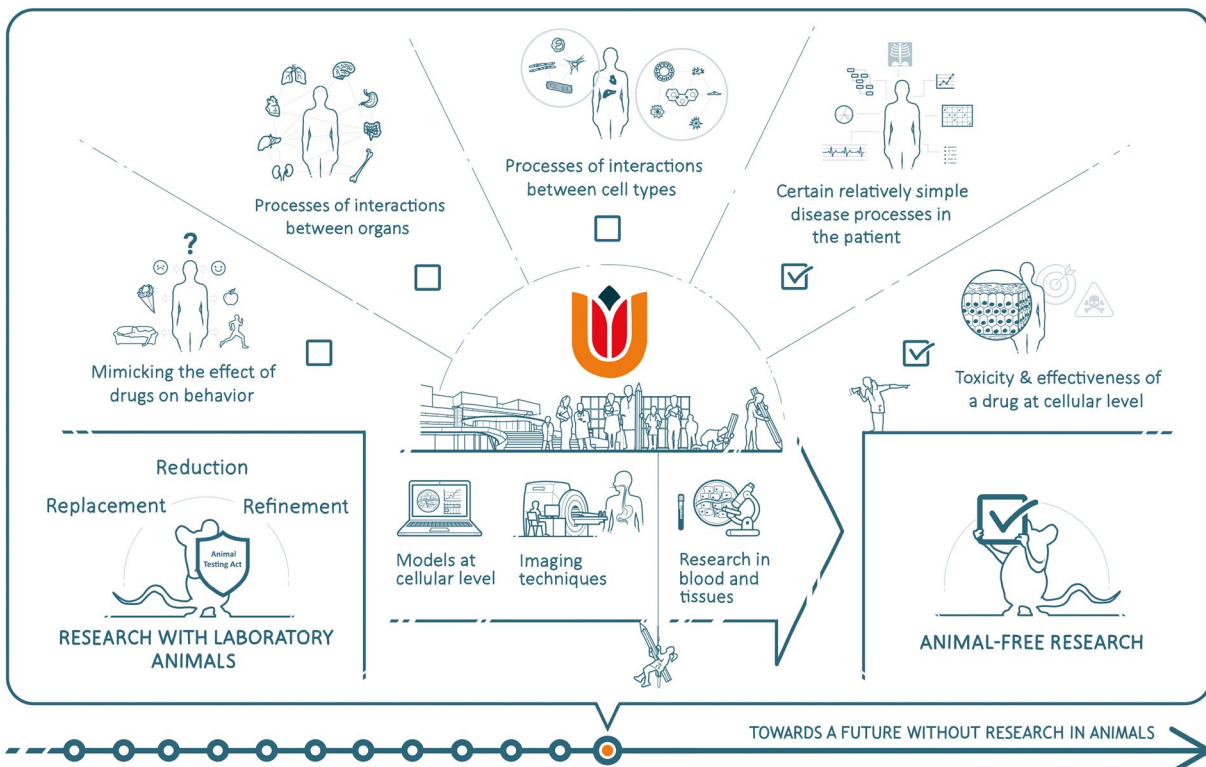
al during experimental design with laboratory animals, to reduce the number of animals and increase animal welfare, thereby increasing the validity of the study. At the end of the symposium there were two panel discussions, each with its own main question:

1. Is animal testing still necessary?
2. What is needed from Amsterdam UMC to be more transparent/open about the use of laboratory animals?

In addition to the two portfolio holders of laboratory animal policy of the [Amsterdam Research Board](#) and the chairman of the Animal Welfare Body of location AMC, the following people were attending the panel discussions: a researcher Ethics and Animal Agency of Wageningen University & Research, senior program manager 'More Knowledge with Fewer Animals' of ZonMw, director of

Proefdiervrij and a science advisor of 'People for the Ethical Treatment of Animals' (PETA).

The symposium was positively evaluated by the audience. There was an interesting discussion and points were raised for our research institute as well as Amsterdam UMC to improve. The meeting will be an annual event to show society and politics what we are doing, and to discuss the new developments but also the challenges that exist to replace research in laboratory animals with animal-free models. A video on animal research in Amsterdam UMC can be found [online](#).



AR&D events 2022



AR&D NETWORK MEETINGS

June 29th, 2022 and September 14th, 2022

In 2022, Amsterdam Reproduction and Development organized two **Network Meetings**. During these meetings researchers had the opportunity to meet live and network with other researchers within AR&D.

Following the symposium's theme Twinning and winning, prior to the first network meeting in June, attendees were asked *What are you good at in terms of research?* and *What can you use help with in the field of research?* The answers given were printed on the name badge, so that people could exchange knowledge/ skills and experience with their 'research twin' during drinks at the end of the afternoon.

The award ceremony for the **AR&D Research Grant** was also part of the program. Grant recipients briefly presented their research plan to the attendees. As a result of these presentations, plans were already made that afternoon for new collaborations and researchers from different departments were able to meet and exchange ideas in carrying out the research. It was nice to immediately see in practice what hearing from each other can bring!

The second network meeting in September focused on valorization and the added value valorization can have for research. From their role as Business Developers at Innovation Exchange Amsterdam (IXA), **Steven van Huiden and Maaïke Alderliesten** explained how their expertise helps researchers to make an impact. In addition to examples of which forms of valorization can be applied within research, the policy on this within Amsterdam UMC was also discussed. The speakers hope AR&D researchers find their way to the **IXA office**.

The second presentation was given by professor **Velja Mijatovic**. Besides being a gynecologist with a sub specialism in reproductive medicine, he is also a principle investigator at the Department of Reproductive Medicine of Amsterdam UMC. He spoke about his experience for the H2Oil trials with investigator initiated studies with financial support of the industry. These trials are about tubal flushing with oil-based contrast during hysterosalpingogram (HSG) in subfertile women. Velja indicated that a fruitful collaboration with an industrial partner is certainly possible and that the financial agreement should be clear on study data property and responsibilities on the conduct of the study. He also stated that a close collaboration with legal support is needed.

After both presentations, an interesting conversation ensued with those present, in which researchers asked questions about their possibilities with valorization and practical advice and tips were given by all three presenters.





AR&D RETREAT 2022 - SHOWTIME – UNMUTE YOURSELF

October 13th and 14th, 2022

On the 13th and 14th of October it was finally Showtime! The theme of this year's Retreat was **Showtime, unmute yourself**. Since, it was the first in-person Retreat after two years of the COVID-19 pandemic, the focus of the Retreat was on getting to know each other and each other's research. The content of the program was based on the theme and songs of the rock band *Queen* were played frequently during the Retreat. The Retreat committee even managed to let everybody dance on a spectacular choreography on *Don't stop me now* during the energizer.

The program kicked off with a keynote by **Dr. Sophie Petropoulos**. As international guest speaker, she walked the attendees through exciting reproductive medicine developments at her two labs situated in Canada and Denmark. She completed her talk with a short insight about her particular position, and the involved science communication, which naturally formed the bridge for the next invited speaker. **Marc van den Broek**, as former writer & spokesman at Amsterdam UMC, gave everyone a glimpse of *"talking science"*, or in other words; how to refine science communication. Both keynote speakers shined a light from a different angle about how to present, communicate and perhaps collaborate on scientific endeavors, to reach the intended target audience or an experimental goal.

After listening, it was *Show Time* for the participants: in breakout rooms, every participant pitched his or her own project with the aid of an ePoster to other AR&D researchers, in

as short as only three minutes! Congratulations to the award winners for this part of the retreat: Féline Voss (best poster) and Jill van Maaren (best pitch)!

How would you explain your research in kindergarten language? Which talent would you use to act in a circus? What do you like the most/least about your research? This and many other questions teased the participants get to know each a bit better, also outside of their research fields. **Interactive workshops** were offered, after booth camp or yoga, on various topics ranging from *"communication in culturally diverse teams"* & *"data visualization"* to *"stress recognition & treatment"* and *"storytelling"*. As a final plenary part of the program, an intriguing **panel discussion** shed light onto principal differences and similarities when it comes to career growth in academia and industry, and the involved decisions. As time flew by, the end of the retreat was there, but not before a final plenary dance of course.

The Retreat was a huge success, thanks to the organization of the Retreat committee consisting of Michelle Romijn, Nienke Halbmeijer, Kavish Kohabir, Hannah Juncker, Wieke Beumer, Danah Kamphuis and Tamar Kruit. ●

AR&D grants 2022



The AR&D research grant round 2022 enabled researchers from Amsterdam UMC to perform research in the field of reproduction and development (the circle of life). All research projects (fundamental (biological) research, clinical or epidemiological research, paramedic, translational research, or research that aim to improve health care within the field of AR&D) were eligible. Multidisciplinary research projects and research projects in the paramedic science field were especially encouraged to be submitted.



These grants could be used to cover personnel costs, bench fee, equipment, conference budget and other related research expenses. For the total grant program €500.000 was available that was distributed over the different grant types (see below).

1. Paramedic Science Grant €25.000
2. Start small, Think big €25.000
3. Move forward €50.000

PARAMEDIC € 25.000



Sarah Michon

Re-use of disposable specula in treatment of fertility patients undergoing multiple inseminations: A discrete choice experiment and small sample pilot study Re-Spec-t

My name is Monique Mochtar. I am a gynecologist, specialized in reproductive

medicine, and working at the Center of Reproductive medicine at Amsterdam UMC. I represent Sarah Michon, our head nurse in this research, because she was on maternity leave.

On a daily base we try to make women pregnant with assisted reproduction techniques for example intra-uterine insemination. Women are inseminated with processed semen at the day she has her ovulation. To insert the semen into the womb we need to use a speculum. After the procedure we throw this speculum away in the bin. This is not very durable, on the contrary, this is a waste of means. So we had the idea to re-use the speculum by cleaning it after use with lukewarm water, dry it with a paper towel and hand it over to the women in a paper bag. We asked her to bring it back for the next insemination. Because most women need repeated attempts before she becomes pregnant.

How will the women react we wondered? Will they refuse because of hygienic reasons? Overall 138 women filled in the questionnaire; 65% were willing to reuse the speculum, 6% was indecisive and 29% would refuse. Age and personality traits did not influence the choice-making. The patient experience study is still ongoing.



Sarah
Michon

Bernadette de Bakker



Judith Dekker

START SMALL, THINK BIG

€ 25.000

Bernadette de Bakker

Using cutting edge imaging modalities to study the intimate hidden security of early life

My name is Bernadette de Bakker and I work as assistant professor in human embryology and fetal imaging at the Department of Obstetrics and Gynecology. In 2017 I founded the Dutch Fetal Biobank, in collaboration with Prof. Eva Pajkrt, Dr. Maurice van den Hoff and others, which enables parents to donate an embryo or fetus to science after termination of pregnancy, preterm labor or an ectopic pregnancy.

Thanks to collaborating gynecologists in various centers in The Netherlands we have collected more than 30 samples of ectopic pregnancies, i.e. excised fallopian tubes containing a complete pregnancy dated roughly between 5 and 9 weeks of pregnancy. With this AR&D grant and together with Prof. Judith Huirne and Prof. Theo Smit we aim to visualize these ectopic pregnancies in 3D with histological resolution, by using contrast-enhanced micro-CT imaging. This valuable material is unique in the world and will provide us with information on stem cells, early placentation, yolk sac development and embryogenesis.

I felt true excitement and scientific curiosity when I noticed that we received the grant which enables us to scan all 30 collected samples. Until then we only scanned one specimen which received immediate fame. Because it was the very first time that we

scanned such a young human embryo in the intimacy of the fetal membranes, Yousif Dawood and I were awarded with the best image award from the journal Radiology in 2021 (see AR&D annual report 2021) and in January 2023 we even won the best cover of the century award!

Judith Dekker

Birth Factors Relating to Early-onset Endometriosis (BIFREE study)

My name is Judith Dekker. I am a gynecologist working at the Department of Reproductive Medicine at Amsterdam UMC with special focus on Endometriosis and special interest in Pediatric and Adolescent Gynecology. Therefore, I see patients with endometriosis varying in age from around 10- 60 years. There is still a delay in diagnosing the disease. Endometriosis, as a chronic disease, is lowering the quality of life in all patients. As endometriosis can already be found in adolescence. The early life origins of endometriosis are insufficiently investigated. Birth characteristics may provide risk stratification for diagnosing endometriosis in adolescence or young adults.

In the spring of 2022, we were awarded an AR&D grant. Our team, consisting of gynecologists, neonatologist, obstetrician and epidemiologist, was very excited about this and we immediately strengthening our collaboration with our Danish colleagues. Thanks to the AR&D grant we are able to use the Danish Health Register and the Danish Medical Birth Register to compare birth related parameters in women with and without endometriosis.

So far, we are now adding the last data to the database, including the data of 2022. This is almost finalized and then statistical analyzing can proceed. The birth cohort data will offer us a unique opportunity to test hypothesized associations between early life environment and endometriosis in large sample sizes over a considerable period of time. Finding parameters will induce earlier recognition of the disease with faster treatment which can resolve symptoms, prevent progression of the disease and preserve fertility later in life.



Emilie
van Limburg
Stirum



Jan-Paul
Roovers

Jan-Paul Roovers

Application of tissue-engineered amniotic membranes for surgical repair of vesicovaginal fistulas

My name is Jan-Paul Roovers and I am a professor of gynecology and urogynecologist in Amsterdam UMC. Most problems that are treated in urogynecology are related or the direct consequence of pregnancy and labor. Incontinence, pelvic organ prolapse and other pelvic floor problems can interrupt the circle of life. The goal in urogynecology is to restore urinary, sexual and reproductive function of women and reintegrate them in the circle of life. We received the AR&D grant for our research on obstetric vesicovaginal fistula. Vesicovaginal fistula are a severe type of pelvic floor injury where an opening is formed between the bladder and vagina as the direct result of prolonged obstructed labor. There are approximately 2-3.5 million women, mostly in Sub-Saharan Africa that suffer from continuous leakage of urine caused by vesicovaginal fistula.

This grant gave one of our PhD candidates, Lennart Maljaars, under supervision of Dr. Zeliha Guler, the opportunity to design a tissue-engineered solution for surgical repair of vesicovaginal fistula. We identified amniotic membranes as a biomaterial with regenerative capacity and used tissue engineering techniques to mechanically reinforce the membranes. In a second research project vaginal cells were grown on the tissue-engineered amniotic membrane to test the biocompatibility. We thank the Amsterdam Reproduction and Development committee for their support through this grant. The grant allowed us to make important steps in our quest for a surgical solution for vesicovaginal fistulas, that may bring direct relief to millions of women worldwide.

Emilie van Limburg Stirum

Cervical length measurement to predict preterm birth

My name is Emilie van Limburg Stirum and I work as a resident not in training and PhD student at the Department of Obstetrics and Gynecology at Amsterdam UMC. With the support of Prof. Martijn Oudijk, Dr. Marjon de Boer, Dr. Janneke van 't Hooft and Dr. Frederik Hermans, I am grateful to have received an AR&D grant. This grant allowed me to start the research project entitled: 'Cervical length measurement to predict preterm birth: overview on population differences, different cut offs and gestational age at measurement using individual participant data analysis' and gives me the opportunity to collaborate with researchers internationally.

The aim of the project is to evaluate the predictive capacity of cervical length measurement in different (high) risk populations at different time-points in pregnancy. This includes studying the differences in cervical length between different geographical populations, as well as determining the most accurate cut-offs and gestational age at measurement. By using individual participant data, statistical power will increase and therefore increase evidence to answer our research questions. With our project we hope to contribute to a more individualized risk profile for each patient at risk for preterm birth.



Larissa van der Windt

Larissa van der Windt

Core outcome measurement instruments to measure late neurodevelopmental morbidity in prevention of preterm birth

My name is Larissa van der Windt and I work as a medical doctor at the Department of Obstetrics and Gynecology in Amsterdam UMC. I received the Start Small, Think Big Grant of the AR&D for the research project: 'Core outcome measurement instruments to measure late neurodevelopmental morbidity in studies investigating prevention of preterm birth'. With this grant, I was able to formalize a big part of my PhD. I still feel super grateful for this opportunity, and also for my team, Dr. Noor Simons, Annemijn de Ruigh, Dr. Janneke van 't Hooft and prof. Eva Pajkrt, since they really helped throughout the process.

Preterm birth strikes 8-12% of all pregnancies worldwide and has significant impact on individual health and society. Several interventions have been introduced to prevent preterm birth. However, effectiveness of these interventions remains uncertain despite several large trials since there is great heterogeneity in primary outcome amongst these studies. To overcome this, a core outcome set (COS) was developed to increase aggregation of evidence. This COS includes 13 core outcomes that should be reported in prevention of preterm birth studies (what to measure). Late neurodevelopmental morbidity is one of these core outcomes. The next step is to decide how to measure this outcome. Currently there is great variety in measurement instruments used to assess long-term neurodevelopment. A more standardized approach would benefit all future preterm birth trials. With the current project we want to select core outcome

measurement instruments (OMI's) for late neurodevelopmental morbidity for prevention of preterm birth studies.

Tjitske Zaat

The importance of vaso-active hormones of the corpus luteum on endometrium and trophoblast in assisted reproduction

My name is Tjitske Zaat, I am a fertility doctor and part-time PhD student at the Centre for Reproductive Medicine at Amsterdam UMC. The focus of my PhD is frozen embryo transfer, the freeze-all strategy, and the obstetrical and neonatal outcomes after different types of endometrial preparation in frozen embryo transfers.

Pregnancies conceived through assisted reproductive techniques (ART) are more often high risk pregnancies with a worse outcome for mothers and babies. The general believe was that an intrinsic factor of infertile couples including age of the mother or the quality of the embryo were the main causes. Nowadays, it is hypothesized that the primary driver of pregnancy health is the quality of the inner lining of the womb, i.e. the endometrium and not the embryo. We performed a follow up study of the ANTARCTICA RCT on the role of the endometrium and found that a pregnancy conceived in an artificially prepared endometrium with medication, is a strong predictor for a high risk pregnancy. The risks for the mother and baby involve hypertensive disorders of pregnancy (HDP) and other risks due to abnormal placentation. If the endometrium is developed in the natural cycle of the woman, only limited risks are involved in these ART pregnancies. We confirmed our findings in our recent systematic review of 100k pregnancies after ART. In our clinics

we now apply the natural cycle in ovulatory women to avoid these risks. However, not all women form their own/natural endometrium because of anovulation. Given the persisting and increasing need for artificial endometrium preparation, there is a critical need to optimize the existing protocol for women who depend on this approach. The aim of our study is to investigate the fundamental changes in endometrium and trophoblast mediated by the vaso-active hormones produced in the natural cycle by the corpus luteum in the ovary, compared to artificially prepared endometrium. We have just started with the experiments and are excited to evaluate the results in the future!



Tjitske Zaat



Jenny van Dongen

Anne Timmermans



MOVE FORWARD € 50.000

Anne Timmermans

COmparative carbon Footprint assessment of trEatment options for utErine fibroids (COFFEE)

My name is Eva Cohen and I am a PhD student at the Department of Obstetrics and Gynecology at Amsterdam UMC. I am working together with a multidisciplinary team that includes members from the AR&D research group (Dr. Wouter Hehenkamp, Dr. Anne Timmermans, Prof. Judith Huirne), Department of Public and Occupational Health (Dr. Dionne Kringos) and Centre for Sustainable Healthcare (Dr. Niek Sperna Weiland). Our research focuses on the environmental impact of treatments within gynecology and on implementing environmental sustainability outcomes in patient decision-making tools. The aim of our research project is to find ways to mitigate the environmental impact of gynecological care pathways, bridging the gap between three apparently distinct but truly intertwined research topics: environmental research, clinical practice and healthcare policy.

When we found out that our proposal was selected for the AR&D grant, we were honored and thankful that environmental research within Amsterdam UMC was given a kick-start. Because of this internal grant, we were able to create our research team and start close collaborations with a critical partner, the National Institute of

Public Health and the Environment (RIVM). We have been working on waste audits of different treatments for uterine fibroids to quantify their environmental impact, we have developed a patient questionnaire to investigate the patient's climate literacy and we have started a review on environmental sustainability in gynecology and obstetrics. We have also recently submitted our first life cycle assessment of surgical attire, the surgical headcover. Furthermore, thanks to the AR&D grant, we were able to secure additional funding for the entire PhD project awarded by the Amsterdam UMC Doctoral School.

Jenny van Dongen

Epigenetic signature of monozygotic twinning: a tool to study the vanishing twin syndrome and genetic influences on twinning

My name is Jenny van Dongen, assistant professor at the Netherlands Twin Register, Vrije Universiteit Amsterdam. I received the AR&D grant with co-applicants Prof. Dorret Boomsma and Dr. Veronika Odintsova. In 2021, we published the discovery of an epigenetic signature in identical twins. The AR&D grant allowed for several extensions of this work, including validation of the epigenetic signature in individuals with a vanished twin, and studying the link between monozygotic (MZ) twinning and amyoplasia, a condition that shows a > 10-fold higher frequency of MZ twins among patients. So far, we received ethical approval, established a survey and sample collection protocol in close collaboration with the

patient society, and established analysis pipelines. Results are expected in fall 2023. We also submitted a review on the etiology of monozygotic and dizygotic twinning, and performed an epigenome-wide association study of assisted reproductive technology in monozygotic twins. I am extremely grateful for receiving the grant, which provided salary support and finances to measure DNA methylation profiles of Amyoplasia patients and individuals with a vanished twin. Moreover, the attention generated for our research through the AR&D grant resulted in valuable extensions of our network, as I was introduced to experts from the Amsterdam UMC expertise center and the international Amyoplasia consortium, who gave valuable advice on the project. I am also grateful for invitations to present this work at several international conferences.

Eva Kontopodi

Antiviral effects of human milk on cytomegalovirus infection in human infant gut organoid models; AVATAR study

My name is Eva Kontopodi, and I work as a Development Specialist in the Expert team “Early Life Nutrition”. The aim of our study was to evaluate the antiviral effects of human milk on human gut organoids, by using a human fetal gut organoid model, that closely mimics human intestinal cellular heterogeneity and organization. We specifically focused on cytomegalovirus (CMV), to get a deeper understanding on the mechanisms through which CMV affects enteroids. Next, the effects of UV-C irradiation on CMV infectivity are focused on, as this is the most promising non-thermal processing method for donor human milk.

We are extremely grateful to AR&D for granting our study. Thanks to this grant, we are able to study for the first time the antiviral effects of CMV-negative and CMV-positive human milk. I am particularly grateful, since this grant gave me the opportunity to continue the work I started as a PhD, on a topic that I was very dedicated

and passionate about. Therefore, I was very excited when I realized that I was given the opportunity to continue. In addition, this grant resulted in a great collaboration among Wageningen University and Research, Amsterdam UMC and Organovir with Prof. Dasja Pajkrt, Dr. Chris van den Akker, Prof. Hans van Goudoever, Prof. Ruurd van Elburg, Prof. Kasper Hettinga, and Dr. Adithya Sridhar.

Jasper Linthorst

Evaluating the accuracy of micro-organisms detection using NIPT data

My name is Jasper Linthorst, I am a bioinformatics researcher at the Department of Human Genetics at Amsterdam UMC. My work mainly revolves around analyzing the sequencing data that originates from the thousands of Non-Invasive Prenatal Tests (NIPT) that are conducted by our department. One of the projects that I have been working on is the analysis of viral DNA fragments that can occasionally be obtained from these tests. Amongst the viruses that we detect in this manner are pathogens, such as Cytomegalovirus and Parvovirus B19. During pregnancy, these viruses can be transmitted trans-placentally and harm the developing fetus. However, as our sequencing-based test is not developed for diagnosing viral infections, we wondered how it compared to typical microbial diagnostic tests. To do so, we teamed up with the Department of Medical Microbiology and (together with Prof. Erik Sistermans and Dr. Matthijs Welkers) we applied for an AR&D grant to perform PCR and serological testing on left-over plasma material of archived NIPT samples. I felt very honored and excited to hear that the grant was awarded to our research proposal!

So far, we have used the grant to retrieve left-over material from hundreds of samples from our biobank and have performed follow-up testing on 187 NIPT samples. Furthermore, we have extended our computational pipeline to screen for thousands of other microbes. Although analyses are not finalized yet, the preliminary results look very promising.

Eva
Kontopodi



Jasper
Linthorst





Iris Sanou

Iris Sanou

Enabling parenthood: Unravelling testicular cell interactions pathways that hamper sperm formation in vitro

My name is Iris Sanou. I am a PhD student at the Reproductive Biology Laboratory under the supervision of Prof. Ans van Pelt and Dr. Callista Mulder at Amsterdam UMC. Our research focusses on male (in) fertility, fertility preservation for those at risk of losing their fertility potential due to necessary gonadotoxic treatment. The aim of my PhD project is to develop a fertility restoration method using a culture system where spermatogonial stem cells differentiate towards fertile sperm outside of the body, so called “in vitro spermatogenesis”. We mine knowledge from a representative mouse model, for which in vitro spermatogenesis is arrested similar as in the human situation. Using novel techniques as single cell sequencing we aim to find molecular cues for this arrest.

Being selected for the AR&D grant for this mouse model project, we are thrilled and incredibly thankful. This grant will open new doors. By obtaining single cell sequencing data from our mouse model, we will further improve the organ culture conditions for human spermatogenesis in vitro.

Successful development of in vitro spermatogenesis will be a major step forward for individuals who are currently unable to become a biological parent with existing assisted reproductive technologies. This innovation will increase their quality of life by fulfilling reproductive desires for patient groups such as pediatric cancer survivors and sickle cell patients and transwomen who started hormonal treatment at prepubertal age. This AR&D grant will help us to move forward to this goal.

Jantine van Voorden

Conversion of patient-derived iPSCs into trophoblast stem cells

My name is Jantine van Voorden. I am a PhD student in the Reproductive Biology Laboratory, working under direct supervision of Dr. Gijs Afink and Prof. Ans van Pelt. My research focuses on the molecular mechanisms of early placenta development and the pathogenesis of placentation disorders, including early-onset fetal growth restriction and pre-eclampsia. For our research, we use human trophoblast stem cells and organoids as an in vitro early placenta model. However, since these trophoblast stem cells need to be isolated from first-trimester placentas, the outcomes later in pregnancy and thus the health status of the starting material are unknown. We therefore came up with the idea to generate trophoblast stem cells from patient-derived induced pluripotent stem cells (iPSCs), with known health status. We were very honored to receive an AR&D grant for this project.

In collaboration with Dr. Wessel Ganzevoort, we will soon collect umbilical cords from pregnancies affected by placental disease and healthy controls. So far, we have spent time optimizing the methods for isolation of mesenchymal stem cells from umbilical cords and we have been able to successfully reprogram these cells into iPSCs. The subsequent conversion into induced trophoblast stem cells requires some more optimization, but as soon as we are able to do that, and obtain permission from the ethical board to biobank iPSCs, we are ready to start with patient material. With this project, our goal is to uncover molecular pathways that are dysregulated in placentation disorders, which may provide leads for predictive biomarkers or pharmacological interventions. ●

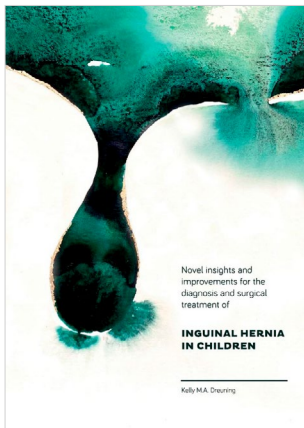


Jantine van Voorden

○○○ AR&D PHD THESES

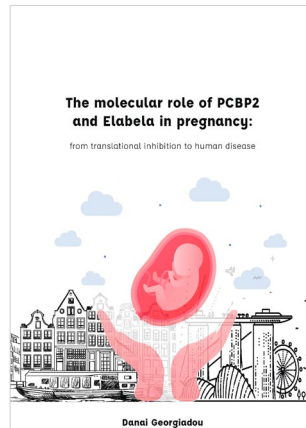
In 2022, 68 researchers obtained their PhD in the area of reproduction and development.

Below a cross section of the PhD theses.



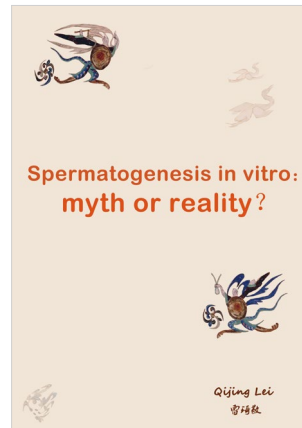
Novel insights and improvements for the diagnosis and surgical treatment of inguinal hernia in children
Kelly Dreuning

Inguinal hernia is the most common congenital surgical disorder in children. This thesis describes the diagnostic and referral strategy of children with suspected inguinal hernia, the clinical manifestations in girls with ovarian hernia, and the current surgical treatment techniques for pediatric inguinal hernia. Also, this thesis aimed to improve current treatment strategies and preparation materials for inguinal hernia surgery by introducing an innovative one-stop-surgery program and age-specific information modalities to prepare children at home for surgery.



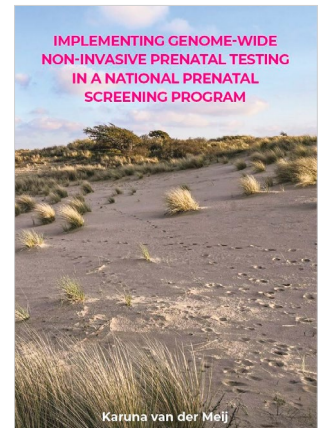
The molecular role of PCBP2 and Elabela in pregnancy: from translational inhibition to human disease
Danai Georgiadou

This thesis demonstrates data on the pathophysiological role of the peptide Elabela and the RNA splicing proteins PCBP1, PCBP2 and YBX1 in human pregnancies by investigating their role in the differentiation of extravillous trophoblasts cells (EVTs). EVT's are placenta cells that are responsible for the remodelling of the maternal artery during placentation, ensuring a healthy pregnancy. This thesis also outlines the work on the identification of the possible elements involved in the translational inhibition of Elabela in embryonic development of vertebrates.



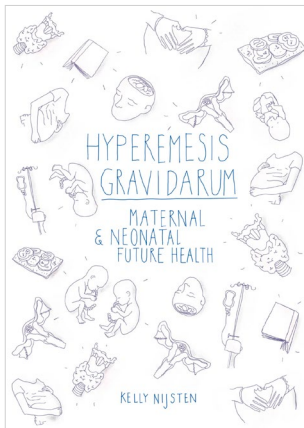
Spermatogenesis in vitro: myth or reality?
Quijing Lei

Successful generation of sperm cells in vitro could be used to treat infertile patients or develop an alternative fertility preservation strategy. Our study showed that sperm-like cells can be observed in our culture system. However, several surveillant checkpoints, which normally guard genomic integrity during sperm formation, seem not to be fully functional in vitro. Therefore, the safety of such artificial sperm should be thoroughly investigated before being clinical use can be considered.



Implementing genome-wide non-invasive prenatal testing in a national prenatal screening program
Karuna van der Meij

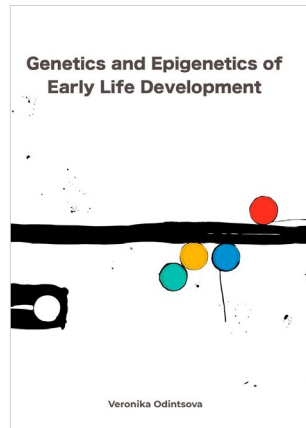
The introduction of non-invasive prenatal testing (NIPT), as a screening test for the detection of fetal aneuploidies has transformed prenatal screening worldwide. NIPT is a safe and reliable screening method to detect fetal aneuploidies in maternal blood. In April 2017, first-tier NIPT was implemented in the Netherlands for all pregnant women as part of the TRIDENT-2 study initiated by the Dutch NIPT consortium. This thesis aimed to evaluate the responsible introduction of first-tier NIPT in the Dutch prenatal screening program. The studies in this thesis focus on aspects related to the implementation of NIPT and the perspectives of pregnant women.



Hyperemesis gravidarum: maternal and neonatal future health

Kelly Nijsten

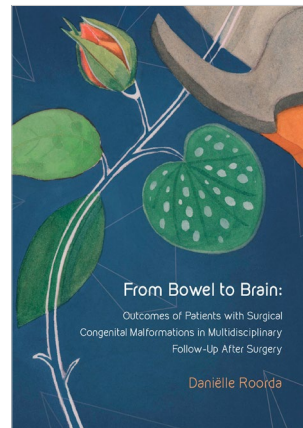
This PhD thesis showed that the Hyperemesis gravidarum (HG) recurrence rate is high and that a large proportion of HG patients have depression, anxiety and post-traumatic stress disorder symptoms. A literature summary also showed that HG can have negative effects for babies born to mothers with HG in the short and long term. Lastly, we found that babies born to mothers with HG had minimal changes in markers of future heart diseases when examining their blood at birth.



Genetics and Epigenetics of Early Life Development

Veronika Odintsova

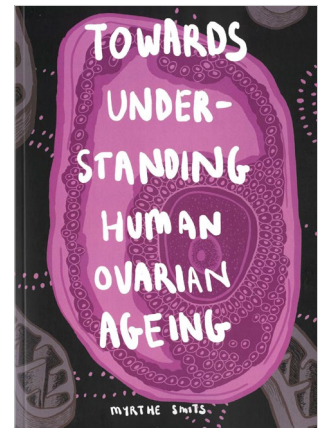
Most epigenetic programming occurs within the first 1000 days of life, and continues to influence gene expression throughout adulthood. The research for this thesis investigated various early-life traits and exposures in twins from the Netherlands Twin Register using advanced molecular genetic and twin methodologies. It showed that DNA methylation can be indicative of prenatal exposures and important later-life outcomes, and may become a useful biomarker in the field of personalized medicine.



From Bowel To Brain: Outcomes of Patients with Surgical Congenital Malformations in Multidisciplinary Follow-Up After Surgery

Daniëlle Roorda

This thesis describes outcomes of patients with surgical congenital malformations in multidisciplinary follow-up after surgery. The first part studies the underlying causes and treatment options for impaired bowel function in patients with Hirschsprung disease, such as constipation, incontinence and Hirschsprung-associated enterocolitis. The second part describes broader outcomes of patients with surgical congenital malformations including quality of life and neurodevelopmental outcome, and explores how standardized follow-up can improve care for patients with surgical congenital malformations.



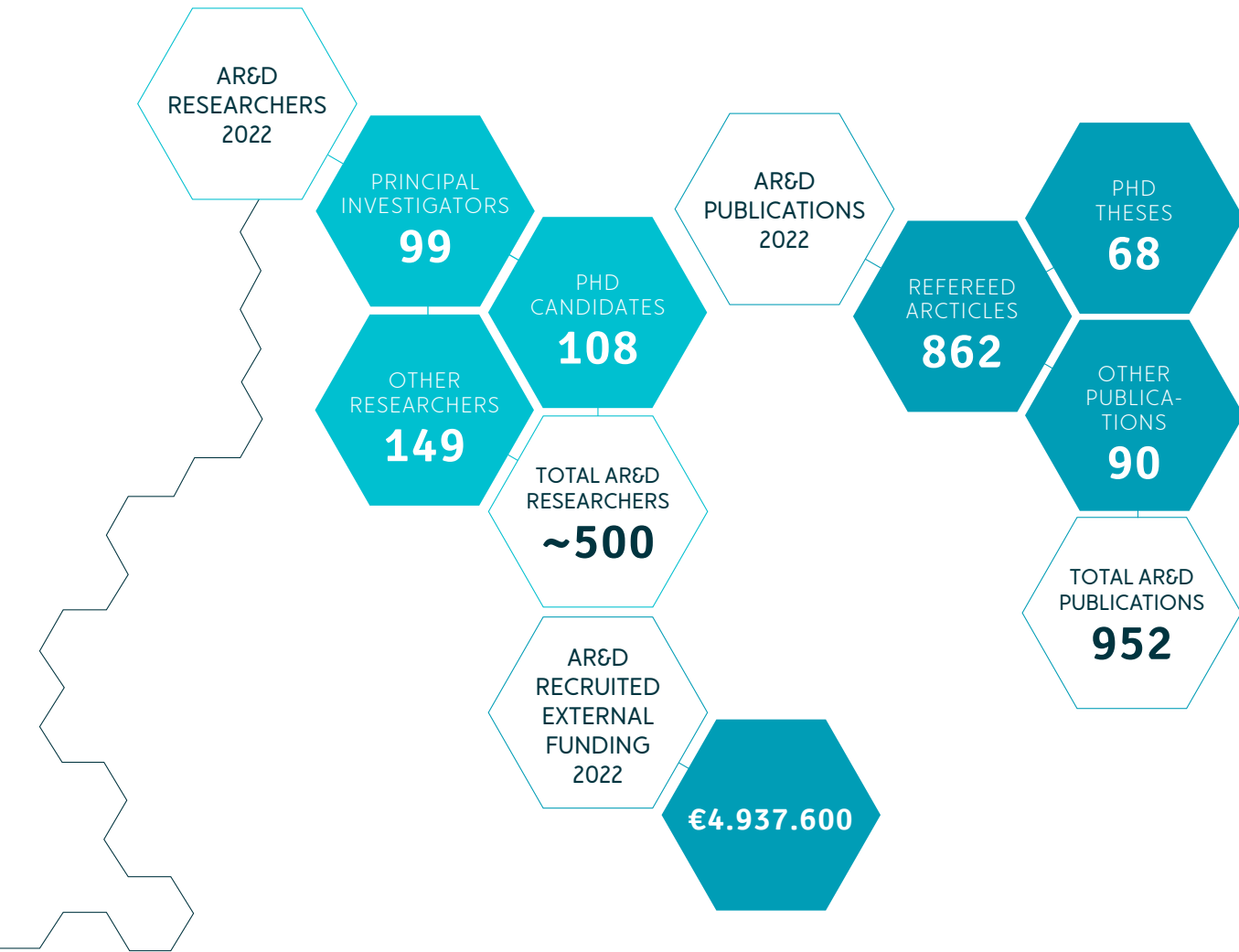
Towards understanding human ovarian ageing

Myrthe Smits

When a woman ages, her oocyte quality declines, which is part of a phenomenon known as ovarian ageing. This results in several fertility problems. In this thesis it is shown that with increasing female age, the expression of pro-longevity pathways decrease, while the expression of anti-longevity pathways increase. Furthermore, it is shown that oxidative stress and mitochondrial dysfunction are involved in ovarian ageing. Future studies on ovarian ageing could focus on targeting oxidative stress and mitochondrial function.

Numbers and highlights

○○○ AR&D IN NUMBERS



DISCLAIMER RESEARCH INFORMATION RESEARCHERS

Information about the number of researchers affiliated with AR&D was collected using the Research Information Systems Pure VUmc and Pure AMC on February 21st, 2023. Registration of research institute affiliation was done by the researchers themselves, by personnel from the Medical Library AMC, by secretary of corresponding AMC/VUmc department or by the policy officers of the AR&D research institute.

PUBLICATIONS

The reported data include all published research output as registered in the Research Information Systems Pure VUmc and Pure AMC on February 21st,

2023. Publications are ascribed to AR&D based on the affiliations of the authors and the content of the publication. A publication can be ascribed to one or more research institutes depending on the affiliations of the authors. Publications registered in the VUmc and AMC Pure instances have been combined and deduplicated. PhD-theses are ascribed to AR&D based on the affiliations of the (co-)supervisors. A thesis can be ascribed to one or more research institutes depending on the affiliations of the (co-)supervisors.

RECRUITED FUNDING

Information about funded research projects has been provided by the separate project administrations from location AMC and location VUmc.

EXTERNAL GRANTS AND PRIZES

In 2022, AR&D researchers were very active in obtaining grants and prizes. Below some of the external grants and prizes awarded to AR&D researchers are highlighted.



ZONMW
€200.000
HELIUS
Wessel Ganzevoort

ZONMW
€100.000
Timing is Key
Callista Mulder

ZONMW
€715.000
TWINC study
Martijn Oudijk

ZONMW
€155.000
SugarDip
Rebecca Painter

ZONMW
€660.000
SUPPORT
Jan-Paul Roovers

VIDI
€800.000
Lotte Havermans

ZONMW DOELMATIGHEIDSGRANT
€575.000
Velja Mijatovic

CHILDREN CANCER-FREE FOUNDATION
€100.000
Mandy Spaan

NWO GRANT OPEN TECHNOLOGY PROGRAMME
€630.000
Anton van Kaam

ANNA REYNVAAN PHD SCHOLARSHIP
€200.000
April Pascual

ZONMW CLINICAL FELLOWSHIP
€200.000
Annemijn Aarts

○○○ KEY PUBLICATIONS

2022 was a very productive year. Here is a selection of peer-reviewed publications that were highlights for our researchers.



Implications of fetal premature atrial contractions: systematic review

Bet et al.

Ultrasound Obstet Gynecol.
2022;60(6):721-730.

Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism [Highlow study]

Bistervels et al.

Lancet.
2022;400(10365):1777-1787.

Extended phenotyping does not preclude the occurrence of delayed haemolytic transfusion reactions in sickle cell disease

Gerritsma et al.

Br J Haematol.
2022;196(3):769-776.

Consensus on revised definitions of Morphological Uterus Sonographic Assessment [MUSA] features of adenomyosis: results of modified Delphi procedure

Harmsen et al.

Acta Obstet Gynecol Scand.
2022;101(10):1036-1037.

Sustainability in gynecology and obstetrics - now or never!

Hehenkamp et al.

Acta Obstet Gynecol Scand.
2022;101(10):1036-1037.

Mapping the effects of pregnancy on resting state brain activity, white matter microstructure, neural metabolite concentrations and grey matter architecture

Hoekzema et al.

Nat Commun.
2022;13(1):6931.

Evaluation of low-dose aspirin in the prevention of recurrent spontaneous preterm labour [the APRIL study]: A multicentre, randomised, double-blinded, placebo-controlled trial

Landman et al.

PLoS Med.
2022;19(2):e1003892.

Effect of pessary vs surgery on patient-reported improvement in patients with symptomatic pelvic organ prolapse

Van der Vaart et al.

JAMA
2022; 328(23):2312-2323.

Machine learning prediction models for neurodevelopmental outcome after preterm birth: A scoping review and new machine learning evaluation framework

Van Boven et al.

Pediatrics.
2022;150(1):e2021056052.

DNA methylation epigenatures: insight into copy number variation

Van der Laan et al.

Epigenomics.
2022;14(21):1373-1388.

More home births during the COVID-19 pandemic in the Netherlands

Verhoeven et al.

Birth.
2022;49(4):792-804.

○○○ SOCIETAL IMPACT

In 2022, AR&D researchers have been contributing to the Societal Impact of research. A selection of societal impact events is presented.

De [te] kleine baby

Sanne Gordijn and Wessel Ganzevoort
in Podcast Verloskundig Baken

Prophylaxis in children with haemophilia
Karin Fijnvandraat and Maria Elisa Mancuso in
Podcast Hemostasis Connect

Een miskraam is geen ziekte die we kunnen behandelen

Norah van Mello in Podcast
Miskraammonologen

Helpt van de zwangere vrouwen werkt onder onveilige omstandigheden
Monique van Beukering in newspaper
De Telegraaf

Gelijk goed beginnen

Tessa Roseboom, book



Het sluimerende virus cytomegalovirus kan kinderen doof maken

Dasja Pajkrť in newspaper NRC

De lotusbevalling

Martijn Oudijk on Linda.nl

Hyperemesis gravidarum: alles over extreme zwangerschapsmisselijkheid
Rebecca Painter on Linda.nl

Abortus ná 24 weken: Angst voor vervolging bij Nederlandse artsen
Eva Pajkrť at NOS

Vaccineren tegen corona als je zwanger bent

Liesbeth van Leeuwen video on Youtube



Eitjes invriezen: 'De ideale leeftijd is 30 tot 36 jaar'

Mariette Goddijn in newspaper
De Telegraaf

Koningin Máxima bij stichting MIND US Hoe hulpverlening aan jongeren met mentale klachten beter moet én kan

Arne Popma at NOS and
AVROTROS EenVandaag

EMMA CENTER FOR PERSONALIZED MEDICINE

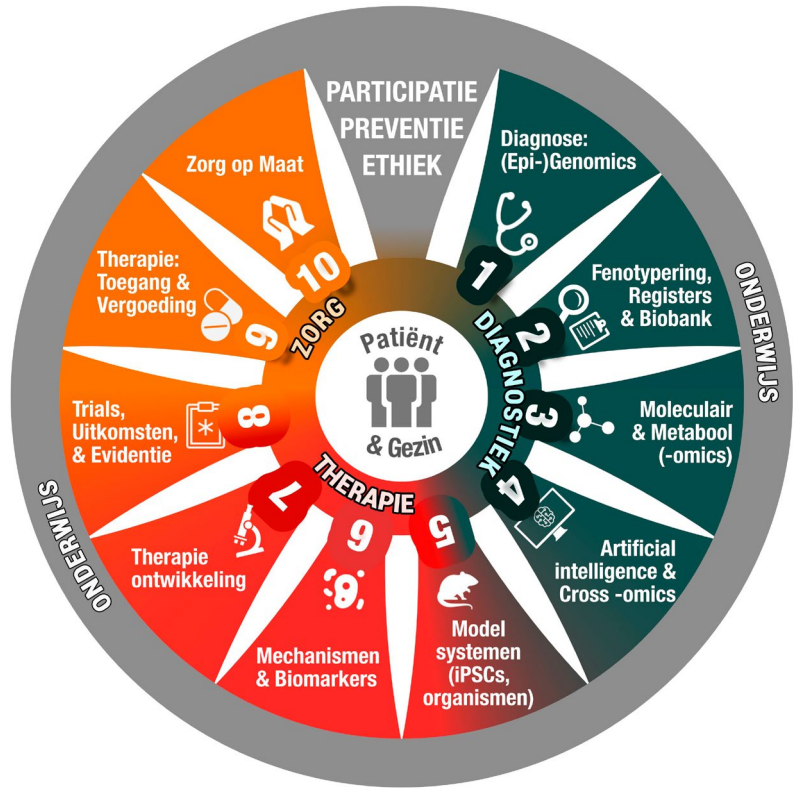
Many children at Emma Children’s hospital Amsterdam UMC have a genetic disorder. Increasingly a genetic diagnosis can be made early in life, due to advances in genome sequencing technologies, enabling personalized care and treatment.



In 2022, a new knowledge infrastructure for children with rare genetic disorders was launched: Emma Center for Personalized Medicine, with many affiliated from AR&D participating. The Emma Center for Personalized Medicine stems from a new collaboration between the different Departments of Emma Children’s Hospital, the Department of Human Genetics and the Laboratory for Metabolic Diseases, co-founded by newly appointed professors van Clara van Karnebeek and Mieke van Haelst (see pages 54-55). Other members of the board include Prof. Arthur Bergen, Prof. Hilgo Bruining, Prof. Riekelt Houtkooper, Prof. Nicole Wolf and Dr. Agnies van Eeghen (see also page 26).



The goal is to accelerate and improve treatment development for patients with rare diseases such as neurodevelopmental disorders and inherited metabolic disorders, in collaboration with experts from all departments, from basic science to trial experts to clinical doctors. The Emma Center for Personalized Medicine organizes monthly meetings ‘Gene Discovery Club’ and ‘Therapy Discovery Club’. See: www.emmacenter.nl



This flywheel demonstrated personalized medicine for all rare disease patients. The flywheel depicts the patient and family at the center of the rare diseases community’s translational research and care activities, aimed at providing accurate diagnosis and counseling, effective and accessible therapies, and ultimately tailored care and prevention [Ref: van Eeghen et al. 2022 Cold Spring Harb Mol Case Stud 8: a006200; Copyright: Health2Media].



Newly appointed professors



In 2022, six professors were appointed at
Amsterdam UMC in the field of AR&D.

PROF. CLARA VAN KARNEBEEK

Clara van Karnebeek is appointed professor of Personalized Medicine for Genetic Metabolic Disorders at the University of Amsterdam since January 2022. She works as a medical specialist and principal investigator in the field of paediatrics and biochemical genetics in the Emma Children's Hospital, Amsterdam UMC. She co-founded the Emma Personalized Medicine Center [see page 53].

She is also program director of United for Metabolic Diseases (UMD,) together with Prof. Hans Waterham. The UMD is a Dutch multidisciplinary partnership of six Dutch academic metabolic centers and the patient umbrella organization for metabolic disorders (VKS) in the Netherlands, funded by Metakids Foundation and the VriendenLoterij. UMD aims to perform innovative research to greatly improve the diagnosis, prevention, treatment and care of patients and families with an inherited metabolic disease.

The acceleration of diagnosis and treatment means that children with serious chronic

diseases continue to live longer. Sometimes this is a life of intensive care and periods of hospitalisation. Because of the great impact this has on parents and a family, Van Karnebeek and others founded The Jeroen Pit House.

PROF. MIEKE VAN HAELST

Mieke van Haelst is appointed as professor of Clinical Genetics since September 2022. She was trained as a clinical geneticist at Erasmus Medical Center, Rotterdam and Great Ormond Street Hospital, London, UK. She worked at Guy's & St Thomas' Hospital and Northwick Park Hospital, London and UMC Utrecht, before she joined the Clinical Genetics team at Amsterdam UMC. She is head of Clinical Genetics and board member of the Department of Human Genetics at Amsterdam UMC.

She is the president of the Dutch Society of Human Genetics (NVHG) and co-initiated HUGE.NL (Human Genome Netherlands), a national platform for scientists, medical doctors and policy makers in the Netherlands to discuss potential implementation of

“The ambition of AR&D is the advancement of knowledge in all aspects of human reproduction and development through interdisciplinary team science aimed at improving health from preconception to adulthood of current and future generations.”

genomic research program results in the Dutch society. She is the initiator of the annual European Clinics for Rare Genetic Disorders and founder of the European Obesity Genetics Collaboration meeting. Her clinical and translational research focuses on the identification of (novel) gene defects and unravelling the pathogenicity obesity-related disorders.

As co-director of Emma Center for Personalized Medicine at Amsterdam UMC (see page 53), she works on the identification and understanding of causal (epi)genetic factors that result in rare diseases. She integrates knowledge and methods of diverse disciplines to accelerate the development of personal treatment for rare genetic disorders. She has established genetic clinics, research and education programs in the Dutch Caribbean and aims to provide equal genetic care for diverse populations.

PROF. REBECCA PAINTER

Good nutrition in pregnancy can be of great benefit to mother and baby’s health across the lifespan. The Vrije Universiteit endowed Professor Rebecca Painter

with the Chair of Maternal Health, Nutrition and Pregnancy on February 1, 2022.

Professor Painter aims to use this chair to pursue research and implementation of a healthier lifestyle in pregnancy for all pregnant persons. The personal and societal impact of healthier nutrition and more exercise during pregnancy translates to 25% fewer cases of gestational diabetes, as well as a marked decrease in children born preterm and NICU admissions. Painter is keen to see implementation of such lifestyle programs being made available to all pregnancies, and not just to those with obesity.



Clara van Karnebeek



Mieke van Haelst



Rebecca Painter



Erik
Sistermans



Baudewijntje
Kreukels



Willem
de Vries

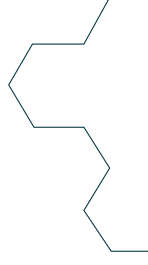
Prof Painter will also use the chair to improve the knowledge base and care for women with extreme vomiting and nausea in pregnancy, also known as hyperemesis gravidarum. Women with hyperemesis gravidarum experience malnutrition in pregnancy, with far-reaching consequences for their own health and wellbeing as well as that of their baby's. Improved access to appropriate care including medication is necessary to avoid the effects of maternal malnutrition in pregnancy. Painter plans work with the international hyperemesis gravidarum collaboration to develop innovative approaches to treat hyperemesis.

PROF. ERIK SISTERMANS

Erik Sistermans is professor of Human Genetics, in particular prenatal genome diagnostics since September 15, 2022. He is head of the Genome Analysis Laboratory of Amsterdam UMC, which includes the Genome Diagnostics lab, the non-invasive prenatal test (NIPT) screening lab and the Core Facility Genomics. He is a national and European registered clinical laboratory geneticist, and board member of the VKGL (Vereniging Klinisch

Genetische Laboratoriumdiagnostiek). He is project leader of the TRIDENT studies that implemented NIPT in the Netherlands.

With the TRIDENT studies ending April 2023, his research focus has shifted towards further improving prenatal screening and diagnostics. Part of his research involves computational analysis of NIPT data, starting with the development of WISECONDOR, a program used for all NIPT analysis in the Netherlands (>500.000), as well as in many other countries worldwide. He initiated the DISTIL studies that use the huge NIPT datasets to expand the possibilities of cfDNA based prenatal testing. This work focusses on the possibilities to test for viral sequences that are relevant for healthy pregnancy and on NIPT based Genome Wide Association Studies (GWAS) to discover genes responsible for fetal and maternal related pregnancy problems such as growth restriction, fetal death, premature birth and pre-eclampsia. He also focusses on technology development, including studies towards use of CRISPR technology for NIPT/NIPD (non-invasive prenatal diagnosis) analysis, and digital MLPA for neonatal screening.



“Unique about the research institute Amsterdam Reproduction & Development is that we investigate human reproduction and development in its totality: from the formation of oocyte and sperm, conception, embryonic and fetal development, pregnancy, birth, and postnatal development as the child grows up, and the circle of life eventually starts again.”

PROF. BAUDEWIJNTJE KREUKELS

Baudewijntje Kreukels was appointed at the VU University as Full Professor of Medical Psychology in 2022, with a special focus on variations in the development of gender and sex.

Her research focuses on the development of gender identity and gender incongruence, and the evaluation of care and treatment for gender incongruence and variations in sex development (differences of sex development, DSD). She is a member of the Steering Committees of the European Network for the Investigation of Gender Incongruence (ENIGI) and the dsd-LIFE consortium, a European study on the outcome of surgical and hormonal therapy and psychological intervention in people with DSD conditions.

Kreukels was a member of the working groups for the chapters on Epidemiology and Intersex conditions of the Standards of Care of the World Professional Association for Transgender Health published in September 2022. Current research interests include aging and effects of hormone treatment on cognitive function and psychological well-being, sexual health in people with gender incongruence and variations of sex development, and the neurobiological substrate of gender incongruence and its treatment.

PROF. WILLEM DE VRIES

Willem de Vries was appointed as professor of Pediatrics and head of the Emma Children's Hospital at Amsterdam UMC in 2022. His areas of interest are healthcare management, healthcare innovation, patient participation, family-centred care.

With his inaugural lecture 'Paediatrics of the future: Caring for tomorrow', he focused on the grand challenges in society, such as inflation, the climate crisis, the energy crisis, and staff shortages in almost every profession, which will have a major impact on tomorrow's care. Currently, there are already long waiting lists and a shortage of nurses and other care staff. De Vries therefore calls for proper research into reasons why it is so difficult to recruit care staff, but especially to then retain them. Work pressure is a big factor in this and he believes that the work-life balance is very important. You can ask yourself whether the long working weeks that young doctors make is still of our time. De Vries also expresses concern about mental problems among young people. His plea is: "Curing is important, but caring for is even more important," He emphasizes the importance of caring for each other as much as we care for our patients. Care is provided for people, by people. We must therefore provide the pediatrics of the future.

If you want to know more about Prof. De Vries, [see this video](#).



**“The ambition
of AR&D is the
advancement of
knowledge in all
aspects of human
reproduction
and development
through
interdisciplinary
team science
aimed at improving
health from
preconception
to adulthood of
current and future
generations”**





“Unique about the research institute Amsterdam Reproduction & Development is that we pay attention to reproduction and development in its totality: the stage before pregnancy, conception, pregnancy, childbirth, the child as it’s growing up, and the resulting health of the adult stages of life”