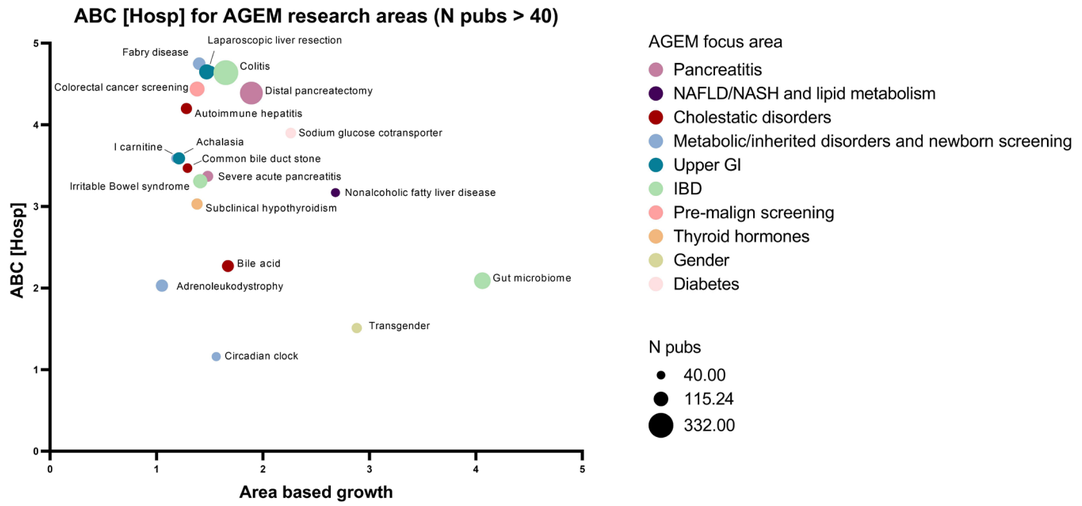


Figure A13 Area Based Connectedness of co-authorship with hospitals, of publication clusters (N > 39) related to AGEM's 10 focus areas.

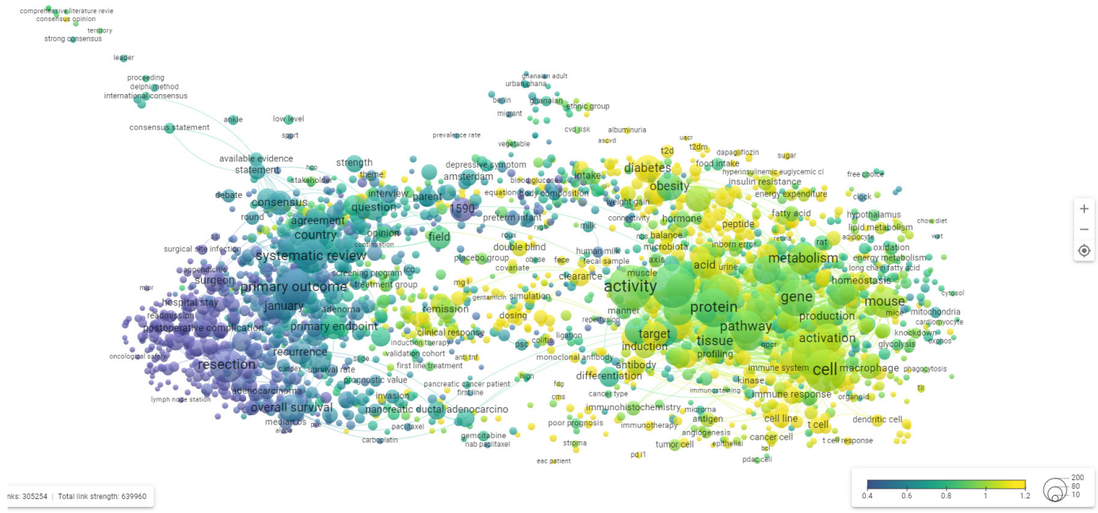


Figure A14 Heat map AGEM publications visualizing co-authorship with the industry, based on the ABC [industry] indicator. The database average is 1. Values above one indicate an above world-average societal connectedness to industry. For a better visualization, access the map online here. The cluster coloring can be changed to show co-authorship with industry by selecting "industry" under "color" in the menu on the left hand side.

Appendix 3 - Case studies

Table A13 Selected case studies and the assessment criteria they demonstrate

Case study	Research Quality	Societal Relevance	Open Science	Academic Culture	PhD policy	HR policy
1. Multidisciplinary research in inflammatory bowel disease	■	■				
2. A new SPRING in lipid metabolism	■	■			■	
3. Dutch Pancreatitic Study Group	■	■	■		■	
4. Sex-specific newborn screening for X-linked adrenoleukodystrophy	■	■	■			
5. The neonatal screening for congenital adrenal hyperplasia in the Netherlands	■	■				
6. Diverse and inclusive HR policies that foster talent development						■
7. Promoting an open and inclusive culture, characterized by scientific integrity				■		
8. PhD development & training					■	
9. Facilitating open science			■			

3.1 Case study 1 – Multidisciplinary research in inflammatory bowel disease

Prof. dr. Geert D'Haens, department of Gastroenterology and Hepatology, Amsterdam UMC; dr. Manon Wildenberg, Tytgat Institute, Amsterdam UMC.

Background

Inflammatory bowel disease (IBD) is a group of chronic inflammatory disorders that affect the digestive tract, including Crohn's disease and ulcerative colitis. The Amsterdam UMC IBD research is highly translational, which involves close collaborations between the Departments of Surgery, Gastroenterology and Hepatology, Imaging, Paediatrics and the Tytgat Institute for Liver and Intestinal research.

The Amsterdam UMC has a long history of providing excellent IBD patient care, as well as conducting both clinical and fundamental research. Fundamental IBD research is carried out at the Tytgat Institute. We own a large biobank containing pediatric and adult IBD surgical resection material (at the Tytgat Institute) and diagnostic biopsies, whole blood and serum in the central Amsterdam UMC biobank (Future-IBD) at the AMC. We also use several relevant animal models for colitis in our lab, including acute and chronic innate-driven colitis mouse models, as well as T-cell driven colitis models. These models have been used to establish basic mechanisms in IBD, as well as pharmacological and dietary intervention strategies. We are also expert in endoscopic, MRI and ultrasound techniques, not only in IBD patients undergoing diagnostic/therapeutic interventions, but also in mouse models for which we developed a validated scoring systems. Analysis of these systems occurs using advanced techniques of single cell and spatial transcriptomics. Working together we hope to develop more effective treatments for this debilitating disease.

Major breakthroughs

Basic science

- Unraveling the critical role of macrophages and IL10 signaling in the clinical effect of anti-TNF therapy (Bloemendaal et al, Gastroenterology 2017, Koelink, Gut 2020).
- Role of Jak-kinase pathways and the specific role of Tyk2 in treatment of IBD (De Vries L et al., J Crohns Colitis. 2021, Fung I et al., DDW 2023).
- Pathological mechanisms in fistulizing Crohns disease (Becker M, J Crohn Colitis 2023).

Translational

- Development of a dietary intervention changing the microbiome and intestinal barrier function resulting in remission in pediatric IBD;
- Identification of epigenetic profiles in the peripheral blood associated with response to various biologic treatments. These findings have led to a massive Horizon Europe grant for a validation clinical trial (12M euro).

Clinical

- Head to head comparison between surgical and medical intervention in early Crohn (Ponsioen et al, Lancet Gastro Hepat 2017)
- The potential of appendectomy in ulcerative colitis, finishing up a 10-year interventional study to prevent UC relapse with appendectomy (collaboration with Surgery).
- We are involved in most pivotal pharma trials related to IBD treatment and we are proud to provide early drug access to otherwise almost untreatable patients this way. These trials are coordinated by the IBD trial office (mirikizumab: D'Haens et al., N Engl J Med 2023, in press; upadacitinib: Colombel et al., N Engl J Med 2023, in press; Risankizumab: D'Haens et al., Lancet 2022).

Who is involved?

IBD research in the Amsterdam UMC has four groups of highly interconnected investigators: Gastroenterologists, Paediatric gastroenterologists, Surgeons and Laboratory Scientists, currently concentrated at the AMC location. In total this comprises a team of 65-70 collaborators working in Principal Investigator groups and, supported by a team of biobankers, project managers, project controllers, medical writers and biostatisticians.

AGEM Principal Investigators focusing on IBD are:

- Geert D'Haens: drug development, pharmacokinetics, biomarkers
- Manon Wildenberg: fibrosis, fistulas, drugs Mechanisms of Actions, mouse models
- Wouter de Jonge: biomarkers, treatments MoA, microbiome
- Anje te Velde: fatigue mechanisms
- Mark Lowenberg: fibrosis, clinical trials, imaging
- Cyriel Ponsioen: microbiome, primary sclerosing cholangitis
- Krisztina Gecse: fistula research, pharmacokinetics, intestinal ultrasound
- Joep Grootjans: dysplasia, peritoneal immune system
- Nanne de Boer: volatile biomarkers, thiopurines
- Gerd Bouma: nutrition, coeliac disease
- Willem Bemelman: positioning of surgery, ileo-anal pouches
- Christianne Buskens: appendix research, perianal fistulas
- Johan van Limbergen: paediatric IBD, dietary interventions

Users and collaborations

Collaborations with PIs in NL/International:

- Pharma: Bristol Myers Squibb, Roche, Pfizer, Takeda, GlaxoSmithKline, Boehringer Ingelheim
- Principal Investigators in the Netherlands: Initiative on Crohn's and Colitis Network, North Holland Gut Club
- CO collaboration; Alimentiv BV
- International clinical trial network: collaboration with approximately 60 clinical sites in France, Italy, Spain, Belgium, Ljubljana, Hungary and the United Kingdom.
- Lab collaborations: Universities of Bonn, Leuven, Kiel, Erlangen
- Imaging collaborations: International Bowel Ultrasound Group

Scientific impact

The research being conducted on IBD in Amsterdam is having a significant scientific impact. IBD is a complex disease with a multifactorial etiology, and the research being conducted in Amsterdam is making important contributions not only to our understanding of underlying mechanisms but also to clinical care worldwide. Examples are the introduction of 'early surgery' for limited Crohn's disease and the use of biologics early in the disease course ('top-down' management). Our papers have been published in top-ranked journals. The impact of our work is supported by a number of large grants from the European Union (EU), such as Horizon, Top consortium for Knowledge and Innovation (TKI), the Helmsley Foundation and countless industry partners and study groups.

Societal impact

The research being conducted on inflammatory bowel disease (IBD) in Amsterdam is also having a significant societal impact. IBD is a chronic condition that affects millions of people worldwide, and it can have a profound impact on a person's quality of life. Through their research, the teams in Amsterdam are working to improve our understanding of the disease and develop more effective treatments, which will have a positive impact on the lives of those living with IBD. The research being conducted in Amsterdam is also contributing to a better understanding of IBD and raising awareness of the disease. This includes patient support groups and advocacy organizations that provide important resources and support for patients and their families.

Future perspectives

Major ongoing programs:

- Single cell and tissue epigenetics
- Unraveling the role of IL-23 in Th17 cell activation (with H Spits and J Bernink)
- Unravelling the peritoneal immune system in cancer and IBD (J Grootjans)
- Single cell transcriptomics of ulcerative colitis and Crohn's disease
- Clinical validation of epigenetic signature from treatment selection in Crohn's disease

3.2 Case study 2 – A new SPRING in lipid metabolism

Prof. dr. Noam Zelcer, department of Medical Biochemistry, Amsterdam UMC

Background

Lipid metabolism is tightly regulated through a myriad of transcriptional and post-transcriptional mechanisms, wherein the Sterol Regulatory Element-Binding Protein (SREBP) transcription factors are master regulators of cholesterol and fatty acid metabolism. To become active SREBPs must traffic from the ER to the Golgi and undergo two sequential proteolytic cleavage events to release their transcriptional domain. The core machinery governing these events has been identified ~20 years ago and is being actively investigated.

Recently, using a genome-wide genetic screen we identified a previously uncharacterized gene, which we named SREBP regulating gene (SPRING), as novel member of the core SREBP activation machinery. Our studies support a key role for SPRING in SREBP signaling, as absence of SPRING severely attenuates activation of SREBPs.

Our ongoing mechanistic studies indicate that SPRING regulates the activity of the first protease that cleaves SPRING (Membrane Bound Transcription Factor Peptidase, Site 1) and is also essential for the proper trafficking of SREBP to the Golgi. As a consequence, liver-specific ablation of SPRING in mice attenuates hepatic SREBP signaling, dramatically reduces circulating plasma lipid levels, and protects mice from diet-induced hepatosteatosis. Identification of genetic variation in human SPRING associating with altered plasma lipid levels support the significance of SPRING as a physiological regulator of lipid metabolism.

Major breakthroughs

- Discovery of SPRING: Using a whole-genome functional genetic screen we identified SPRING, and were the first to demonstrate that SPRING is a critical determinant of SREBP activation. We found that retrograde trafficking of SCAP, an essential SREBP chaperone, depends on SPRING (Loregger et al, Nat. Comm, 2020).
- SPRING and S1P undergo intermolecular proteolysis to regulate SREBP signaling: To become transcriptionally active SREBPs must undergo two sequential proteolytic cleavage events in the Golgi. The first cleavage is mediated by the protease S1P. Our studies indicate that SPRING enhances the activity of S1P, and that reciprocally, S1P promotes the cleavage of SPRING in addition to that of SREBPs. This results in the production of a secreted SPRING protein (Hendrix et al1, under review).
- SPRING governs hepatic SREBP signaling and protects mice from diet-induced hepatosteatosis: We developed liver-specific SPRING knockout mice. As a consequence, hepatic SREBP signaling is attenuated. This results in reduced hepatic and plasma lipid levels, and protects mice from diet-induced hepatosteatosis (Hendrix et al2, under review).
- Genetic variation in SPRING associates with circulating lipoprotein levels: We identified both rare and common SPRING variants associated with circulating levels of lipoproteins in humans (Hendrix et al2, under review).

Who is involved?

The SPRING project in the Zelcer group at the Department of Medical Biochemistry (Amsterdam UMC, location AMC) is spearheaded by a PhD candidate, Sebastian Hendrix. He is regularly assisted by two technicians Jenina Kingma and Masoud Valiloo, and by an animal biotechnician Roelof Ottenhoff. Former group members, Anke Loregger and Josephine Tan, who were involved in the initial discovery and characterization of SPRING are also regularly involved in discussions.

User and collaborators

The SPRING project is supported by local, national, and international collaborators including (but not limited to):

- AMC: dr. A Jongejan (Trascriptomics and RNA sequencing analysis) and dr J Levels (Lipid and lipoprotein analysis)
- UMCG: Prof. B v/d Sluis (Analysis of hepatic lipid metabolism and generation of Spring knock-in mice), Prof. F. Kuipers & dr JF de Boer (Analysis of in vivo cholesterol and fatty acid biosynthesis)
- University of Milan: Prof GD Norata, dr M. Svecla (Shotgun proteomics of liver tissue and immune phenotyping of Spring knock-out models)
- University of Nantes: dr A Rimbert (Human genetics of hepatic and lipid traits).

Scientific impact

The SREBP-regulated transcriptional pathway is a central determinant of lipid homeostasis. The core machinery that governs SREBP activation has been defined ~20 years ago. Given the centrality of the SREBP pathway in cell biology, SREBPs and components of this machinery are extensively studied in a wide-range of conditions and human diseases.

Our discovery of a new component of this core machinery, SPRING, represents an important addition to the understanding of how lipid homeostasis is maintained and regulated. This finding has been recognized in the field, resulted in well-cited publications (several under review/revision), and has been presented in prestigious international scientific meetings as invited talks (e.g. Gordon, Deuel, European Atherosclerosis Society etc.). Furthermore, the investigation of SPRING is a major component of two ongoing grants (NWO VICI, NWO-ENW M2).

From a broader perspective, the genetic strategy that we have pioneered and was at the base of identifying SPRING is now being used in the research group to interrogate other fundamental aspects of lipid metabolism.

Societal impact

The primary impact of the project is scientific and geared towards the scientific community. Nevertheless, there is clear societal impact beyond this. Namely, components of the SREBP activation machinery are considered as potential therapeutic targets. Our results showing that hepatic SPRING ablation decreases hepatic and plasma lipids, fasting glucose levels, and protects mice from development of diet-induced hepatosteatosis positions SPRING as a potential metabolic target. This possibility will be pursued (see below). Furthermore, as genetic variation in SPRING modulates circulating lipoprotein levels in humans, one could consider integrating SPRING when assessing genetic dyslipidemias.

Future perspectives

Several key lines of investigation related to SPRING will be pursued in the coming years:

- Mechanism of action: We aim to define the mechanistic details of SPIRNG action. Specifically how it interacts with S1P & SCAP, and the significance of S1P and SPRING cleavage for SREBP signaling.
- Does the cleaved and secreted form of SPRING have biological function? We will develop models to study the potential physiological role(s) the secreted SPRING fragment we identified. Is secretion regulated? Does the secreted form have biological function? Is there a receptor? Does it have therapeutic value?
- Structure of SPRING: In collaboration of Prof D Kober (University of Texas Southwestern Medical Center), an expert is structural biology, we are attempting to solve the 3 dimensional structure of SPRING together with S1P and/or SCAP. We anticipate these structures to inform on subsequent mechanistic studies.
- SPRING function beyond the liver and metabolic disease: The SREBP pathway is critical in immune responses and cancer. We are therefore interested to interrogate the role of SPRING in these disease models, initially in mouse models.
- Therapeutic targeting of SPRING: We will test whether targeting hepatic SPRING using antisense oligo technology (collaboration Ionis) is effective in ameliorating dyslipidemia, diabetes, and development of diet-induced hepatosteatosis in preclinical models.

3.3 Case study 3 – Dutch Pancreatitis Study Group

Marc Besselink, professor of Surgery; Paul Fockens, professor of Gastroenterology; Rogier Voermans, gastroenterologist; Marcel Dijkgraaf, professor of Health Technology Assessment (HTA); Marja Boermeester, professor of Surgery.

Background

The Dutch Pancreatitis Study Group (DPSG) has been one of the world's leading research groups in acute and chronic pancreatitis since 15 years. Researchers from the AGEM institute and Amsterdam UMC have a leading role in this Study Group. No other group published more practice changing randomized trials than this group. Acute pancreatitis is a top-3 most common gastrointestinal reason for acute hospitalization. It has been an 'orphan disease' with high disease burden, long hospitalization and high mortality due to systemic inflammatory response syndrome (SIRS) and organ failure. Chronic pancreatitis, leading to chronic lifelong pain, is a poorly understood disease with a very large loss of quality of life.

Major breakthroughs

1. The DPSG has provided numerous breakthroughs in the field of pancreatitis:
2. Probiotics should not (i.e. no longer) be used in the treatment of acute pancreatitis because it increases mortality (PROPATRIA trial)
3. A minimally invasive step-up approach to infected necrotizing pancreatitis should be used as compared to primary open necrosectomy as it prevents new onset organ failure and lowers mortality (PANTER trial)
4. A minimally endoscopic step-up approach can be preferred over a surgical step-up approach to infected necrotizing pancreatitis as it reduces hospital stay and prevents pancreatico-cutaneous fistula (PENGUIN, TENSION, extension trials)
5. Enteral feeding can be started after 72 hours if a patient with acute pancreatitis has insufficient oral intake, not needed to start urgently <24 hours, prevents a two-thirds of patients of receiving a nasojejunal feeding tube (PONCHO trial)
6. It is not required to perform an urgent endoscopic retrograde cholangiopancreatography (ERCP) in patients presenting with biliary pancreatitis, only when cholestasis persists after 48 hours. This approach prevents two-thirds of patients of receiving an ERCP (APEC trial)
7. It is not required to perform interventions (endoscopic or percutaneous catheter drainage) urgently within 24 hours in patients with infected necrotizing pancreatitis. This approach prevents intervention and surgery in a third of patients, who will be successfully treated with only antibiotics (POINTER trial)
8. Early surgery in patients with painful chronic pancreatitis should be the preferred first approach in these patients based on short-term and long-term outcome data (ESCAPE trial).
9. Plastic stents for endoscopic drainage of infected necrotizing pancreatitis result in equal outcome as large lumen apposing metal stents (AXIOMA trial)

Who is involved?

The 30 largest hospitals in the Netherlands are involved including all 7 university medical centers. Per center at least one gastroenterologist and one gastrointestinal surgeon is involved. In the university medical centers also radiologists, interventional radiologists, microbiologists and PhD candidates are involved. The first two PhD candidates have become professor at University of Amsterdam (Besselink) and Utrecht (Van Santvoort). PIs of the DPSG trials have come from departments of surgery and gastroenterology from Amsterdam UMC (TENSION, ESCAPE, POINTER, PICUS-2, AXIOMA, PIANO), UMC Utrecht (PROPATRIA, PYTHON, PANTER), St. Antonius (PONCHO, COMBO), Erasmus MC Rotterdam (APEC), Radboud UMC/ Maastricht UMC (FLUYT, PLANCTON), and LUMC (PANDA).

Users and collaborations

The group is invested heavily in training and giving a leading role to PhD candidates. As example all of them go for a dedicated training program in Randomized Controlled Trials in Oxford University, next to the standard research training in Dutch university medical centers. The 30 largest hospitals in the Netherlands are involved including all 7 university medical centers. Per center at least one gastroenterologist and one gastrointestinal surgeon is involved. In the university medical centers also radiologists, interventional radiologists, microbiologists and PhD candidates are involved. Collaborations exist with all leading groups in pancreatitis research worldwide. This has led to numerous publications including the international guidelines and practice seminars in leading journals as BMJ, The Lancet and Gastroenterology.

Scientific impact

The research output is shown here. The figure shows the first 9 Randomized Controlled Trials published by the DPSG:

2008	PROPATRIA	THE LANCET
2010	PANTER	The NEW ENGLAND JOURNAL of MEDICINE
2012	PENGUIN	JAMA The Journal of the American Medical Association
2014	PYTHON	The NEW ENGLAND JOURNAL of MEDICINE
2015	PONCHO	THE LANCET
2018	TENSION	THE LANCET
2019	ESCAPE	JAMA The Journal of the American Medical Association
2020	APEC	THE LANCET
2021	POINTER	The NEW ENGLAND JOURNAL of MEDICINE

Societal impact

The Dutch Pancreatitis Study Group has had a major societal impact in the past 15 years. The international guidelines for the treatment of acute and chronic pancreatitis include all Dutch evidence gathered from the randomized trials and numerous non-randomized cohort studies. In fact, the 2012 International Association of Pancreatology /American Pancreatic Association guidelines are written and coordinated by DPSG members.

Future perspectives

The DPSG has obtained grants in the last 2 years from ZonMW for three nationwide randomized controlled trials:

1. PICUS-2, PI Marc Besselink, on the merits of laparoscopic cholecystectomy in patients with idiopathic acute pancreatitis to prevent recurrence.
2. PIANO, PI Rogier Voermans, on the merits of antibiotic stewardship in patients with necrotizing pancreatitis.
3. PLANCTON, PI Stefan Bouwense, on the merits of omega-3 fatty acids in predicted severe pancreatitis.

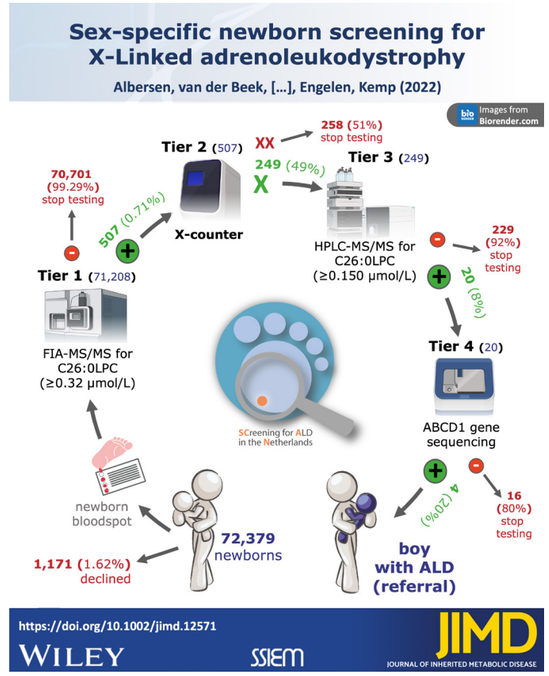
Furthermore, numerous prospective and non-randomized prospective trials are ongoing aiming at improving disease understanding and treatment outcomes for patient with acute and chronic pancreatitis. The POEMA trial has focused on dysbiosis in patients with acute pancreatitis developing infected necrosis. Dysbiosis of the gut microbiota with Enterococcus or Staphylococcus is a predictive factor for infected pancreatic necrosis in patients with acute pancreatitis (van der Berg, Van Santvoort, Verdonk, Boermeester). One clear desire is to expand the preclinical research within the DPSG. For this contact has been made with leading researchers within AGEM, Cancer Center Amsterdam and Amsterdam Institute for Infection & Immunity.

3.4 Case study 4 - Sex-specific newborn screening for X-linked adrenoleukodystrophy

Dr. Stephan Kemp, Genetic Metabolic Diseases, project leader SCAN study

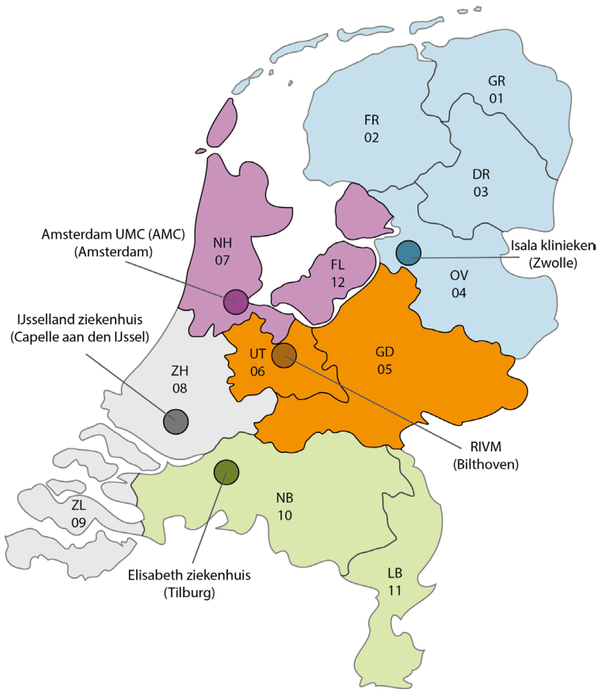
Background

X-linked adrenoleukodystrophy (ALD) is a genetic neurometabolic disorder that affects the adrenal glands and central nervous system. Pathogenic variants in ABCD1 result in elevated levels of very long-chain fatty acids, including C26:0-lysophosphatidylcholine (C26:0-LPC). Males with ALD are at high risk for developing adrenal dysfunction and/or inflammatory demyelinating brain lesions (cerebral ALD) at an early age, which is often fatal without treatment. Adrenal insufficiency and/or cerebral ALD are exceedingly rare in women with ALD. Newborn screening has revolutionized the care of boys with ALD as it enables prospective monitoring and timely therapeutic intervention, thereby preventing irreversible damage and saving lives. In 2015, the Dutch Health Council recommended to screen only male newborns for ALD without identifying untreatable conditions associated with elevated C26:0-LPC, like other peroxisomal beta-oxidation defects. The novelty of sex-specific newborn screening and the lack of an example for a boys-only screening algorithm required a pilot study before ALD can be included in the nationwide screening program.Commissioned by the Ministry of Health, Welfare and Sport (VWS), the ALD group of the Amsterdam UMC, together with the National Institute for Public Health and the Environment (RIVM) designed this pilot study.



Major breakthroughs

The SCAN (Screening for ALD in the Netherlands) study is the first sex-specific newborn screening program worldwide. Using a 4-tier algorithm, males with ALD are identified based on the combination of: 1) elevated C26:0-LPC levels, 2) the presence of one X-chromosome and 3) a variant in ABCD1, in heel prick dried bloodspots. Screening of 71,208 newborns resulted in the identification of four boys with ALD who, following referral to the pediatric neurologist and confirmation of the diagnosis, enrolled in a long-term follow up program. The results of this pilot show the feasibility of employing a boys-only screening algorithm that identifies males with ALD without identifying untreatable conditions. This approach will be of interest to countries that are considering ALD newborn screening but are reluctant to identify girls with ALD because for girls there is no direct health benefit. We also analyzed whether gestational age, sex, birth weight and age at heel prick blood sampling affect C26:0-LPC concentrations and demonstrate that these covariates have a minimal effect. Following the successful pilot, the Ministry of VWS decided to add ALD to the Dutch newborn screening program. As of October 2023 all Dutch male newborns will be screened for ALD.



Who is involved?

The SCAN study was a participation between the Amsterdam UMC and the RIVM. The screening algorithm included 2 of the 5 Dutch newborn screening labs (Tier 1), the lab Human Genetics (Tier 2) and Lab Genetic Metabolic Diseases (Tiers 3 and 4). Obstetric care providers, screeners and family physicians in the 4 participating provinces (Noord Holland, Flevoland, Utrecht and Gelderland). The department of pediatric neurology of the Amsterdam Leukodystrophy Center of the Amsterdam UMC.

Users and collaborators

The ALD research team at Amsterdam UMC collaborates with all ALD groups and stakeholders around the globe. Especially within newborn screening there is open communication (through ALD Alliance and ALD Connect) and sharing of knowledge with the aim to continuously improve the screening and follow-up of newborns and their families. Within several European countries, preparations to include ALD in the national newborn screening program are underway. Our team helps these countries in their efforts, both with technical questions as well as the needed samples for testing the various tiers.

Scientific impact

The Netherlands has a unique screening program in which RIVM, physicians and disease experts participate and collaborate. This allowed us to answer questions that could not be addressed in other countries. For example, with permission of the relevant committee of the Department for Vaccine Supply and Prevention Programs of the RIVM, we received anonymized information of >70.000 newborns (of whom the parents had consented to participate in the pilot) regarding gestational age, sex, birth weight and age at heel prick blood sampling was obtained for covariate analysis. Analysis of these data demonstrates that these covariates have a minimal effect on C26:0-LPC not requiring rescreening of preterm babies at term age.

Societal impact

The SCAN study has shown that it is feasible to employ a boys-only screening algorithm that identifies males with ALD without identifying unsolicited findings, based on elevated C26:0-LPC levels, the presence of one X-chromosome and a variant in ABCD1 in heel prick dried bloodspots. This approach will be of interest to countries that are considering ALD newborn screening but are reluctant to identify girls with ALD because for girls there is no direct health benefit. Finally, the identification of four male newborns with ALD allows prospective monitoring and timely therapeutic intervention, thereby preventing irreversible damage and saving lives.

Future perspectives

As of October 2023 all Dutch male newborns will be screened for ALD. Our goal is to help as many countries as possible in their efforts to include ALD in their newborn screening program. Newborn screening also uncovered new challenges. In the current landscape there is no test available to assess a boy's true risk to develop ALD. As a consequence, all boys identified through newborn screening are subjected to the same rigorous follow-up protocol, with adrenal function testing (starting at age 6 months) and brain MRI scans (starting at age 2 years) every 6 months. One of the major goals of our research is focused on the identification of prognostic biomarkers allowing the development of a test to determine an individual's true risk of developing adrenal disease and/or cerebral ALD. Such a test will allow physicians to make informed decisions about treatment and management (in a practical sense this may be the need for less intense screening for an individual), leading to better outcomes for affected individuals and their families.

3.5 Case study 5 - The neonatal screening for congenital adrenal hyperplasia in the Netherlands; improved by adding second-tier testing.

Prof. dr. Anita Boelen, Endocrine Laboratory, department of Laboratory Medicine, Amsterdam UMC.

Background

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders of the adrenal steroid synthesis. Ninety-five percent of CAH cases are caused by 21-hydroxylase deficiency (21-OHD) due to mutations in the CYP21A2-gene. In the remaining 5% of cases other enzyme deficiencies are involved with 11ß-hydroxylase deficiency as the most common one. In classic CAH due to 21-OHD the conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol is limited, leading to deficient production of cortisol and in 75% of cases also of aldosterone, and a concomitant increase of precursor steroids, notably 17-OHP. Patients with aldosterone deficiency are classified as the salt-wasting phenotype and are at risk of life-threatening hyponatremia, hyperkalemia and acidosis. Furthermore, a shortage of cortisol may predispose to life-threatening hypoglycemia. The lack of cortisol also leads to an increased secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland. This, in turn causes hyperplasia of the adrenal cortex, which subsequently results in the excessive production of precursor steroids, which shunt into the non-affected androgen pathway. The severity of the illness, the availability of a screening test (17-OHP) and possibility of life-saving in-hospital treatment led to the inclusion of the disorder in the Dutch newborn screening (NBS) program in 2002.

Major breakthroughs

The screening for CAH is based on a 17-OHP measurement in dried blood spots (DBS) using a sophisticated algorithm, based on gestational age or birth weight and refined by adding a second DBS in case of an inconclusive first result. Despite this, a substantial number of children is still referred with a false-

positive NBS result due to the non-specificity of the 17-OHP measurement. In CAH due to 21-OHD, the enzyme 11ß-hydroxylase catalyzes the conversion of 17-OHP into 21-deoxycortisol (21-DF). 21-DF is a specific and promising marker for 21-OHD but is unsuitable as a primary marker in neonatal screening due to the long analysis time. Second-tier profiling of 21-DF in DBS using LC-MS/MS is a possibility to improve the specificity of the screening. We recently developed a method to measure 21-DF in DBS and confirmed 21-DF as the only specific marker for 21-OHD, correctly identifying eight patients in a cohort of 92 screened neonates with positive NBS results. As a result, 21-DF was implemented in the Dutch NBS program since October 2021 as a second-tier marker in all inconclusive first DBSs. Further evaluation needs to be done but a substantial reduction in the number of false-positive referrals has been observed already.

Who is involved?

Prof. dr. Anita Boelen and Prof. dr. Annemieke Heijboer, Endocrine Laboratory, department of Laboratory Medicine, Amsterdam UMC.

User and collaborations

Regional screening laboratories; Isala, Zwolle; IJselland ziekenhuis, Capelle a/d IJsel; Elisabeth ziekenhuis, Tilburg; Paediatricians from various academic and peripheral hospitals; RIVM; screenings laboratory (GZB); Centrum voor bevolkingsonderzoeken.

Scientific impact

Our recent developed method to measure 21-DF might also be used for the diagnosis of patients with late onset CAH with 21-DF being an possible ideal marker for this from of CAH, which often presents with sign of hyperandrogenism or subfertility. The application in DBS makes it possible for follow up of patients with CAH at home. A blood sample can be easily taken using a finger prick without the need for the presence of a phlebotomist.

Societal impact

In extensive collaboration, with both laboratory specialists and pediatricians from various academic and peripheral hospitals and the RIVM, a study with broad social relevance has been carried out. We have shown that a new laboratory test developed by our laboratory (LC-MS/MS method for 21-deoxycortisol in blood spots) can be successfully implemented in the heel prick screening and that as a result 100% of all second heel pricks within the framework of the condition CAH can be prevented. This has important consequences for the parents involved. Parents of a child who has to undergo a second heel prick have to deal with psychological consequences because of the idea that their child may have a serious illness. They appear to be extra alert to the health of their child for a long time to come. As a result, these children appear to require more care later than peers who have not received an extra heel prick. The result of our research, which has been directly implemented in the national government's heel prick screening, therefore has a major social impact. This message was picked up by the Amsterdam UMC (website and interview for the magazine 'Janus') and distributed via other websites.

Future perspectives

Evaluation of the revised program has to carry out in order to determine the positive predictive value of the program including the second tier. More research will be done on the usefulness of 21-DF in late-onset CAH.

3.6 Case study 6 - diverse and inclusive HR policies that foster talent development

Amsterdam UMC

The mission of Amsterdam UMC 'Together we discover the healthcare of tomorrow' expresses the vision of being an organization in which research staff with diverse backgrounds flourish and jointly contribute to excellent team science.

Diversity & Inclusion policy

Amsterdam UMC has endorsed the Charter 'Talent to the top', by which it committed itself to improve the gender balance in (sub)top levels. The Gender Equality Plan of Amsterdam UMC, which is in line with EU policy guidelines, goes a step further by expressing the vision of becoming an inclusive organization that represents the cultural and sexual diversity of its environment. This Gender Equality Plan is part of the broader 'Action Plan for 2021 and after: Diversity & Inclusion at Amsterdam UMC: Differences make us stronger together'. To strengthen gender equality and diversity, Amsterdam UMC has dedicated resources and expertise to promote equal opportunities for women and people from underrepresented groups, such as a Diversity & Inclusion (D&I) Office, Principal D&I investigators and educators. Amsterdam UMC offers several workshops and trainings to raise awareness and help employees integrate diversity in their own teams and collaborations. To help female researchers progress to higher levels on the career ladder, part of the Aspasia Grant of the Dutch Research Council (Nederlandse Organisatie voor Wetenschappelijk Onderzoek; NWO) funds have been transferred to the Women in Science Fund, financially supporting young female scientists to go on international work visits.

Talent policy

Amsterdam UMC has a Committee for Talent and Appointments (CTA) that has been assigned by the Executive Board to shape the talent policies of scientific staff and to provide advice to the Deans of the Medical Faculties of the VU and the UvA on the appointment of mid-career and top level academics (i.e. Associate Professors and Professors). The CTA also provides advice on the implementation of Recognition and Rewards (R&R), which advocates a broader evaluation of academic staff, in line with the current national and international discussion on this topic. The goal of the CTA is to make appointment policies of Amsterdam UMC more transparent for talents from within, as well as from outside of Amsterdam UMC who wish to make career steps. The CTA is a subcommittee of the Amsterdam Research Board (Figure 1). Diversity and Inclusion will also be integrated into the talent policies by the CTA. The CTA has developed a Qualification Portfolio along the principles of R&R to evaluate resumes. In this Portfolio, candidates can present themselves by way of an 'evidence based resume' by combining narratives providing context to their career choices, with qualitative and quantitative indicators of their academic achievements. They need to excel in at least two of the following domains: research; education; clinical work; valorization and/or academic leadership. The development of new talent policies by the CTA will build on existing career instruments, such as the Principal Investigator system, Postdoc Career Bridging Grant, Amsterdam UMC Fellowship and Tenure Track. Currently, the CTA broadens its scope towards talented researchers in different stages of their careers by developing postdoc policies and providing advice on Starters Grants for Assistant Professors and nurses with aspirations in research. Also, an Amsterdam UMC-wide mentoring