SELF-EVALUATION
2017 - 2022

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)
research institute

Amsterdam UMC
University Medical Centers

Self-evaluation report AGEM 2017 - 2022

Colophon

Board of directors
Stan van de Graaf - co-director (2017 - present)
Anita Boelen - co-director (2022 - present)
Gerd Bouma - co - director (2015 - 2022)

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Abbreviations

ABC	Area Bases Connectedness
AG&M	Amsterdam Gastroenterology & Metabolism
AGEM	Amsterdam Gastroenterology Endocrinology Metabolism
AMC	Academic Medical Center
BD	Business Developer
CTA	Committee for Talent and Appointments
ERC	European Research Council
GI	Gastrointestinal
GLS	Glutaminase
IBD	Inflammatory Bowel Disease
IEM	Inborn errors of metabolism
ISO	International Organization for Standardization
IXA	Innovation Exchange Amsterdam
KNAW	Royal Netherlands Academy of Arts and Sciences
METC	Medical Ethical Assessment Committee
MNCS	Mean Normalized Citation Score
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Non-alcoholic steatohepatitis
NWO	Dutch Research Council (Nederlandse Organisatie voor Wetenschappelijk Onderzoek)
OA	Open Access
PhD	Doctor of philosophy
PI	Principal Investigator
RIVM	National Institute of Public Health and Environment
SEP	Strategy Evaluation Protocol
SWOT	Strengths Weaknesses Opportunities Threats
UMC	University Medical Center
UMD	United for Metabolic Diseases
UvA	University of Amsterdam
VU	Free University Amsterdam
VUmc	VU Medical Center
ZonMw	ZorgOnderzoek Nederland Medische Wetenschappen

Word from the directors

The body's intricate mechanisms that regulate food intake, digestion, and metabolism play a vital role in maintaining our overall health. This remarkable machinery of individual components serving a common purpose mirrors the essence of our institute. Founded in Amsterdam, the Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) research institute stands as one of the eight esteemed research institutes within the Amsterdam University Medical Centers.

At AGEM, we bring together experts from various disciplines associated with metabolism, digestion, and endocrinology to cultivate a comprehensive understanding of these processes and their impact on human health. Our institute serves as a collaborative platform, bridging the gap between clinicians and basic scientists, thereby fostering translational science. By synergizing our efforts and fostering collective learning and exploration, we strive to make a significant difference in gastrointestinal, endocrine, and metabolic health on a global scale.

Contained within this self-evaluation report is a showcase of the quality and societal impact of the research conducted within our institute. This evaluation encompasses the initial six years of AGEM, which commenced following the merger of the VU Medical Center (VUmc) and Academic Medical Center (AMC) in 2017. Throughout this period, approximately 700 to 800 AGEM researchers have actively contributed to diverse research fields and programs, driving crucial scientific advancements to enhance health and mitigate the burden of diseases within our areas of focus.

Within this report, we will present key highlights from AGEM's research accomplishments over the past six years, as well as elaborate on our institute's mission, vision, and strategic aims. We take pride in the achievements of our researchers thus far and eagerly anticipate the next six years. Our commitment remains unwavering as we strive to further empower our researchers and amplify their impact in the pursuit of improved health outcomes.

Stan van de Graaf
Co-director

Anita Boelen
Co-director

Executive summary

The Amsterdam Gastroenterology, Endocrinology and Metabolism (AGEM) research institute unites the research at Amsterdam UMC involved at the intersection of digestion, metabolism, endocrinology microbiology, cancer and public health. Together, we aim to improve gastrointestinal, endocrine and metabolic health and to connect our efforts to major societal and healthcare challenges, thereby preventing and reducing the burden of common and rare diseases.

The AGEM institute consists of approximately 700 Amsterdam UMC researchers working in the fields of gastroenterology, endocrinology and metabolism. The multidisciplinary nature of the AGEM research institute is amply illustrated by the diversity of the participating (sub-) departments and reflected accordingly in the diversity of our AGEM research board. The AGEM institute is currently led by two directors, two policy officers and one business developer.

The last six years, research within the institute has been divided into four programs: (1) re-generation and neoplasms of the digestive system; (2) digestive function and pathology; (3) endocrinology, metabolism and nutrition, and; (4) inborn errors of metabolism. In order to guide the evaluation, the institute has defined ten focus areas. These are clusters of research in which many Principal Investigators are collaborating. Whereas some of the focus areas can be categorized under a single research program, others are placed at the cross-section of two or more research programs. This illustrates the cross-disciplinarily of the institute.

Mission, vision, aims and strategy

The AGEM mission is: to perform research that promotes healthy nutrition and metabolism, prevents or cures gastrointestinal, endocrine and inherited and acquired metabolic disease and improves the outcomes for our patients. The AGEM vision and goal is: to unite the Amsterdam UMC research on gastrointestinal, endocrine and metabolic health and disease into a single research organization. To achieve this mission and vision, five strategic aims were formulated:

1. Talent development and retention: recruit, train and retain the next generation of excellent researchers for research programs of AGEM;
2. Promote and foster multidisciplinary research approaches within the institute between different research programs and amongst scientists from bench to bedside;
3. Provide an attractive platform for preclinical and clinical development for external partners active in our disease areas, thereby strengthening partnerships to generate societal and healthcare impact;
4. Create a sense of belonging within the institute. This involves i) creating an atmosphere of intellectual excitement and cross-fertilization that encourages researchers to expand their understanding of biology and disease processes, in order to make important contributions to modern medicine, and ii) a safe, social and inclusive environment where individuals all contribute to team-science with their own strength;
5. Develop a branding & communication strategy, which is used to target the general public, patients, press, academic colleagues and charities. For this aim, we focus on those areas of research where the full chain of translational research is at an international top level and multiple PIs collaborate in teams.

In order to work towards these five aims, the institute has chosen the following strategy: 1) distribute annual grants; 2) organize symposia and lectures; 3) stimulate collaborations; 4) hire a business developer; 5) contribute to talent development; 6) communicate science to the scientific and general public; and 7) foster research integrity.

Evidence

Research quality

The AGEM institute has been active in the biomedical and health sciences fields for several years, and its researchers have produced a diverse range of research output. Collaboration, both internal and external, has been an essential component of the research produced. A significant proportion of AGEM's publications have been made available to the public and 20% of its publications have been ranked in the top 10% most cited in their field in their respective year. AGEM's research efforts have yielded notable scientific outcomes, resulting in publications in high-impact journals and an increasing number of collaborations with external institutions. Next to these scientific collaborations, the use of AGEM research products is demonstrated by the numerous (systematic) reviews published by AGEM researchers as well as the relatively high Mean Normalized Citation Score. Despite the challenge of balancing data sharing with participant privacy, many research groups within AGEM are actively promoting data sharing within their respective fields. The AGEM institute is dedicated to producing high-quality research that is highly valued and well recognized by the scientific community. Many research groups within the institute play a crucial role in patient care and research in their respective disease areas at both regional and international levels: researchers are part of international consortia, received prestigious awards and grants and participate in various editorial boards and scientific organizations.

Societal relevance

Next to the impact of AGEM research on filed patents, research conducted within the AGEM institute has gathered significant media attention over the last six years. AGEM research also has a significant impact on patients and patient care, particularly through its influence on clinical guidelines: the majority of AGEM focus areas scores above the world average with regards to

the uptake of research in clinical guidelines. In addition to the impact of AGEM research on policy documents, the AGEM institute actively collaborates with non-academic hospitals, companies, and patient organizations. The impact of co-authorship collaborations between the AGEM institute and non-academic hospitals was observed to be above world average for all AGEM's research focus areas. These collaborations are crucial in bridging the gap between academic research and clinical practice, ultimately resulting in better patient outcomes. The AGEM institute also communicates its research to society by publishing news articles and research highlights on its website. And, despite AGEM's primary focus on research rather than education, which is entrusted to the graduate schools and the Doctoral School, AGEM researchers actively contribute to the education of undergraduate, graduate, and PhD candidates in diverse roles. The public has shown appreciation for research conducted by AGEM researchers through public awards and prizes, as well as appointments of AGEM researchers in the boards or advisory committees of societal organizations or patient associations.

Accomplishments

Research quality and societal relevance

The chosen case studies reflect the broad range of research conducted within the AGEM institute and demonstrate that the AGEM institute excels at fundamental, clinical and translational science. The high quality of AGEM research is shown by the fact that research has led to well-cited publications in top journals as well as invitations to prestigious international scientific meetings. Further, the AGEM institute houses some unique research projects such as those about newborn screening. Despite the fact that some of AGEM's research projects are primarily geared towards the scientific community, the societal relevance of research conducted within the AGEM institute is apparent. A prominent example of this, is the improvement of the Dutch newborn screening program by adding second-tier testing for congenital adrenal hyperplasia.

AGEM's contribution to the four SEP-specific aspects

The AGEM institute shares Amsterdam UMC's commitment to be an organization in which research staff with diverse backgrounds flourish and jointly contribute to excellent team science. Despite AGEM's limited influence on HR-related aspects due to its role as network institute, the institute aims to contribute to this aim in whatever ways it can, e.g. through the AGEM Talent Development Grant and the AGEM International Student Fellowship. Second, AGEM aims to promote scientific integrity in several ways, e.g. through its Responsible Research Dinner Debate. Third, even though PhD policy is the main responsibility of the Amsterdam UMC Doctoral School and Amsterdam UMC departments, AGEM aims to provide extra support to PhD candidates, for instance by organizing an annual PhD candidate retreat and the AGEM PhD candidate course. Last, in addition to fostering Open Science, the AGEM institute aims to create a transparent environment with regards to its policies and choices and places great emphasis on stakeholder involvement.

Strategy for the next six years

Based on the AGEM-wide SWOT analysis, it was concluded that redefining AGEM's four research programs into three research programs reflected in AGEM's name (gastroenterology, endocrinology and metabolism) will help researchers better identify themselves with the programs, thereby increasing their sense of belonging and commitment. In addition, AGEM should make clear what the centers of excellence are within the institute and actively stimulate interdisciplinary collaboration. This will benefit further internal and external positioning of AGEM. It is important to continue to develop the aspects that we are good at, namely offering a safe and enthusiastic environment for young investigators and PI's alike.

This analysis, together with the ones conducted for AGEM's three newly defined research programs, led to the conclusion that the institute is making commendable progress towards achieving its five strategic aims. Since these aims accurately represent the core mission and vision of AGEM, the institute will continue to prioritize these five aims over the next six years. While these aims will serve as the overarching framework for AGEM's strategy, this self-evaluation has highlighted specific focus points that can further refine the institute's alignment with its mission and vision:

1. More focus on PI level to stimulate involvement and interdisciplinary research within AGEM

It was identified that there are opportunities to enhance cohesion among PIs working in similar research fields. A comprehensive inventory of all AGEM research will be conducted to identify common interests. Further, the institute will organize events specifically designed to stimulate interaction and collaboration among Principal Investigators, organized top-down and centered around specific research themes. These events will play a vital role in fostering a spirit of cooperation and knowledge exchange within the AGEM community. Lastly, an AGEM database will be made and updated, to enhance communication and facilitate connections between researchers. This will contribute to a more streamlined research environment and encourage fruitful collaborations.

2. Strengthen and further define AGEM talent policy.

Aligned with our strategic objectives, talent development and retention hold significant importance within the institute's mission. AGEM has taken the initial steps to establish Young AGEM, a board comprising early- to mid-career researchers who will offer advice and support to the AGEM research board. Furthermore, the institute is committed to furthering the implementation of an Amsterdam UMC-wide mentoring program. Lastly, AGEM aspires to assume a more prominent role in Amsterdam UMC-wide talent policy, e.g. through the Committee for Talent and Appointments and by making a strategic talent management plan.

3.National and international positioning.

To provide strategic direction for the institute, AGEM aims to strengthen its positioning within the national and international research landscape. It is crucial to identify the specific research areas in which AGEM currently holds a leading role, both on a national and international level. This determination will serve as a compass for future decision-making and enable the institute to establish a unique and appealing profile for collaboration.

Introduction

About the institute

We have to sustain our daily energy expenditure by efficient digestion and metabolism. The body's machinery required to manage this task is one of the most important organ systems burdened by disease in the Western World. Obesity, diabetes, thyroid diseases and chronic inflammatory diseases of the gastrointestinal tract, pancreas and liver are some of the major illnesses that affect our society. Millions of people are affected by these highly prevalent diseases that can be influenced by lifestyle, while having such a disease affects the well-being of these people dramatically. On the other hand, rare diseases as inborn errors of metabolism (IEM) and rare endocrine diseases require highly specialized care but also offer a unique opportunity to study human metabolism in health and disease. The Amsterdam Gastroenterology, Endocrinology and Metabolism (AGEM) research institute unites the research at Amsterdam UMC (appendix 1.1) involved at this intersection of digestion, metabolism, endocrinology microbiology, nutrition, cancer and public health. Together, we aim to improve gastrointestinal, endocrine and metabolic health and to connect our efforts to major societal and healthcare challenges, thereby preventing and reducing the burden of common and rare diseases.

The last six years, research within the institute has been divided into four programs: (1) re-generation and neoplasms of the digestive system; (2) digestive function and pathology; (3) endocrinology, metabolism and nutrition, and; (4) inborn errors of metabolism. Within these research programs we aim to develop centers of expertise that belong to the top of the international basic, translational and clinical research in our field by contributing to important scientific advances and improving health and limiting the impact of disease in our focus areas. We will elaborate further on the research programs and focus areas in chapter 3.

From AG&M to AGEM

In 2017, the institute was initiated under the name Amsterdam Gastroenterology & Metabolism (AG&M). Even though endocrinology had always been an important line of research within the institute, with many researchers, grants and PhD candidates, this was not reflected properly in the name of the institute. From April 2020, the institute continued under the name Amsterdam Gastroenterology Endocrinology Metabolism. This better reflects the broader research scope of the institute and further emphasizes the importance of multidisciplinary research.

Organization and governance

The AGEM institute consists of Amsterdam UMC researchers working in the fields of gastroenterology, endocrinology and metabolism. Over the last six years, the institute has always hosted approximately 700-800 researchers. The Principal Investigator (PI) structure used by Amsterdam UMC aptly illustrates the diversity of research lines and groups represented within the AGEM institute (appendix 1.2, table A1). Upon appointment, new PIs are officially appointed to one or two research institutes.

At the start of the institute, the AGEM office consisted of two directors and a policy officer. They were supported by a research board, consisting of senior AGEM researchers (at least one representative from each of the four research programs). The research board meets the AGEM office approximately once per two months to discuss AGEM policy, and plays an important role in reviewing scientific strategy, the institute's position within Amsterdam UMC, research support and talent development among others.

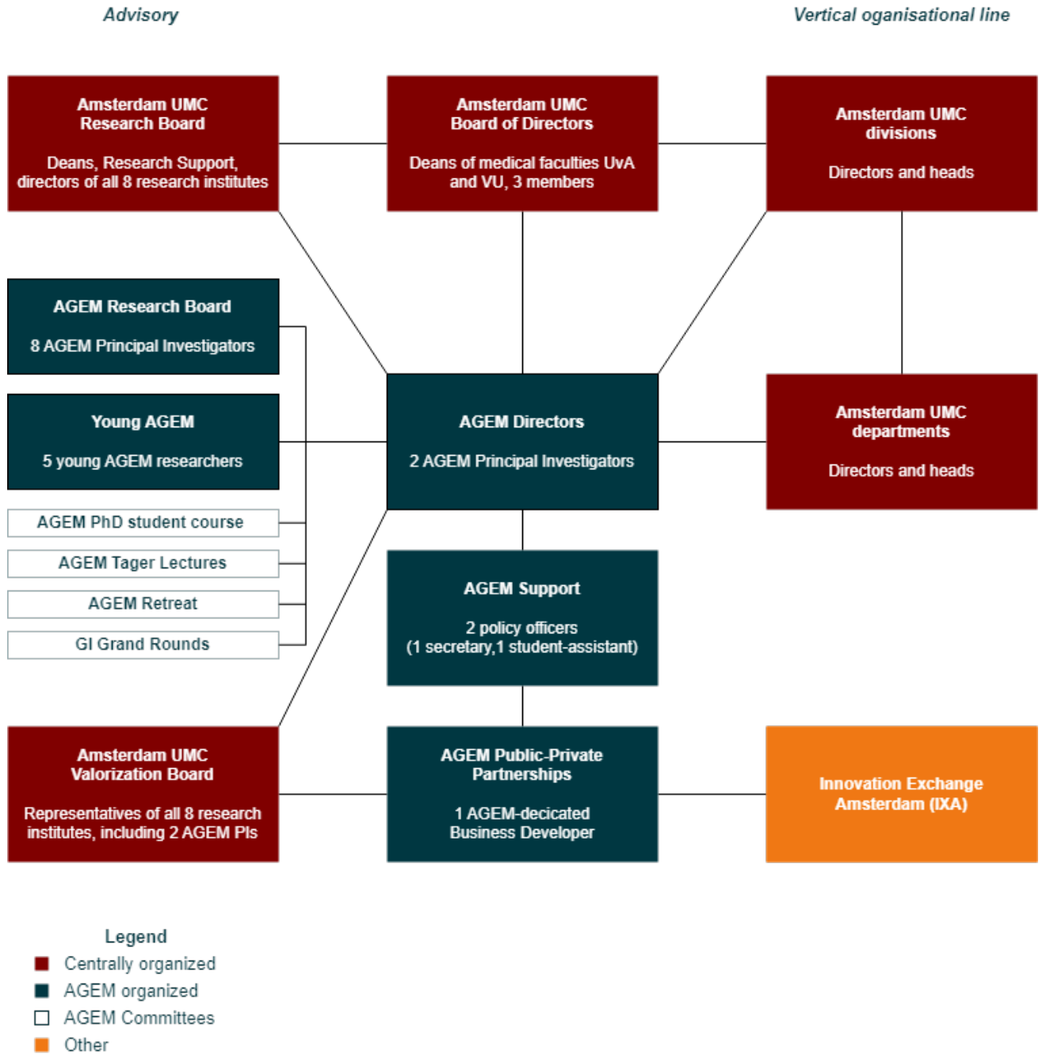


***Figure 1**. Organizational structure AGEM research institute*

Since 2022, by a second policy officer. Later that year, an AGEM-dedicated Business Developer was appointed through our Innovation Exchange Amsterdam[1] (IXA) bureau. From time to time, the institute was also supported by a student assistant and/or secretary. The current governance of AGEM is visualized in figure 1. As one of eight research institutes of Amsterdam UMC, AGEM's governance is directly linked to Amsterdam UMC's research organization and policy (see appendix 1.1 for further explanation).

The multidisciplinary nature of the AGEM research institute is amply illustrated by the diversity of the participating (sub-)departments (appendix 1.2, table A2) and reflected accordingly in the diversity of our AGEM research board (appendix 1.2, table A3).

Mission, vision & aims

Mission, vision and aims

Mission and vision

AGEM unites the research at the Amsterdam UMC involved at the intersection of nutrition, microbiology, digestion, endocrinology and metabolism and aims to make an important contribution to improve gastrointestinal, endocrine and metabolic health and reduce the burden of diseases such as pancreatitis, inflammatory bowel disease (IBD), thyroid disorders, diabetes mellitus and galactosemia. The AGEM mission is:

To perform research that promotes healthy nutrition and metabolism, prevents or cures gastrointestinal and inherited and acquired metabolic disease and improves the outcomes of our patients.

The researchers of the AGEM institute closely collaborate with internal and external academic and commercial parties to perform research with a true impact on the understanding and treatment of pathological processes. This impact is achieved at three important levels:

1. Making discoveries that help unravel the fundamental mechanisms that maintain organ homeostasis in health and the way these are dysregulated in disease;
2. Translating the revolutionary advances made in biomedical research to healthcare or modern medicine;
3. Performing (pre)clinical research that truly improves our current pathways for disease prevention and cure.

The AGEM vision and goal is: to unite the Amsterdam UMC research on gastrointestinal, endocrine and metabolic health and disease into a single research organization.

AGEM researchers Vanesa Dijkstra-Muncan and Francesca Giugliano

Strategic aims

Upon its inception, the institute formulated 10 specific aims to achieve its mission and vision by promoting the quality and visibility in the institute:

1. Familiarize the researchers of the VUmc and AMC with each other and promote a spirit of common purpose;
2. Create an atmosphere of intellectual excitement and cross-fertilization that encourages researchers to expand their understanding of biology and disease processes, in order to make important contributions to modern medicine;
3. Identify key research questions for the coming decade in line with todays' major societal and healthcare challenges, and actively work within the AGEM research programs to address these questions;
4. Promote and foster multidisciplinary research approaches within the institute between different research programs and amongst scientists from bench to bedside;
5. Focus on those areas of research where the full chain translational research is at an international top level;
6. Talent development: recruit and train the next generation of excellent researchers for research programs of AGEM;
7. Collaborate closely with colleagues at the top of our international academic field and develop stable partnerships with their institutes;
8. Provide an attractive platform for preclinical and clinical development for commercial entities active in our disease areas;
9. Increase quality of the Core Facilities required for the research at the highest international academic level;
10. Develop a branding & communication strategy, which is used to target the general public, patients, academic colleagues, charities and industry.

Mid-term evaluation 2019

In order to ensure the scientific and societal relevance of its research, the AGEM institute is subjected to national evaluation cycles, in which the strategy of the institute is evaluated each six years. Since the institute was constituted in 2017, this will be the first external evaluation the institute conducts. Nevertheless, the institute conducted an internal mid-term evaluation in 2019, following the Strategy Evaluation Protocol (SEP), in order to reevaluate its mission and vision and to refine its strategic aims.

The 2019 self-evaluation (appendix 1.3) revealed that the institute had already made significant progress towards achieving several of its ten strategic aims, particularly to familiarize researchers of the VUmc and AMC with each other, to create an atmosphere of intellectual excitement, and to identify key research questions. Since the Amsterdam UMC's Core Facilities are separate entities on which the AGEM institute does not have financial or managerial influence, this aim was excluded from the institute's strategy. Overall, the 2019 evaluation provided valuable validation that the institute was heading in the right direction, and identified some strategic aims that had not received adequate attention before. Consequently, this served as an opportunity to redirect the institute's focus and reformulate its previous aims to:

1. Talent development and retention: recruit, train and retain the next generation of excellent researchers for research programs of AGEM;
2. Promote and foster multidisciplinary research approaches within the institute between different research programs and amongst scientists from bench to bedside;
3. Provide an attractive platform for preclinical and clinical development for external partners active in our disease areas, thereby strengthening partnerships to generate societal and healthcare impact;
4. Create a sense of belonging within the institute. This involves i) creating an atmosphere of intellectual excitement and cross-fertilization that encourages researchers to expand their understanding of biology and disease processes, in order to make important contributions to modern medicine, and ii) a safe, social and inclusive environment where individuals all contribute to team-science with their own strength;
5. Develop a branding & communication strategy, which is used to target the general public, patients, press, academic colleagues and charities. For this aim, we focus on those areas of research where the full chain of translational research is at an international top level and multiple PIs collaborate in teams.

Strategy

of the past six years

Strategy

The last six years, AGEM research has been divided into four research programs (box 1). In order to guide this evaluation, the institute has defined ten focus areas (figure 2). These are clusters of research in which many PIs are collaborating. Whereas some of the focus areas can be categorized under a single research program, others are placed at the cross-section of two or more research programs. This aptly illustrates the cross-disciplinarily of the AGEM research institutes.

Description of strategy to achieve aims

Grants

AGEM strives to cultivate a stimulating academic environment that encourages a collaborative and multidisciplinary approach to research, between scientists at the bench and bedside. To achieve this, AGEM offers various types of internal grants annually since its inception in 2017. On the website, we have provided some exemplary cases of success stories resulting from the Talent Development Grant and the Innovation Grant. In 2020, AGEM introduced additional grants for one year only, explicitly designed to promote clinical research, reflecting its commitment to supporting research initiatives across diverse areas of study. The AGEM grants, albeit small in size compared to grants from (inter)national funders, are valued greatly by AGEM Principal Investigators[2] - mainly since the grants can easily be used to implement new and innovative projects. An overview of all grant laureates can be found on the website.

Symposia and lectures

Within its strategic aims, AGEM has always placed a strong emphasis on further developing its role as a network institute, by promoting internal and external multidisciplinary collaborations. In line with this, the institute organizes a multitude of recurring lectures, such as the Tager lectures, focusing on metabolic and endocrine research and given by well-known (inter) national scientists, and the Grand Rounds in Digestive Diseases, its gastroenterological counterpart. Furthermore, the institute has also organized a series of well-attended symposia addressing various research themes and hosting distinguished lecturers from Amsterdam UMC and beyond. In order to promote inter-institutional collaboration within Amsterdam UMC, AGEM co-organizes and supports an annual meet & greet between PIs from AGEM and the Amsterdam institute for Infection and Immunity (AII); a symposium focusing on hepato-(liver)-pancreato-biliary (HPB) organs with Cancer Center Amsterdam (CCA); and regular ImmunoMetNet symposia and meetings. All of the above symposia and lectures are highly appreciated and valued by the PIs[3].

***Box 1**. Description of AGEM research programs 2017-2022*

1 Re-generation and neoplasms of the digestive system

The groups embedded in this research program focus on the postnatal development, carcinogenesis and repair of the digestive tract. The mechanisms regulating gut-development, post-surgical healing, and tumorigenesis, as well as the development of novel treatment strategies are important areas of study.

2 Digestive function and pathology

This program focusses on the function of the human digestive system in health and disease. The main research areas are: (patho)physiology of the digestive tract, the role of the microbiome, the mechanism of action of therapies, the development of novel surgical and medical treatment strategies and nutrition.

3 Endocrinology, metabolism and nutrition

In this research program, metabolism and hormonal regulation play a central role. The ultimate aim of this research program is simple: to improve (metabolic) health of patients with metabolic and endocrine pathologies.

4 Inborn errors of metabolism

Within this program, rare IEM manifesting from (pre)neonatal period into adulthood are investigated. The focus is to unravel the cause of a metabolic derangement in patients suspected of a genetic metabolic disorder and to develop and improve treatment for these patients.

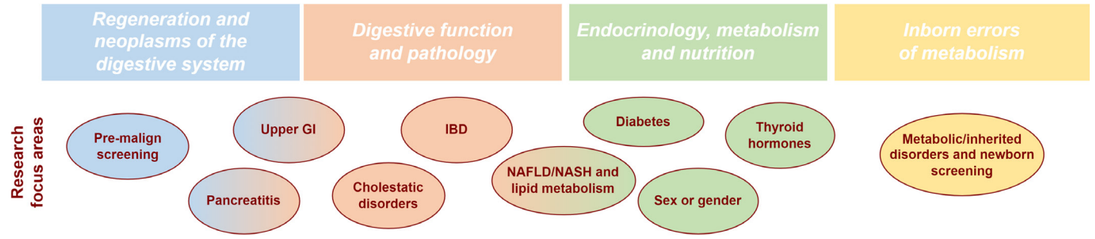


***Figure 2**. AGEM research programs with focus areas.*

Collaborations

Regionally, AGEM collaborates with the other research institutes of Amsterdam UMC and other teaching hospitals in the Amsterdam region. The institute's main national partners are the academic medical centers in the Netherlands. Furthermore, most of the AGEM principal investigators have a large international network. Even though these are not restricted to specific institutes, some of these partnerships reflect long-term and productive collaborations (p. 9)

AGEM-dedicated business developer

To further enhance external collaboration, the institute hired a Business Developer (BD) in 2022. For a broadly positioned (pre)clinical research institute like AGEM, this brings great opportunities. Besides capitalizing on existing knowledge and expertise, the BD identifies valuable synergies within AGEM, and crafts new propositions for external partnerships. The BD assists in setting up collaborations with various stakeholders and clients; academic/technology institutes, food/pharma industries, health care providers, and patient organizations. The BD helps translate science into innovative clinical and technological applications and is partly embedded in IXA.

Talent policy

The institute has implemented various initiatives to support the academic and personal growth of PhD candidates and ensure their well-being. One prominent example is the annual AGEM retreat, organized by PhD candidates. The retreat offers a platform for all PhD candidates to present their research, thereby providing a comprehensive overview of the full width of research conducted within the institute. This retreat aims to bring researchers together to explore, exchange and learn from each other's research. Furthermore, the institute conducts a highly regarded PhD candidate course to provide valuable information to new and current PhD candidates, in the areas of gastroenterology, endocrinology, and metabolism. This course covers essential topics that may fall outside the scope of their own research and also provides practical information and hands-on practice with broader academic skills. Each year, AGEM also organizes the Best Publication Battle, in which talented PhD candidates and junior postdocs get the opportunity to pitch their publication in a high-impact journal, thereby competing for the honoree prize of 'Best AGEM publication' of that year.

1. Talent development and retention: recruit, train and retain the next generation of excellent researchers for research programs of AGEM

- Annual AGEM Talent Development grant
- Contribution to establishing Amsterdam UMC mentoring program
- Annual AGEM PhD student course
- Continued AGEM international student fellowship
- AGEM contribution printing costs PhD theses

2. Promote and foster multidisciplinary research approaches within the institute between different research programs and amongst scientists from bench to bedside

- Promoting inter-departmental collaboration
- Eligibility requirements AGEM Grants
- Organization symposia and lectures
- Annual AGEM Retreat
- AGEM annual report
- Communication through various channels

3. **Provide an attractive platform for preclinical and clinical development for external partners active in our disease areas, thereby strengthening partnerships to generate societal and healthcare impact**

- Promoting technological innovation through AGEM innovation grant
- AGEM-dedicated Business Developer

4. Create a sense of belonging within the institute. This involves i) creating an atmosphere of intellectual excitement and cross-fertilization that encourages researchers to expand their understanding of biology and disease processes, in order to make important contributions to modern medicine, and ii) a safe, social and inclusive environment where individuals all contribute to team-science with their own strength

- Regular meetings with AGEM Principal Investigators and department heads
- Annual AGEM retreat
- Communication through various channels

5. Develop a branding & communication strategy, which is used to target the general public, patients, press, academic colleagues and charities. For this aim, we focus on those areas of research where the full chain of translational research is at an international top level and multiple PIs collaborate in teams

- Communication through various channels
- Contribution to organizing the Anatomische Les
- AGEM-dedicated Business Developer

***Figure 3**. AGEM aims with a summary of strategic choices to achieve those aims*

In addition to the institute's own initiatives, AGEM closely collaborates with the Amsterdam UMC Doctoral School, which aims to be a well-known and appreciated partner for PhD candidates and their supervisors. Through this collaboration, the AGEM institute contributes to PhD administration.

The AGEM institute is dedicated to creating a supportive and nurturing environment that encourages growth, learning, and success for all its researchers: junior to senior. The AGEM Talent Development Grant, for example, is specifically designed to support exceptionally talented researchers who have obtained a PhD degree within the last eight years. The grant provides funding for researchers who want to establish their own research line or further develop their existing research line.

Another noteworthy initiative is the institute's International Student Fellowship, encouraging (bio)medical students to participate in a research internship at an international top institute. The majority of these students return to Amsterdam UMC to obtain a PhD degree. In 2022, the AGEM institute has started drafting an Amsterdam UMC-wide mentoring program in collaboration with the seven other research institutes of Amsterdam UMC. This program will provide researchers with mentorship and guidance as they navigate their careers. To support development of senior researchers, AGEM has funded a well-appraised course for starting group leaders for several of its talented researchers. Finally, AGEM has an advisory role with regard to Amsterdam UMC talent policy and recruitment. This role is reflected in the institute's participation in nominating individuals and teams for local and international awards, in supporting promotions from assistant to associate or full professorships and in recruiting talent through e.g. the Amsterdam UMC fellowship and in participation in bi-annual research strategy sessions with Amsterdam UMC divisions and the board of directors.

Overall, AGEM's dedication to talent development is reflected in its various initiatives and advisory roles. These efforts ensure that the institute remains at the forefront of research and fosters the growth and development of its researchers.

Communication

The institute makes use of several communication channels, aimed at internal and external audiences, such as the bi-monthly newsletter, the AGEM website, and the AGEM LinkedIn page. Further, the AGEM annual report, distributed internally and externally, is an important initiative to highlight the high-quality research that happens within the institute and to reflect on the last year, summarizing the most important developments. Finally, the AGEM-dedicated BD plays an important role in establishing and growing collaborations with the industry and external partners. When interviewing PIs in 2023, the appreciation for the institute's clear and professional communication, specifically through its bimonthly newsletter, was expressed often.

Research integrity

Scientific integrity is an important topic of Amsterdam UMC's research policy. Since the AGEM institute highly values this theme as well, the AGEM staff is actively bringing this to the attention of AGEM department heads and PIs in face-to-face meetings. Furthermore, AGEM has also organized a Responsible Research Dinner Debate. During this event, researchers from all career phases (PhD candidate to PI) had open discussions around the theme of scientific integrity and how to foster responsible research practices in their departments and groups. This initiative has already snowballed to new efforts at different departments, such as the Tytgat Institute of Liver and Intestinal Research (group sessions with Dilemma Games[4]) and the Endocrine Laboratory (monthly meetings of technicians, PhD candidates and master students to discuss research and ethical issues).

Evidence

Research quality & societal impact

Evidence

An overview of chosen indicators to evaluate the institute can be found in appendix 2.1, table A4. AGEM consists of approximately 730 researchers, primarily PhD candidates (appendix 2.2, table A5). The institute is funded through the Amsterdam UMC, and its research is funded through the first until fourth funding stream[5] (appendix 2.2, table A6 and A7).

Research quality

Research products

The AGEM institute has been active in the biomedical and health sciences fields for several years, and its researchers have produced a diverse range of research output, as shown in appendix 2.3, table A8. Collaboration between PIs has been an essential component of the research produced (figure 4). Additionally, the majority of AGEM publications are the result of collaborations with external institutes, indicating a commitment to interdisciplinary research (appendix 2.3, table A9). AGEM's dedication to Open Access (OA) is also noteworthy, as a significant proportion of its publications have been made available to the public. Finally, a clear indication of the high quality of research conducted at AGEM is the fact that, over the past six years, 20% of its publications have been ranked in the top 10% most cited in their field in their respective year.

Appendix 2.3, figure A5 and A6 present a visual representation of the key terms extracted from all AGEM publications based on their co-occurrence. Although AGEM's three research

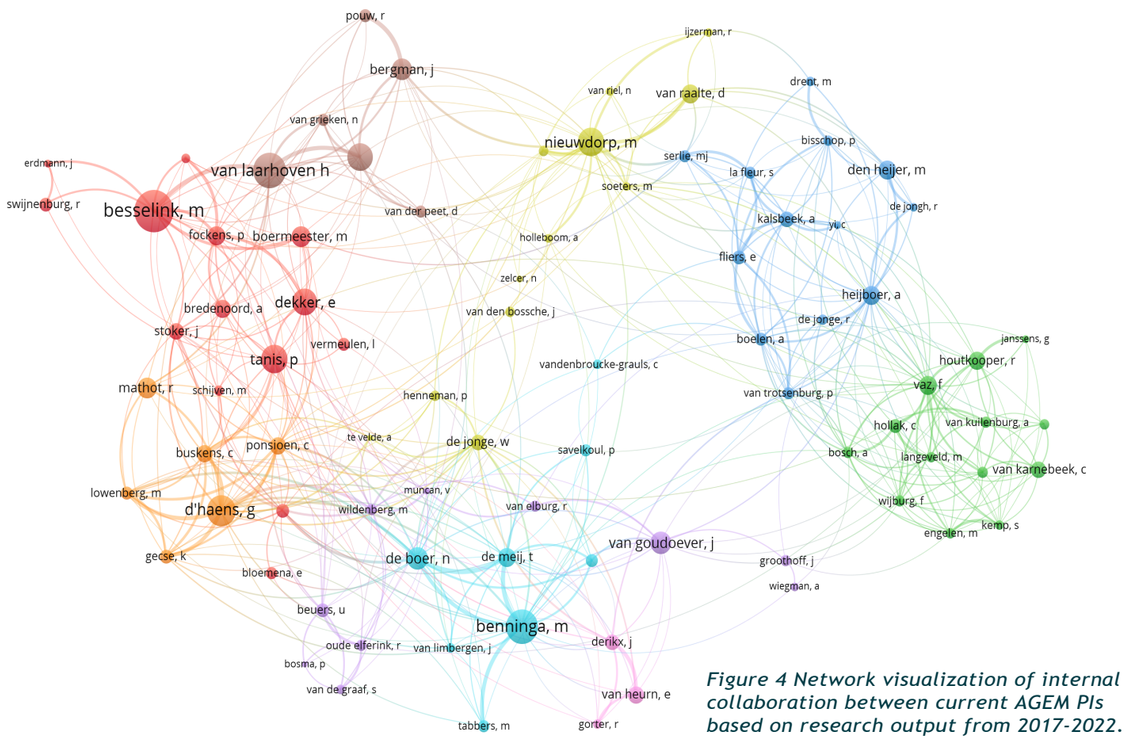


Figure 4 Network visualization of internal collaboration between current AGEM PIs based on research output from 2017-2022.

programs are evident in certain areas of the term map, the density of all key terms presented in the map suggests these research themes are closely related. This finding suggests that AGEM researchers are working together in a combined field to achieve a shared goal, rather than treating the three research themes as separate entities.

Use of research products

AGEM's research efforts have yielded notable scientific outcomes, resulting in publications in high-impact journals and collaborations with other academic institutions. For instance, Dr. Van Kuilenberg and his research group published their findings on Glutaminase (GLS) deficiency, the first IEM caused by a short tandem repeat expansion in GLS, in the New England Journal of Medicine in April 2019. This discovery has paved the way for new collaborations and a clinical trial to treat GLS patients. Moreover, an increasing majority of peer-reviewed articles published by AGEM researchers are the result of collaborations between AGEM and external institutes (figure 4 and table 1). These collaborative efforts demonstrate the AGEM institute's commitment to advancing biomedical and health sciences through a multidisciplinary approach.

Next to these scientific collaborations, the use of AGEM research products is demonstrated by the numerous (systematic) reviews published by AGEM researchers as well as the relatively high Mean Normalized Citation Score (MNCS) (appendix 2.3, table A8 and A9). Despite the challenge of balancing data sharing with participant privacy, many research groups within AGEM are actively promoting data sharing within their respective fields. Chapter 5 will delve more deeply into data sharing practices and OA policies.

Marks of recognition

The AGEM institute is dedicated to producing high-quality research that is highly valued and well recognized by the scientific community. Many research groups within the institute play a crucial role in patient care and research in their respective disease areas at both regional and international levels. They are also part of various international consortia[6]. Numerous AGEM researchers have received prestigious awards and grants for their outstanding work[7] and they participate in various editorial boards and scientific organizations. In conclusion, AGEM researchers are highly committed to producing cutting-edge research and are leaders in their fields, both nationally and internationally. The institute's numerous awards, grants, and collaborations with external institutes are a testament to its commitment to excellence.

Societal relevance

In order to assess the societal relevance of AGEM research, we analyzed the so called Area Based Connectedness (ABC) (appendix 2.4, box A1) of publication clusters (N publications > 39) related to the institute's aforementioned ten focus areas (appendix 2.4, table A11).

Research products

Next to the impact of AGEM research on filed patents (appendix 2.4.1), research conducted within the AGEM institute has gathered significant media attention over the last six years (appendix 2.4.2). AGEM's research regularly appears in reputable newspapers[8] as well as in patient organisation magazines[9]. Furthermore, AGEM's research is frequently featured on other news platforms[10]. AGEM researchers are regularly invited to speak at international conferences, seminars hosted by patient organizations, and guest on podcast episodes[11]. They also actively contribute to several websites and online webinars for patients with specific diseases[12]. One striking example is the website for children with abdominal pain, launched by Prof. Benninga and colleagues, which has been translated into many languages and provides a way to treat functional abdominal pain and irritable bowel

Dutch universities	P	International universities	P	Research organizations	P
Erasmus University	250	Katholieke Universiteit Leuven	39	Royal Netherlands Academy of Arts and Sciences (KNAW)	24
Utrecht University	209	University of British Columbia	31	Netherlands Comprehensive Cancer Organisation (IKNL)	21
Leiden University	204	Harvard University	30	Sanquin Blood Supply Foundation	12
Maastricht University	143	Karolinska Institutet	22	National Institute of Public Health and Environment (RIVM)	10
Radboud University	138	University of Copenhagen	19	Oncode Institute	9

Table 1. Five most important scientific collaborative partners (Dutch universities, International universities or Research organizations) of AGEM researchers, in terms of number of co-authored publications (fractional counting). Based on peer-reviewed publications in the period 2017-2022.

syndrome in children. Other researchers contribute to websites to inform the general public about their research in plain language. The group of Prof. Den Heijer, for example, has written thirteen articles for the wetenschap.nu platform. Overall, AGEM's research has had a significant impact on public health, and its researchers have been successful in disseminating their findings to a wider audience.

The research conducted within AGEM also has a significant impact on patients and patient care, particularly through its influence on clinical guidelines (appendix 2.4.3). Figure 5 shows that the majority of AGEM focus areas scores above the world average with regards to the uptake of research in clinical guidelines. One noteworthy example is the work done by the Dutch Pancreatitis Study Group (Case study 3, appendix 3): the international guidelines for the treatment of acute and chronic pancreatitis all include Dutch evidence gathered from the randomized trials and numerous non-randomized cohort studies. In addition to their significant involvement in clinical guidelines, AGEM researchers are active in organizing conferences and webinars for healthcare providers[13].

Use of research products

In addition to the impact of AGEM research on policy documents (appendix 2.4.4), the AGEM institute actively collaborates with non-academic hospitals, companies, and patient organizations (appendix 2.4.5). The impact of co-authorship collaborations between the AGEM institute and non-academic hospitals was observed to be above world average for all publication clusters (N > 39) related to AGEM's ten focus areas (appendix 2.4.5, figure A11). These collaborations are crucial in bridging the gap between academic research and clinical practice, ultimately resulting in better patient outcomes.

An important showcase of such a collaboration is United for Metabolic Diseases (UMD). Prof. van Karnebeek and prof. Waterham, both AGEM PIs, founded UMD: a multidisciplinary collaboration between six Dutch academic metabolic centers and the Patient Organization for Metabolic Disorders. Moreover, the AGEM institute has been expanding its collaborations with research organizations such as the National Institute of Public Health and Environment (RIVM), particularly on implementation and improvement of the Dutch neonatal screening program[14] (case studies 4 and 5, appendix 3).

The AGEM institute also communicates its research to society by publishing news articles and research highlights on its website, which attracts a significant number of monthly visitors. In addition, the AGEM LinkedIn page and newsletter (sent bi-monthly to over 800 people) serve as other means of communication, aimed at AGEM researchers as well as the general public and all those interested.

Marks of recognition

There are numerous examples of the public's appreciation of research conducted by AGEM. The public has shown appreciation for research conducted by AGEM researchers through public awards and prizes, as well as appointments of AGEM researchers in the boards or advisory committees of societal organizations or patient associations[15]. Several AGEM researchers have also been awarded grants or awards by societal or patient organizations, such as the 2019 Huibregtsenprijs for prof. Hollak, prof. Schijven who won the Medical Inspirator Prize for her work on StoMakker in 2020, and prof. Van Karnebeek, who was awarded Royal Honors[16] for her work on the Jeroen Pit Huis in 2022.

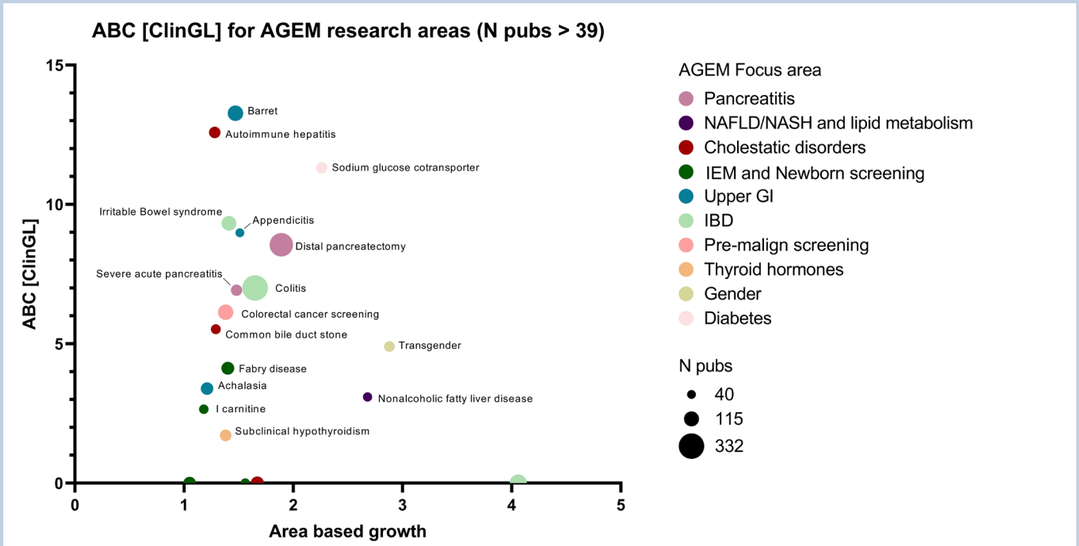


Figure 5 Area Based Connectedness to clinical guidelines of publication clusters (N > 39) related to AGEM's ten focus areas.

Translating science to students

Despite AGEM's primary focus on research rather than education, which is entrusted to the graduate schools and the Doctoral School, AGEM researchers actively contribute to the education of undergraduate, graduate, and PhD candidates in diverse roles. Dr. Seppen, for instance, is the director of the master program Biomedical Science at the University of Amsterdam (UvA) and prof. Van Trotsenburg is the director of the master program Medicine at the UvA. Further, most AGEM PIs actively contribute to a variety of courses for master students. For example, the master track Experimental Internal Medicine (University of Amsterdam) is built around the courses 'Neuroendocrinology and Translational Medicine' (coordinated by prof. Kalsbeek and prof. Houtkooper) and 'Gastrointestinal, Metabolic and Cardiovascular Disease' (coordinated by dr. Te Velde, dr. Seppen and prof. Zelcer). At Amsterdam University College, prof. de Vries and dr. Hochstenbach provide a 3-moths course for last-year bachelor students entitled 'Metabolic Biochemistry'. Most importantly, the institute translates its science to students through the AGEM PhD candidate course. In this two-week course, approximately 40 AGEM PIs give lectures to AGEM PhD candidates about basic concepts from their research.

Accomplishments

Research quality & societal impact

Achievements

To illustrate the institute's accomplishments in terms of research quality and societal impact), we have selected nine case studies (appendix 3, table A13).

Research quality & societal relevance

In alignment with the quantitative information showcased in chapter 4, the selected case studies effectively exemplify the broad range of high-quality and societal relevant research conducted within the AGEM institute. The case studies also demonstrate that the AGEM institute excels at both fundamental[17] and clinical research[18], as well as at the cross-section of both fields[19]. The high quality of AGEM research is shown by the fact that research has led to well-cited publications in top journals[20] as well as invitations to prestigious international scientific meetings[21]. Further, the AGEM institute houses some unique research projects such as those about newborn screening[22]. Since the Dutch screening program brings together RIVM, physicians and disease experts, this allows AGEM researchers to gather information on large groups of newborns, helping them to answer questions that could not be addressed in other countries.

Despite the fact that some of AGEM's research projects are primarily geared towards the scientific community[23], the societal relevance of research conducted within the AGEM institute is apparent. A prominent example of this, is the improvement of the Dutch newborn screening program by adding second-tier testing for congenital adrenal hyperplasia[24]. The results of this research have been directly implemented in the national government's heel prick screening and therefore aptly illustrates the major social impact of the institute's research. AGEM aims to stimulate its researchers to increase the societal impact of their research. This is done, for instance, through hiring a business developer, who helps translate science into innovative clinical and technological applications with the societal, healthcare and commercial impact in mind. The institute also holds a lobbying position towards Amsterdam UMC's divisions, departments and Board of Directors. In order to reward researchers for making an impact on society, the institute nominates talented researchers for various societal prizes which are often granted[25]. In conclusion, these case studies show the AGEM's institutes commitment to producing high quality research with a clear impact on society.

AGEM's contribution to the four SEP-specific aspects

Amsterdam UMC aims to be an organization in which research staff with diverse backgrounds flourish and jointly contribute to excellent team science. Case study 6 (appendix 3.6) provides examples of how Amsterdam UMC's HR policies are aimed at promoting diversity, inclusion and talent development. The AGEM institute wholeheartedly shares this commitment and, despite its limited influence on HR-related aspects due to its role as network institute, AGEM aims to contribute to diversity, inclusion and talent development in whatever ways it can. Two notable initiatives are 1) the AGEM Talent Development Grant, which is specifically designed to support exceptionally talented researchers and 2) the AGEM International Student Fellowship, to encourage (bio)medical students to conduct a research internship at an international top institute. A more elaborate explanation of all AGEM's initiatives with regards to HR policies is provided in case study 6 (appendix 3.6).

Secondly, Amsterdam UMC takes measures to promote an open and inclusive academic culture, characterized by scientific integrity (appendix 3.7). The AGEM institute aims to promote scientific integrity in several ways. For example, AGEM staff actively raises awareness of this topic during face-to-face meetings with department heads and PIs. Additionally, the institute organizes the Responsible Research Dinner Debate. This event brings together researchers from different career stages, ranging from PhD candidates to PIs, to have open discussions about scientific integrity and responsible research practices within their departments and research groups. AGEM PIs appreciate the efforts the institute takes on this topic. They mention that scientific integrity should be one of the core responsibilities of the organization as a whole and that the theme should be woven into other events and information, rather than be addressed separately. In case study 7 (appendix 3.7), all measures to promote an open and inclusive academic culture are described in greater detail.

AGEM retreat

Thirdly, PhD policy and training is one of the core values of Amsterdam UMC as well as the AGEM institute (appendix 3.8). The Amsterdam UMC Doctoral School plays a pivotal role in this and this theme is also prioritized on the department level, according to AGEM PIs. Wherever possible, the AGEM institute aims to provide additional support for PhD candidates, with a specific focus on the AGEM research field. The most notable examples of this are the AGEM annual PhD candidate retreat and the AGEM PhD candidate course. This effort is recognized by AGEM PIs, who are positive about AGEM's initiatives to support PhD training and wellbeing. Case study 8 (appendix 3.8) elaborates on all initiatives that are undertaken to support PhD candidates.

Lastly, Open Science is greatly valued by both Amsterdam UMC as well as the AGEM institute. Case study 9 (appendix 3.9) describes the various efforts that are undertaken on the different organizational levels. As a result of these initiatives, the majority of peer-reviewed articles from AGEM researchers are Open Access publications and this trend is seen to increase over the last six years (appendix 2.3, table A9). In addition to fostering Open Science, the AGEM institute also aims to create a transparent environment with regards to its policies and choices and places great emphasis on stakeholder involvement (appendix 3.9). When interviewing AGEM PIs in early 2023, many mentioned to feel the institute's appreciation for their work and involvement in the institute, e.g. by being invited to brainstorm sessions about the strategy of the institute and face-to-face update meetings.

Teaching-research nexus

The AGEM institute is committed to creating an enriching nexus between research, learning, and teaching. Our mission is to ensure that research enhances the quality of education, and we are proud to be a part of Amsterdam UMC: a collaboration between the renowned research universities Vrije Universiteit (VU) and UvA. Further, as a research institute, AGEM's initiatives and actions are deeply connected to the teaching-research nexus, given the institute's focus on facilitating both PhD candidates and graduate students (chapter 3 and appendix 3). Apart from its own initiatives, AGEM supports policies set by Amsterdam UMC to further strengthen the teaching-research nexus.

Strategy

for the next six years

Strategy for the next 6 years

The strategic evaluation of the AGEM institute was conducted in several steps (figure 6). Since the institute-wide Strength Weaknesses Opportunities Threats (SWOT) analysis (box 2) concluded that the previously defined four research programs did not adequately represent all research represented in AGEM, it was decided to continue with three research programs: Gastroenterology, Endocrinology and Metabolism. SWOT analyses were conducted for all three newly defined research programs.

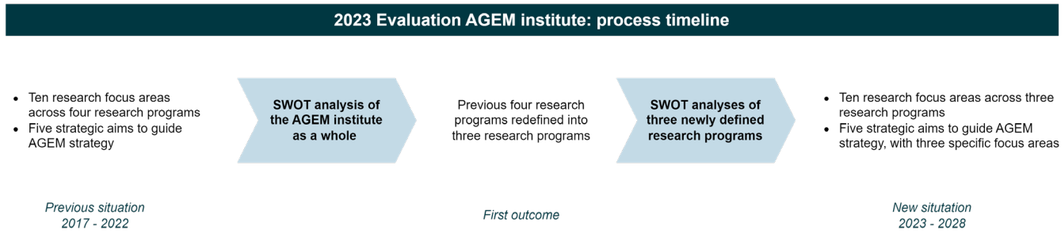


Figure 6. Visualization of the 2023 evaluation process

Box 2: SWOT analysis AGEM institute as a whole

Strengths

The AGEM research institute is multidisciplinary and has a connecting role between various disciplines and different research institutes of the Amsterdam UMC. The most urgent societal and healthcare needs require such a multidisciplinary approach, which makes such intensive cooperation of vital importance. Furthermore, studies on underlying mechanisms of disease development are translated into targeted application and intervention in relevant clinical cohorts. In conjunction with clinical study data and human biological samples, this strengthens our understanding of disease processes, and further guides our preclinical research programs. The institute has close ties with in-house clinical trial units and established centers and laboratories[38]. Last, the institute unites strong research lines on several overarching research themes of growing academic and societal interest, such as nutrition and the microbiome.

Weaknesses

Our profile to the outside world requires further attention. AGEM shows too little what it is good at, its unique capabilities, and what it wants to be strong at. Internally, several PIs find it difficult to get a grasp of the scope of the institute. The institute has an advising role with regards to Amsterdam UMC-wide talent policy, e.g. in appointments and nominations. However, the impact of AGEM is considered to be indirect, as its advisory role is positioned towards the end of the process rather than at the forefront.

Opportunities

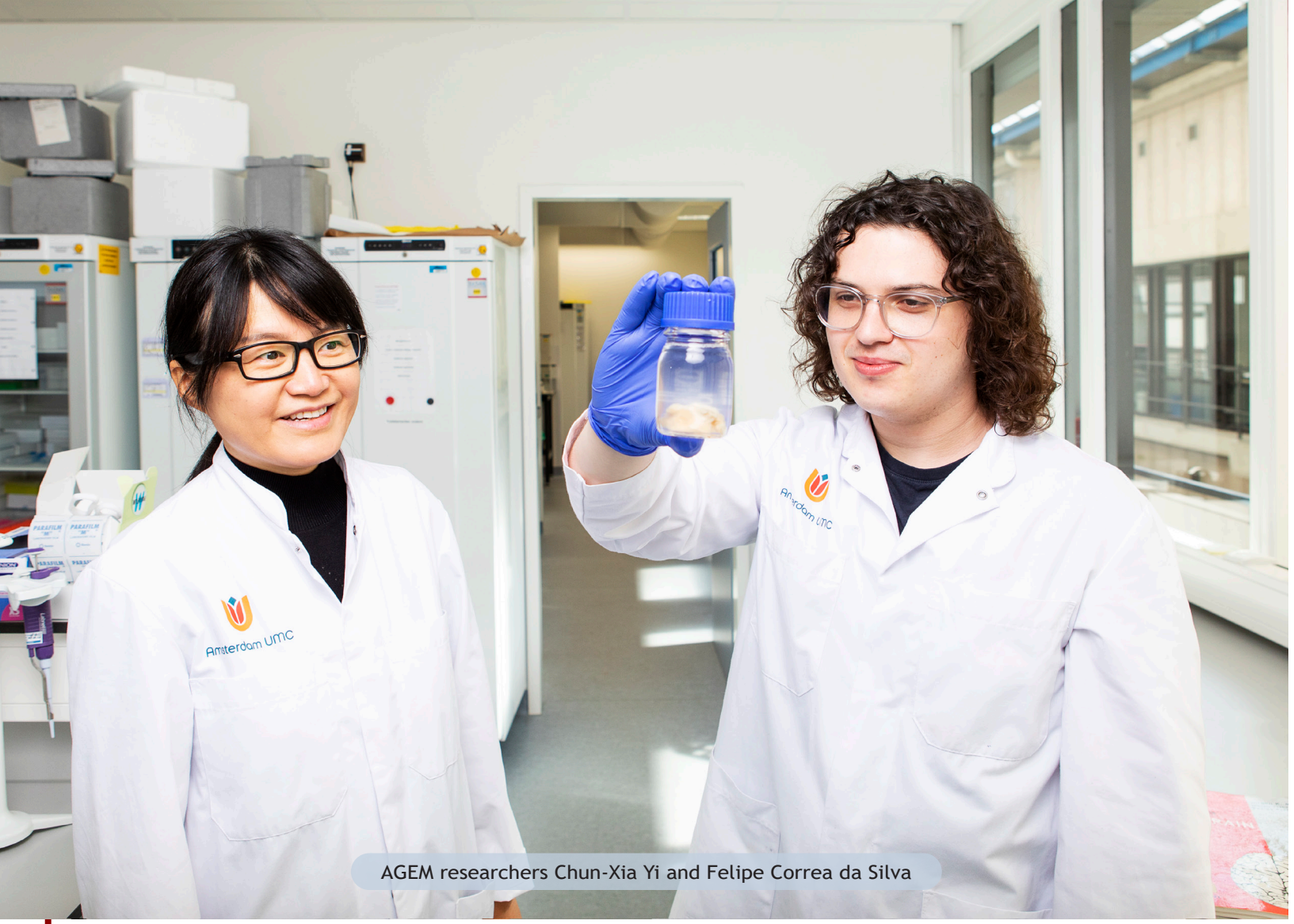
AGEM sees opportunities in (inter)national collaborations and consortia that will eventually yield large grants and/or synergy. This should be coupled with a communication/dissemination strategy to better showcase AGEM's capabilities and to position the institute as the go-to partner for collaborations in designated research areas. The recent recruitment of a business developer will expand our partnerships and drive societal and healthcare innovations. Further, AGEM PIs feel that the institute mainly serves younger researchers. Organizing events specifically geared towards the PI level could further enhance synergy between research groups. Lastly, an intuitive database of AGEM researchers could further enhance internal collaboration.

Threats

Sub-areas that belong to several research institutes do not have their own AGEM profile with the risk losing these researchers (for example diabetes research which has a clear connection with AGEM but belonged to the cardiovascular research institute pre-alliance). Further, due to the two locations, PIs working on a similar topic are physically far apart, lowering spontaneous meetings and exchange of ideas[39]. This is recognized as a difficulty by several AGEM PIs. Inspiring activities/events are mainly geared towards students and PhD candidates, but could also serve and enthuse PIs to increase their involvement with the institute. Last, increased costs of our animal facilities coupled with the societal pressure to reduce laboratory animal use.

Future plans

Redefining AGEM's four research programs into three research programs reflected in AGEM's name (gastroenterology, endocrinology and metabolism) will help researchers better identify themselves with the programs, thereby increasing their sense of belonging and commitment. In addition, AGEM should make clear what the centers of excellence are within the institute and actively stimulate interdisciplinary collaboration. This will benefit further internal and external positioning of AGEM. It is important to continue to develop the aspects that we are good at, namely offering a safe and enthusiastic environment for young investigators and PIs alike. Lastly, the institute aims to further develop its own talent policy, as well as strengthen its position in Amsterdam UMC-wide talent policy. To do so, the AGEM directors and research board will develop a strategic talent management plan (bi)annually, which will be shared with AGEM department heads and divisions. This plan should focus on research themes that are of growing academic and societal interest and on foreseen changes (e.g. retirements) in academic staff, thereby allowing the institute to make strategic decisions with regards to talent attraction, development and retention.



AGEM researchers Chun-Xia Yi and Felipe Correa da Silva

1. Gastroenterology

The focus of this research program is the function of the human digestive system in health and disease. The main research areas encompass (patho)physiology of the liver, pancreas and intestine, including gastrointestinal motility, the role of the microbiome in digestive health and disease, the mechanism of action of therapies of diseases of the digestive system, nutrition, and the development of novel surgical and medical treatment strategies.

Strengths - – This program consists of very well-cooperating translational research groups, conducting research in all age categories and covering the whole gastrointestinal tract, including the liver and pancreas, with a strong portfolio of collaborative studies with pharma, food and med tech companies. Particularly the clinical groups collaborating with the groups of the Tytgat Institute for Liver and Intestinal Research[26], who provide a solid basic research component. Clinical questions are thus answered quickly in the laboratory setting, thereby ensuring rapid application of knowledge in the clinic[27]. All research groups in this program have ample international collaborations and work together in many successful consortia. Furthermore, the bi-weekly 'Grand Rounds in Digestive Diseases', in which a gastroenterology topic is highlighted by a leading scientist/physician, is well-attended by doctors, nurses, researchers etc.

Weaknesses - Much of the research is still focused within the frameworks of different organs such as the liver, esophagus, intestine and pancreas. Second, education on the gastrointestinal tract is not prominently present in the current (bio) medical curriculum. Third, there is no implementation of lifestyle in gastrointestinal health care. In 2025, lifestyle must be an integral part of regular care, so that lifestyle interventions can be used effectively to prevent and treat health complaints, disorders and diseases[28]. Last, collaboration with patients (organizations), while often obligatory when applying for grants, is difficult to implement and is therefore done sometimes as a matter of form.

Opportunities - As the role of the microbiome in various diseases becomes increasingly clear, this provides a connection between the various organ systems. Also, the fact that the diet is playing an increasingly important role, as a medicine too, provides more and more associations. Opportunities are seen to expand further in the area of Personalized Medicine. Within AGEM, making an inventory of all the research in this area and looking for common interests can reinforce each other, as can strengthening cooperation with other universities. In education, community service learning can be used to bridge society and academia by involving students in contact with patients, for example by monitoring and supporting patient communities to research and patient self-examination[29].

Threats – First, the aforementioned divide of gastroenterological research over two locations. Second, the high costs of ethical approval for patient-related/clinical research[30] and the increased administrative/financial burden to perform research on anonymized patient material inhibit the possibility of doing retrospective research with students and makes collaboration with patients or involving patient material more difficult.

2. Endocrinology

The endocrine system regulates and integrates a wide range of body functions. Endocrine dysfunction therefore can contribute to a broad range of diseases affecting virtually every organ system of the body. Endocrinology research within AGEM spans a large spectrum of translational research from basic science, including technical innovations, to experimental medicine and from clinical studies of new treatments to population-related research. Together these studies aim to enhance our understanding of the physiology, pathophysiology, diagnosis, and treatment of endocrine disorders. Research topics within this program include: 1) Neuroendocrinology; 2) Hypothalamic-pituitary-thyroid axis/thyroid; 3) Bone; 4) Gonadal endocrinology; and 5) Obesity and Diabetes (appendix 4.1).

Strengths - Translational research where clinical studies are combined with wetlab[31] and computational approaches to deal with large and complex data sets. This ensures a strong position in the field. Technical innovative lab for hormone measurements. Recently, the endocrinological research became more involved in European Research Networks.

Weaknesses - The endocrinology research is scattered around several locations (VUmc and AMC) and several research institutes. There is not enough overview of ongoing business; connection between clinical and basic scientists and wishes within this relatively new program. There is little financial support for 'structural' personal that guarantee stability and consistency (knowledge as well as skills) in the lab (e.g. techs, senior staff, non-PI). Lastly, there is a gap between AGEM Research Board members (mostly established scientists) and younger PIs/postdocs.

Opportunities - The increased incorporation of endocrinology research into the AGEM institute is an opportunity to improve overview and collaboration. Including young talents in the AGEM directorate will better facilitate communication between junior and senior scientists and tailor AGEM strategy according to mutual needs. Improving collaboration between clinical and basic/technical/data scientists, e.g.

through PI meetings, can optimize the translational character of endocrinology research within AGEM.

Threats - The research focus within AGEM, although connected, is not focused around one concise theme. This can lead to scattering of resources and reduced excellence. It is important to prevent wetlab/bioinformatics becoming 'service-providing' (only to process clinical samples) and improve activities and identity of scientists in this area of research.

3. Metabolism

This program focusses on (non-)inherited metabolic disorders, both common and rare, manifesting from (pre)neonatal period into adulthood . Major aims are improving (early) diagnosis, unraveling the genetic, biochemical and clinical causes and consequences of the metabolic derangements in patients, and developing and improving treatment for patients. The program encompasses clinical, pre-clinical and translational research and houses state-of-the-art diagnostic facilities for metabolic disorders (metabolite, enzyme and DNA) and the central core facility for metabolomics and lipidomics (appendix 4.2).

Strengths – Metabolism is one of the spearheads of the Amsterdam UMC and research in this field aims to combat the increasing clinical, societal and economical burden of metabolic diseases. This program consists of multi-disciplinary research, spanning the fundamental-translational-clinical spectrum that is supported by experts and facilities[32]. There is a lot of clinical and pre-clinical expertise in a large number of inherited metabolic disorders, which is also strongly supported by state-of-the-art diagnostic facilities. There are close collaborations and interactions between clinical departments, laboratory for Genetic Metabolic Diseases, neurology, human genetics, and with national and international partners (clinical and pre-clinical). The program encompasses a Center of Expertise for Metabolic Disorders and there is national[33] and international[34] recognition, including eleven disease specific centers of expertise on rare inborn errors of metabolism. Lastly, the program has a Strong record on academia driven pharma by "Medicijn voor de Maatschappij"[35] and houses PIs with an established, strong track record with demonstrated and ongoing capacity to obtain prestigious competitive personal grants[36] as well as project/consortia grants[37].

Weaknesses – Obtaining national and European funding remains a challenge for research focused around rare metabolic diseases. The AGEM institute, hosting a broad range of metabolic research topics, is broadly spread across the Amsterdam UMC campus which leads to suboptimal interactions between the different themes. There is insufficient structural support for core metabolic facilities and associated dedicated staff and there are limited future career perspectives for talented metabolic researchers.

Opportunities – The merging of all inborn errors of metabolism research on location AMC (completed at end 2022) will improve expertise, efficiency and collaborations. The newly established large national Expertise Center Metabolic Diseases will increase patient flow and enable registries, biobanking and consolidation of research lines. The establishment and active participation in UMD will increase national (and local) strength, awareness and opportunities for metabolic diseases. New possibilities for metabolic research will be created due to a) the inclusion of more IEM in newborn screening programming, b) the increasing burden of metablic disorders (such as NAFLD/diabetes/obesity) in the general population; c) increased attention from industry, potentially allowing more public-private partnerships for academia

AGEM researchers Hilde Herrema and Peter Henneman

driven drug development, e.g. through Medicines for Society and; d) the increased interest of pharmaceutical companies to fund research, due to registries and large prospective rare disease cohorts. More durable funding for the Metabolomics/Lipidomics facility with spatial metabolomics as new target (requiring external funding) will increase possibilities for collaborations and funding.

Threats – Metabolic diseases such as diabetes and NAFLD represent a highly competitive field, whereas the research on rare inborn errors of metabolism remains very specific. There is a decrease in (inter)national public research funding opportunities and a lack of durable funding for bio-informatic support and expertise in the age of "big metabolic data". Last, researchers experience the burden of regulations and protocols is too high and there is insufficient cohesion between AGEM PIs leading to lack of "brand" recognition.

Stategy for the next six years

The results of this evaluation indicated that the institute is making commendable progress towards achieving its five strategic aims as outlined in Chapter 2. Further, the institute has shown to be viable, since AGEM conducts research in areas that are rising in disease incidence, societal costs, total publication output and funding . In the following years, AGEM will seek strategic alliances with other institutes to unite research in such areas: e.g. Wageningen University for nutrition research and Amsterdam Public Health for prevention research. The identified opportunities for improvement from this evaluation strongly align with the predefined five strategic aims. Therefore, the institute will continue to prioritize these five aims over the next six years, as they accurately represent the core mission and vision of AGEM. While these aims will serve as the overarching framework for AGEM's strategy, this self-evaluation has highlighted specific areas of focus that can further refine the institute's alignment with its mission and vision (figure 7). In the next six years, the institute will dedicate special attention to the following three points while keeping its five strategic aims at the core.

AGEM strategic aims 2023 - 2028

1. Talent development and retention: recruit, train and retain the next generation of excellent researchers for research programs of AGEM;
2. Promote and foster multidisciplinary research approaches within the institute between different research programs and amongst scientists from bench to bedside;
3. Provide an attractive platform for preclinical and clinical development for external partners active in our disease areas, thereby strengthening partnerships to generate societal and healthcare impact;
4. Create a sense of belonging within the institute. This involves i) creating an atmosphere of intellectual excitement and cross-fertilization that encourages researchers to expand their understanding of biology and disease processes, in order to make important contributions to modern medicine, and ii) a safe, social and inclusive environment where individuals all contribute to team-science with their own strength;
5. Develop a branding & communication strategy, which is used to target the general public, patients, press, academic colleagues and charities. For this aim, we focus on those areas of research where the full chain of translational research is at an international top level and multiple PIs collaborate in teams.

More focus on PI level to stimulate involvement and interdisciplinarity within AGEM

Strengthen and further define AGEM talent policy

National and international positioning

Figure 7. AGEM's envisioned strategic aims for the years 2023-2028, with three underlying focus points

1.More focus on PI level to stimulate involvement and interdisciplinary research

There are opportunities to enhance cohesion among PIs working in similar research fields. Therefore, AGEM will prioritize efforts to stimulate collaboration and interdisciplinary research. To promote a stronger sense of belonging among AGEM researchers, we have already taken the initial step of redefining the four research programs into three. Additionally, AGEM will commence organizing events specifically designed to stimulate interaction and collaboration among PIs, organized top-down and centered around specific research themes that span the three research programs. These events will play a vital role in fostering a spirit of cooperation and knowledge exchange within the AGEM community. Furthermore, we recognize the importance of maintaining an up-to-date AGEM researchers database. This will contribute to a more streamlined research environment and encourage collaborations.

2. Strengthen and define AGEM talent policy

Aligned with our strategic objectives, talent development and retention hold significant importance within the institute's mission. AGEM has taken the initial steps to establish Young AGEM, a board comprising early- to mid-career researchers who will offer advice and support to the AGEM research board. Young AGEM will serve as a platform for young researchers to enhance their policymaking, strategic, and advisory skills. This initiative aims to provide valuable opportunities for professional growth and development. Furthermore, the institute is committed to furthering the implementation of an Amsterdam UMC-wide mentoring program, as previously mentioned. This program, tailored for researchers at the PhD level and beyond, will offer mentorship and guidance to support their career progression and success. In order to strengthen AGEM's position in Amsterdam UMC-wide talent policy, the AGEM directors and research board will develop a strategic talent management plan to be shared with AGEM department heads and divisions. This (bi)annual plan will focus on research themes that are of growing academic and societal interest and on foreseen changes (e.g. retirements) in academic staff, thereby allowing the institute to make strategic decisions with regards to talent attraction, development and retention. Related to this, AGEM aspires to assume a more prominent role within the Committee for Talent and Appointments (CTA) of Amsterdam UMC. By participating in the CTA, the institute can actively contribute to talent management and decision-making processes, ensuring that AGEM's expertise and perspectives are well-represented. The institute envisions to advise the CTA on attracting talents in certain areas of research, which should be determined in close consultation with the divisions and departments of Amsterdam UMC.

3. National and international positioning

To provide strategic direction for the institute, AGEM aims to strengthen its positioning within the national and international research landscape. It is crucial to identify the specific research areas in which AGEM currently holds a leading role, both on a national and international level. This determination will serve as a compass for future decision-making and enable the institute to establish a unique and appealing profile for collaboration. Recognizing this importance, AGEM has engaged the services of an external consultancy agency to assist in answering this pivotal question. Their expertise will contribute to a comprehensive assessment of AGEM's research strengths, which will help improve the efficiency of the institute's procedures and which can serve as inspiration for research areas and groups to learn from each other.

Endnotes

Endnotes

1 IXA is the valorization-contracting department of Amsterdam UMC, that manages projects with third parties, starting new ventures, and intellectual property, all supported by in-house legal and financial resources.

2 From: interviews with AGEM Principal Investigators, early 2023

3 From: interviews with AGEM Principal Investigators, early 2023

4 The Dilemma Game (developed by Erasmus University) confronts researchers with difficult dilemmas in the context of a critical dialogue, supporting them in further developing their own 'moral compass'.

5 Dutch research funding is allocated through three 'funding streams' (geldstromen). The first funding stream consists of the block grant that universities receive directly from the government to pay for their teaching and research activities. The second funding stream originates from independent public organisations such as ZorgOnderzoek Nederland Medische Wetenschappen (ZonMw) and the Dutch Research Council (NWO). The third funding stream consists of funding from not-for-profit organisations. The fourth funding stream comes from for-profit organisations (source: https://zoek.officielebekendmakingen.nl/blg-337795.pdf)

6 E.g. the involvement of several AGEM Principal Investigators and research groups in the international GROWTH consortium (a consortium consisting of 8 individual research project, together aimed at setting up a new European platform that trains young scientists in the industry-led exploration of innovative routes to fully exploit the potential of early life nutrition to prevent inflammatory disease)

7 For example: NWO VICI Grants (Prof. Zelcer, 2017; Prof. Van de Graaf, 2020; Prof. Nieuwdorp, 2020; Prof. Vermeulen, 2021); NWO VIDI Grants (dr. Derikx, 2018; dr. Engelen, 2018); European Research Council (ERC) grants (Zelcer, Houtkooper, Van de Graaf, Vermeulen); ZonMw Collaborative Grants (Dr. Vaz; Prof. Kalsbeek)

8 For example De Volskrant ('Baby Julius was bijna dood, artsen leerden ervan' and 'Verzwakte muur om kankercellen biedt chemo een kans'); NRC Handelsblad ('Er is een ziekelijke behoefte projecten te laten slagen'); and Algemeen Dagblad ('Nieuwe behandeling biedt hoop aan diabetespatiënten')

9 For example 'Een goede hielprikaandoening - VKS Wisselstof'

10 For example NOS ('Nieuwe behandeling kan insuline spuiten voorkomen voor diabetespatiënten'); RTL Nieuws ('Immuunsysteem voorbereiden op nieuwe pandemie: 'Lockdown voorkomen''); radio shows (BNR radio and Pointer); and documentaries (Brandpunt).

11 For example dr. Schijven in podcasts, Best Barrett Talks Podcast, Voor een fitter en gezonder leven Podcast

12 For example www.barrett.nl and Acnes

13 For example the organization of conferences for nurses, such as the FIOCA conference: aimed at updating nurses about the latest updates in gastroenterology

14 The endocrine laboratory is one of the five regional laboratories performing the neonatal screening under the control of the RIVM (Head neonatal screening Amsterdam UMC Prof. Boelen). In recent years, research regarding the neonatal screening was done under the supervision of Prof. Boelen and Prof. Heijboer (Head of the Endocrine Laboratory) and Prof. Bosch (head paediatric metabolic department)in order to evaluate and optimize a variety of endocrine and metabolic neonatal screening programs. They also developed a second tier test for congenital adrenal hyperplasia which was successfully implemented. Dr. Kemp, Dr. Vaz and colleagues (Laboratory for Metabolic Diseases) have been closely collaborating with the RIVM on improving the Dutch newborn screening for years.

15 Such as Dr. Savelkoul who won the Gazelle award (of the Financieel Dagblad) for his Microbiome business.

16 "Ridder in de Orde van Oranje Nassau"

17 E.g. case study 2

18 E.g. case study 3

19 E.g. case study 1

20 Case study 1, 2, 3

21 Case study 2

22 Case study 4 and 5

23 E.g. case study 2

24 Case study 5

25 E.g. prof. Schijven who won the Societal Impact Award 2022

26 International Organization for Standardization (ISO) approved

27 For example, rectal surgery in patients with Crohn's disease now removes mesorectal fat because this was shown to contribute to inflammation after bowel removal

28 See: Coalitie Leefstijl in de Zorg, Ministry of Health

29 This could be initiated together with a recently started self-research network NL (ZONN), a platform for citizen science around health.

30 "METC approval"

31 ISO approved

32 Metabolomics/Genomics/Imaging/Microbiome unit/Clinical trial unit

33 From the Nederlandse Federatie van Universitair Medische Centra

34 European Reference Network for Hereditary Metabolic Disorders

35 In 2019, the platform Medicines for Society ("Medicijn voor de Maatschappij") was launched by AGEM PI prof. Hollak that aims to improve access to orphan drugs, including essential medicines for metabolic diseases, through "academia-driven pharma". The platform, in collaboration with regulators, has recently launched the pilot program "Orphan Drug Access Protocol" financially supported by insurance companies. In addition, focus is on development of novel public private partnerships on socially responsible terms. Pilot projects are running, that should translate cases to systems solution, by scientific research (current output is 18 peer reviewed publications and several media presentations and Hollak was awarded the Academy Medal for her scientific achievements in 2023).

36 NWO VENI, VIDI,VICI, ERC, etc

37 Joint Programming Initiative, NWO, Innovative Training Networks, etc

38 E.g. the Microbiota Center and the Metabolomics Facility.

39 Examples are Gastroenterology/Hepatology: where clinical science is bundled at location VUmc, while Pediatric Gastroentrology and Tytgat institute (department concentrating pre-clinical gut/liver research) remains at location AMC for several more years.

40 The group of prof. Boermeester, for example, is initiator in sharing databases on individual patient data meta-analysis (IPDMA) initiatives.

Appendices

Abbreviations

AG&M	Amsterdam Gastroenterology & Metabolism
AGEM	Amsterdam Gastroenterology Endocrinology Metabolism
ALD	X-linked adrenoleukodystrophy
AMC	Academic Medical Center
ARB	Amsterdam Research Board
ASAP	Association of Amsterdam UMC PhD Candidates
CAH	Congenital adrenal hyperplasia
CCD	Central Authority for Scientific Procedures on Animals (Centrale Commissie Dierproeven)
CTA	Committee for Talent and Appointments
DBS	Dried Blood spots
DEC	Animal Experiments Committee (Dierexperimentencommissie)
D&I	Diversity & Inclusion
ECTS	European Credit Transfer and Accumulation System
EoE	Eosinophilic Esophagitis
EU	European Union
FAIR	Findable, Accessible, Interoperable and Reusable
GDPR	General Data Protection Regulation (Algemene Verordening Gegevensbescherming; AVG)
GI	Gastrointestinal
IBD	Inflammatory Bowel Disease
KNAW	Royal Netherlands Academy of Arts and Sciences (Koninklijke Nederlandse Akademie van Wetenschappen)
MREC	Medical Research Ethics Committee (Medisch Ethische Toetsingscommissie; METC)
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Non-alcoholic steatohepatitis
NBS	Dutch newborn screening
NFU	Netherlands Federation of University Medical Centers
NWO	Dutch Research Council (Nederlandse Organisatie voor Wetenschappelijk Onderzoek)
OA	Open Access
PhD	Doctor of philosophy
PI	Principal Investigator
R&R	Recognition and Rewards
RIVM	National Institute of Public Health and Environment (Rijksinstituut voor Volksgezondheid en Milieu)
SCAN	Screening for ALD in the Netherlands
SPRING	SREBP regulating gene
SREBP	Sterol Regulatory Element-Binding Protein
TKI	Top consortium for Knowledge and Innovation (Topconsortium voor Kennis en Innovatie)
UMC	University Medical Center
UvA	University of Amsterdam
VU	Vrije Universiteit Amsterdam
VUmc	VU University Medical Center
VWS	Health, Welfare and Sport (Volksgezondheid, Welzijn en Sport)
WMO	Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met mensen)

Appendix 1

1.1 Research at Amsterdam UMC - organization and policy

Amsterdam University Medical Centers (Amsterdam UMC) are combined one of the most prominent research institutes in the Netherlands, as well as one of the largest academic hospitals. Amsterdam UMC has arisen from the administrative merger of Amsterdam's two academic hospitals, the Academic Medical Center (AMC) and the VU University Medical Center (VUmc), in 2018. Amsterdam UMC represents the medical faculties of the two universities associated: the University of Amsterdam (UvA) and the Vrije Universiteit (VU) Amsterdam. This merger enables Amsterdam UMC to further develop its core tasks together: complex patient care, scientific research, and education and training. Amsterdam UMC is a member of NFU, the Netherlands Federation of University Medical Centers (UMC's) that binds and supports the seven Dutch UMC's in their core tasks. UvA is a member of the League of European Research Universities and VU Amsterdam is a member of Aurora Alliance and hence, Amsterdam UMC is connected to both networks.

Amsterdam UMC research organization

The Amsterdam UMC Executive Board consists of five members. Professor Chris Polman is chair and dean of the VU Faculty of Medicine, Professor Hans van Goudoever is vice-chair and dean of the UvA Faculty of Medicine, Mr. Henk Snapper is the Chief Financial Officer, and the other members are Professor Mark Kramer and Dr. Karen Kruijthof. Besides the combined Executive Boards, Amsterdam UMC also shares a research policy advisory organ, called the Amsterdam Research Board (ARB). The ARB represents the Amsterdam UMC research community and advices the Executive Board on research policy. Together with the deans and administrative staff, the ARB aims to promote scientific quality and responsible research conduct. The ARB consists of one to two research institute directors from each research institute, a selected number of independent researchers and some positional members including the chairs of the three ARB subcommittees: the Amsterdam Valorisation Board, the Good Research Practice committee and the Committee Talent and Appointments (Figure A1). Each of the ARB members is portfolio holder of specific research policy topics. The ARB is chaired by Professor Mat Daemen, the vice-dean research of Amsterdam UMC. Both deans are attendant members of the ARB. Together, these people oversee all fundamental, translational and clinical research within Amsterdam UMC. The board of the Amsterdam UMC Doctoral School, which is chaired by Professor Christa Boer, coordinates the training and supervision of PhD candidates. The board has six members, one of whom is a PhD candidate.

The research structure is organized in a matrix with divisions and research institutes (Figure 1). Amsterdam UMC has ten divisions, each headed by a division chair, and encompasses multiple departments and sub-departments. Each department/sub-department head has integral responsibility for patient care, education and research, as well as for management and finances. The ten current divisions are: 1. Specialisms in Medicine, 2. Surgical Specialisms, 3. Heart Center, 4. Mother and Child Center, 5. Neuro/Head/Neck, 6. Operating Center and Intensive Care, 7. Imaging Specialisms, 8. Outpatient Clinics, 9. Laboratory Specialisms and 10. Primary Care, Public Health and Methodology.

Research institutes

To enhance focus and stimulate interdisciplinary collaboration between departmental research groups as well as between the medical faculties and other faculties of VU and UvA, there are eight Amsterdam UMC research institutes, namely Amsterdam Cardiovascular Sciences, Amsterdam Gastroenterology

Endocrinology and Metabolism, Amsterdam institute for Infection and Immunity, Amsterdam Movement Sciences, Amsterdam Neuroscience, Amsterdam Public Health, Amsterdam Reproduction and Development and Cancer Center Amsterdam. Each research institute covers the whole spectrum from basic biomedical research, through translational and clinical research to the assessment of innovations in actual clinical practice. Each institute has its own Board of Directors, a four-year project plan and an annual budget of €554,000 to stimulate innovation based upon the specific project plan. Five of the institutes that stem from former VUmc institutes receive additional historical budgets. The directors discuss progress and strategic issues during the monthly ARB meetings.

Research Support

Amsterdam UMC has a central support organization to create an environment in which researchers can excel, both by contributing to a stimulating context and by providing practical advice. The Management Team of Research Support is chaired by Professor Mat Daemen, who is also chair of the Amsterdam Research Board. The other members of the Board of Research Support are Dr. Jessika van Kammen, who is also a member of the Amsterdam Research Board, and Mr. Jan Brand. The double positions of Professor Daemen and Dr. van Kammen are intentional and help to align the development and the execution of research policies, and vice versa: namely, the development of policies that respond to the needs of researchers. This organization – Research Support – provides hands-on support to researchers, from the development of early ideas into fundable research proposals to the implementation of the outcomes. Research Support is comprised of the following units: Research Policy Office, Research Grant Support, Medical Research Ethics Committee Office, Research Data Management, Clinical Monitoring Center, Legal Research Support, Project administration, Medical Library and output registration, and Innovation Exchange Amsterdam, as depicted in Figure 1. Amsterdam UMC has a quality framework in place, the co-called Research Roadmap, that clearly states the steps that need to be followed to carry out research in different settings (i.e., preclinical research, clinical trials, research involving human subjects): from experimental design and collection of data, to closure and publication of the results. Dedicated Research Support teams are in place to provide hands-on support and help researchers comply with integrity and quality requirements.

Furthermore, methodological and statistical support for researchers is available as well and coordinated by the Department of Epidemiology and Data Science. Amsterdam UMC-broad Core Facilities, such as the Core Facilities for Genomics, Metabolomics, Microscopy and Cytometry, and Human Induced Pluripotent Stem Cells are available for researchers as well.

Amsterdam UMC research policy

The following parties are involved in Amsterdam UMC's research policies:

- Executive Board: In general, strategic research decisions are made by the Executive Board. Specifically, this holds for the appointment of professors, major research investments and strategic participation in national and international initiatives. For particular topics, such as advice on the awarding of fellowships and scholarships for PhD candidates, special committees have been set up by the Executive Board.
- Division chairs and department heads: Nomination of candidates for Principal Investigator (PI) appointments or (associate) professorships are the responsibility of the department heads. Content issues, such as the definition of new and existing research lines and the formation of centers are discussed in the matrix: division and departments together with the research institutes. Additionally, division chairs and department heads can stimulate research activities by, for example, investing in equipment and laboratory facilities.
- Amsterdam Research Board: Important topics for the ARB are for example talent policy, societal impact and visibility of research, quality of research and the development of policies on scientific integrity. The ARB has an executive committee that meets twice a year with each of the Division boards in order to inform each other about relevant developments concerning research policy.
- Research Policy Office: The Research Policy Office plays a role in preparing most central research policies, including the alignment with (inter)national developments and the research policies of the two universities: UvA and VU Amsterdam.

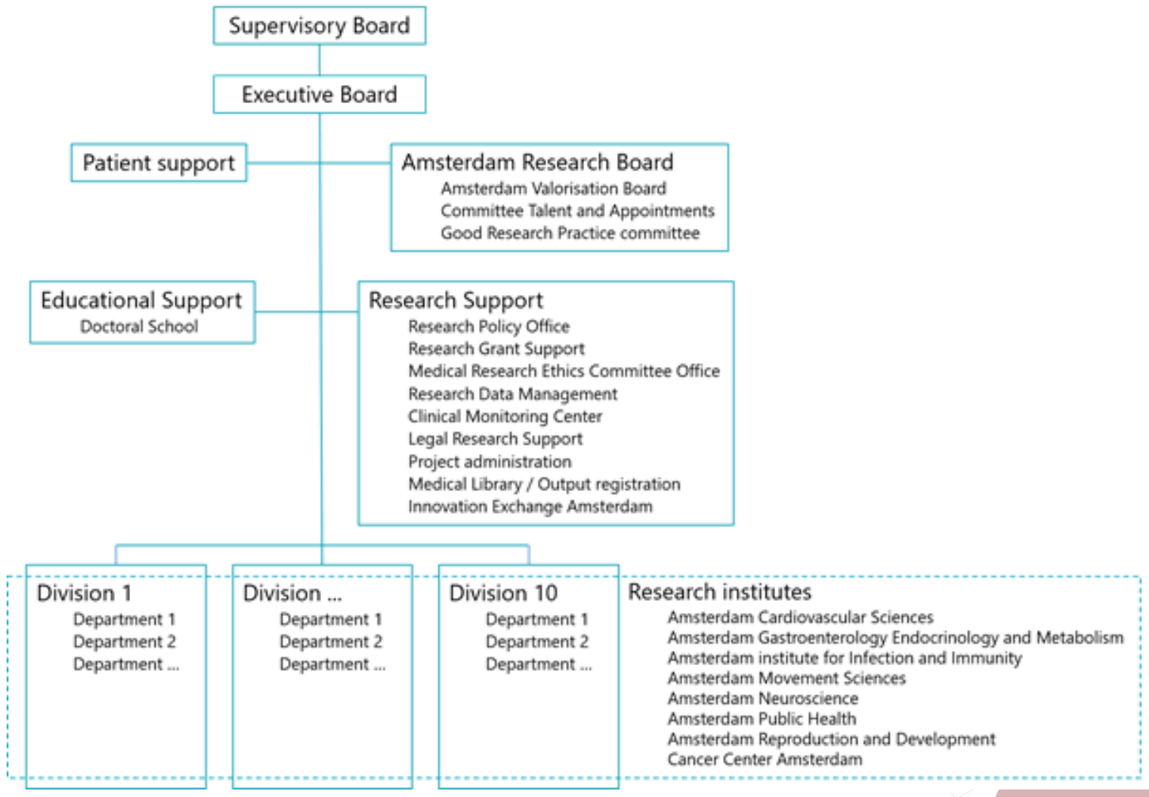


Figure A1: Organizational structure of Amsterdam UMC research.

1.2 Organizational structure AGEM

Table A1 PIs AGEM on December 31, 2022.

Name	(sub-)department	Research line
Prof. dr. Benninga	Paediatrics – gastroenterology	Functional gastrointestinal disorders in children and adolescents with follow-up into adulthood
Prof. dr. Van Berge Henegouwen	Surgery	Gastrointestinal surgery- esophageal and gastric surgery
Prof. dr. Bergman	Gastroenterology & Hepatology	Endoscopic imaging studies using high resolution endoscopy, optical chromoscopy, and volumetric laser endomicroscopy
Prof. dr. Besselink	Surgery	Hepato-Pancreato-Biliary surgery
Prof. dr. Beuers	Gastroenterology & Hepatology	Pathogenetic and therapeutic aspects of chronic cholestatic and immune-mediated liver diseases
Prof. dr. Bisschop	Internal Medicine- Endocrinology	Internal medicine, clinical endocrinology
Prof. dr. Boelen	Clinical Chemistry – Endocrine Laboratory	Thyroid hormone metabolism, neonatal screening
Dr. De Boer	Gastroenterology & Hepatology	Drug rediscovery & Volatile organic compounds/electronic nose technology
Prof. dr. Boermeester	Surgery	Clinical and preclinical aspects of abdominal infections and intestinal failure
Prof. dr. Bosch	Paediatrics – Metabolic Diseases	Metabolic disorders: Phenylketonuria, Galactosemia, Riboflavin Transporter Deficiency
Dr. Bosma	Tytgat Institute	Liver directed gene therapy for inherited severe liver disorders
Dr. ir. Van den Bossche	Molecular Cell Biology and Immunology	Immune/metabolic profiling and targeting of macrophages and other immune cells
Prof. dr. Bouma	Gastroenterology & Hepatology	Chronic Inflammatory Bowel Diseases, Celiac disease, autoimmune hepatitis
Prof. dr. Bredenoord	Gastroenterology & Hepatology	Neurogastroenterology and benign esophageal disorders
Dr. Buskens	Surgery	Gastro-intestinal surgery, predominantly focusing on colorectal carcinoma and inflammatory bowel disease
Dr. Cillessen	Pathology	T-Cell Lymphoma, Non-Hodgkin Lymphoma, Anaplastic Large Cell Lymphoma, and Celiac Disease
Prof. dr. Dekker	Gastroenterology & Hepatology	Gastrointestinal Oncology, special interest in screening and diagnosis of colorectal cancer
Dr. Derikx	Paediatrics – surgery	Translational research with the aim to reveal pathophysiology of intestinal ischemia-reperfusion, anastomotic leakage and intestinal maturation (including the derailment of the inflammatory response leading to necrotizing enterocolitis)
Prof. dr. D'Haens	Gastroenterology & Hepatology	Inflammatory Bowel diseases, Biologic therapy, Trial design and execution, Mucosal immunology, Drug development, Imaging of the GI tract
Dr. Dijkstra-Muncan	Gastroenterology & Hepatology	Intestinal epithelial homeostasis and disease, organoids, gut development, nutrition
Prof. dr. Drent	Internal Medicine- Endocrinology	Growth hormone, hormones and the brain (hypofyse, MEN1, psychology)
Dr. Den Dunnen	Internal Medicine – Immunology/ Rheumatology	Role of antibodies during infections, rheumatoid arthritis, and inflammatory bowel disease, with the aim to identify new targets for therapy of these diseases
Prof. dr. Van Elburg	Paediatrics	Early Life Nutrition
Dr. Engelen	Paediatrics – Neurology	Peroxisomal metabolic disorders, Leukodystrophies
Dr. Finken	Paediatrics – Endodrinology	Long-term impact on development of abberrations in hormonal systems, in paricular the hypothalamus-pituitary-adrenal axis, in early life
Prof. dr. La Fleur	Clinical Chemistry – Endocrine Laboratory	Neurobiology of Energy Metabolism
Prof. dr. Fockens	Gastroenterology & Hepatology	Advanced diagnostic and therapeutic gastrointestinal endoscopy, GI oncology (colrectal & pancreato-biliary), Neurogastroenterology
Dr. Gecse	Gastroenterology & Hepatology	Perianal fistulizing Crohn's disease, intestinal ultrasound in inflammatory bowel diseases and predictive markers in optimizing treatment response
Dr. Gorter	Paediatrics – surgery	Appendicitis, Viral Gastroenteritis, Pinworms, Appendectomy, and Ileostomy.
Prof. dr. Van Goudoever	Paediatrics	Fetal and Neonatal Nutrition and Metabolism. Neonatal Gastroenterology. Long term outcome patient (parent) empowerment.
Prof. dr. Van de Graaf	Tytgat Institute	Metabolite dynamics and liver-centered organ crosstalk
Dr. Van Grieken	Pathology	Stomach cancer, CRC, Predictive markers, genetics, DNA, mutations, copy number changes
Prof. dr. Groothoff	Paediatrics – Nephrology	Kidney diseases in children
Dr. Hanssen	Vascular Medicine	The role of the microbiome in maintenance of residual beta cell function and immunological tone in type 1 diabetes and on the atherosclerotic complications of diabetes, and the role of the innate immune system, microbiome and glucose as well as amino-acid metabolism herein.
Prof. dr. Heijboer	Clinical Chemistry – Endocrine Laboratory	Development and implementation of methods for diagnostics and research endocrinology
Prof. dr. Den Heijer	Internal Medicine- Endocrinology	Diabetes, transgender, bone metabolism
Dr. Henneman	Clinical Genetics	Epigenetics of complex and non-complex diseases in order to detect novel associated genetic and epigenetic loci
Dr. Herrema	Vascular Medicine	Translational and integrative research on development of cardiometabolic diseases. Special interest in the gut microbiome, particularly bacteriophages.
Prof. dr. Van Heurn	Paediatrics – surgery	Pediatric surgery
Prof. dr. Hollak	Internal Medicine- Endocrinology	Natural history, pathophysiology and treatment of lysosomal storage disorders
Dr. Holleboom	Vascular Medicine	Translational projects in non-alcoholic fatty liver disease
Prof. dr. Houtkooper	Lab. Genetic Metabolic Diseases	Molecular and translational aspects of metabolism, and how this contributes to health and disease
Dr. IJzerman	Endocrinology & Metabolism	Obesity and diabetes in relation to the brain
Dr. Janssens	Lab Clinical Chemistry	Multi-omics data integration studying the molecular determinants of healthy aging
Prof. dr. De Jonge	Clinical Chemistry	One-carbon metabolism (folate, vitamin B12) in health and disease
Prof. dr. De Jonge	Tytgat Institute	Mechanisms of functional and inflammatory gastro-intestinal disease
Dr. De Jongh	Internal Medicine- Endocrinology	Vitamin D and elderly, diabetes and obesity, diet and lifestyle
Prof. dr. Kalsbeek	Clinical Chemistry – Endocrine Laboratory	Role of the hypothalamus in neuro-endocrine regulation of energy metabolism, Autonomic innervation of liver and adipose tissue, Circadian control of hormone rhythms
Dr. Van Karnebeek	Paediatrics – Metabolic diseases	Personalized medicine for genetic metabolic diseases
Dr. Kemp	Lab. Genetic Metabolic Diseases	Unravel the pathophysiology of ALD, to predict the clinical outcome of newborns with ALD, to develop a treatment for ALD, and implement ALD newborn screening in the Netherlands
Dr. Kroon	Lab. Experimental Vascular Medicine	Vascular and Valve Inflammatory and metabolic responses
Dr. Van Kuilenburg	Lab. Genetic Metabolic Diseases	Inborn errors of metabolism, Pharmacogenetic consequences of defects of the pyrimidine degradation pathway, Biochemical aspects of pediatric oncological diseases
Prof. dr. Van Laarhoven	Internal Medicine – oncology	Upper GI cancer, esophagogastric and pancreatic cancer
Dr. Langeveld	Endocrinology & Metabolism	Inherited metabolic diseases in adults, with an emphasis on lysosomal storage disorders (LSDs) and fatty acid oxidation disorders (FAOD)
Dr. Van Limbergen	Paediatrics – Gastroenterology	Clinical and Translational research in pediatric Inflammatory Bowel Disease: focus on multi-omics of nutritional therapy
Dr. Lowenberg	Gastroenterology & Hepatology	Optimizing treatment strategies with biologicals and immunomodulators in patients with inflammatory bowel diseases
Prof. dr. Mathôt	Hospital Pharmacy	Clinical Pharmacology
Dr. De Meij	Paediatrics – Gastroenterology	The role of the gut environment, including microbiota and metabolomics
Prof. dr. Nieuwdorp	Experimental Vascular Medicine	Internal Medicine with a special focus on Diabetes Mellitus.
Prof. dr. Oude Elferink	Tytgat Institute	Hepatic transport processes
Dr. Van der Peet	Surgery	Surgical treatment of esophagus and gastric diseases
Prof. dr. Ponsioen	Gastroenterology & Hepatology	Inflammatory Bowel Disease, Primary Sclerosing Cholangitis
Dr. Pouw	Gastroenterology & Hepatology	Improving management of patients with early oesophageal adenocarcinoma & Identification and validation of biomarkers, for risk stratification of patients with Barrett's oesophagus
Dr. Van Raalte	Endocrinology & Metabolism	Diabetes
Prof. dr. Van Riel	Experimental Vascular Medicine	Computational modelling of metabolic diseases, in particular diabetes.
Prof. dr. Salomons	Lab. Genetic Metabolic Diseases	Genetic neuro-metabolic disorders, Creatine deficiency, 2-Hydroxyglutaric aciduria (link with oncology), Polyol metabolism (glucose- sorbitol-aldose reductase), Aminoacyl tRNA synthetase (DNA translation)
Prof. dr. Savelkoul	Medical Microbiology	Molecular epidemiology of tuberculosis
Prof. dr. Schijven	Surgery	Simulation, Serious Gaming and Applied Mobile Healthcare
Dr. Serlie	Internal Medicine- Endocrinology	Translational research in the field of obesity
Dr. Soeters	Internal Medicine- Endocrinology	(Patho)physiology of Energy Metabolism- Glucose/Lipid Metabolism
Prof. dr. Stoker	Radiology & Nuclear Medicine	Abdominal imaging
Dr. Swijnenburg	Surgery	Multimodality molecular imaging to allow integration of diagnostic and intraoperative imaging in patients suffering from tumors in the liver, pancreas and biliary tract
Dr. Tabbers	Paediatrics – Gastroenterology	Intestinal failure, evidence-based guideline development and functional gastrointestinal disorders
Prof. dr. Tanis	Surgery	Colorectal cancer; Complications after pelvic surgery
Dr. Van Tol	Surgery	Surgery: Liver metastases (from CRC)
Prof. dr. Van Trotsenburg	Paediatrics – Endocrinology	Thyroid metabolism, endocrinology

Dr. Vaz	Lab. Genetic Metabolic Diseases	Metabolism of complex lipids and their role in genetic disease, acquired disorders and aging
Dr. Te Velde	Tytgat Institute	Gastroenterology; Inflammatory Bowel Diseases
Prof. dr. Vermeulen	Center for Experimental Molecular Medicine	Cancer stem cells, Colorectal cancer, Cancer subtypes, Tumor evolution
Dr. Voermans	Gastroenterology & Hepatology	Gastroenterologist with special interest in Hepato-Pancreato-Biliary diseases and endoscopic interventions
Dr. Voskuijl	Paediatrics- Immunology	Global Child Health: Childhood malnutrition, Nutritional status & acute illness, Minimally Invasive Tissue Sampling (MITS), Early Risk Prediction/Early Warning Score
Prof. dr. De Vries	Medical Biochemistry	Medical Cell Biochemistry
Prof. dr. Waterham	Lab. Genetic Metabolic Diseases	Functional genetics and molecular biology of metabolic disorders
Dr. Weissenbruch	Neonatology	Nutrition, metabolism and endocrinology in neonates: premature infants: growth and development
Dr. Wiegman	Paediatrics – Metabolic Diseases	Paediatric metabolic diseases
Prof. dr. Wijburg	Paediatrics – Metabolic Diseases	Inborn errors of metabolism, clinical
Dr. Wildenberg	Tytgat Institute	Translational gastroenterology, in particular in inflammatory bowel disease (IBD)
Dr. Yi	Endocrinology & Metabolism	Neuron-glia interactions in metabolic diseases
Prof. dr. Zelcer	Medical Biochemistry	Fundamental mechanisms underlying the molecular regulation of lipid metabolism in health and disease

Legend
Blue: PI since 2020
Orange: PI since 2021
Green: PI since 2022

Table A2 Departments and sub-departments participating in AGEM

Div	Division name	Department	Sub-department	Head
1	Internal specialisms			L. Schuijs
1	Internal specialisms	Internal medicine	Endocrinology	A.M. Pereira Arias
1	Internal specialisms	Internal medicine	Medical Oncology	H.W.M. van Laarhoven
1	Internal specialisms	Internal medicine	Vascular Medicine	M. Nieuwdorp
1	Internal specialisms	Gastroenterology & Hepatology		P. Fockens
2	Surgical specialisms	Surgery		H.J. Bonjer
4	Woman-Child	Paediatric surgery		L.W.E. van Heurn
4	Woman-Child	Paediatrics	General Paediatrics	C.C. de Kruijff
4	Woman-Child	Paediatrics	Paediatric Gastroenterology	M.M. Tabbers
4	Woman-Child	Paediatrics	Paediatric Metabolic Diseases	A.M. Bosch
4	Woman-Child	Paediatrics	Paediatric Endocrinology	A.S.P. van Trotsenburg
4	Woman-Child	Paediatrics	Paediatric Nephrology	J.W. Groothoff
7	Imaging	Clinical pharmacology & pharmacy		E.L. Swart
7	Imaging	Radiology & Nuclear Medicine		C. van Kuijk
9	Laboratories	Center of Exp. & Molecular Med		J.P. Medema
9	Laboratories	Human Genetics		J.J. Meij
9	Laboratories	Clinical Chemistry	Laboratory for Endocrinology	A.C. Heijboer
9	Laboratories	Clinical Chemistry	Laboratory Genetic Metabolic Diseases	G.S. Salomons
9	Laboratories	Clinical Chemistry		R. de Jonge
9	Laboratories	Laboratory Exp. Vascular Medicine		M. Nieuwdorp
9	Laboratories	Medical Biochemistry		C.J.M. de Vries
9	Laboratories	Pathology		M.J. de Vijver
9	Laboratories	Tytgat Institute		K.F.J. van de Graaf

Table A3 Previous and current AGEM directors, research board members and young AGEM members

Date	Name	(sub-)department
Directors		
2014 - 2022	Gerd Bouma	Gastroenterology & Hepatology
2017 - current	Stan van de Graaf	Tytgat Institute
2022 - current	Anita Boelen	Laboratory for Endocrinology
Research Board		
2016 - 2018	Gajja Salomons	Laboratory Genetic Metabolic Diseases
2016 - 2019	Riekelt Houtkooper	Laboratory Genetic Metabolic Diseases
2016 - 2019	Louis Vermeulen	Center of Experimental and Molecular Medicine
2016 - 2019	Max Nieuwdorp	Experimental Vascular Medicine
2019 - 2021	Clara van Karnebeek	Paediatrics
2019 - 2020	Marc Besselink	Surgery
2020 - 2022	Hans Waterham	Laboratory Genetic Metabolic Diseases
2017 - present	Anje te Velde	Tytgat Institute
2018 - present	Annemieke Heijboer	Laboratory for Endocrinology
2019 - present	Annet Bosch	Paediatric Metabolic Diseases
2020 - present	Richard IJzerman	Internal Medicine - Endocrinology
2020 - present	Hilde Herrema	Experimental Vascular Medicine
2021 - present	Joris Erdmann	Surgery
2022 - present	Joep Derikx	Paediatric Surgery
2022 - present	Noam Zelcer	Medical Biochemistry
2022 - present	Stephan Kemp	Laboratory Genetic Metabolic Diseases
2022 - present	Ric van Tol	AGEM-dedicated Business Developer
Young AGEM		
2022 - present	Bruno Sovran	Tytgat Institute
2022 - present	Signe Nielsen	Laboratory Genetic Metabolic Diseases
2022 - present	Patrick de Jonge	Experimental Vascular Medicine
2022 - present	Dirk Jan Stenvers	Internal Medicine - Endocrinology

1.3 Outcomes mid-term evaluation AGEM 2019

In 2019, the AGEM institute conducted an internal mid-term evaluation. The report included a reflection on the institute's previously defined ten strategic aims and on what the institute had already achieved by that time. These results are presented below.

1. Familiarize the researchers of the VUmc and AMC with each other and promote a spirit of common purpose. & 2. Create an atmosphere of intellectual excitement and cross-fertilization that encourages researchers to expand their understanding of biology and disease processes, in order to make important contributions to modern medicine.
These two goals have been achieved for as much as reasonably possible in the first three years of AGEM. Multiple departments (endocrinology, gastroenterology/hepatology/surgery/clinical chemistry) have merged in 2020, or before, and are already working on one location. The various AGEM activities have led to sense of common purpose in a bottom-up fashion, where starting PhD candidates realize from the start they are in a single organisation. Due to the enormous size of the Amsterdam UMC, it remains important that research staff 'feels at home' within the institute and is encouraged to collaborate with other scientists

3. Identify key research questions for the coming decade in line with todays' major societal and healthcare challenges, and actively work within the AGEM research programs to address these questions.
We have initially phrased four research programs that cover these critical research questions. Later, we rephrased these to limit redundancy with other institutes, although it remains very important to work together with the other institutes. Also the name of the institute was adapted from AG&M to AGEM, to better reflect the importance of Endocrinology in our institute.

4. Promote and foster multidisciplinary research approaches within the institute between different research programs and amongst scientists from bench to bedside & 5. Focus on those areas of research where the full chain of translational research is at an international top level.
The Innovation grants were designed to stimulate collaboration between disciplines. The analysis of co-authorhips between clinical PIs with pre-clinical PIs demonstrates the extensive multidisciplinary interaction within the institute.

6.Talent development: recruit and train the next generation of excellent researchers for research programs of AGEM.
The Talent program of AGEM seems to be effective. This is illustrated by the competitive grants won by AGEM Talent grant awardees and the multiple master students that started a PhD position after finishing their AGEM-supported internship abroad. For scientists at a more senior level, the role of AGEM can be further improved. Also, talent retention could be given more attention in the aims for the next years.

7.Collaborate closely with colleagues of the top of our international academic field and develop stable partnerships with their institutes. & 8.Provide an attractive platform for preclinical and clinical development for commercial entities active in our disease areas.

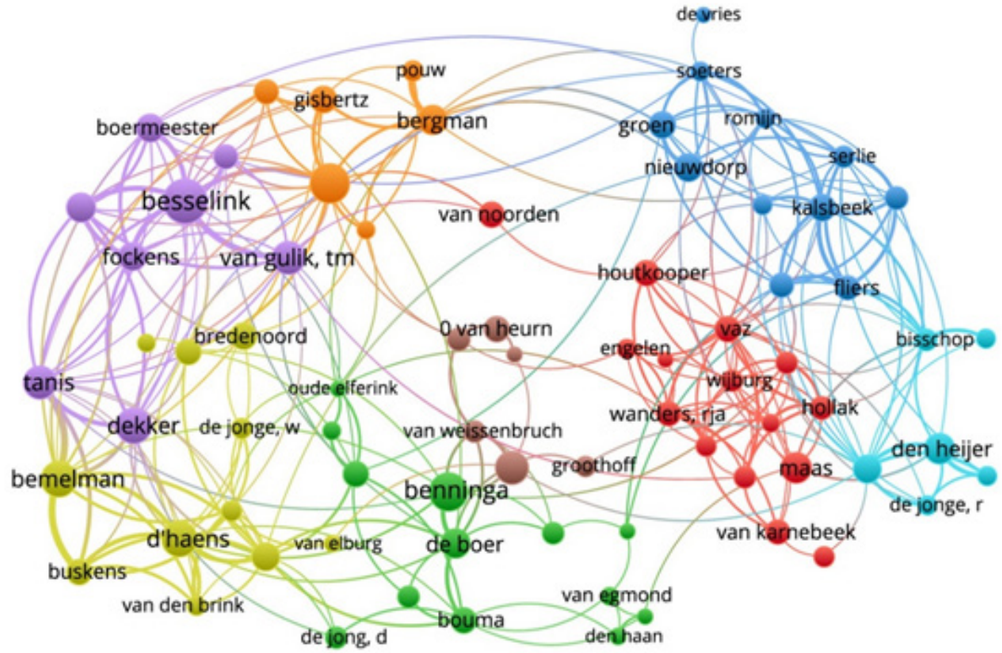


Figure A2. Peer-reviewed papers with at least 1 AGEM PI were used as input for co-authorship analysis using Vosviewer. Only PIs with at least 10 papers were depicted and not all names are shown for graphic purposes. Although the various AGEM programs and focus areas can be loosely distinguished also in output, this co-authoring analysis also shows the connectivity within the entire institute.

AGEM has been very successful both in international and national collaborations, both with academic and commercial partners. This is illustrated by the various consortium publications in the leading journals as well as by the high level of funding with commercial partners. Nevertheless, the alliance did consume considerable energy focusing inward, and this aim should receive more attention in the coming years. This aim should, however, focus on creating a societal and healthcare impact rather than serve a commercial purpose. This should be rephrased in the future aims.

We analysed which organizations have >40 joint publications with at least 1 AGEM PI as co-author. (Legally)distinct organizations that are closely affiliated (VU/Vu/UvA/AMC and UU/UMCU for example) were combined in this analysis. This graph shows the connection with local hospitals, national (academic) hospitals and universities. Internationally, our most important partners are university medical centers of Leuven, Cambridge, Oxford, Harvard, Oslo, Pisa, etc as indicated on the left.

9.Increase quality of the Core Facilities required for the research at the highest international academic level.
The Core Facilities have an improved governance and financial structure, where income and costs are more clearly separated from departmental finances. Virtually all core-facilities now work with a system of user fees to (partially) cover costs. As AGEM we have supported some of the facilities with financial and administrative support in organizing starting symposia, invitations of the managing directors for

lectures and PhD training to ensure AGEM scientists are aware of the possibilities and by funding novel add-on capacities for existing facilities, such as the fluxomics addition of the Metabolomics facility and the anaerobic culture facility and nanostring sequencing for the Microbiota facility. However, since the

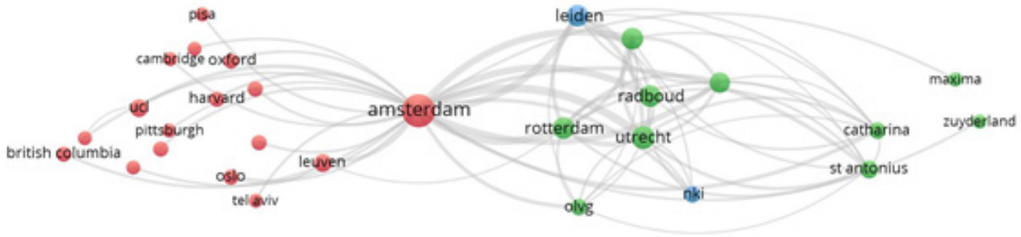


Figure A3. External collaborative partners with whom AGEM researchers have co-published peer-reviewed articles in the period 2017-2019.

Amsterdam UMC's Core Facilities are separate entities on which the AGEM institute does not have financial or managerial influence, this aim should be excluded from the institute's strategy.

10.Develop a branding & communication strategy, which is used to target the general public, patients, academic colleagues, charities and industry.

We have a better website where AGEM PIs, programs and successes are visible to the world. We recently included the various podcasts produced by PhD candidates of AGEM. We have annual reports to provide similar overviews that are send to internal and external stakeholders. We have an annual lunch with representatives of charity foundations, patient organisations and industry followed by a visit to the Anatomische les to involve these parties with AGEM. Individual departments such as Gastroentrology/ Hepatology have annual events to showcase the state-of-the-art endoscopy apparatus and techniques to an international audience of academic colleagues. Nevertheless, this aim should receive more priority in the coming years.

Appendix 2 - Evidence

2.1 List of chosen indicators

Table A4 List of chosen indicators and their reasoning

RESEARCH QUALITY			
1. Research products for peers			
Category	**Type**	**Indicator**	**Reasoning**
Publications	Peer-reviewed articles	Number of peer-reviewed articles	High quality reseach leads to high quality output. These can include different types of publications. Another important assett of the quality of research, is its availability to the research community (open access)
		% open access	
	Non-peer reviewed articles	Number of publications	
	Books	Number of publications	
	Book chapters	Number of publications	
	PhD theses	Number of publications	
	Conference papers	Number of publications	
	Professional publications	Number of publications	
	Publications aimed at the general public	Number of publications	
	Other research output	Number of publications	
	Key terms	Term-map of key terms publications	
Co-authorship	PI collaborations	Collaboration web AGEM PIs	High quality researched is characterized by strong internal and external collaboration
		Proportion of publications involving collaboration	
2. Use of research products by peers			
Category	**Type**	**Indicator**	
Use of data	Reviews published	Number of publications	Research output can be used by scientific peers in multiple ways. These indicators indicate the most common ways of sharing research output.
	expertise centers	Descriptive (examples)	
	data platforms	Descriptive (examples)	
	exploitation data sets	Descriptive (examples)	
	Citations	Number of citations	The most well-known indicator to measure the use of research products by scientific peers
Co-authorship	Collaboration with external institutes	Collaboration web with external institutions (all) Collaboration web with external institutions (non-academic network)	High quality researched is characterized by strong internal and external collaboration
	Contract research & collaborations	Collaborations based on funding	Next to co-authorship, external funding also indicates collaboration with external partners.
3. Marks of recognition by peers			
Category	**Type**	**Indicator**	
Personal grants	Veni, vidi, vici	Name researcher, type of grant, year	Individual grants awarded to AGEM researchers indicate the institute houses excellent researchers
	ERC	Name researcher, type of grant, year	
Consortia	Involvement in (inter)national consortia	Descriptive (examples)	Other examples of the appreciation of the institute's research by the scientific community, include the involvement in international consortia, editorial boards, scientific committees, etc.
	Science awards/scholarly prizes	Descriptive (examples)	
	Membership of scientific committees, editorial boards, etc.	Descriptive (examples)	

SOCIETAL RELEVANCE			
1. Research products for societal target groups			
Category	**Type**	**Indicator**	
Publications	Books	Descriptive (examples)	The societal impact of research can be visualized by the types of research output aimed at societal target groups. These include products for both the general public (books, documentaries, etc.) as well as professional public (patents, applications, etc.). An important target group in the case of the AGEM institute are patients.
	Patents	Uptake in patent citaitons	
	Documentaries / films / TV / podcasts	Descriptive (examples)	
	Websites	Descriptive (examples)	
	Digital infrastructures (e.g. applications)	Descriptive (examples)	
Clinical impact	Clinical trials	Descriptive (examples)	One of the most important societal target groups in the case of the AGEM institute, are patients suffering from gastroenerological, endocrine or metabolic diseases. Therefore, the societal impact of the institute can be measured by the impact of its research on the clinic.
	Clinical guidelines	Uptake in clinical guidelines	
	Ontwikkelde tests	Descriptive (examples)	
Other	Other projects with societal partners	Descriptive (examples)	Other projects with societal partners may also indicate the societal relevance of the research
2. Use of research products by societal target groups			
Category	**Type**	**Indicator**	
Communication	Website	Description of website	The outreach of research conducted within the AGEM institute can be visualized by the number of visitors on the (publicl available) AGEM website and LinkedIn page
		Number of visitors	
	News / Social media	Number of followers	
		Uptake of key terms in news	
Policy	Research used in policy documents	Uptake in policy documents	The uptake of research in policy documents indicates research output is used by societal target groups
Co-authorship	Collaboration with industries	Co-authors from industries	Collaboration with external partners, such as industries and non-academic hospital, indicate the use of research products by these societal target groups
	Collaboration with non-academic hospitals	Co-authors from non-academic hospitals	
3. Marks of recognition by societal target groups			
Category	**Type**	**Indicator**	
Awards	Grants by societal partners	Descriptive (examples)	Individual grants and prizes awarded to AGEM researchers indicate the institute houses excellent researchers
	Public awards and prizes	Descriptive (examples)	
Appointments	Appointments at societal organisations	Descriptive (examples)	The appointment of AGEM researchers in societal / patient organisations, indicates the institute houses excellent researchers
	Appointments at patient associations (committees, boards)	Descriptive (examples)	

2.2 AGEM in numbers

Table A5 Number of researchers registered at the AGEM institute, 2017-2022.

	2017	2018	2019	2020	2021	2022
Principal Investigators*	88	90	91	93	99	101
PhD students**	495	443	470	416	432	415
Other researchers***	289	262	228	293	221	214
Total******	872	795	789	802	752	730

** Based on official Amsterdam UMC Principal Investigator registration*

*** Based on the AGEM institute's own registration system as well as Hora Finita (registration system for VUmc PhD students)*

**** Based on the Research Information Systems Pure VUmc and Pure AMC in each respective year. Registration of research institute affiliation was done by the researchers themselves, by representatives of the department of the researcher, by personnel from the Medical Library AMC or by the policy officer of the AGEM research institute. Researchers affiliated with AGEM registered in the VUmc and AMC Pure instances have been combined and deduplicated. In 2020, the rule was introduced that each researcher could be affiliated to a maximum of 2 research institutes, to prevent long affiliations. This could be the reason for the decrease in number of researcher in 2020/2021.*

***** The numbers presented here are an estimation of the total number of researchers registered and/or affiliated at the AGEM institute. Due to the self-registration aspect of the Pure registration system and the fact that one central Doctoral School registration system has been launched only in 2023, these numbers are likely to be an underrepresentation of reality. Therefore, the numbers presented here are solely meant to give an indication of the order of magnitude of the institute over time.*

Table A6 Funding AGEM institute 2017-2022. The institute has a budget of approximately EUR 550.000 each year. Main expenditures are the AGEM grants, lectures and symposia and personnel costs (AGEM staff).

Funding AGEM institute	2017	2018	2019	2020	2021	2022
AMC	250.000	308.500	308.500	308.500	308.500	305.415
VUmc	250.0000	250.000	250.000	250.000	253.789	251.251
Total	500.000	558.500	558.500	558.500	562.289	556.666

Table A7 Total funding AGEM research in EUR for the second until fourth funding stream, 2017-2022.

Funding stream	2017	2018	2019	2020	2021	2022
2	2.726.159	5.020.955	5.524.833	1.635.670	3.852.350	4.149.495
	1.196.589	3.989.612	2.918.739	129.702	2.573.323	160.962
	3.922.748 (16)	**9.010.567 (20)**	**8.443.572 (21)**	**1.765.372 (16)**	**6.425.673 (18)**	**4.310.457 (9)**
3	4.663.433	5.523.132	6.172.802	5.235.684	2.029.801	4.303.070
	2.892.864	3.043.653	4.366.619	2.829.899	536.853	8.273.349
	7.556.297 (19)	**8.566.785 (32)**	**10.539.421 (22)**	**8.065.583 (24)**	**2.566.654 (21)**	**12.576.419 (24)**
4	7.573.802	14.053.234	4.758.711	3.484.397	9.455.223	1.973.092
	3.255.643	1.066.988	4.210.452	2.687.687	4.419.472	1.450.403
	10.829.445 (22)	**15.120.222 (28)**	**8.969.163 (28)**	**6.172.084 (22)**	**13.874.695 (27)**	**3.423.495 (20)**
Total	**22.308.490 (57)**	**32.697.574 (80)**	**27.952.156 (71)**	**16.003.039 (40)**	**17.073.912 (66)**	**20.310.371 (53)**

The table includes funding information for each Principal Investigator affiliated to AGEM, even if PIs are affiliated to more than 1 institute and their funding is registered at another institute. In blue, all funding that is registered at AGEM. In green, the funding from PIs who are affiliated to AGEM but their funding is registered at their second research institute. In bold, the totals of these two. The numbers in brackets are the number of PIs who have received this funding. Due to the large variety in size of the grants, the fact that these numbers also include consortium grants partially granted to Amsterdam UMC, and the COVID-19 pandemic in 2020 - 2021, there is some variety in the total funding over time. Nonetheless, the number of PIs who have received grants remains relatively stable over time (with the exception of 2020).

2.3 Research quality

Table A8 Research output AGEM researchers 2017-2022

	2017	2018	2019	2020	2021	2022	Total
Refereed article	1.396	1.552	1.492	1.485	1.624	1.447	8.996
***of which review articles**	162	175	158	189	246	161	1.091
Non-refereed article	50	83	68	78	100	54	433
Book	3	0	0	0	0	0	3
Book chapter	27	29	23	19	20	3	127
Conference paper	4	3	8	6	9	6	36
Professional publication	64	58	59	43	38	16	278
Publication aimed at the general public	0	2	1	0	0	0	3
Other research output	35	20	24	6	21	5	111
Total	1.597	1.474	1.675	1.637	1.821	1.537	9.987

These numbers are based on the Registration Systems Pure AMC and Pure VUmc. Again, due to aforementioned reasons, these numbers are likely to be an underrepresentation of reality and are therefore solely meant to give an indication of the order of magnitude of the publication output of the institute over time

Table A9 Publication statistics of peer-reviewed articles published by researchers from the AGEM institute, over the total period 2017-2022

A)

	Overall
P [full]	6.293
P [fract]	2.138
P [OA]	5.177
PP [OA]	75%
PP [collab]	88%
PP [industry]	9%
PP [top full]	20%
PP [top fract]	15%
MNCS [full]	1.85
MNCS [fract]	1.39

B)

	2017	2018	2019	2020	2021	2022	Overall
P [full]	1.216	1.306	1.234	1.237	1.300		6.293
P [fract]	456	458	408	397	419		2.138
P [OA]	809	941	940	1.055	1.060	372	5.177
PP [OA]	0.66	0.71	0.75	0.85	0.80	0.71	0.75
PP [collab]	0.84	0.87	0.88	0.89	0.89	0.93	0.88

(A) and publication statistics AGEM institute divided per year (B). Indicators not included in this table, remained relatively stable over the last six years and are therefore only presented as overall number in Table 1. Information about 2022 is not available for P [full] and P [fract] since these numbers are based on the number of citations each publication receives - this information is not yet available for 2022. Similarly, information about open access is not yet available on Unpaywall for all publications of 2022, resulting in a likely underreporting of P [OA] in 2022.

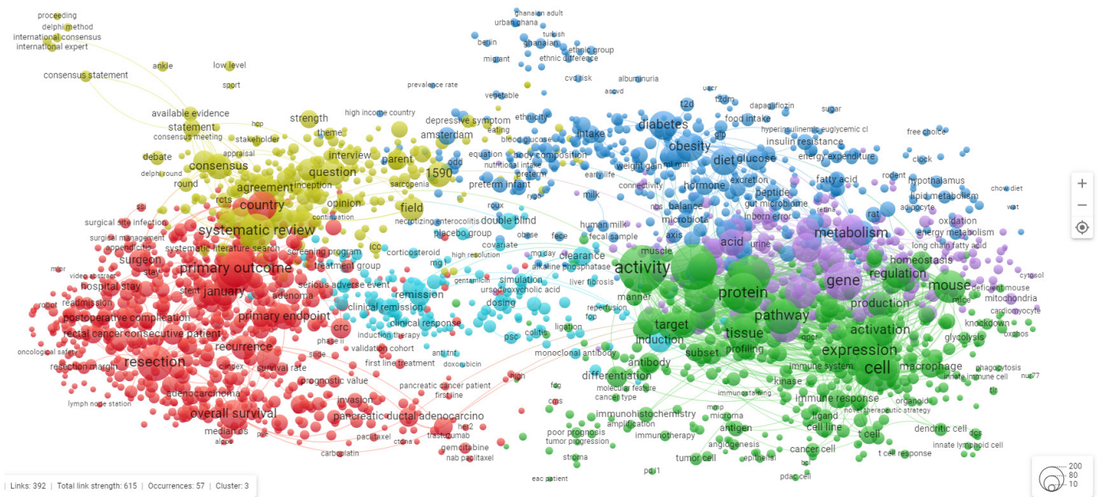


Figure A5 Term map of all AGEM publications in the year 2017-2022. Each publication is authored by at least one AGEM researcher. Each dot represents a cluster in which AGEM researchers publish articles. The dots are key terms extracted from textual data. The closer the dots are, the more often two terms co-occur in publications. For a better visualization and possibility to zoom in, access the map online here.

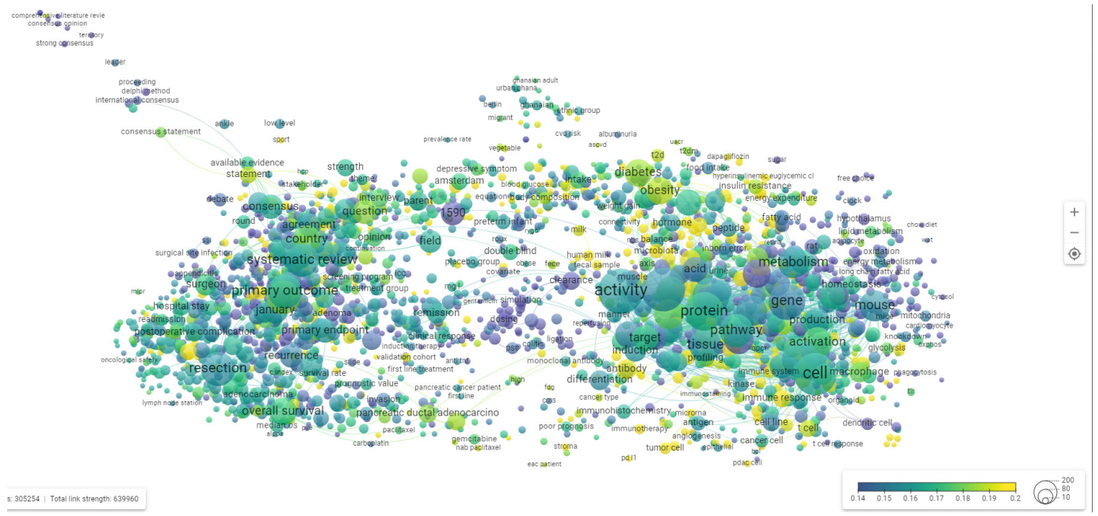


Figure A6 Heat map of key terms from AGEM publications. The color scale indicates the relative growth of the cluster. This map highlights the relative growth in several clusters in which AGEM researchers are publishing their work. These areas of growth are dispersed across the entire map, indicating growth of publications in all three of AGEM's research themes. For a better visualization and possibility to zoom in, access the map online here. The cluster coloring can be changed to show relative growth of publication clusters, by selecting "clusters" under "color" in the menu on the left hand side.

Table A10 External collaborators of the AGEM institute. The table shows all external institutes with which AGEM has a fractional number of co-authored publications of >5

		P [copub fract]
Erasmus University Rotterdam	NL	250
Utrecht University	NL	209
Leiden University	NL	204
Santeon	NL	161
Maastricht University	NL	143
Radboud University	NL	138
University of Groningen	NL	117
Netherlands Cancer Institute- Antoni van Leeuwenhoek Hospital	NL	68
Katholieke Universiteit Leuven	BE	39
Wageningen University & Research	NL	32
University of British Columbia	CA	31
Harvard University	US	30
Royal Netherlands Academy of Arts and Sciences (KNAW)	NL	24
Reinier Haga Groep	NL	22
Karolinska Institutet	SE	22
Spaarne Gasthuis	NL	21
Netherlands Comprehensive Cancer Organisation (IKNL)	NL	21
University of Copenhagen	DK	19
University of Toronto	CA	18
Ghent University	BE	18
Isala	NL	18
Beijing Normal University	CN	18

Tergooi Medical Center	NL	17
University of Oslo	NO	16
Ludwig-Maximilians-Universität München	DE	15
Heidelberg University	DE	15
University College London	GB	15
Medical University of Vienna	AT	15
Amsterdam University of Applied Sciences	NL	15
Máxima Medical Center	NL	15
Eindhoven University of Technology	NL	14
Western University, Canada	CA	14
University of California, San Diego	US	13
Imperial College London	GB	13
Stanford University	US	13
Icahn School of Medicine, Mount Sinai	US	12
University of Pisa	IT	12
Sanquin Blood Supply Foundation	NL	12
Nationwide Children's Hospital	US	12
Amphia Ziekenhuis	NL	12
University of Oxford	GB	12
Mayo Clinic	US	12
Universität Hamburg	DE	11
University of Gothenburg	SE	11
University of Birmingham	GB	11
University of Colorado, Denver	US	11
University of Cambridge	GB	11
Noordwest Ziekenhuisgroep	NL	11
Johns Hopkins University	US	10
University of Cincinnati	US	10
University of Palermo	IT	10
University of Parma	IT	10
University of Bonn	DE	10
National Institute of Public Health & Environment	NL	10
University Hospital Southampton NHS Foundation Trust	GB	10
Haaglanden Medisch Centrum	NL	10
University College Dublin	IE	10
Oxford University Hospitals NHS Foundation Trust	GB	10
Gelre Ziekenhuis	NL	9
Oncode Institute	NL	9
Meander Medical Center	NL	9
Humanitas University	IT	9
University of Calgary	CA	9
Jeroen Bosch Ziekenhuis	NL	9
National Institutes of Health	US	9
Zuyderland Medisch Centrum	NL	9
University of Strasbourg	FR	9

Medical University of Graz	AT	9
University of Helsinki	FI	9
Delft University of Technology	NL	9
Massachusetts General Hospital	US	9
University of Milan	IT	9
Great Ormond Street Hospital for Children NHS Foundation Trust	GB	9
Dalhousie University	CA	8
University of Zurich	CH	8
Netherlands Organisation for Applied Scientific Research (TNO)	NL	8
Rijnstate	NL	8
University of Padova	IT	8
University of Bologna	IT	8
University of Naples Federico II	IT	8
University of North Carolina, Chapel Hill	US	8
Tel Aviv University	IL	8
University of Pennsylvania	US	7
University of Pittsburgh	US	7
University of Antwerp	BE	7
University of Twente	NL	7
University of Cologne	DE	7
Yale University	US	7
Johannes Gutenberg University Mainz	DE	7
Hospices Civils de Lyon	FR	7
Ziekenhuis Gelderse Vallei	NL	7
University of Bergen	NO	7
Slotervaartziekenhuis	NL	7
Technical University of Munich	DE	6
The University of Edinburgh	GB	6
Guy's & St. Thomas' NHS Foundation Trust	GB	6
King's College London	GB	6
Case Western Reserve University	US	6
Goethe University Frankfurt	DE	6
Sichuan University	CN	6
Centre National de la Recherche Scientifique	FR	6
Hannover Medical School	DE	6
Newcastle University	GB	6
Humboldt-Universität zu Berlin	DE	6
University of Alberta	CA	6
Freie Universität Berlin	DE	6
University of Ottawa	CA	6
French Institute of Health and Medical Research (INSERM)	FR	6
Washington University in St. Louis	US	6
Université Libre de Bruxelles	BE	6
University of Washington, Seattle	US	6
National Institute of Biology	SI	6

University of São Paulo	BR	6
Hospital Clínic de Barcelona	ES	6
University of Sydney	AU	6
University of Chicago	US	6
University of Barcelona	ES	6
Université de Paris	FR	6
London North West University Healthcare NHS Trust	GB	6
Sapienza University of Rome	IT	5
Royal Free London NHS Foundation Trust	GB	5
San Raffaele Hospital	IT	5
University of Lausanne	CH	5
Amsterdam Rheumatology and Immunology Center	NL	5
Albert Schweitzer Hospital	NL	5
University of Eastern Finland	FI	5
University of Melbourne	AU	5
HAN University of Applied Sciences	NL	5
University of Porto	PT	5
Cambridge University Hospitals NHS Foundation Trust	GB	5
Northwestern University	US	5
University of Turin	IT	5
University of Florence	IT	5
Charles University	CZ	5
Leibniz Institute for Experimental Virology (Heinrich Pette Institute)	DE	5
Ospedale Pediatrico Bambino Gesù	IT	5
GlaxoSmithKline	GB	5
Emory University	US	5
Ohio State University	US	5
University of Bern	CH	5
University of California, Los Angeles	US	5
Robarts Research Institute	CA	5
Nanjing University	CN	5
Memorial Sloan Kettering Cancer Center	US	5
Washington State University	US	5
University College London Hospitals NHS Foundation Trust	GB	5
German Cancer Research Center	DE	5
McGill University	CA	5
University of Glasgow	GB	5
Manchester University NHS Foundation Trust	GB	5
University of Verona	IT	5
RWTH Aachen University	DE	5
University of California, San Francisco	US	5
Medisch Centrum Leeuwarden	NL	5
Hôpitaux Universitaires Paris Nord Val-de-Seine	FR	5
Université de Lorraine	FR	5

2.4 Societal relevance

Box A1. Background information about Area Based Conectedness (ABC).

One way to measure societal impact of the papers published by AGEM researchers, is to look at Area Based Connectedness.

- ABC[policy] = The relative connectedness of the areas (publication clusters) in which an institute published, as measured by the share of output (worldwide) being cited in policy documents.
- ABC[news] = The relative connectedness of the areas (publication clusters) in which an institute published, as measured by the share of output (worldwide) being cited in news articles
- ABC[ClinGL] = The relative connectedness of the areas (publication clusters) in which an institute published, as measured by the share of output (worldwide) being cited in clinical guidelines.
- ABC[industry] = The relative connectedness of the areas (publication clusters) in which an institute published, as measured by the share of output (worldwide) being published by or with a company. This indicator is related to PP[industry] which applies to the output of the institute only.
- ABC[hosp] = The relative connectedness of the areas (publication clusters) in which an institute published, as measured by the share of output (worldwide) being published by or with a (non-academic) hospital.
- ABC[patent cits] = The relative connectedness of the areas (publication clusters) in which an institute published, as measured by the share of output (worldwide) being cited in patents.

Table A11. ABC scores for publications clusters categorized by AGEM research focus area. Only publications clusters with N pubs > 39 were categorized.

AGEM focus area	Publication cluster	N pubs	Area based growth	ABC [ClinGL]	ABC [Hosp]	ABC [News]	ABC [Patent cits]	ABC [policy]
1	distal pancreatectomy	281	1,89	8,55	4,39	0,96	0,81	0,51
1	severe acute pancreatitis	65	1,48	6,92	3,37	0,94	0,76	0,5
2	nonalcoholic fatty liver disease	44	2,68	3,09	3,17	1,76	1,22	0,35
3	laparoscopic liver resection	89	1,67	0	4,67	0,37	0,35	2,6
3	autoimmune hepatitis	68	1,28	12,58	4,2	1,2	0,71	1,07
3	common bile duct stone	50	1,29	5,52	3,47	0,34	0,14	0,28
3	bile acid	77	1,67	0	2,27	0,86	2,5	0,14
4	fabry disease	85	1,4	4,12	4,75	1,34	2,91	0,59
4	l carnitine	46	1,18	2,65	3,59	0,67	1,83	1,62
4	adrenoleukodystrophy	81	1,05	0	2,03	1,73	2,28	0
4	circadian clock	45	1,56	0	1,16	3,13	0,89	0,08
5	appendicitis	40	1,51	8,98	4,67	0,74	0,38	0,47
5	barrett	123	1,47	13,27	4,65	1,32	0,98	0,64
5	achalasia	80	1,21	3,39	3,59	1,41	0,73	0,84
6	colitis	332	1,65	7	4,64	1,76	1,69	1,68
6	irritable bowel syndrome	110	1,41	9,32	3,31	1,82	1,37	0,55
6	gut microbiome	150	4,06	0	2,09	3,19	1,47	0,22
7	colorectal cancer screening	120	1,38	6,13	4,44	0,67	2,53	0,93
8	subclinical hypothyroidism	69	1,38	1,71	3,03	0,51	1,41	0,65
9	transgender	57	2,88	4,9	1,51	0,16	3,11	0,01
10	sodium glucose cotransporter	62	2,26	11,31	3,9	3,19	3,04	0,91

AGEM focus areas: 1) Pancreatitis; 2) Non-alcoholic fatty liver disease (NAFLD) / Non-alcoholic steatohepatitis (NASH) / lipid metabolism; 3) Cholestatic disorders; 4) Metabolic/inherited disorders and newborn screening; 5) Upper GI: barrett's / eosinophilic esophagitis (EoE) / achalasia; 6) IBD; 7) Pre-maligne screening (barrett's / colon); 8) Thyroid hormones; 9) Gender; 10) Diabetes.

2.4.1. AGEM Societal impact - patents

The research carried out at the AGEM institute not only results in publications in peer-reviewed journals but also leads to the development of products aimed at societal target groups. For instance, the institute's research has resulted in the filing of several patents, including one for a Cerebrotendinous Xanthomatosis newborn screening method. As is shown in the figure below, the filing of patents is mainly observed in the institute's focus areas metabolic/inherited disorders and IBD. These patents highlight the practical implications of the research and its potential to benefit society by providing solutions to real-world problems.

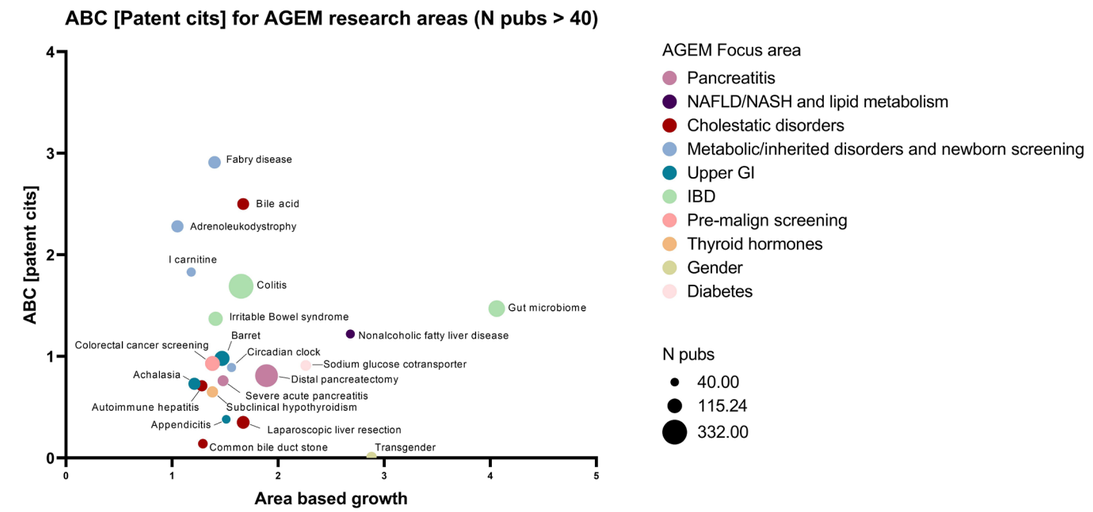


Figure A7 Area Based Connectedness with patent citations of publication clusters (N > 39) related to AGEM's 10 focus areas

2.4.2. AGEM Societal impact - news articles

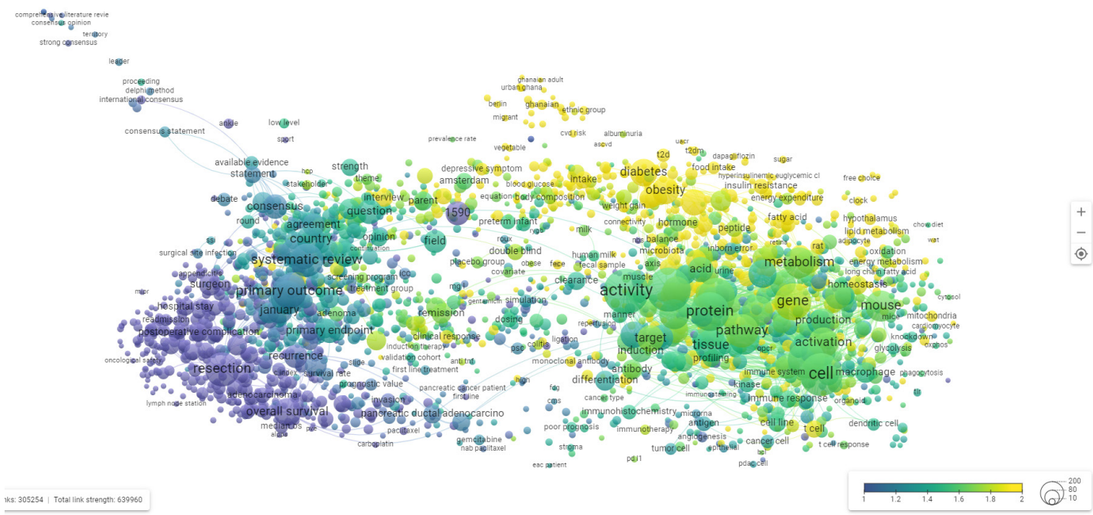


Figure A7 Heat map AGEM visualizing the uptake of key terms in news articles For a better visualization, access the map online here. The cluster coloring can be changed to show the uptake of key terms in news articles, by selecting "news" under "color" in the menu on the left hand side.

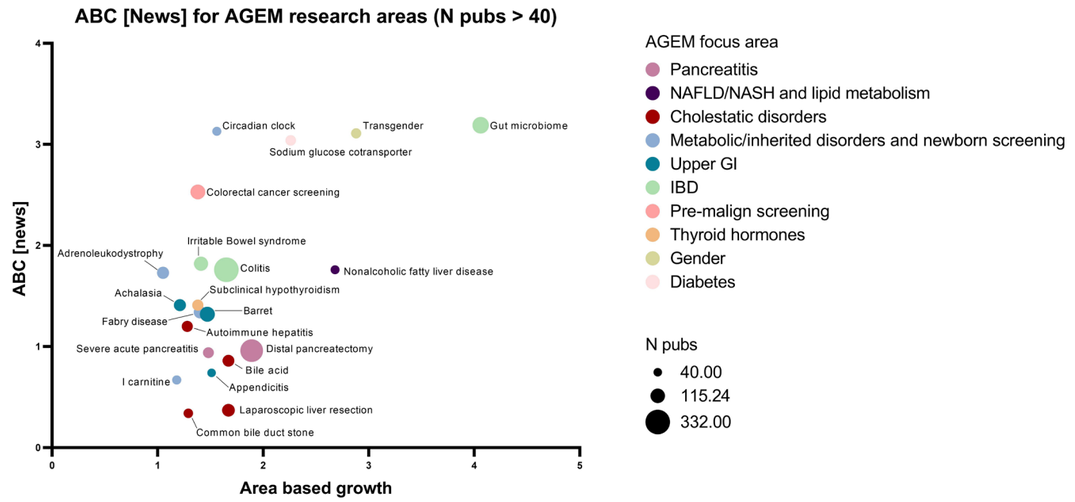


Figure A8 Area Based Connectedness to news articles of publication clusters (N > 39) related to AGEM's 10 focus areas.

2.4.3. AGEM Societal impact - clinical guidelines

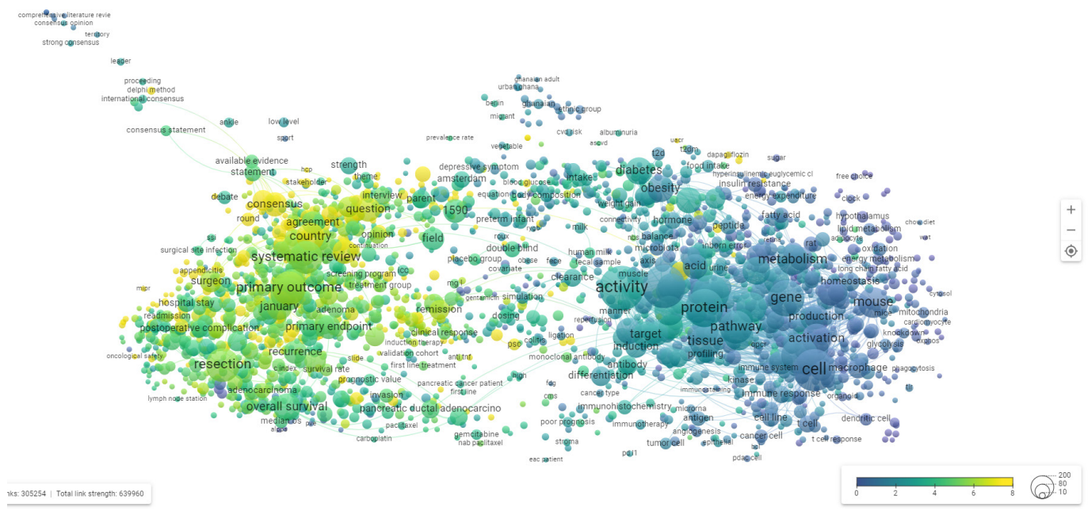


Figure A9 Heat map AGEM publications visualizing the uptake of research output in clinical guidelines, based on the ABC [clinGL] indicator. The database average is 1. Values above one indicate an above world-average societal connectedness to clinical guidelines. For a better visualization, access the map online here. The cluster coloring can be changed to show the uptake in clinical guidelines, by selecting "ClinGL" under "color" in the menu on the left hand side.

2.4.4. AGEM Societal impact - policy documents

Next to the impact of AGEM publications on patent citations and clinical guidelines, key terms from different research topics within the total body of AGEM publications are also observed to frequently be used in policy documents (figure A10). For some of AGEM's publication clusters (N > 39) an above world-average connectedness to policy documents was observed. This impact was observed to be biggest in AGEM's focus area on transgender research.

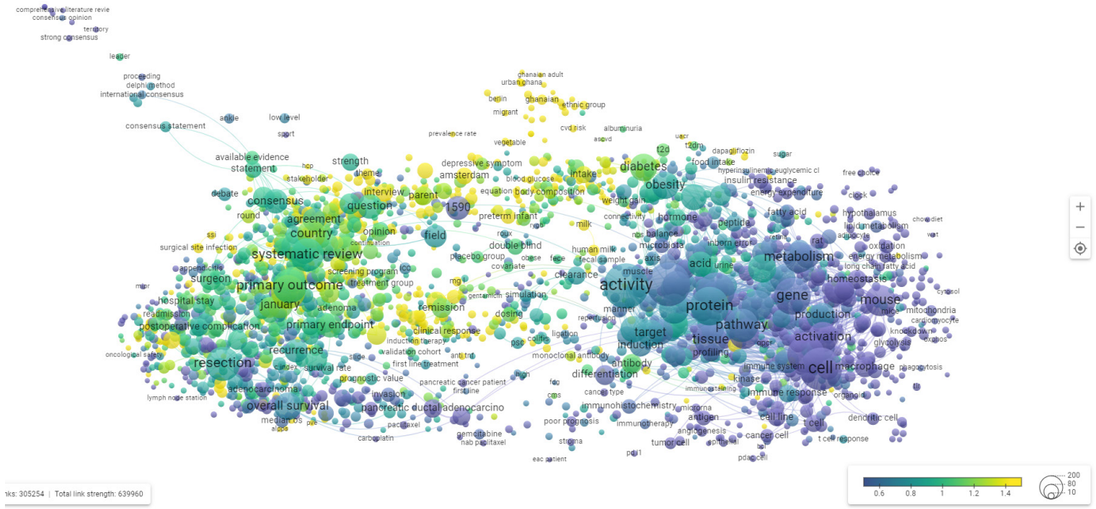


Figure A10 Heat map AGEM publications visualizing the uptake of research output in policy documents, based on the ABC [policy] indicator. The database average is 1. Values above one indicate an above world-average societal connectedness to policy. For a better visualization, access the map online here. The cluster coloring can be changed to show the uptake in policy documents, by selecting "policy" under "color" in the menu on the left hand side.

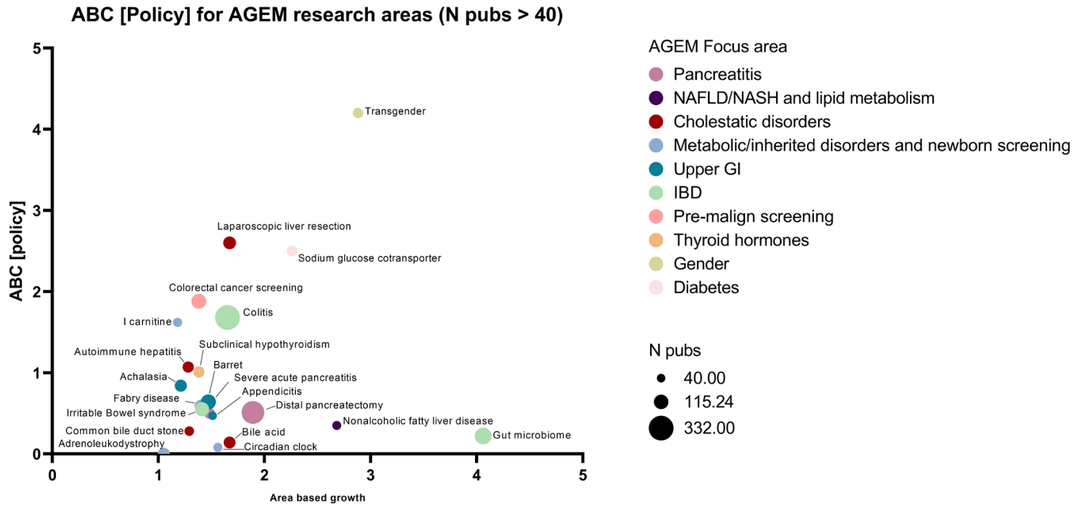


Figure A11 Area Based Connectedness with policy documents of publication clusters (N > 39) related to AGEM's 10 focus areas.

2.4.5. AGEM Societal impact - co-authorship hospitals and industry

Table A12 Five most important societal collaborative partners (Hospital and Hospital groups) of AGEM researchers, in terms of number of co-authored publications (fractional counting) (P). Based on peer-reviewed publications in the period 2017-2022.

Hospital	P	Hospital group	P
Antoni van Leeuwenhoek Hospital	67.6	Santeon	161.2
Netherlands Comprehensive Cancer Organization (IKNL)	20.7	Reinier Haga Group	22.1
Isala	17.9	Spaarne Gasthuis	21.1
Tergooi Medical Center	16.8	Noordwest Ziekenhuisgroep	10.5
Máxima Medical Center	14.6	University Hospital Southampton NHS foundation trust	9.9

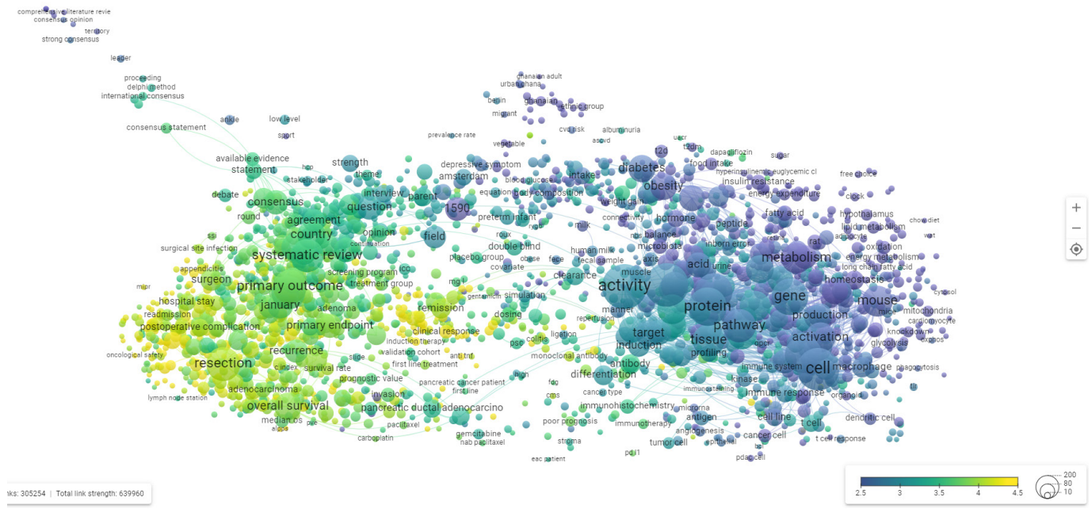


Figure A12 Heat map AGEM publications visualizing co-authorship with (non-academic) hospitals, based on the ABC [hosp] indicator. The database average is 1. Values above one indicate an above world-average societal connectedness to (non-academic) hospitals. For a better visualization, access the map online here. The cluster coloring can be changed to show co-authorship with hospitals by selecting "Hosp" under "color" in the menu on the left hand side.

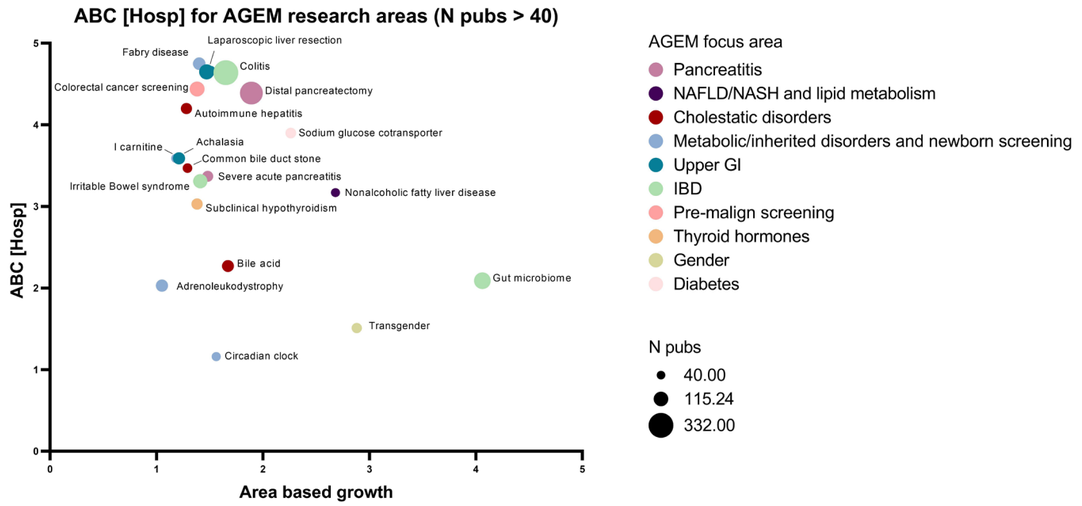


Figure A13 Area Based Connectedness of co-authorship with hospitals, of publication clusters (N > 39) related to AGEM's 10 focus areas.

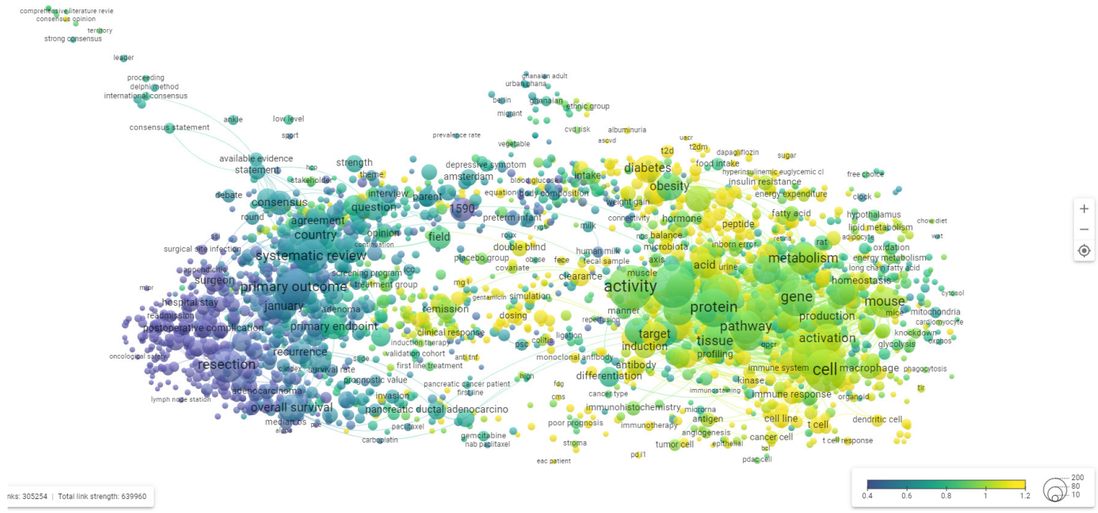


Figure A14 Heat map AGEM publications visualizing co-authorship with the industry, based on the ABC [industry] indicator. The database average is 1. Values above one indicate an above world-average societal connectedness to industry. For a better visualization, access the map online here. The cluster 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.

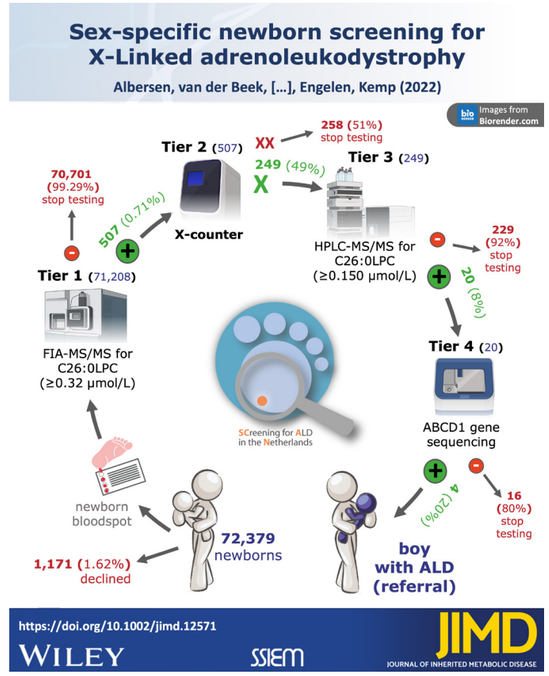
Furthermore, numerous prospective and non-randomized prospective trials are ongoing aiming at improving disease understanding and treatment outcomes for patient with acute and chronic pancreatitis. The POEMA trial has focused on dysbiosis in patients with acute pancreatitis developing infected necrosis. 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

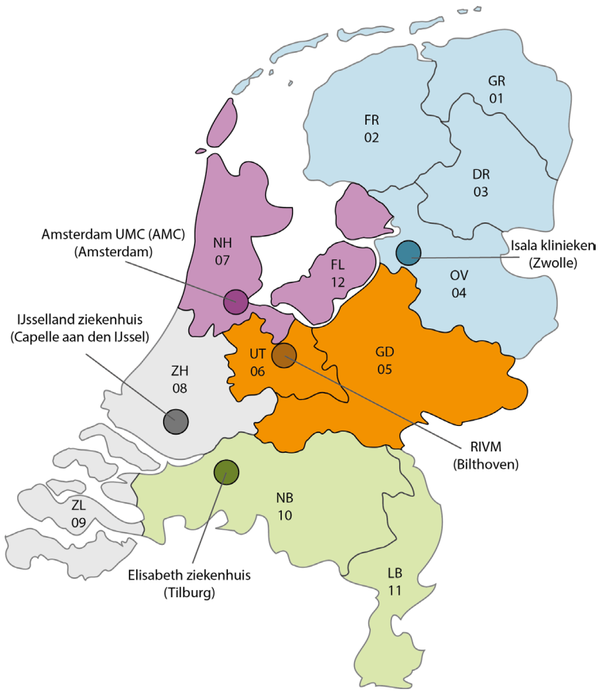
Background

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

system is being set up for researchers from the level of PhD candidate to Professor, by bundling existing mentoring programs of the research institutes. Furthermore, a digital Postdoc portal is being launched to support postdocs in making career advancement, by offering information, courses and coaching.

Amsterdam UMC aims to stimulate research excellence by recognizing professionals who are in the lead. The scientific careers of talented young researchers are stimulated by the Principal Investigator (PI) system for researchers who have taken up leadership and developed their own lines of research. Currently, there are approximately 750 PIs within Amsterdam UMC. PIs can be nominated by their department head and, after a strict selection procedure, are appointed by the Executive Board of Directors. The recognition and increased visibility as PI supports them when forming collaborations and applying for research grants.

At postdoc level, Amsterdam UMC offers up to four Postdoc Career Bridging grants per year to young researchers. The Amsterdam UMC Postdoc Network deploys activities to attract attention to the specific needs of postdocs, among others by organizing courses on scientific and transferable skills and networking events, thereby stimulating professional and career development. For very talented senior postdocs or mid-career level researchers, an Amsterdam UMC Fellowship exists, consisting of one 5-year Fellowship per year to set up an own research group. In 2022, an additional Diversity & Inclusion Talent Fellowship was granted in collaboration with the UvA to a researcher belonging to an underrepresented group in the Netherlands. Fellowship laureates are embedded in the Tenure Track scheme of Amsterdam UMC that guides a limited group of very talented mid-career level researchers to a tenured position in five years. In addition, Amsterdam UMC has several incentive arrangements to stimulate research excellence. The incentive policy is designed to encourage researchers to focus on strategically important grants and to attract and retain mid-career talent by awarding laureates of specific prestigious grants with supplemented budget or an additional PhD or postdoc position. The Research Grant Support helps to stimulate, retain or attract researchers at mid- and high-career level to obtain prestigious (inter-)national and EU research grants. The Research Policy Office is involved in the development of research policy advice and offers support to Amsterdam UMC researchers.

AGEM

Diversity & inclusion policy

The AGEM institute adheres to the Human Resources policies set by Amsterdam UMC. As a network institute that does not employ any staff, the institute does not have diversity promoting practices integrated into its structure. Instead, the responsibility for promoting diversity lies within Amsterdam UMC's divisions and departments. Despite this, the AGEM institute strives to promote diversity in whatever ways it can. For instance, it places a strong emphasis on selecting lecturers from diverse backgrounds for symposia and events.

Talent policy

The AGEM institute is dedicated to creating a supportive and nurturing environment that encourages growth, learning, and success for its researchers. The AGEM Talent Development Grant, for example, is specifically designed to support exceptionally talented researchers who have obtained a PhD degree within the last eight years. The grant provides funding for researchers who want to establish their own research line or further develop their existing research line.

Another noteworthy initiative is the institute's International Student Fellowship, encouraging (bio) medical students to participate in a research internship at an international top institute. The majority of these students return to Amsterdam UMC to obtain a PhD degree. In 2022, the AGEM institute has started drafting an Amsterdam UMC-wide mentoring program in collaboration with the seven other research institutes of Amsterdam UMC. This program will provide researchers with mentorship and guidance as they navigate their careers. Finally, AGEM has an advisory role with regard to Amsterdam UMC talent policy and recruitment. This role is reflected in the institute's participation in nominating individuals and teams for local and international awards, in supporting promotions from assistant to associate or full professorships and in recruiting talent through e.g. the Amsterdam UMC fellowship.

Overall, the AGEM institute's dedication to talent development is reflected in its various initiatives and advisory roles. These efforts ensure that the institute remains at the forefront of research and fosters the growth and development of its researchers.

3.7 Case study 7 - Promoting an open and inclusive culture, characterized by scientific integrity

Amsterdam UMC

Amsterdam UMC takes measures to ensure openness, (social) safety, inclusivity and research integrity. The office of the ombudsman is responsible for the social safety policy and the complaints procedure. This office aims to improve social safety and to combat unethical and/or undesirable behavior, to increase ownership and responsibility of employees and managers regarding safety signals and to promote an open reporting culture. Moreover, Amsterdam UMC is developing an active diversity and inclusion policy (see case study 6 for more details).

Regarding research integrity, Amsterdam UMC aims to provide an academic culture in which researchers are stimulated and supported to perform research to the highest ethical standards. Elaborating on the European and the Netherlands Code of Conduct for Research Integrity, that articulate broad values and principles characterizing research integrity, the Amsterdam UMC Research Code defines local guidelines and expectations for researchers when conducting research at Amsterdam UMC. The Executive Boards have appointed several independent confidential counselors, including counselors specifically for PhD candidates, who focus on research integrity. Next to confidential counselors for undesirable behavior and integrity, there are specific counselors for any employee or external party involved in research at Amsterdam UMC who has a question about research integrity or suspects research misconduct. These confidential counselors can mediate and advise on whether or not to file a complaint. Furthermore, they can support the submission of a formal complaint to the research integrity committees, that are

established by the Executive Boards of the UvA and VU Amsterdam which are responsible for research done in their institutions. Moreover, the confidential counselors provide research integrity training. Research integrity training is also part of the PhD trajectory, and is offered by the department of Ethics, Law and Humanities as well as the Research Policy Office of Research Support.

Transparency is one of the five principles of the Netherlands Code of Conduct for Research Integrity, which also form the base of the Amsterdam UMC Research Code. Therefore, Amsterdam UMC publicize the external professional activities (nevenwerkzaamheden) that full professors carry out according to the Human Resources registration systems. All Amsterdam UMC employees, including employees who perform research tasks, must declare their external activities in the registration system. This concerns activities that are relevant in light of the societal impact of research and also activities that can potentially lead to the risk of a conflict of interest.

Ethical review

Medical research involving human subjects, human material or laboratory animals has to be carried out according to national law and regulations. Within Amsterdam UMC, dedicated ethical committees review research protocols to ensure human and animal safety, and research quality.

Research with humans

All medical scientific research in which human participants are subjected to (medical) procedures or are required to follow rules of behavior, falls under the Medical Research Involving Human Subjects Act (Wet Medisch wetenschappelijk onderzoek met mensen; WMO). The Amsterdam UMC MREC (Medical Research Ethics Committee) has to approve research subject to WMO. Research proposals are only approved if the MREC establishes that the risks and burden for participants are in balance with the potential benefit for medical science or healthcare. All Amsterdam UMC clinical investigators performing WMO research are obliged to follow the Basic course on Regulations and Organization of Clinical Trials (Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers). Amsterdam UMC employees other than clinical researchers who are involved in clinical research (such as research nurses, data managers, students and study coordinators) are obliged to follow a Good Clinical Practice course.

All other research with humans, such as research with medical data or interviews, is not subject to the WMO (nWMO). Since 15 March 2023, there is a dedicated review board under the responsibility of the MREC that assesses all nWMO research proposals (including research involving setting-up a biobank or conducting research with material from an existing biobank) according to predefined ethical and legal criteria. Applicable legislation and regulations include the Medical Treatment Contracts Act (Wet Geneeskundige Behandelingsovereenkomst), General Data Protection Regulation (GDPR; AVG in Dutch), the Code of Conduct for Responsible Use and the Code of Conduct for the Use of Data in Health Research. The two Codes describe rules of conduct for care providers and researchers who wish to use patient material (i.e., biomaterials or data). Moreover, research involving the processing of personal data is regulated by the GDPR. The Amsterdam UMC Research Data Management department, Legal Research Support, privacy officer and data protection officer all support researchers in the proper use and organization of research data, ownership of data and data protection.

Research with laboratory animals

The Experiments on Animals Act (Wet op de dierproeven) stipulates that animal experiments can only be conducted after authorization by the national Central Authority for Scientific Procedures on Animals (Centrale Commissie Dierproeven; CCD). For each research proposal using laboratory animals, a 'Section 9 officer' from the department has to apply for a project license at the CCD. Project permission is based on ethical assessment by an independent local committee of experts known as the Animal Experiments Committee (Dierexperimentencommissie; DEC). The DEC focuses on protecting laboratory animals and weighs the degree of animal discomfort caused by the procedures and decides if this is proportional to the scientific and/or social benefits of the study.

AGEM

Research integrity

Amsterdam UMC places great importance on scientific integrity, and the AGEM institute shares this commitment. AGEM staff actively raise awareness of this topic during face-to-face meetings with department heads and Principal Investigators. Additionally, the institute organizes the Responsible Research Dinner Debate. This event brings together researchers from different career stages, ranging from PhD candidates to Principal Investigators, to have open discussions about scientific integrity and responsible research practices within their departments and research groups. As a result of these discussions, various departments have already implemented initiatives to promote scientific integrity, such as the Tytgat Institute of Liver and Intestinal Research (group sessions with Dilemma Games[4]) and the Endocrine Laboratory (monthly meetings of technicians, PhD and master students to discuss research and ethical issues).

Openness, (social) safety and inclusivity

The AGEM institute serves researchers working in various divisions and departments of Amsterdam UMC. As a network institute, its ability to promote openness, social safety, and inclusivity on the work floor is limited. However, the institute remains committed to fostering an environment that is open, safe, and inclusive, welcoming individuals from all backgrounds, ages, and walks of life. To facilitate effective communication, the institute exclusively uses English as the primary language of communication. Additionally, news items from Amsterdam UMC that are originally in Dutch are regularly translated to ensure that non-Dutch speaking AGEM researchers can understand them.

3.8 Case study 8 - PhD development & training

Amsterdam UMC

PhD policy

As a PhD degree is obtained at a university, distinct doctorate regulations apply for the UvA and VU Amsterdam. Supplementary regulations apply, to ensure that the thesis-requirements correspond as much as possible for the whole Amsterdam UMC PhD candidates community. Due to these different university regulations also the rules on training differ. For VU PhD candidates a training of 30 European Credit Transfer and Accumulation System (ECTS) is mandatory, while for UvA PhD candidates this is recommended. The Amsterdam UMC executive committee has determined that all theses must contain a portfolio of education of about 30 ECTS. The aim is to ensure that PhD candidates are trained as independent researchers and that their expertise and knowledge is broadened. General PhD support and training is centralized and provided by the Doctoral School and training in a specific field by the involved research institute. The Amsterdam Doctoral School collaborates with the International Offices of both universities UvA and VU. Each year, Amsterdam UMC awards five to six PhD Scholarships to excellent Amsterdam UMC students who hold a Master's degree. With these Scholarships, that are financed from core government funding, students can perform a four-year PhD trajectory at Amsterdam UMC.

Services and training

Support services of the Doctoral School include providing information and advice to PhD candidates. PhD candidates can always contact one of the PhD advisors, when they need coaching or a confidential consultation. In order to monitor all PhD trajectories at fixed milestones, these are centrally registered. In addition, the individual PhD trajectories are administered more detailed by using a paper archive (AMC/UvA) or the digital registration system Hora Finita (VUmc/VU). Besides services for PhD candidates, the Doctoral School offers services to their supervisors. Specially designated Doctoral School employees can be contacted for information and confidential consultations.

At the start of the PhD trajectory, the PhD candidate mandatory files a Training Plan (also including a paragraph on supervision) to be evaluated and monitored by the PhD supervisors up to the moment of graduation. By pre-establishing a balanced Training Plan, the candidates should think early in their PhD trajectory about what skills they want to learn. At the end of the process, the portfolio is assessed compared to the initial plan (VUmc) and/or (part of it) is added to the thesis (AMC and VUmc).

The Doctoral School offers trainings on general academic skills (like writing, presenting, personal development, research ethics, scientific integrity, scientific methods), research skills (broadening and deepening of scientific understanding) and social (personal) competences. The Doctoral School strives to develop guidance more specific on the group of PhD candidates towards the job market and career prospects in the near future. Research institutes also organize trainings and activities on their research focus. The initiatives of the AGEM institute are described in the main text of the report, and below.

The active Association of Amsterdam UMC PhD Candidates (ASAP) cooperates with the Doctoral School. They organize social events and are involved in the training of PhD candidates. They represent Amsterdam UMC PhD candidates in the Amsterdam Doctoral School Board and in national PhD candidate associations.

AGEM

The institute has implemented various initiatives to support the academic and personal growth of PhD candidates and ensure their well-being. One prominent example is the annual AGEM retreat, which is organized mainly by PhD candidates. The retreat offers a platform for all PhD candidates to present their research, thereby providing a comprehensive overview of the full width of research conducted within the institute. This retreat aims to bring researchers together to explore, exchange and learn from each other's research. Furthermore, the institute conducts a highly regarded PhD candidate course to provide valuable information to new and current PhD candidates, in the areas of gastroenterology, endocrinology, and metabolism. This course covers essential topics that may fall outside the scope of their own research and also provides practical information and hands-on practice with broader academic skills. Each year, AGEM also organizes the Best Publication Battle, in which talented PhD candidates and junior postdocs get the opportunity to pitch their publication in a high-impact journal, thereby competing for the honoree prize of 'Best AGEM publication' of that year.

In addition to the institute's own initiatives, AGEM closely collaborates with the Amsterdam UMC Doctoral School, which aims to be a well-known and appreciated partner for PhD candidates and their supervisors. Through this collaboration, the AGEM institute maintains close ties with the Doctoral School and contributes to PhD administration.

3.9 Case study 9 - Facilitating Open Science

Amsterdam UMC

Open Access publishing

As part of Open Science, Amsterdam UMC encourages Open Access (OA) publishing and the reuse of data for future research by other groups. Amsterdam UMC policy is to publish all scientific articles of which the corresponding author is working at Amsterdam UMC OA. Therefore, Amsterdam UMC researchers can publish OA via the golden route free of charge in more than 10.000 journals. More than 80% of the articles submitted by Amsterdam UMC authors is published Gold OA, the other 20% is mostly open available through Green OA. Support and information regarding OA publishing is provided by the Medical Library for location AMC and by the UBVU for location VUmc.

FAIR data

For the reuse of data, it is a prerequisite that research data is stored in a Findable, Accessible, Interoperable and Reusable (FAIR) way. The Research Data Management department facilitates the creation of FAIR datasets by providing researchers the tools and support for drawing up Data Management

Plans. Amsterdam UMC researchers can use the open data repository DataverseNL to share metadata and publish their research FAIR data sets, open or under conditions for reuse.

Public engagement

Amsterdam UMC has several online platforms to spread news and stories from Amsterdam UMC to the research community and the public: Amsterdam UMC Vandaag (in Dutch), Amsterdam UMC Spotlight (in English) and the websites of the research institutes. In addition, involving patients in various stages of the research cycle, i.e., in the design, conduct, and dissemination of research, can improve research in multiple ways. The Research Grant Support provides advice to researchers about patient involvement in research proposals. Currently, Amsterdam UMC-broad policies are being developed for collaboration with external (societal) stakeholders and patient involvement in research.

AGEM

Amsterdam UMC places great importance on Open Science, and the AGEM institute shares this commitment. While, again, the main responsibility of promoting Open Science lies with the line organization of Amsterdam UMC, the AGEM institute and its researchers try to contribute in whatever ways they can. Acknowledging the importance of protecting the privacy of patients and study participants, AGEM researchers have found ways to share research data in a sensitive and transparent manner. This is mainly done by making data available upon request (for instance by publishing core outcome data sets). Further, datasets of clinical trials are often combined with those of certain other European or international research groups[40]. Some research data is also uploaded anonymously into online repositories, such as data produced by the group of dr. Van Limbergen, where they can be accessed by the public. The Dutch Institute of Clinical Auditing facilitates data sharing by anonymizing research data.

In addition to Open Science, the AGEM institute also places great importance on transparency of its policies and stakeholder involvement. One prominent example is the involvement of AGEM researchers in the evaluation and reformulation of the institute's strategy and future plans. The institute conducted an internal mid-term evaluation in 2019, during which several key researchers from the institute were invited to think along about the direction the institute was heading in. Again, in 2022, strong emphasis was placed on stakeholder contribution to the external evaluation of the institute's strategy: all AGEM's Principal Investigators were invited for interviews and/or working sessions, aiming at a joined effort to evaluate the last six years of the institute and to redefine its strategy and strategic aims for the next six years. Young AGEM was also actively involved in the evaluation process, thereby ensuring participation of the younger generation of researchers as well. Additionally, the institute evaluates each activity or initiative that it implements, by asking participants to fill out evaluation forms. All in all, the institute's efforts to actively involve its researchers in the preparation and execution of its aims and strategy was very well appreciated, as was mentioned frequently when interviewing the Principal Investigators.

Appendix 4 - Strategy

4.1 Research topics within the endocrinology research program

The endocrine system regulates and integrates a wide range of body functions. Endocrine dysfunction therefore can contribute to a broad range of diseases affecting virtually every organ system of the body. Endocrinology research within AGEM spans a large spectrum of translational research from basic science, including technical innovations, to experimental medicine and from clinical studies of new treatments to population-related research. Together these studies aim to enhance our understanding of the physiology, pathophysiology, diagnosis, and treatment of endocrine disorders. Research topics within this program include:

- Neuroendocrinology, in which pituitary tumors are central as well as metabolic and behavioral effects of classic (thyroid hormone, insulin) and novel (leptin, GLP-1) hormones on the hypothalamus, thereby modulating circadian organization, eating behavior and metabolism.
- Hypothalamic-pituitary-thyroid axis/thyroid. Thyroid research is focused on a) central hypothyroidism and b) thyroid hormone metabolism and action during illness and also includes research on methodology. Novel genetic causes and their mechanistic role in central hypothyroidism and sensorineural hearing loss have been discovered in this theme.
- Bone. In addition to its mechanical properties, bone is also a source of growth factors and hormones, which interact with phosphate homeostasis and energy metabolism. Focus is on neural and endocrine regulation of bone metabolism; Interaction between bone and energy metabolism; Vitamin D and osteoporosis / Vitamin D-FGF23-klotho axis; Rare genetic metabolic bone disorders (osteogenesis imperfecta, fibrodysplasia ossificans progressive).
- Gonadal endocrinology. Part of this research focusses on the (side) effect of the hormonal treatment (long- and short-term effects of cross sex hormonal treatment). Another part of the research focusses on the effects of sex hormones an sich. This is done in international collaboration (European Network for the Investigation of Gender Incongruence cohort). Also preanalytical, analytical and postanalytical regarding androgen and estrogen methods are performed within this theme.
- Obesity and type 2 diabetes. Within this theme, lifestyle and dietetary impact on development of these endocrine disorders are studied. An additional layer strongly embedded herein is the role of the gut microbiome, which converts dietary components into metabolically active, hormone-like metabolites which act on human metabolism and the endocrine system.

4.2 Research program: inborn errors of metabolism (IEM)

This research area, within the research program Metabolism, focusses on inherited metabolic disorders manifesting from (pre)neonatal period into adulthood. The IEM area currently includes 7 clinical PIs, including 4 full professors and 7 pre-clinical PIs, including 3 full professors. Currently there are >40 PhD candidates in this combined program and in the past 5 years, >35 PhD candidates completed a doctoral thesis in these departments.

Major aims are improving (early) diagnosis, unraveling the genetic, biochemical and clinical causes and consequences of the metabolic derangements in patients, and developing and improving treatment for

patients. The program encompasses clinical, pre-clinical and translational research and houses state-of-the-art diagnostic facilities for metabolic disorders (metabolite, enzyme and DNA) and the central core facility for metabolomics and lipidomics. Since 2022, both the clinical and preclinical research groups of the VUmc and AMC location have merged at location AMC. Within the program there is close collaboration with other departments, including human genetics, oncology, immunology , endocrinology and others. In 2021, the joined departments of this research program have been recognized by the Nederlandse Federatie van Universitair Medische Centra (NFU) as national center of expertise for Metabolic Diseases, including diseases of creatine metabolism, familiar hypercholesterolemia, galactosemia, gyrate atrophy, lysosomal storage diseases, peroxisomal diseases, phenylketonuria, riboflavin transporter deficiency, fatty acid oxidation disorders.

In 2019, the platform Medicines for Society (“Medicijn voor de Maatschappij”) was launched by AGEM PI prof. Hollak that aims to improve access to orphan drugs, including essential medicines for metabolic diseases, through “academia-driven pharma”. The platform, in collaboration with regulators, has recently launched the pilot program “Orphan Drug Access Protocol” financially supported by insurance companies. In addition, focus is on development of novel public private partnerships on socially responsible terms. Pilot projects are running, that should translate cases to systems solution, by scientific research (current output is 18 peer reviewed publications and several media presentations and Hollak was awarded the Academy Medal for her scientific achievements in 2023).

Also in 2019, AGEM PIs prof. Waterham and prof. Van Karnebeek co-founded and co-direct the aforementioned UMD consortium. UMD unites clinicians, laboratory specialists and researchers from the six Netherlands Academic Metabolic Centers and the patient organization VKS with the aim to improve diagnostics, treatment, care and research of and increase awareness on inherited metabolic diseases.