CELEBRATING 40 YEARS OF MEDICAL GENETICS AT VUB

HISTORY AND DEVELOPMENT OF THE CMG VUB- UZ-BRUSSELS

Inge Liebaers and many others

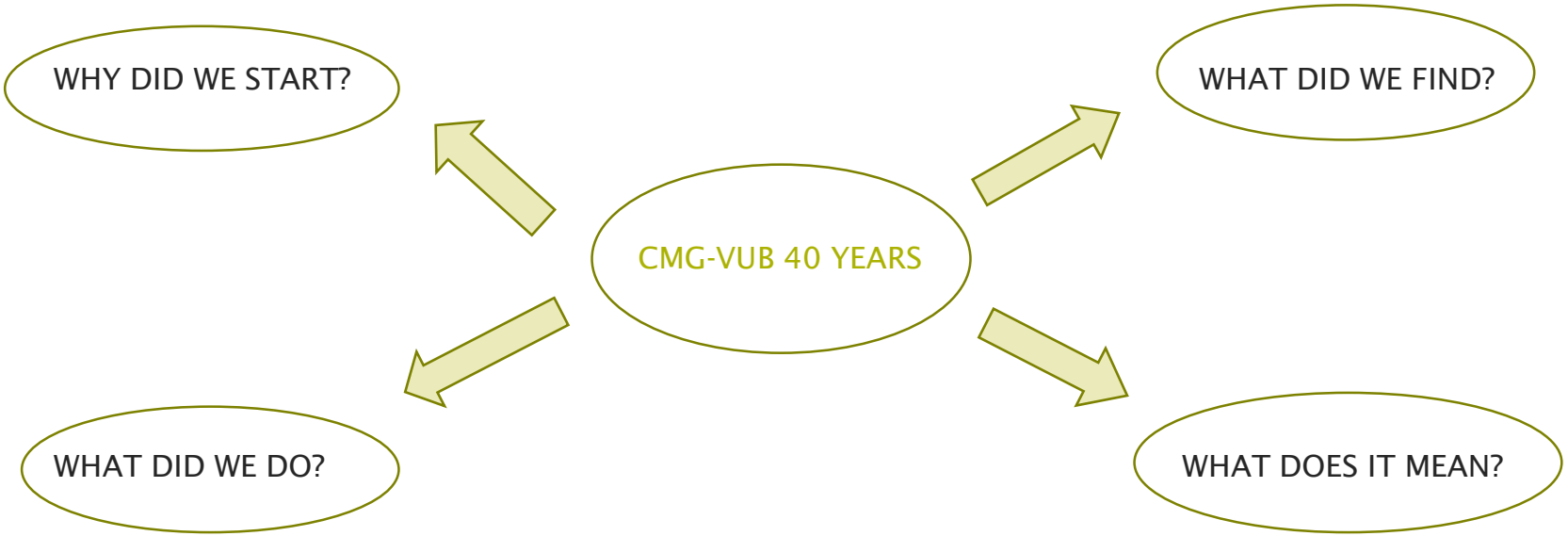
INGE LIEBAERS
1982 - 2010

MARYSE BONDUELLE
2010 - 2018

FREDERIK HES
2019 -

Bozar,Brussels,October 1, 2022

LAYOUT OF PRESENTATION



From the Tim Albert training

WHY DID WE START ?

Before 1982, the VUB had no Center for Medical Genetics

In 1978 Prof Charles Suzanne proposed to create a CMG

The aim was to be complementary to the existing centers by offering a more liberal approach to prenatal diagnosis and … reproductive options in general….

This was followed up in collaboration with the CRM by offering IVF, including insemination with donor sperm, PGD…. and much more

WHAT DID WE DO ?

IN BRIEF

A Center for Medical Genetics (CMG) was created at the VUB

in 1982

To provide a genetic service to the public, education in medical genetics to students, colleagues and the public, and develop research activities.

A clinic and necessary technology was developed

A course in medical genetics was scheduled

Research projects were written

Funding was obtained from the University and UZ Brussel, the government, the RIZIV, the FWO and other funding agencies

WHAT DID WE DO

THE BELGIAN TEXT

In 1966 the first 'Center for Medical Genetics' was created by Professor Herman Vandenberghe at the KUL and soon thereafter some 'genetic activity' followed by the establishment of CMG's occurred at the other universities in the seventies.

In 1973 the HIGH COUNCIL FOR ANTROPOGENETICS (HRA) – later the COLLEGE (2014) was founded

In 1979 (Circular Letter) and in 1987 (Royal Decree) the criteria to obtain recognition as a CMG were published and in 1988 (Royal Decree) the 8 current CMG's were recognized

In 1989 art 33 concerning the reimbursement of genetic tests by the RIZIV was published (Royal Decree)

In 1995 A Decree of the Flemish Government regulated the recognition, the financing and the activity reporting by the 4 Flemish CMG's

WHAT DID WE DO

THE BELGIAN CONTEXT

2000: reactivation of the Belgian Society of Human Genetics

2007: KCE report (Federaal Kenniscentrum/Centre Fédéral d'Expertise)

2011: start accreditation (ISO-15189) of the laboratories

2012: Royal Decree: art 33 revisited + art 33 bis

2013: Agreement RIZIV and CMG reimbursement for the genetic counselling activity

- standard: 2 contacts with physician + 1psycho/social contact + adm (250 euro)
- complex: 3 contacts with physician + 2 psycho/social contacts + adm (650 euro)

2017: Medical Genetics recognized as a specialty

- 2 years of medical specialty
- 4 years in CMG(2y clinic, 1y lab, 1 year free to choose)

2017: General NIPT – reimbursement

2022: Nomenclature for accredited Medical Geneticists: 27 euro

WHAT DID WE DO ?

AT THE VUB

In 1978 Prof C Suzanne suggested to create a Center for Medical Genetics at VUB

After many meetings and discussions, the Faculty was convinced that Inge Liebaers (IL) returning from the NIH/USA was going to be the right person to do the job

In 1978, IL appointed in the research unit 'health care' of the VUB, started with consultations in the department of pediatrics (Prof. Loeb) and gynecology/obstetrics (Prof. Amy and Foulon) in the AZ-VUB (now UZ-Brussels)

At that time IL was also appointed as pediatrician in training in the St Pieters Hospital in Brussels and performed lysosomal enzym tests in the clinical laboratory of the same hospital (Prof Franckson). Karyotypes were performed in close collaboration with the ULB (E Vamos, N Van Regemorter and F Hayez)

WHAT DID WE DO ?

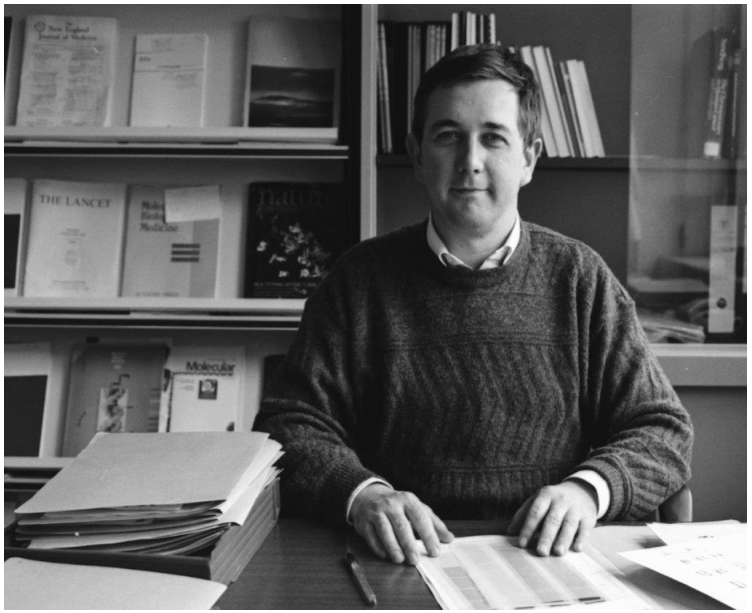
AT THE VUB

In 1980 IL became a member of the High Council of Anthropogenetics (HRA)

In 1981 the genetic activity at the VUB expanded in the research unit KGEN

Willy Lissens, enzymology

Luc Hens, cytogenetics



+ part time technician and administrative person

WHAT DID WE DO ?

AT THE VUB

In 1982 IL had a FT position at VUB and was a part-time consultant in the AZ-VUB

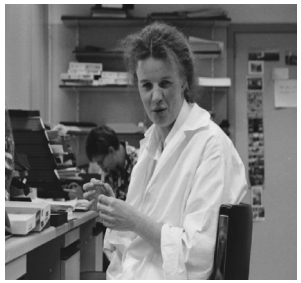
In 1983-1984

- Willy Lissens, PhD became a FT collaborator in the biochemistry laboratory and his first technician was Mia Vercammen
- Luc Hens, PhD became FT in the cytogenetics lab and was joined by A.M. Maes, E. Van Assche, both scientists and soon Linda Nolmans, technician joined
- Maryse Bonduelle - pediatrician and Karen Sermon – physician interested in research joined the team
- Jo Heulaerts started as secretary

WHAT DID WE DO ?

AT THE VUB

MORE PEOPLE JOINED THE CMG

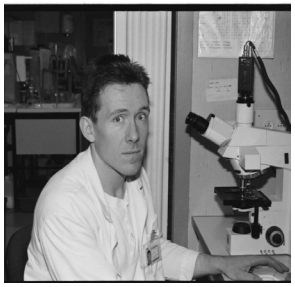


A.M. Maes 1983

E. Van Assche 1983

L. Nolmans 1984

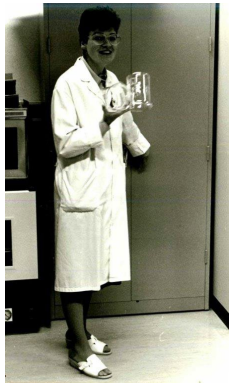
E. Van Emelen 1983?



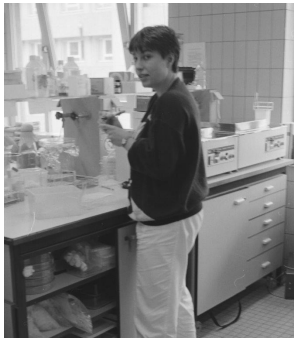
D. De Smedt 1986

K. Sermon 1984

J. Heulaerts 1983



M. Vercammen 1984



G. De Dobbelaere 1987

S. Seneca 1991

WHAT DID WE DO ?

AT THE VUB

In 1985 we were a ‘complete’ but still small CMG with

from left to right
Willy, Elvire, Jo, Mireille, Linda
Mia, Eric, Inge, Anne-Mia, Luc

A clinical service unit offering genetic counselling - based on clinical and laboratory diagnostics: karyotyping, enzymology, DNA-testing

Education activities including a course in clinical genetics for the medical and bio-medical students, seminars for colleagues, talks to the public….. to patient-associations

Research activities ongoing and increasing

WHAT DID WE DO ?

AT THE VUB

WE DID GROW AND EXPANDED

We needed space and moved several times

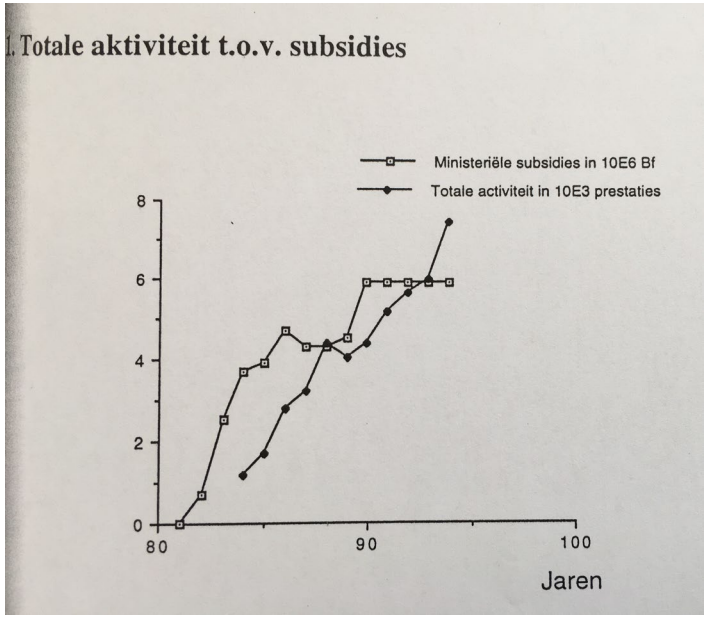
< 1982 till 1989 faculty building E/R2

- 1990 to KRO building / today still outpatient clinic
- 2005 laboratories to main hospital building
- 2020 offices to Thielemans building

We needed funding

Ministry of Health subsidies became available

- in 1982: 700,000 BEF on a total of 45.000.000 BEF, thanks to the generosity of other the centers
- later: see graph



RIZIV money as soon as we were an official center

-1983: 3.200.000 BEF (1983)

- 1985: 7.600.000 BEF (1985)

leading to difficult discussions with the hospital management; this improved with time

Research projects were funded by the VUB, the FWO, EU and several other agencies

WHAT DID WE DO ?

AT THE VUB

FURTHER DEVELOPMENTS

1992: Celebration 10 years of CMG

2002: Celebration 20 years of CMG with a symposium & start WEBSITE

2013: Accreditation of most (80%) genetic tests; is ongoing

2015: Bright Core Facility: high throughput NGS platform (VUB/ULB)
miSeq-HiSeq-NovaSeq acquired

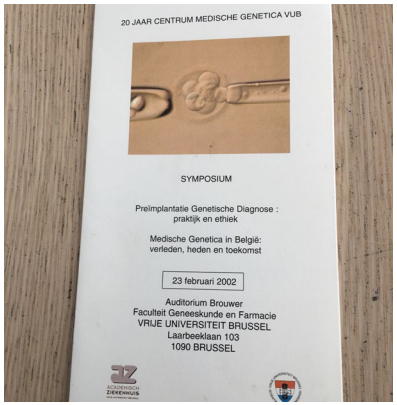
IB2 informatics platform (VUB/ULB)

2017: IGencare project/Innoviris
increase in NIPTs
AMPLiUZ next to the CMG

WHAT DID WE DO ?

AT THE VUB

CELEBRATING 20 YEARS OF MEDICAL GENETICS


20 JAAR CENTRUM MEDISCHE GENETICA VUB

SYMPOSIUM

Preïmplantatie Genetische Diagnose : praktijk en ethiek

Medische Genetica in België: verleden, heden en toekomst

23 februari 2002

Auditorium Brouwer
Faculteit Geneeskunde en Farmacie
VRIJE UNIVERSITEIT BRUSSEL
Laarbeeklaan 103
1090 BRUSSEL


Pre-implantatie genetische diagnose, voorkomt genetische afwijkingen

Zoal hoger vermeld werd tien jaar geleden, onder de leiding van Prof. Liebaers, aan het Centrum voor Reproductieve Geneeskunde van de VUB voor de eerste maal een pre-implantatie genetische diagnose verricht. Ouders die omwille van een bepaalde genetische belasting niet aandurfden een kind te hebben, kregen zo via IVF/ICSI en PGD toch de mogelijkheid aan hun kinderwens te voldoen.

Prof. Liebaers lichtte de PGD-techniek toe, die wordt uitgevoerd op een in vitro embryo, vooraleer het teruggeplaatst wordt in de baarmoeder, tussen dag drie en vijf na de bevruchting. Men haalt één of twee cellen uit het embryo en analyseert ze terwijl het embryo zelf verder ontwikkelt. De chromosomen kunnen onderzocht worden met fluorescente merkers en met aangepaste moleculaire technieken kan men de aan- of afwezigheid van specifieke DNA-sequenties bepalen (**zie foto**).

Met PGD kan men tegemoetkomen aan de vraag van ouders met een gekend herhalingsrisico, bijvoorbeeld voor de X-gebonden spierziekte van Duchenne. Vroeger had men enkel de genetische counseling, waarbij uitgelegd werd dat de kans bij een gekende draagster één op vier was om de ziekte over te dragen en dat prenatale diagnose en abortus de enige alternatieven waren om nog een ziek kind te vermijden. Preventieve diagnose, voor de inplanting in de baarmoeder kan nu door onderzoek van een embryobiopsie in het achtcellige stadium.

Vijftig ziekten

Na het begin met Duchenne en mucoviscidose in 1993, is het nu mogelijk om meer dan 50 monogene ziekten op te sporen, naast bijna elke denkbare chromosomale translocatie. De conditio sine qua non voor de ouders met een hoog herhalingsrisico voor een ernstige genetische ziekte is uiteraard het doorlopen van een volledige IVF-procedure.

Het probleem is nog wel de slaagkans. Onder de beste omstandigheden en bij terugplaatsing van één tot twee embryo's ligt de slaagkans per gestarte cyclus rond de 20%. Door de kosten van de vrij ingewikkelde procedure zal de klassiek prenatale diagnose zeker niet vervangen worden. PGD blijft een optie, hoewel de vraag de afgelopen 10 jaar sterk toegenomen is.

PGD kan vandaag ook aangeboden worden aan families met een ziek kind dat om te kunnen genzen een trans-

▲ Biopsie van een embryo.

▲ Chromosomen ge


…braak in Wapenbank te Luik

…bekenden zijn vrijdagnacht ingebroken in de Luikse Wa…enbank. Uit een lokaal zijn tientallen vuurwapens gestolen, …oofdzakelijk revolvers van het merk Smith and Wesson.

Gazet van Antwerpen

Zaterdag 23 en zondag 24 februari 2002

"Onderzoeken van jonge embryo vermijdt abortus"

BRUSSEL - "Ik voel me gelukkig dat ik 120 koppels, bij wie de erfelijke kaarten zeer ongunstig lagen, aan een gezonde baby heb kunnen helpen." Dat zegt professor Inge Liebaers, 20 jaar geleden één van de oprichters van het *Centrum Medische Genetica* van de VUB, wereldleider inzake *Preïmplantatie Genetische Diagnose*. Daarbij worden embryo's op erfelijke afwijkingen getest in het allervroegste stadium: in de 'proefbuis'.

Centrum Medische Genetica VUB bestaat 20 jaar

Jos Vranckx

"Twintig jaar geleden had ik me onmogelijk kunnen voorstellen dat ik een genetisch defect in één enkel cel zou kunnen opsporen. Want dat moet je kunnen om een 'ziek' van een 'gezond' embryo te kunnen onderscheiden", aldus Inge Liebaers uit België. Het Brusselse centrum is immers het enige ter wereld dat zo'n groot aantal genetische afwijkingen kan opsporen. "Het gaat om ziekten die niet zo vaak voorkomen maar voor de betrokkene wel zware gevolgen hebben, zoals mucoviscidose, de ziekte van Huntington. Te paarde…

kunnen nemen. We dringen nooit een bepaalde keuze op." Medische erfelijkheid is een dure onderneming. "Eén behandeling kost 1.500 euro (60.000 frank) waarvan 495 euro (20.000 frank) vergoed. Maar de eigenlijke kostprijs ligt nog veel hoger. Embryo's ma…


Génétique

Choisir l'enfant sain

Le diagnostic préimplantatoire permet de sélectionner l'embryon en fonction de ses gènes

A la VUB, on pratique couramment le diagnostic préimplantatoire. Malgré ses difficultés techniques et les questions éthiques que ce type d'acte médical peut soulever.

CATHERINE PAGAN

L'utilisation d'une technique médicale, qui permet de sélectionner l'enfant à naître en fonction de ses gènes, soulève de lourdes questions éthiques aux Etats-Unis. En cause, le cas d'une Américaine de 30 ans, porteuse d'une mutation génétique qui lui donne un très fort risque de développer une forme familiale précoce de la maladie d'Alzheimer, même si elle a aussi d'infimes chances d'y échapper (1). Porteuse de la même mutation, sa sœur aînée avait été atteinte du mal à 38 ans et s'était vite vue dans l'incapacité de s'occuper de ses deux jeunes enfants. A l'âge de 30 ans, la jeune femme, toujours en bonne santé, choisit d'avoir recours à la sélection génétique d'embryon et donne naissance à un enfant exempt de la mutation. Pari sur la vie ou désir égoïste d'enfant ? Qui pourra juger ?

En Belgique, si cette technique, appelée diagnostic préimplantatoire, est encore relativement marginale, elle se dévelop-

Des bébés exempts de l'une ou l'autre mutation génétique présente chez leurs parents, tel est le but du diagnostic préimplantatoire.
Photo Thienpont

Universitair Ziekenhuis Brussel

VUB

WHAT DID WE DO ?

AT THE VUB

OTHER ACTIVITIES

European dysmorphology meetings in Strasbourg (1990)

Belgian National Committee on Bioethics (1993): research on embryos

Ad-hoc ethical committee Brussels IVF and CMG

BRUMA (1996) to BRUMASTRA (2006): meetings concerning PGD/PGT

PGD consortium of ESHRE (1997): founding members and still active

Retirement of Inge Liebaers in 2010 and in 2015 and …

BeSHG meeting in 2013

PND/PGD meeting 2017 in BOZAR (VUB/ULB)

Retirement of Maryse Bonduelle in 2018

Appointment of Frederik Hes in 2019

WHAT DID WE DO ?

AT HET VUB

ESHRE PGD CONSORTIUM

1997

From L to R: Catherine Staessen; Joep Geraedts; Karen Sermon; Joyce Harper; Stéphane Viville; Inge Liebaers; Alan Handyside

2022

Martine De Rycke (CMG VUB) and Veerle Goossens (ESHRE office) et al.

WHAT DID WE FIND ?

AT THE VUB

IN THE CLINIC

The clinical activities

did grow and evolved from communication with and to patients and their families to communication with computers and administration

The lab- technologies

went from simple to complex investigations of chromosomes and DNA by scientists and analysts and more recently by bioinformaticians to help coming to a diagnosis

WHAT DID WE FIND ?

AT THE VUB

CONCERNING TEACHING

The course in medical genetics had to be updated more and more frequently

Master and PhD theses were defended

Seminars were given to different specialties

Presentations were given to the public

Communication with patient associations increased gradually

WHAT DID WE FIND ?

AT THE VUB

PUBLICATIONS

Metabolic diseases

Follow-Up of children born after ART

Preimplantation Genetic Diagnosis (PGD), now PGTesting

Infertility

Brain malformations

Mitochondrial diseases

Cardiogenetics

Oncogenetics

Stem cell-research and embryo-research

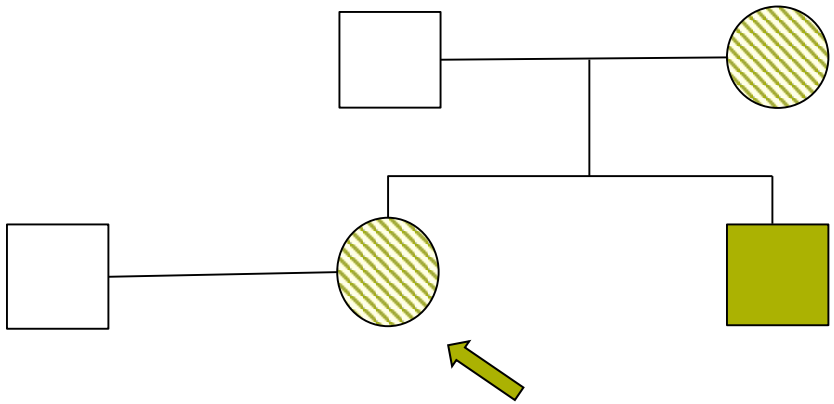
WHAT DID WE FIND?

AT THE VUB

PGD now PGT: first request in 1990

DMD affected

DMD carrier



- The lady was a proven DMD deletion carrier (C Van Broeckhoven, UA)
- She would rather take the risk than do a PND+TOP
- Sexing by PCR and detection of the deletion by PCR, to be developed, were discussed

WHAT DID WE FIND ?

AT THE VUB

PGD now PGT: cycles and outcome

C-nb	date	method	COC	2PN	D Es	unaff	aff	car	cryo	ET	preg	child
1	1993	Sex PCR	28	12	4	1	3	_	(3)	1	_	_
2	1994	Del PCR	23	11	6	4	2	_	_	3	+	02/10/1994
3	1997	Del PCR	31	23	22	14	4	_	9	2	_	OHSS
4	1998	FRET								3	_	_
5	2001	Del + Mark	12	10	5	2	1	_	_	1	_	_
6	2002	Del + Mark	37	25	15	8	4	3	9	_	_	OHSS
7	2002	FRET								3	+	13/03/2003
8	2006	FRET								2	_	STOP

WHAT DID WE FIND ?

PGD now PGT: children follow up

Baby 1, oldest daughter, came to see me with her mother in 2014, at the age of 20y for counselling

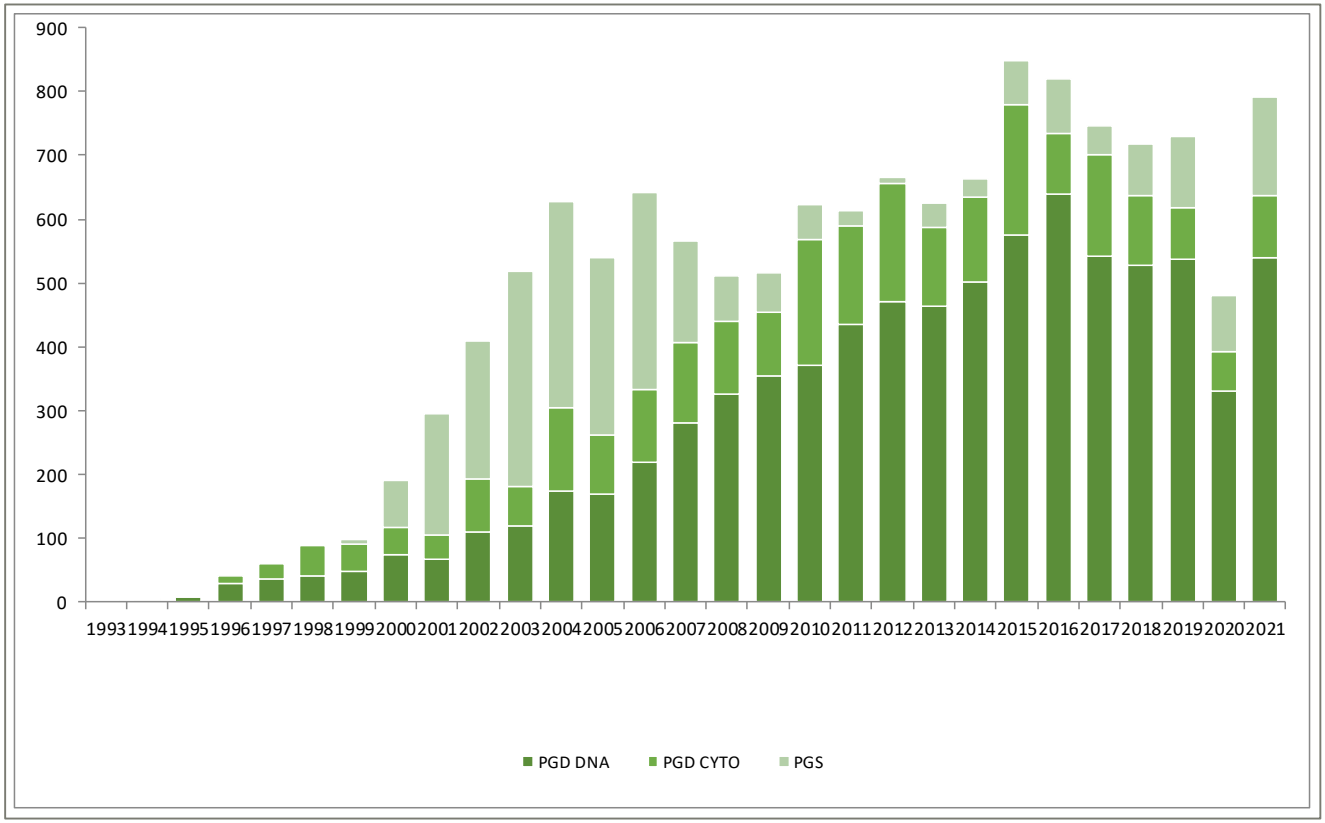
We confirmed that she was not a carrier of DMD

Baby 2, younger sister, 14y at the moment, was healthy but did not request counselling so far

WHAT DID WE DO

AT THE VUB

PGT 1993 TO 2021



Dip in 2021 was COVID-19 related

WHAT DID WE FIND

AT HET VUB

STEM CELLS …… LEFT THE CMG

Derivation, culture, and characterization of VUB hESC lines.
Mateizel I, **Spits C**, De Rycke M, Liebaers I, **Sermon K .**
In Vitro Cell Dev Biol Anim. 2010 Apr;46(3-4):300-8

Research more directed to early embryo development is ongoing on this campus in Reproductive Genetics (REGE) by K Sermon, C Spits and H Van de Velde with a third Methusalem project

WHAT DID WE FIND ?

AT THE VUB

ONGOING RESEARCH TODAY

- Sophie Uyttebroeck: Unraveling the molecular etiology of Pompe's disease
- Randy Osei: A multi-omics approach to improve the diagnosis of genetic disorders
- Ellen Rijckmans: Combining exome and transcriptome data to unravel the genetic base of lissencephalies
- Saartje Van Pottelberghe: IGenCare Integrated Personalised Medical Genomics Care Solution for Patients with Rare Genetic Diseases: Psycho-Social Care in Cardiogenetics
- Doan Vo Ngoc: Unraveling the molecular etiology of lysosomal storage diseases: Pompe disease
- Annelore Van Der Kelen: Unraveling the genetic etiology of female infertility
- Ileen Slegers: Reproductive decision-making in times of whole genome sequencing
- Kim Van Berkel: on mosaic embryos

WHAT DOES IT MEAN ?

The CMG-VUB has been able to earn its place on the market

WHAT DOES IT MEAN ?

IN A NUTSHELL

To be able to offer quality counseling, up to date education, and peer-accepted research, close collaboration within a multidisciplinary team is mandatory and this is what happened during the past 40 years in our center.

THANKS TO ALL PAST AND PRESENT CMG MEMBERS, AND ALL THE BEST,

INGE LIEBAERS