Fondation 101 Génomes

Genomics for Rare Diseases

The 101 Genome Marfan project: Where are we now?

MEN - Paris

September 16th 2022

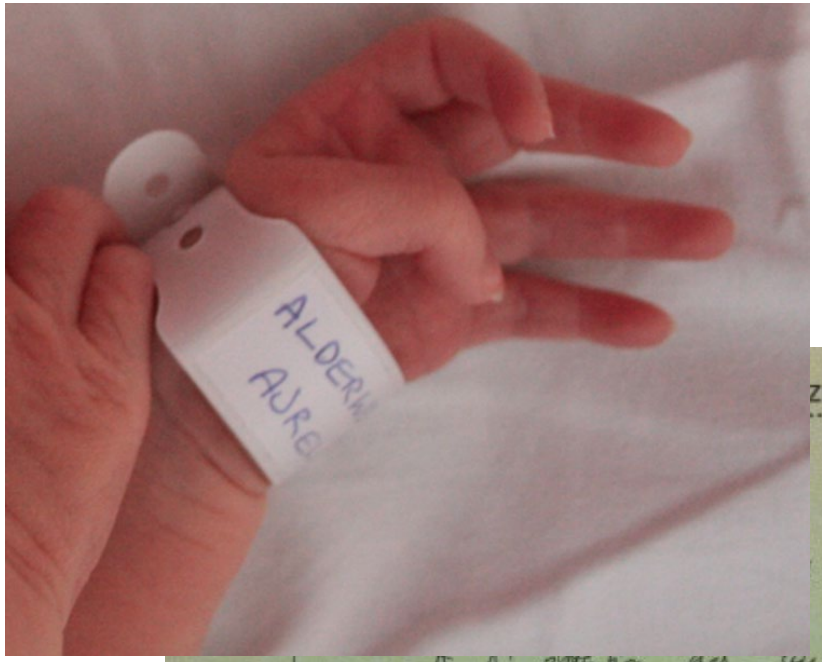
Reminder

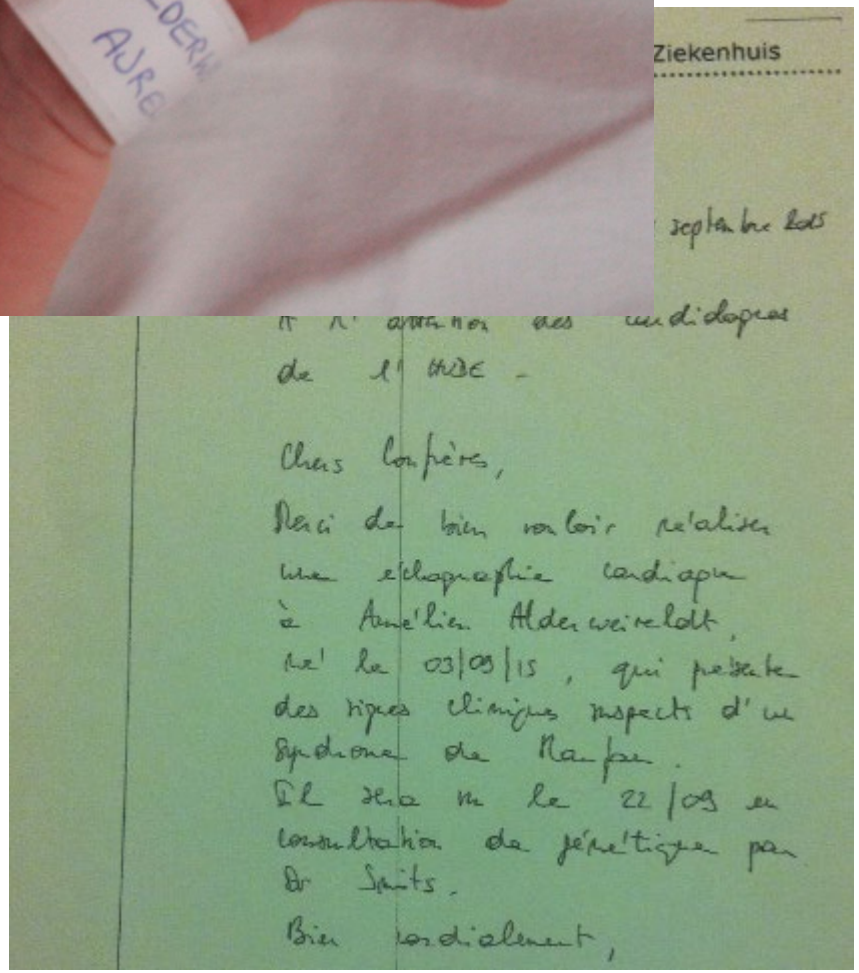
Diagnostic Odyssey

Diagnostic Odyssey (1/2)

September 2015

- Aurélien was born on **September 3rd 2015**.
- Eight days after his birth, on September 11th , the pediatrician who examined him at birth tells us that she suspects a **connective tissue anomaly**.
- She talks about connective tissue abnormalities and **Marfan syndrome** is "evoked" for the first time
- Despite a request from the Brussels geneticist who examined Aurélien, the reference center for Belgium that he contacted refused to carry out a genetic analysis
- A far too long diagnostic odyssey then began



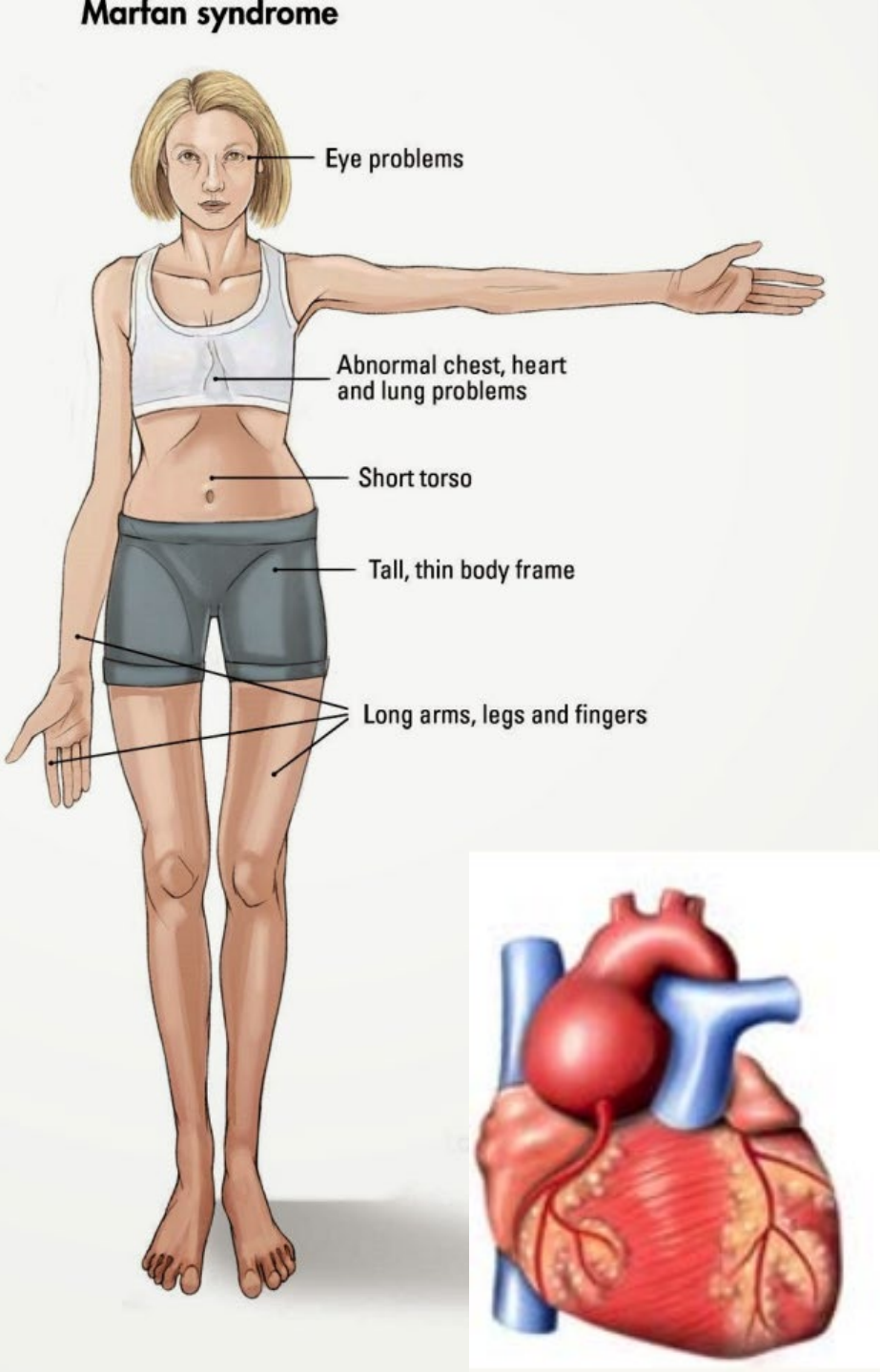


Diagnostic Odyssey (2/2)

August 2016

- **The diagnostic odyssey** ended 11 months later with the discovery of a ***de novo*** **mutation on exon 26 of our child's FBN1 gene**.
- This discovery confirmed that, as a result of a **spontaneous mutation**, Aurélien is suffering from a **rare disease called Marfan Syndrome**.
- Aurélien was diagnosed during his first year of life, and it is explained to us that he falls into the category of people with a "neonatal" or " early onset" form of Marfan syndrome.

Marfan syndrome (MFS)
& neonatal Marfan Syndrome (nMFS)



Marfan syndrome (1/4)

FBN1 & fibrilline

- Marfan syndrome results from an **anomaly in the connective tissues** that hold the cells that make up the human body together.
- This abnormality is caused by a **defect in the fibrillin protein** encoded by the **FBN1 gene** following a pathogenic mutation.
- **The disease is multisystemic** and affects, among other things, the **musculoskeletal, pulmonary, ocular and cardiovascular systems**.
- The main danger for patients with the syndrome is that of **aortic dissection**, the consequences of which are generally fatal.

Marfan syndrome (2/4)

The intensity of the afflictions is very variable (even within families)

Javier Botet

- Some people affected by the syndrome have few disorders.
- While others are severely affected, sometimes severely handicapped and their life expectancy can be quite reduced.
- Between these two extremities, we find the majority of Marfan patients who are sometimes severely handicapped by the disease and who must regularly control the dilation of their aorta.

In the current state of scientific knowledge, the cause of this great variability in the extent and intensity of the damage is not yet well understood.

Neonatal Marfan Syndrome (3/4)

Statistical life expectancy

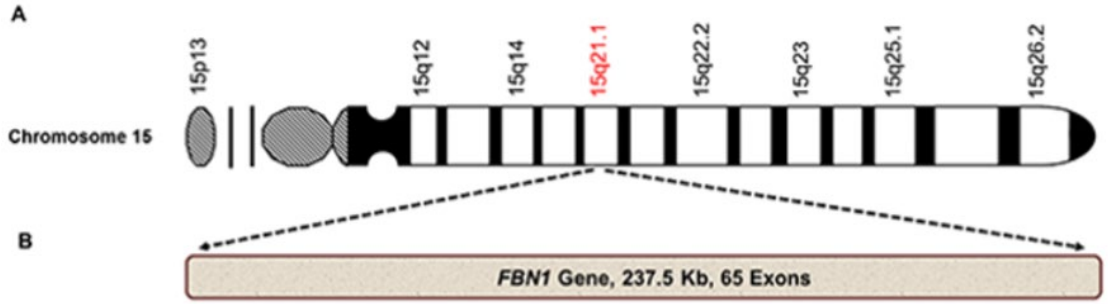
- Some authors report that the **statistical life expectancy** for this particular form is as low as **16.3 months:**

  « *Marfan syndrome (MFS) (OMIM 154700) is an autosomal dominant disorder of fibrous connective tissue involving the ocular, skeletal, and cardiovascular systems. MFS patients present with clinical variability, in which the rare neonatal Marfan syndrome (nMFS) has the most severe presentation in early childhood. The prognosis of nMFS is very poor,* ***with a mean survival age of only 16.3 months****. Valvular insufficiencies and diaphragmatic hernias have been associated with shorter survival in patients diagnosed before the age of 1 year. […] The term neonatal Marfan syndrome was first used in 1991 to describe the most severe phenotype of MFS similar to cases previously known as infantile Marfan syndrome, congenital Marfan syndrome, and severe perinatal Marfan syndrome. Recently, it has been suggested that the term neonatal MFS should be replaced by early onset and rapidly progressive MFS to represent the most severe features of MFS in early childhood* »

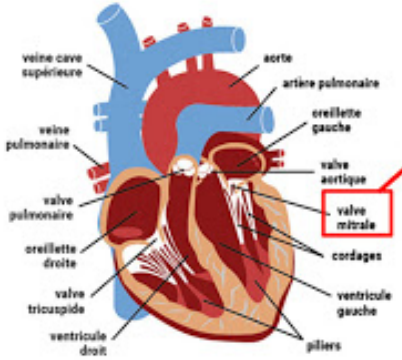
  PENG Q. et al., « *A novel fibrillin-1 gene missense mutation associated with neonatal Marfan syndrome : a case report and review of the mutation spectrum* », BMC Pediatrics, 30 avril 2016, 16:60, DOI 10.1186/s12887-016-0598-6

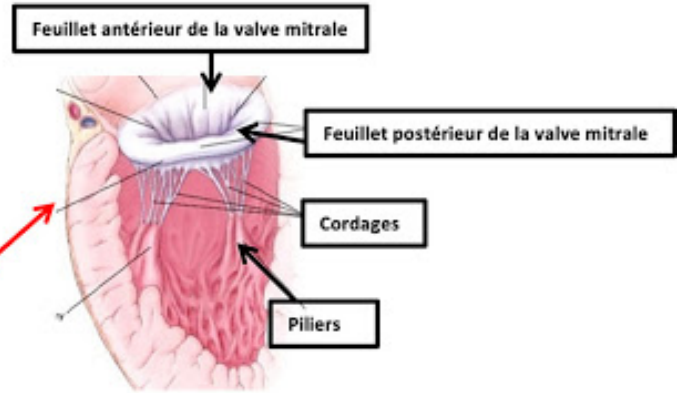
Neonatal Marfan Syndrome (4/4)

Exons 24-32 et mitral valve



- These are almost always spontaneous cases: **de novo**
- Genetic analysis reports that these cases are usually (but not always) found when a pathogenic mutation occurs in the core of the FBN1 gene on **the interval of exons 24 to 32**
- A signature of this form is the rapid affection of the **mitral valve**





Genomics

Genomics (1/4)

Prof. Guillaume Smits (IB)² | HUDERF – ERASME

- After the shock of the diagnosis, **we returned to the geneticist** who follows Aurélien since his second week of life: Prof Guillaume Smits.
- He **patiently answered** our **very many** questions.
- With his explanations, **we progressively understood** that we could, perhaps, **try to help our son and other children living with rare diseases**.

Genomics (2/4)

Sequencing

Today the emergence of new generation sequencers has paved the way to three different approaches to the study of genes:

1. The **"traditional" sequencing** of **individual genes (or by panels of a few genes);**
2. New generation sequencing (NGS) of the whole exome called **Whole Exome Sequencing (WES)** **3% of the genome** and;
3. New Generation Sequencing (NGS) of **the entire genome** called **Whole Genome Sequencing (WGS)**.

With the new sequencers, scientists have gradually entered the era of genomics

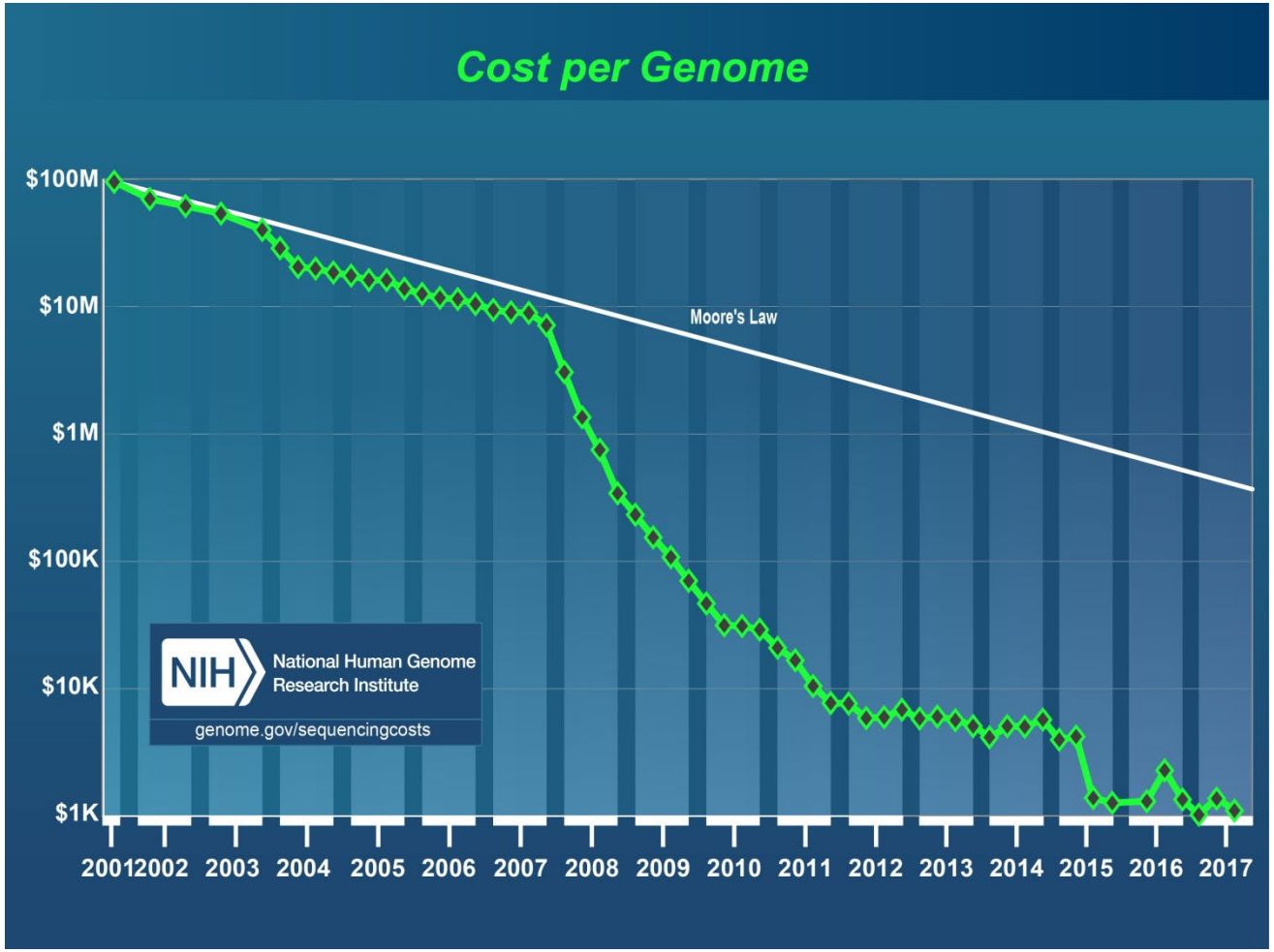
Genomics	vs	Genetics
• The study of an organism's complete set of genetic information. • 'Genome'- the complete genetic information of an organism. • The genome includes both genes and non-coding DNA.		• The study of heredity • The study of the function and composition of single genes. • 'Gene'- specific sequence of DNA which codes for a functional molecule.

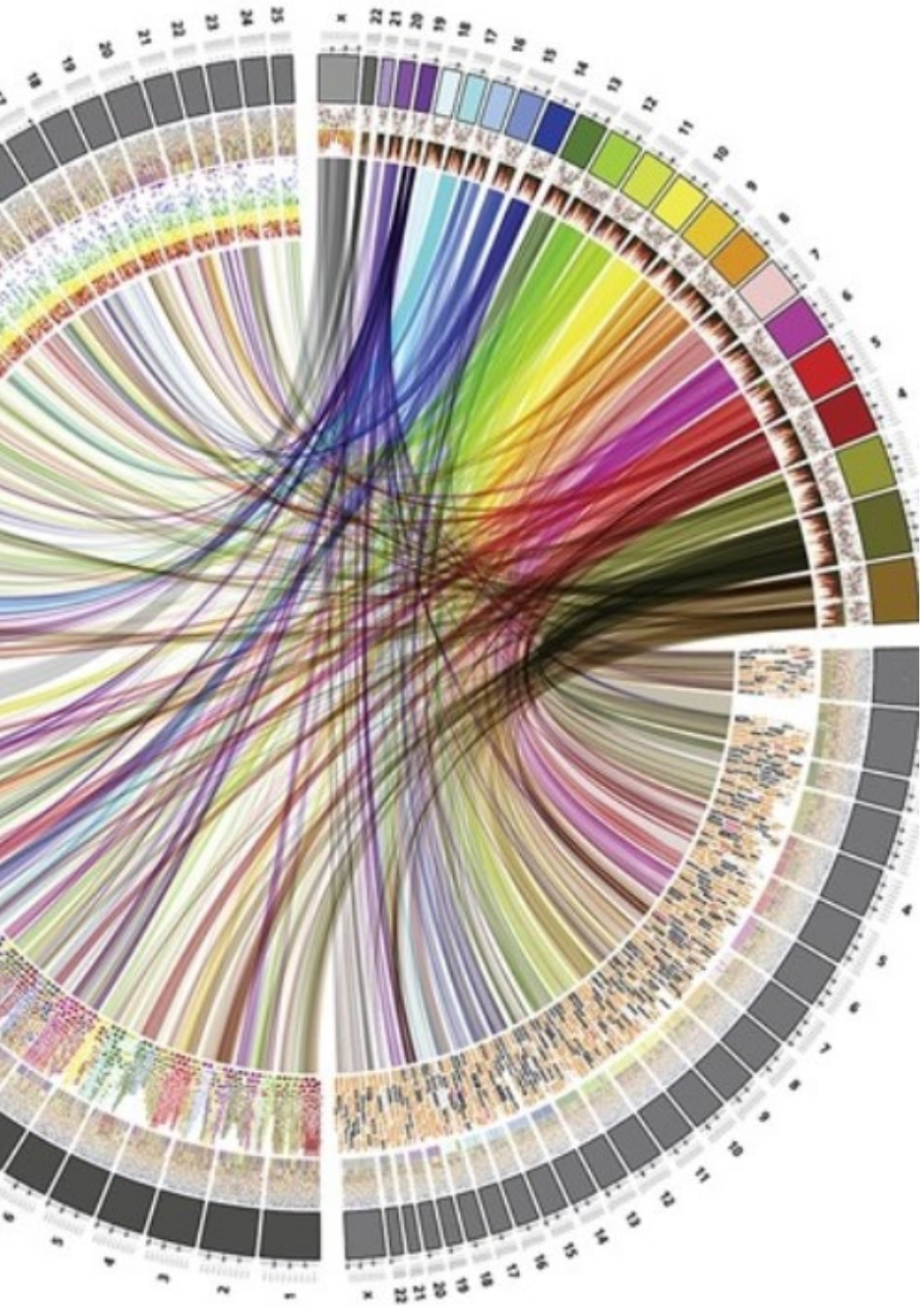
Genomics (3/4)

$1000 for a Whole Genome Sequencing

And the progressive reduction of sequencing costs facilitates this transition:

- The cost of sequencing has thus decreased from **$100,000,000** per genome in **2001** to
- **$1000** per genome since **2017**!





Genomics (4/4)

Genome mapping

- The addition of each new sequenced genome progressively **improves** the understanding of the **“human genome”**.
- Each new sequenced genome - shared and coupled with phenotypic data - contributes to “**mapping the genome”** and to **understanding the interactions between different genes.**
- Genome knowledge opens the way to **personalized medicine**.

Protective Genes

Protective Genes (1/3)

The Resilience Project

nature biotechnology

ARTICLES

Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases

Rong Chen[1,2,12], Lisong Shi[1,2,12], Jörg Hakenberg[1,2], Brian Naughton[3,11], Pamela Sklar[1,2,4], Jianguo Zhang[5], Hanlin Zhou[5], Lifeng Tian[6], Om Prakash[7], Mathieu Lemire[8], Patrick Sleiman[6], Wei-yi Cheng[1,2], Wanting Chen[5], Hardik Shah[1,2], Yulan Shen[5], Menachem Fromer[1,2,4], Larsson Omberg[9], Matthew A Deardorff[6], Elaine Zackai[6], Jason R Bobe[1,2], Elissa Levin[1,2], Thomas J Hudson[8], Leif Groop[7], Jun Wang[10], Hakon Hakonarson[6], Anne Wojcicki[3], George A Diaz[1,2], Lisa Edelmann[1,2], Eric E Schadt[1,2] & Stephen H Friend[1,2,9]

CHEN R. et al., « *Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases* », Nature Biotechnology, 34, 531–538 (2016) doi:10.1038/nbt.3514, Received 29 July 2015 Accepted 12 February 2016 Published online 11 April 2016. Disponible à l'adresse: https://www.nature.com/nbt/journal/v34/n5/pdf/nbt.3514.pdf

- In this project, **589,306 "genomes"** (actually a combination of WES and WGS) collected **at random** in other contexts **have been re-examined.**
- This study identified **13 apparently healthy adults** who carry pathogenic mutations that should have caused severe rare diseases in them that normally develop in childhood.

- The people discovered by the **Resilience Project should have been sick but are not**.
- These people may be protected by the **action of protective modifier genes**.

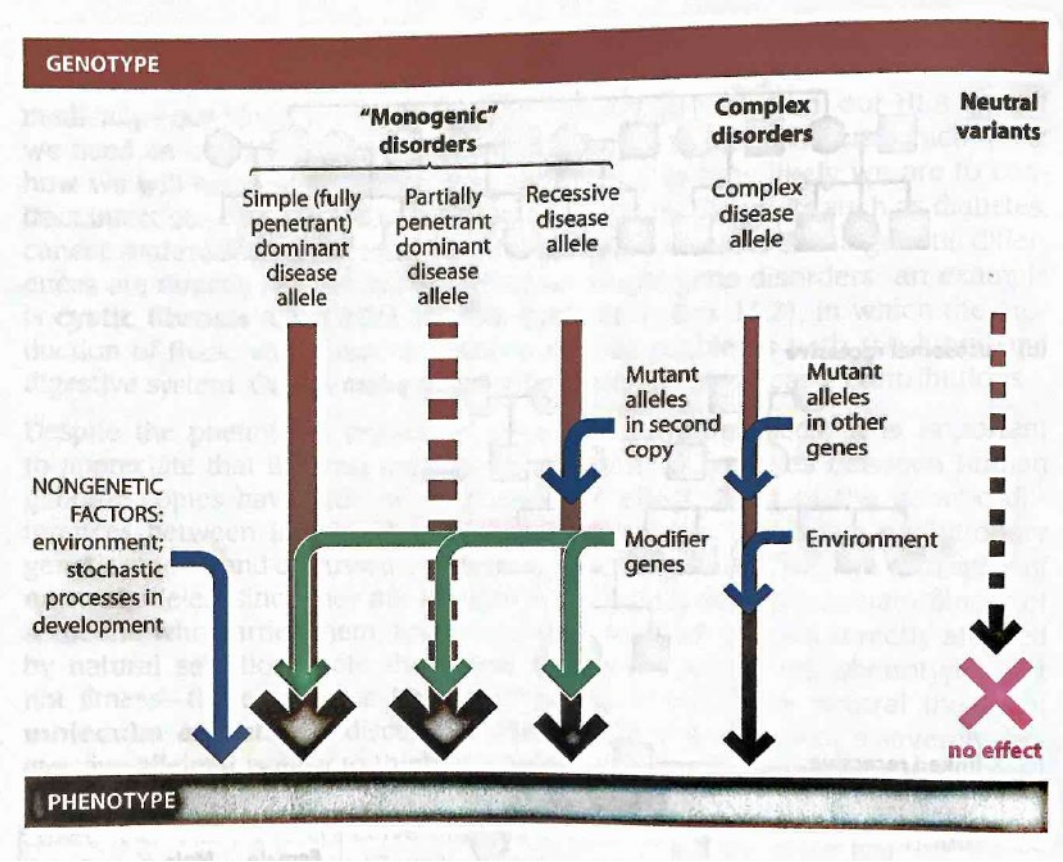
gnomAD

genome aggregation database

Protective Genes (2/3)

Modifier & protective gene

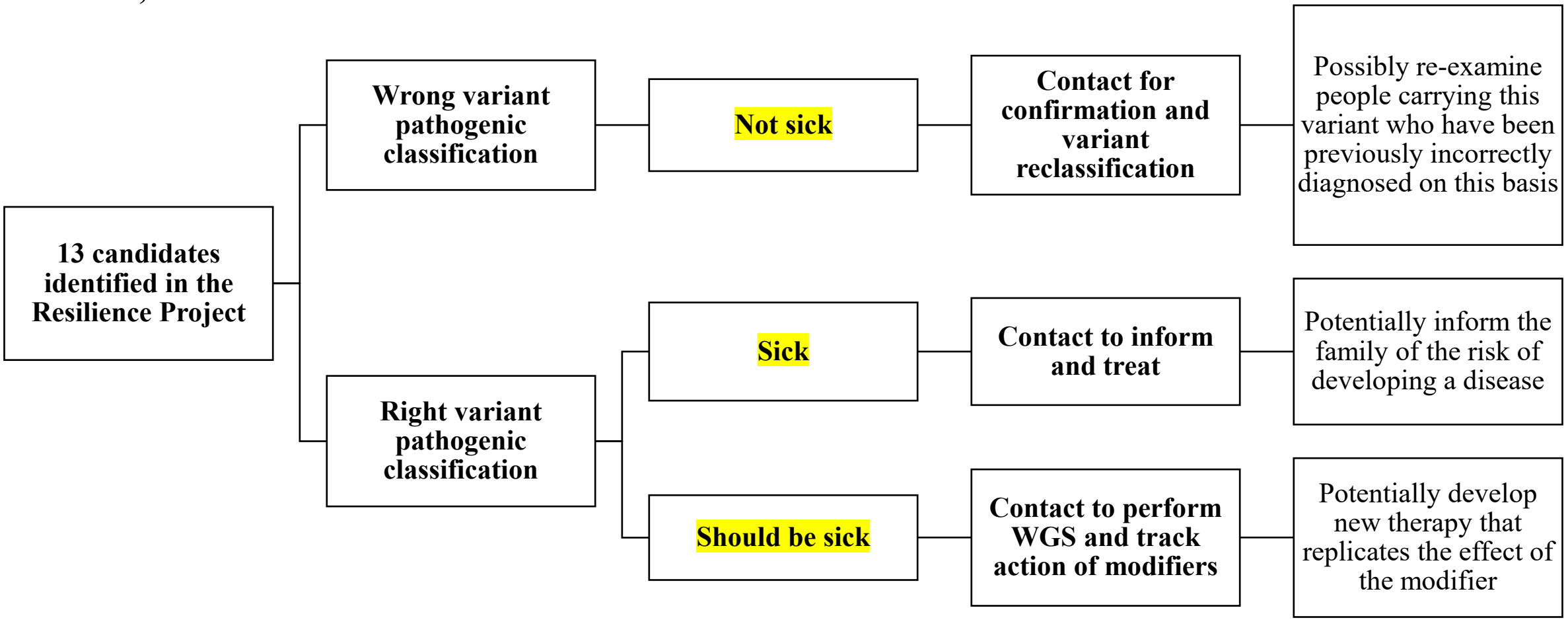
- A **modifier gene** is a gene that affects the expression of one or more genes (=**epistasis**).
- A **protective gene** is a modifier gene (= **epistatic gene**) whose action protects an individual from the harmful influence of a gene carrying a pathogenic mutation (= **hypostatic gene**).



TYLER-SMITH et al., Human evolutionary genetics (second edition), Garland Science, 2014, ISBN 978-0-8153-4148-2, page 46

Protective Genes (3/3)

Not sick, sick or should be sick

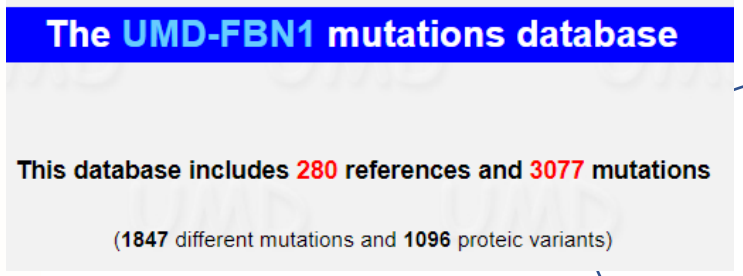


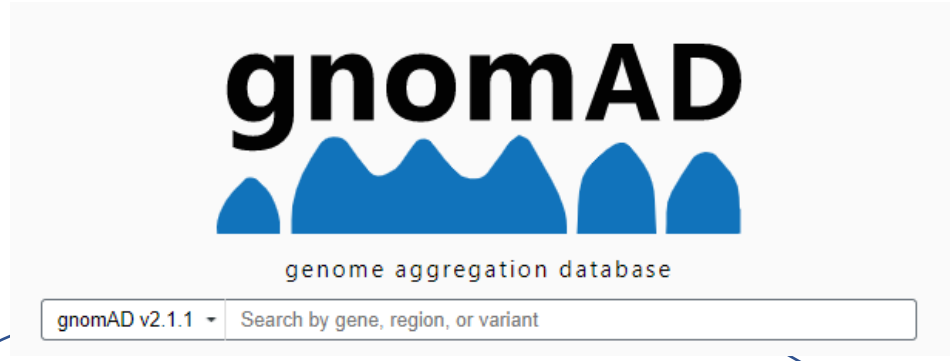
Recontact? No re-contact possible (68% of the total cohort come from …23andMe!)

What about FBN1?

What about FBN1? (1/3)

2016 | UMD-FBN1+HGMD+Franken vs gnomAD





Pathogenic variants
www.umd.be/FBN1/

Benign, non-pathogenic variants
https://gnomad.broadinstitute.org/

FBN1 Mutations				
GnomAD database (2017)	24-juin-17	0	http://gnomad.broadinstitute.org/	
HGMD (2017)	14-sept-17	1.311	http://www.hgmd.cf.ac.uk/	
UMD-FBN1 Mutations database (2014)	28-août-14	3.077	http://www.umd.be/FBN1/	
Francken (2017)	03-mai-17	314	Heart	
			Exomes	Genomes
Identical mutations in at least two databases		122	64	58
GnomAD / HGMD		*45*	*23*	*22*
GnomAD / UMD-FBN1		*75*	*40*	*35*
GnomAD / Franken		*2*	*1*	*1*
Identical mutations in three databases		66	*35*	*31*
Identical mutations in four databases		4	*2*	*2*

This observation was subsequently confirmed in the scientific literature in 2019. See BAUDHUIN L. ET AL., « *Variability in gene-based knowledge impacts variant classification: an analysis of FBN1 missense variants in ClinVar* », EJHG, 21 May 2019, https://doi.org/10.1038/s41431-019-0440-3.

Of the **122 individuals** whose data are in gnomAD, **24 individuals**, (12 exomes and 12 genomes) have a previously identified pathogenic mutation responsible for Marfan syndrome that is located in the risk zone of **exons 24 to 32 where nMFS is found**.

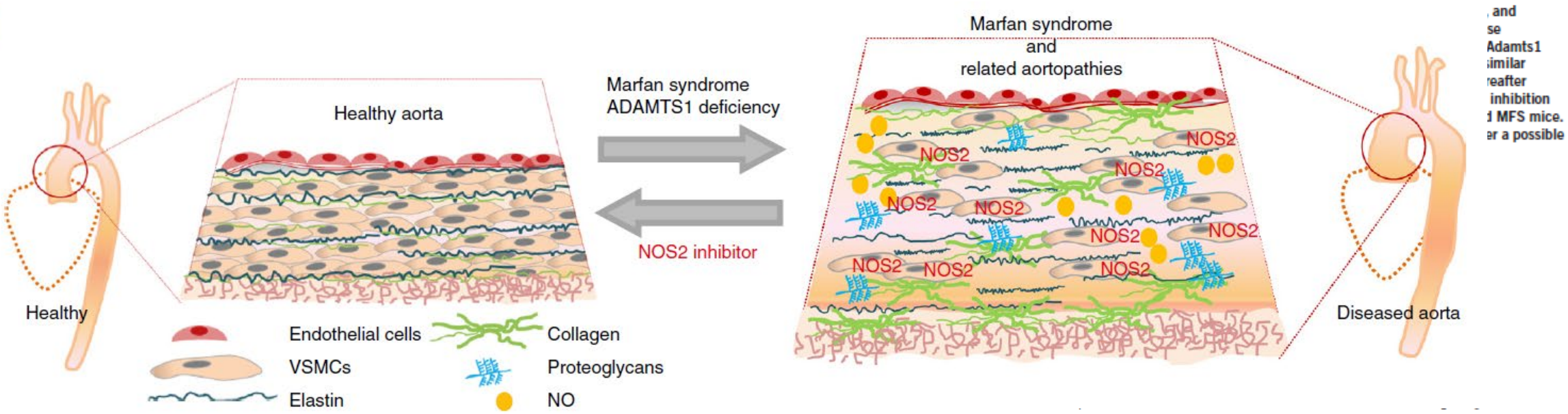
N°	EXON	Chrom	Source	Protein Consequence	Transcript Co
574	32	15	E	p.Gly1334Asp	c.4001G>A
577	31	15	E	p.Gly1313Ser	c.3937G>A
	30	15	E	p.Tyr1266Phe	c.3797A>T
	29	15	E	p.Pro1225Leu	c.3674C>T
	28	15	E G	p.Asp1191Asn	c.3571G>A
	28	15	E G	p.Val1172Met	c.3514G>A
	27	15	E G	p.Pro1148Ala	c.3442C>G
	25	15	E	p.Lys1043Arg	c.3128A>G
	24	15	E G	p.Val984Ile	c.2950G>A
	30	15	E	p.Asn1247Ile	c.3740A>T
	32	15	E	p.Gly1353Arg	c.4057G>A
	31	15	E	p.Asn1282Ser	c.3845A>G
	29	15	E	p.Ile1198Thr	c.3593T>C
	28	15	E G	p.Arg1170His	c.3509G>A
	28	15	E	p.Asn1168Ser	c.3503A>G
	27_29	15	G	p.Asp1155Asn	c.3463G>A
	27	15	E G	p.Ala1152Val	c.3455C>T
	27	15	E G	p.Pro1141Leu	c.3422C>T
	25	15	E	p.Leu1038Phe	c.3112C>T
	24	15	E G	p.Thr1020Ala	c.3058A>G
	24	15	E	p.Ala1015Thr	c.3043G>A
	24	15	G	p.Cys996Arg	c.2986T>C
	24	15	E G	p.Ala986Thr	c.2956G>A
	24	15	E G	p.Arg976His	c.2927G>A

What about FBN1? (2/3)

2017 | NOS2 ?

Nitric oxide mediates aortic disease in mice deficient in the metalloprotease Adamts1 and in a mouse model of Marfan syndrome

Jorge Oller[1,10], Nerea Méndez-Barbero[1,10], E Josue Ruiz[1], Silvia Villahoz[1], Marjolijn Renard[2], Lizet I Canelas[1], Ana M Briones[3], Rut Alberca[1], Noelia Lozano-Vidal[1], María A Hurlé[4], Dianna Milewicz[5], Arturo Evangelista[6], Mercedes Salaices[3], J Francisco Nistal[4], Luis Jesús Jiménez-Borreguero[7], Julie De Backer[3], Miguel R Campanero[8,11] & Juan Miguel Redondo[1,9,11]



OLLER, J. et a., « *Nitric oxide mediates aortic disease in mice deficient in the metalloprotease Adamts1 and in a mouse model of Marfan syndrome* », NATURE, published online 9 January 2017; doi:10.1038/nm.4266.

Considering that NOS2 inhibitors have been safely used in clinical trials for endotoxemia, rheumatoid arthritis and migraine (https://clinicaltrials.gov/ct2/home identifiers: NCT00184990, NCT00370435 and NCT00242866), our results point to NOS2-specific inhibitors as a promising alternative for the treatment of aortic disease that could be implemented with minimal delay.

What about FBN1? (3/3)

Fondation 101 Génomes

My wife and I then realized that:

- That there was **hope of discovering a modifier gene for FBN1** (NOS2 ?)
- **That the researchers did not have the necessary tools to conduct this research.**

We therefore decided to make the missing resources available to all scientists.

And to do so, we created the "*Fondation 101 Génomes*"

Fondation 101 Génomes

Genomics for Rare Diseases

Fondation 101 Génomes
&
101 Genomes Marfan Projet

101 Genomes (1/4)

Fondation 101 Génomes : creation & purpose

- The **101 Genomes Foundation (F101G)** aims **<u>to advance research</u>** by 10 years through the creation of **an innovative genomic databank** that will allow researchers to better understand and treat rare diseases.
- **The disruptive innovation** of the **genomics and bioinformatics revolution** makes this objective possible today.

Genomics in the Cloud

According to Professor Anne De Paepe, ProRector of Ghent University, this is "*a unique and unprecedented example of* ***patient participation in scientific research***".

101 Genomes (2/4)

101 Genomes Marfan Project

- **The 101 Genomes Marfan Project (P101GM) is the pilot project of the F101G**. This Project is dedicated to **Marfan syndrome.**
- It is built on an extensible starting cohort of **101 patients**.
- The creation of the **Genomic Cloud** is an integral part of this pilot project.
- When the **Genomic Cloud** is set-up it will be able to host **other projects dedicated to other rare diseases** that will benefit from the experience gained.






101 Genomes (3/4)

Scientific Committee

- **The P101GM Scientific Committee** is composed of **leading scientists in Marfan Syndrome and algorithmics**.
- Among the members of the committee are the professors **Julie De Backer, Bart Loeys, Guillaume Smits, Guillaume Jondeau, Catherine Boileau and Anne De Paepe.**
- The Committee is **co-chaired** by **Julie De Backer & Bart Loeys**

101 Genomes (4/4)

& European Associations

DECLARATION OF COOPERATION

TO THE 101 GENOMES PROJECT DEDICATED TO MARFAN SYNDROME

OF THE 101 GENOMES FOUNDATION

BETWEEN

The 101 Genomes Foundation (F101G) was founded in November 2017. Its objective is to advance
a bioinformatics database containing complete genomic (Whole
ypic cross data of patients with rare
community through a secure inter
e F101G pilot project is dedicated to
reinafter P101GM);

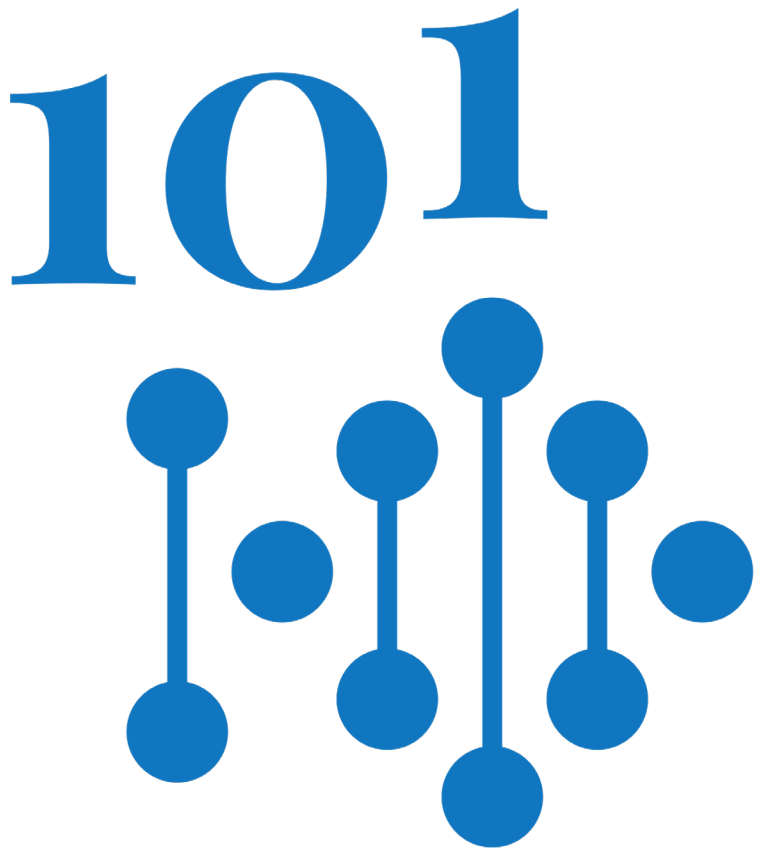
The P101GM is supported by **several European Marfan patient associations**:

- **Belgian Marfan Syndrome Association;**
- **French Marfan Syndrome Association;**
- **den-i (Luxembourg);**
- **…**

It received the **2018 Edelweiss Award** from the Belgian alliance for rare diseases: RaDiOrg

What is new since Drammen?

Dimensions



Phenotypic data

Data forms:

MAC
MONTALCINO AORTIC CONSORTIUM

Specific:
P101GM FBN1 common template VASCERN

"AORta Automatic Measurement"

AORAM cytomine

FARI AI FOR THE COMMON GOOD INSTITUTE BRUSSELS

Reference centres MFS

European Reference Network

VASCERN

Patients MFS

Fondation 101 Génomes
Genomics for Rare Diseases

Scientific Community

Genomic data

GEMS: "Genome-wide Epistasis for cardiovascular severity in Marfan Study"

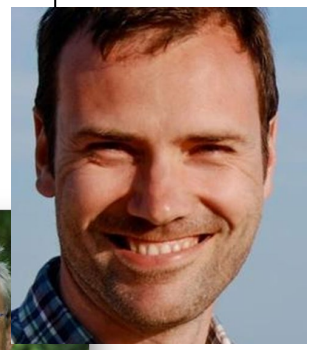
FBN1 mutation	A	B	C	D	E	F	G	H	I	J	K	L	M	Total
c.247+1G>A		1												33+1= 34
c.640G>A	1(2)		1	1										23+5= 28
c.2645C>T			1		0									77+1= 78
c.5788+5G>A		1(2)		3										60+6= 66
c.7039_7040del AT			1(2)											50+3= 53
c.7454A>T														1
c.7754T>C	1(1)	4(2)	1(1)	1	0									162+11 = 173

Sequencing WGS 30x + pipeline VCF:

illumina macrogen EUROPE

GEMVAP: Classification, ancrage & quête

B2 ULB Center of Human Genetics MLG MACHINE LEARNING GROUP



AORAM

Aorta Automatic Measurements

FARI AI FOR THE COMMON GOOD INSTITUTE BRUSSELS

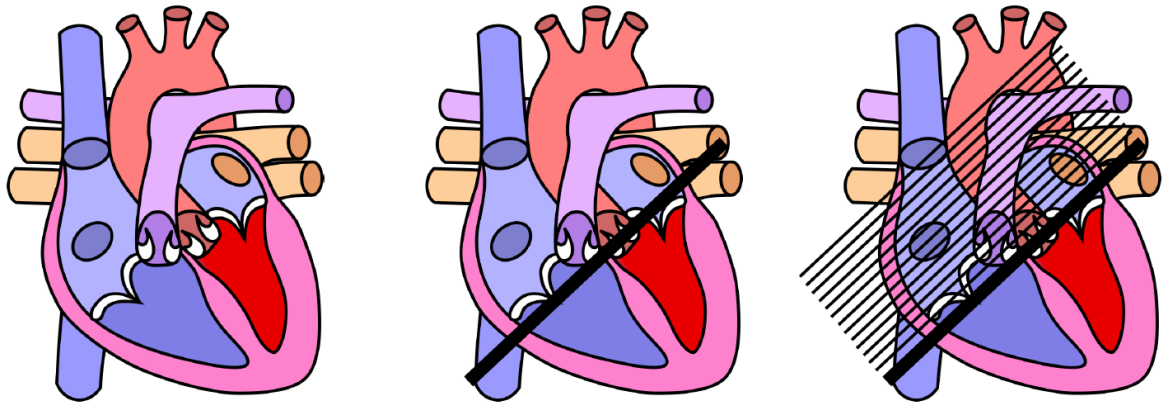
cytomine

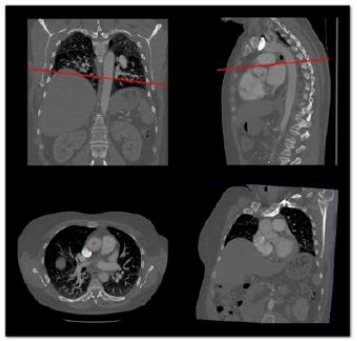
COLLABORATIVE BIOMEDICAL IMAGE ANALYSIS

- **Alpha 1** - manual tool to explore medical images, annotate them and train algorithms
- **Alpha 2** - expand Alpha 1 for automatic detection of the aortic valve reference plane
- **Alpha 3** - logical workflow managing Alpha 1 and Alpha 2

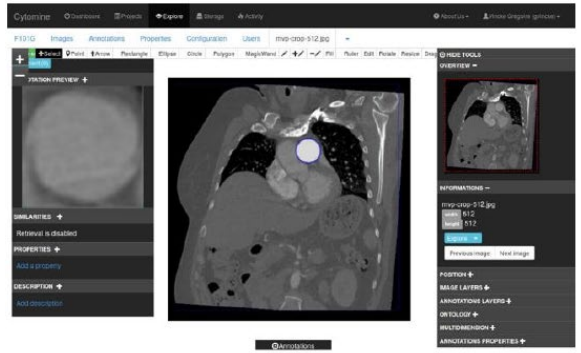
Challenge

Extraction of slices throughout the 10 first centimeters of the aorta and AI computation of metrics





Osimis : CT/MRI slicer

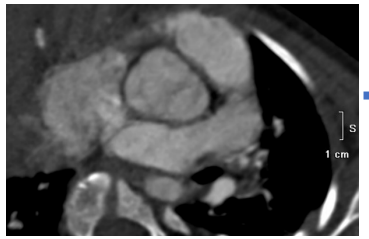


Cytomine : annotation and AI

Image capture
Prof. REGA UZ Leuven

CT-SCAN

Dicom files



Storage & Access
101 Genomes Foundation

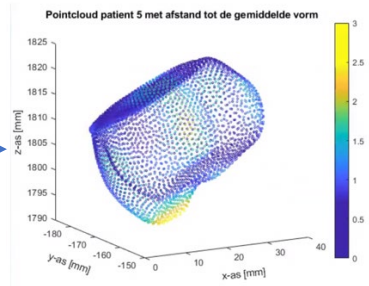
F101G Genomic Cloud

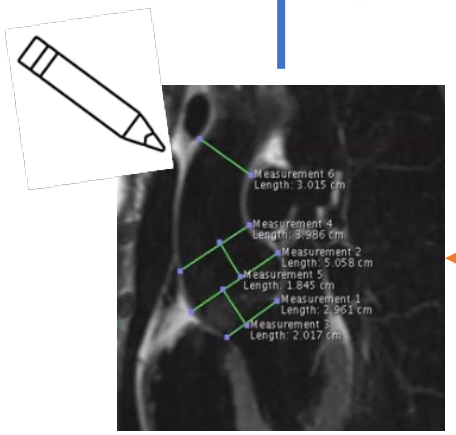
Interface visualization & Annotation

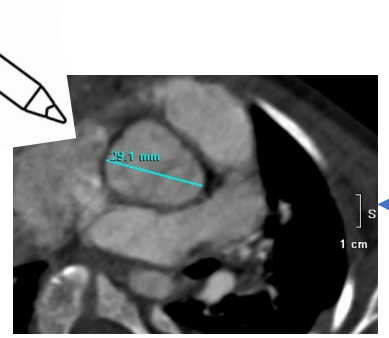
ORTHANC

OSIMIS
IMAGING · RE-WIRED

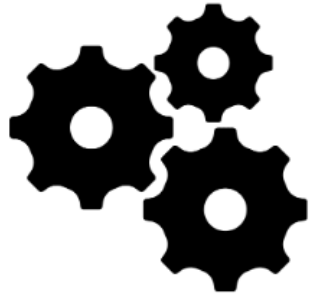
Collaborative human annotation
Prof. JONDEAU APHP

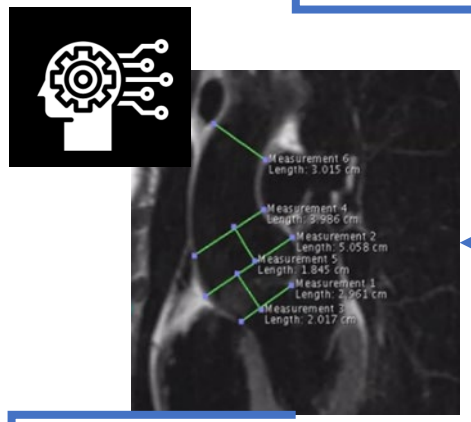


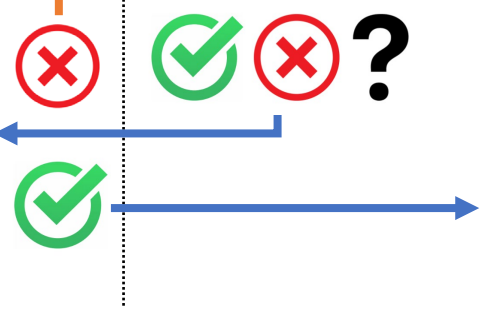




Human-Assisted Machine Learning
FARI: MLG, (ib)^2, ULB & VUB







GEMVAP+

Improve clinical diagnosis of rare genetic disorders with a GEne-specific Missense VAriant Predictor framework

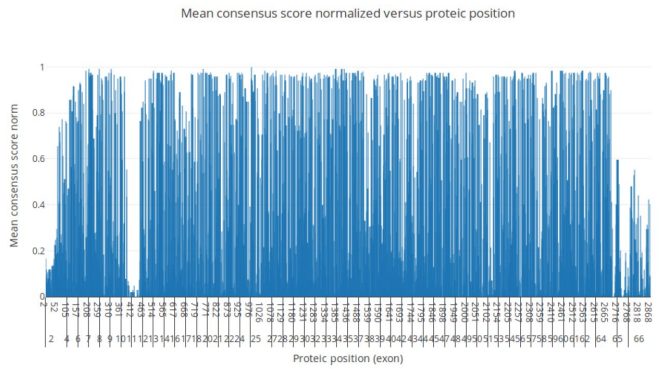
Missense variant interpretation is challenging

DNA HAS ALL YOU CAN ASK FOR .
DNA HAS ALL YOO CAN ASK FOR .

DNA HAS ALL YOU .
DNA HAS ALY OUC ANA SKF OR

DNA HAS ALL LOU CAN ASK FOR .

GEMVAP FBN1 top5 whole gene prediction



Interuniversity Institute of Bioinformatics in Brussels

ULB Center of Human Genetics

MLG MACHINE LEARNING GROUP

"Artificial Intelligence (AI) for the diagnosis of Marfan Syndrome" by Professor Guillaume Smits

ABSM 20 GALA, 2019

Professor Guillaume SMITS, Université Libre de Bruxelles, member of the Scientific Committee of the 101 Genomes Marfan Project, explains the "GEne specific Missense VAriant Predictor (GEMVAP)" tool developed thanks to F101G and the role of artificial intelligence in the diagnosis of Marfan syndrome at the Gala des 20 ans [...]

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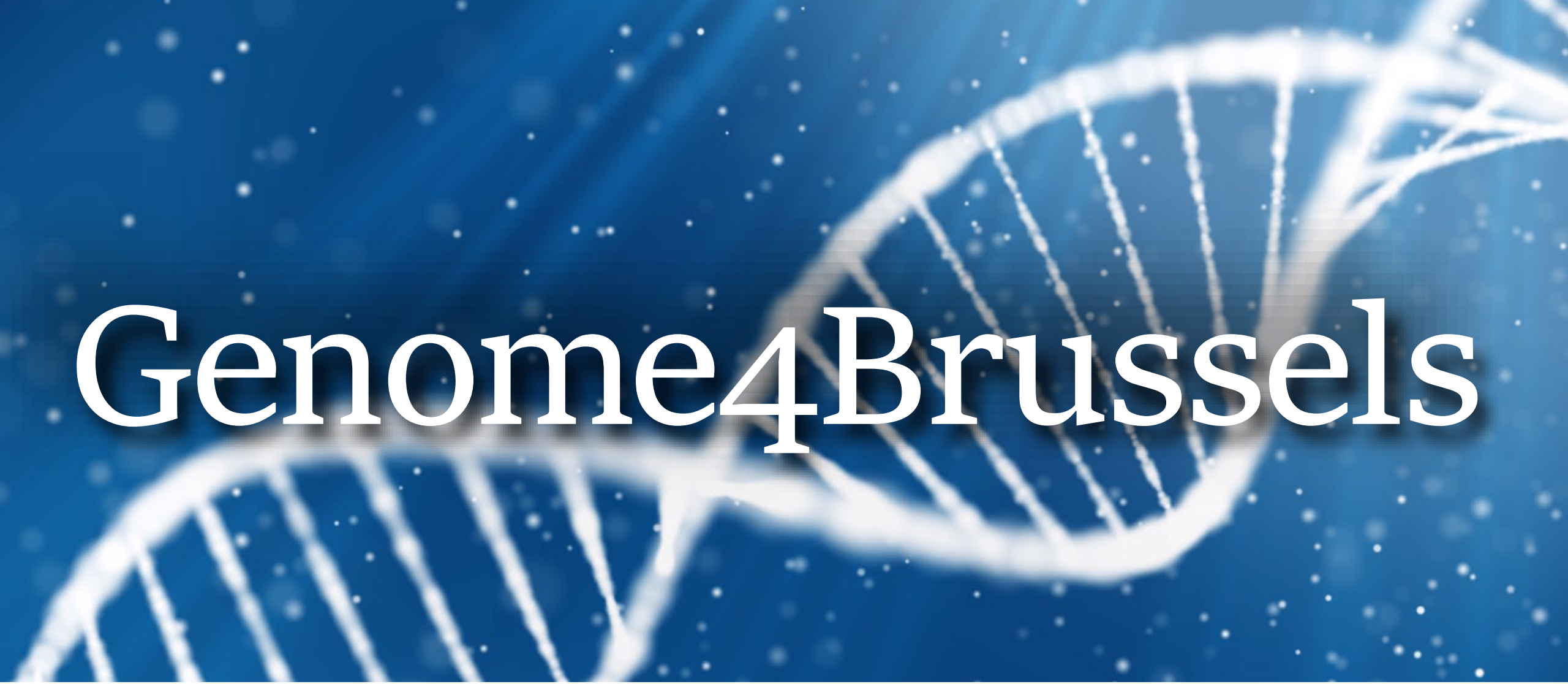

MLG
MACHINE LEARNING GROUP

B²
INTERUNIVERSITY INSTITUTE OF
BIOINFORMATICS IN BRUSSELS

Fondation 101 Génomes
Genomics
for Rare Diseases

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GEMS

Genome-wide Epistasis for cardiovascular severity in Marfan Study

Genomic data

GEMS: "Genome-wide Epistasis for cardiovascular severity in Marfan Study"

FBN1 mutation	A	B	C	D	E	F	G	H	I	J	K	L	M	Total
c.247+1G>A		1												33+1= 34
c.640G>A	1(2)		1	1										23+5= 28
c.2645C>T			1		0									77+1= 78
c.5788+5G>A		1(2)		3										60+6= 66
c.7039_7040delAT			1(2)											50+3= 53
c.7454A>T														1
c.7754T>C	1(1)	4(2)	1(1)	1	0									162+11 = 173

Sequencing WGS 30x + pipeline VCF:

Humanizing Genomics macrogen EUROPE

GEMS

'Our' GEMS

- GEMS is the **acronym** of ***Genome-wide Epistasis for cardiovascular severity in Marfan Study***
- The **objective** of GEMS is to identify protective modifier genes (= epistatic genes) within the whole human genome that can explain the variability of cardiovascular disease found in people with Marfan syndrome. Such a discovery would make it possible to contemplate new therapeutic approaches that would replicate the protective effects identified in order to prevent cardiovascular events
- **This research is at the heart of the Fondation 101 Génomes's action**. It is led by **Professor Bart Loeys** and the entire scientific committee of the Project 101 Genomes Marfan
- It is actively supported by the **VASCERN Network dedicated to vascular diseases** and by the main members of the HTAD group within it.

"An evocation of current research and future perspectives" by Professor Bart Loeys

ABSM 20 GALA, 2019

Professor Bart LOEYS, University of Antwerp & Co-Chair of the Scientific Committee of the 101 Genomes Marfan Project, presents the state of research initiated by the action of F101G: Genome-wide Epistasis for cardiovascular severity in Marfan Study (GEMS) and its vision for the future at the Gala des 20 ans de [...]

Share: Tweet Partager 28 Whatsapp SHARE E-mail Print More

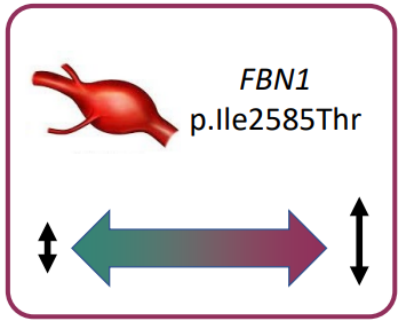
20191012

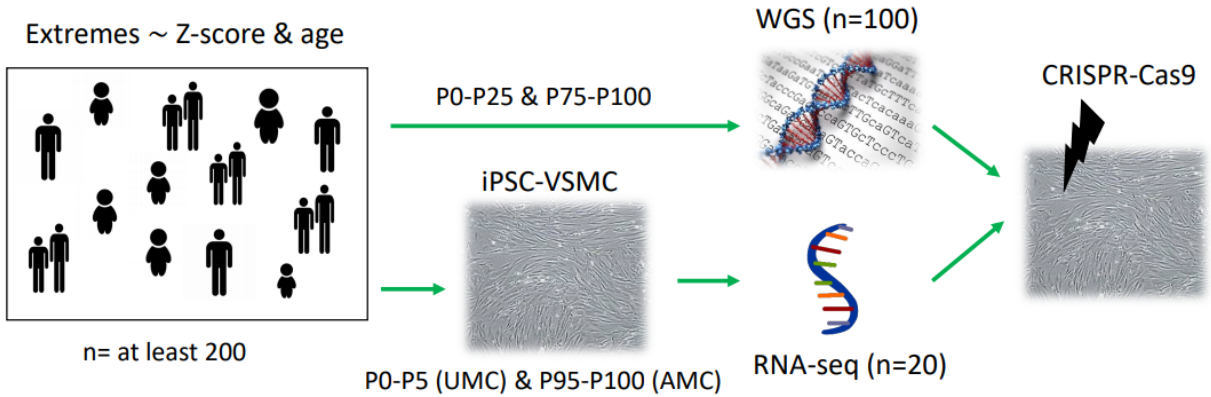
GEMS

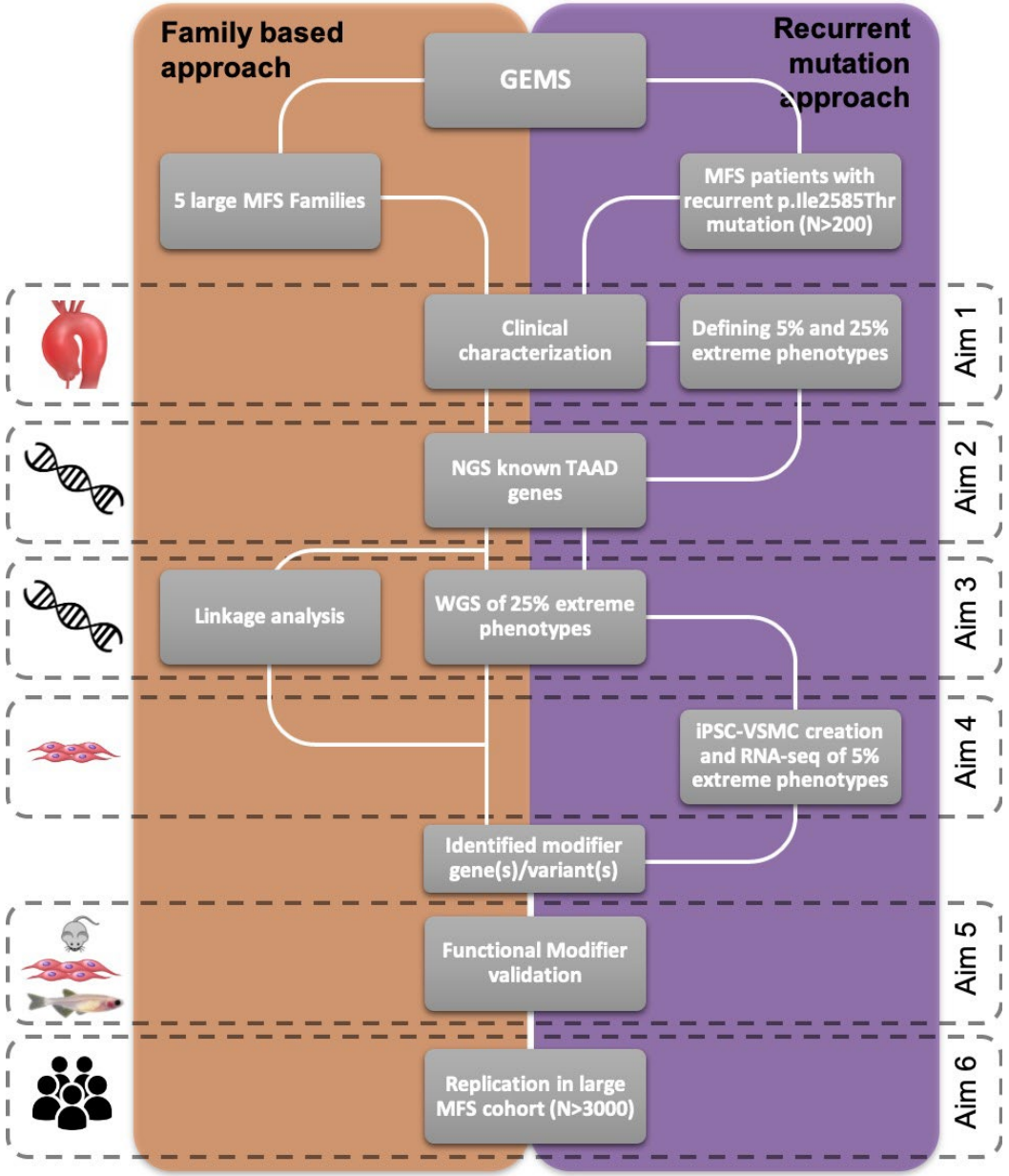
Methodology

3. Methodology: identification of modifier genes

Cohort of **more than 260 carriers** of the two selected mutations







GEMS

262 patients!

Antwerp, Ghent, Leiden, Nijmegen, Groningen, Amsterdam, Paris, London, Hamburg, Sheffield, Zurich, Milan, Pavia, Bologna, Barcelona, Rome, Vienna, Umea, Ottawa, Baltimore, …

26 Centers of reference responded to the request of the GEMS project so far. (See ANNEXE 1: List with precise addresses)

21 Centers of references follow patients eligible for the investigation cohort.

An investigation cohort of at least 262 patients can be mobilised via these centres.

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	
FBN1 mutation	**Antwerp**	**Ghent**	**Leiden/ Nijmegen/ Gronigen**			**Amsterdam**	**Paris**	**London**	**Berlin**	**Munich**	**Hamburg**	**Sheffield**	**Zurich**	**Milan**	**Pavia**	**Bologna**	**Barcelona**	**Rome**	**Umea**	***Ottawa***	***Baltimore***	**TOTAL**
#3 p.Ala882Val; c.2645C>T – exon 21	0	4	1			0	53	6	0	0	1	3	3		1	3					*4*	79
#7 p.Ile2585Thr; c.7754T>C – exon 62	8	13	20			2	93	12	10	0	2	1		3	2		3	1	4	*6*	*3*	183
Number of patients	**8**	**17**	**21**			**2**	**146**	**18**	**10**	**0**	**3**	**4**	**3**	**3**	**3**	**3**	**3**	**1**	**4**	***6***	***7***	**262**
	3%	*6%*	*8%*			*1%*	*56%*	*7%*	*4%*	*0%*	*1%*	*2%*	*1%*	*1%*	*1%*	*1%*	*1%*	*0%*	*2%*	*2%*	*3%*	*100%*
Distance from UZA (km)	0	60	138			180	348	378	722	777	564	654	693	947	984	1161	1376	1519	2166	*5655*	*6145*	

It cannot be guaranteed at this stage that it will be possible to carry out grouped collections followed by grouped shipments. At this stage, the cautious approach would be **to plan for 262 individual shipments**.

However, Centers will be encouraged to organise group collections for 2-5 people. **Bearing in mind that, at reception, the UZA can only perform a maximum of 20 IPSC and PBMC extractions per day.**

Bioflow

GEMS2Center:

Tubes 2 for **stem cell culture** (***I**nduced **P**luripotent **S**tem **C**ell*) and Tube 3 for **PBMC extraction** (***P**eripheral **B**lood **M**ononuclear **C**ell*) must reach within **48 hours** the UZA laboratory (Antwerp, Belgium).

IPSC & PBMC extracted from **Tubes 2 & 3** will stay in UZA. **IPSC & PBMC** should be stored at a temperature lower than -80° at UZA (in a local additional nitrogen tank).

DNA extracted from **Tube 1** is divided in two lots: **(1) 'Lot 500 ng'** that contains 500 nanograms (ng) of DNA for whole genome sequencing (*1 DNA storage tube*); **(2) 'Lot Rest'** that contains the rest of DNA extracted that will be placed in Biobank for long storage (*4 DNA storage tubes*).

In transit, 'Lot 500 ng' and 'Lot Rest' should be stored at Room T°.

When 50 DNA samples are collected, they are shipped (Shipping 2 & 3).

Antwerp, Ghent, Leiden, Nijmegen, Groningen, Amsterdam, Paris, London, Hamburg, Sheffield, Zurich, Milan, Pavia, Bologna, Barcelona, Rome, Vienna, Umea, Ottawa, Baltimore, …

UZA

Shipping 1: Controlled Room T°

T° between +15°C & +25C°

48h MAX

Tube	Extract	Transit (T°)	Long (T°)
Tube 1/DNA	Lot 500 ng: WGS	Yes (Room T°)	No
	Lot Rest: BioBank	Yes (Room T°)	Yes (<-80°)
Tube 2/IPSC	N.A.	N.A.	N.A.
Tube 3/PBMC	PBMC	Yes (<-80°)	No

Shipping 2 Ambiant Room T°

50 lots 'Rest' (=50*4) are shipped for long storage in Paris at <-80°

Air Liquide HEALTHCARE

Biobank Fondation 101 Génomes

Centers of reference collect **three tubes of EDTA blood** per patient: :

- **Tube 1 DNA (5 ml)**
- **Tube 2 IPSC (10 ml)**
- **Tube 3 PBMC (10 ml)**

For 262 patients, **786 samples** (=262 x 3 tubes) are required. **Tubes 1, 2 & 3 are sent to UZA.**

Shipping 3: Ambiant Room T°

50 lots '500 ng' (=50*1) are shipped for sequencing batch to Amsterdam in the Netherlands

Humanizing Genomics macrogen EUROPE

WGS 30x Pipeline

Fondation 101 Génomes

101 Genomic Cloud

Bioflow

GEMS2Patient:

Kits need to be transported at room temperature. With room temperature we mean the environmental temperature at which the samples are transported.

DNA extracted from '**Kits**' is divided in two lots: **(1) Lot 500 ng** that contains 500 nanograms (ng) of DNA for whole genome sequencing (*1 DNA storage tube*); **(2) Lot Rest** that contains the rest of DNA extracted that will be placed in Biobank for long storage (55,000 ng - 500 ng = 54,500 ng) (*4 DNA storage tubes*).

In transit, 'Lot 500 ng' and 'Lot Rest' should be stored at Room T°.

When 50 DNA samples are collected, they are shipped (Shipping 2 & 3).

500 to 1000 Individual donors

Individual saliva collection kits **DNAGenotek 'Oragene-DNA OG-610'** in **ACP-055 mailing box.**

Kits are delivered to individuals, picked up and shipped **to UZA**.

UZA

Shipping 1: Ambiant Room T°

Tube	Extract	Transit (T°)	Long (T°)
Tube 1/DNA	Lot 500 ng: WGS	Yes (Room T°)	No
	Lot Rest: BioBank	Yes (Room T°)	Yes (<-80°)

Shipping 3:
Ambiant Room T°

50 lots '500 ng' (=50*1) are shipped for sequencing batch to Amsterdam in the Netherlands

Humanizing Genomics macrogen EUROPE

WGS 30x Pipeline

Shipping 2
Ambiant Room T°

50 lots 'Rest' (=50*4) are shipped for long storage in Paris at <-80°

Air Liquide HEALTHCARE

Biobank Fondation 101 Génomes

Fondation 101 Génomes

101 Genomic Cloud

What do we store?

We store DNA

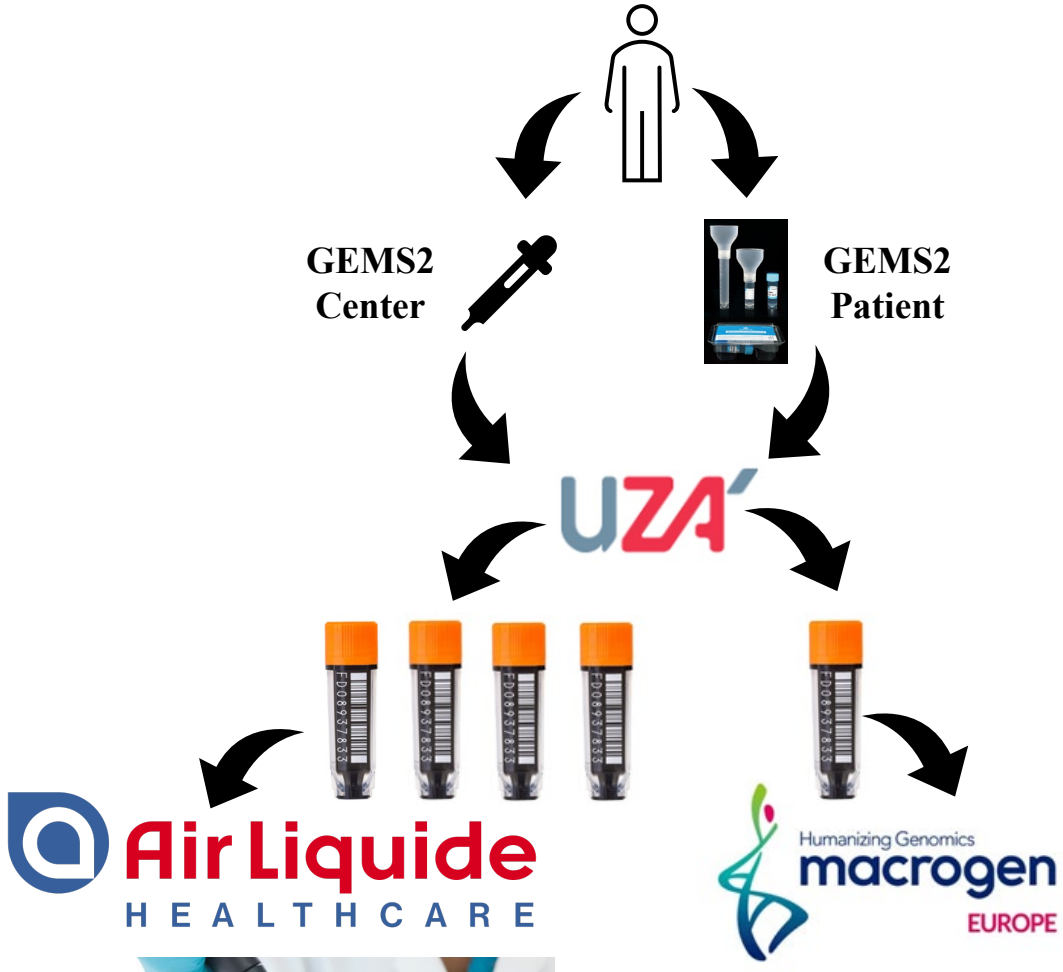
Both in the dimension involving centers and, in the dimension involving individuals, the samples are gathered in the laboratory in Antwerp.

There the DNA is extracted* and distributed for each patient in 5 DNA storage tubes sealable with screw caps. **One DNA** storage tube is sent to *MacroGen* for sequencing and **4 DNA** storage tubes are stored in BioBank.

The DNA storage tubes are for example: "68-0703-10 | FluidX 96-Format, 0.5ml External Thread, Next-Gen Jacket, Tri-Coded Tube, Capped | Barcode & HRN (Side) Detail68-0703-11 | FluidX 96-Format, 0.5ml External Thread, Next-Gen Jacket, Tri-Coded Tube, Capped, Racked (in 66-51004 Rack) | 2" (https://www.brookslifesciences.com/products/fluidx-96-format-0.5ml-external-thread-next-gen-jacket-tri-coded-tube).

For the 252 individuals, we will need 1260 DNA storage tubes. 252 tubes will be destroyed after use by *MacroGen* and **1008 tubes will be stored long-term at -80° at Air Liquide**.

** Research is currently ongoing at the UZA and ULB to determine whether it is feasible, and at what cost, to extract DNA in such a way as to enable long-read sequencing and not just short-read sequencing. The current technological evolution seems to indicate that within a few years long-read sequencing (or a combination of long and short-read) could be the norm.*



Storage

Biobank:

- Biologic : BioB
- Bioinformatic : Genomic Cloud

Biologic storage

CryopAL Biobanque Solutions

Draft convention

CBS BIOBANQUE SOLUTIONS

Catégories	Recherche portant sur un médicament	Recherche impliquant la personne humaine (RIPH)		
Titre	Recherche interventionnelle portant sur un médicament	Recherche interventionnelle ne portant pas sur un médicament	Recherche interventionnelle à risques et contraintes minimes	Recherche non interventionnelle
Abbréviation	EC médicament	RIPH1	RIPH2	RIPH3
Exemple		• Collecte de sang hors conditions de l'arrêté du 12/04/2018	• Prélèvement de sang effectué spécifiquement pour la recherche hors contexte de soin • Collecte dans les conditions de l'arrêté du 12/04/2018	• Prélèvement supplémentaire pour la recherche réalisé dans le cadre du soin
Autorisations recherche	Autorisation UE Portail européen CPP	Autorisation ANSM Avis favorable CPP	Enregistrement ANSM Avis favorable CPP	

Entre les soussignés :

La société CryopAL Biobanque Solutions, une société anonyme à conseil d'administration dont le numéro de SIRET est le 529 218 638 00029, le numéro de TVA intracommunautaire est le FR 84 529 218 638 et dont le siège social est situé Parc Gustave Eiffel, 8 avenue Gutenberg, 77600 Bussy Saint Georges

représentée aux fins des présentes par Monsieur Yves Patin, Directeur Général

Ci-après dénommée **« CryopAL Biobanque Solutions »**

D'une part,

Et

La Fondation 101 Génomes (F101G), fondation privée de droit belge, inscrite à la banque carrefour belge des entreprises sous le numéro BE0684609172 et dont numéro de TVA intracommunautaire est le BE 684 609 172 et dont le siège social est situé avenue de Sumatra, 6 à 1180 Bruxelles, Belgique.

représenté aux fins des présentes par Romain Alderweireldt, administrateur de la F101G.

Ci-après dénommé le **« Déposant »**

D'autre part,

CryopAL Biobanque Solutions et le Déposant étant individuellement désignés par la « Partie » et collectivement par les « Parties ».

ERASME-ULB ethic committee

5 April 2022: 'Avis favorable'

- **Comité·d'Ethique·Hospitalo-Facultaire·Erasme-ULB**¶

¶

https://www.erasme.ulb.ac.be/fr/ethique¶

¶

¶

Pour·un·contact·avec·le·secrétariat·du·CE¶

tél°:·32·2·555·3707¶

e-mail°:·comite.ethique@erasme.ulb.ac.be¶

¶

Pour·la·soumission··de·votre·dossier·au·format·papier¶

A·l'attention·de·Mme·Hélène·François¶
Comité·d'Ethique·Erasme-ULB·(local·0W7010,·route·843)↵
Route·de·Lennik·808¶
1070·Bruxelles¤

¶

Pour·la·soumission·de·votre·dossier·au·format·électronique¶

e-mail°:·comite.ethique@erasme.ulb.ac.be¶

¶

¶

Demande·d'avis·du·Comité·d'Ethique·↵
constitution·/·renouvellement·d'agrément¶
Etablissement·de·Matériel·Corporel·Humain·(MCH)¶

¤

¶

Cliniques universitaires de Bruxelles
Route de Lennik 808
B-1070 Bruxelles
T +32 (0)2 555 31 11
M contact@erasme.ulb.ac.be
S www.erasme.ulb.ac.be

Hôpital Erasme — ULB

Dr VERBOOGEN Michel
Médecin, Neuropsychiatre,
Président du Conseil d'administration
de la Fondation 101 Génomes
Rue Cambron, 31
7500 Tournai

Bruxelles, le 05/04/2022

Comité d'Ethique
hospitalo-facultaire
Erasme - ULB
(021 / 406)

Secrétariat
T 02 555 37 07
02 555 37 11
F 02 555 46 20
M comite.ethique@erasme.ulb.ac.be
www.erasme.ulb.ac.be/ethique

Cher VERBOOGEN Michel,

Dans le cadre de sa mission légale définie à l'article 7, §1er, alinéa 3, de la loi du 19 décembre 2008 relative à l'obtention et à l'utilisation de matériel corporel humain destiné à des applications médicales humaines ou à des fins de recherche scientifique, le Comité d'Ethique hospitalo-facultaire Erasme-ULB a pris connaissance du dossier de soumission de la biobanque de MCH « Biobanque de matériel corporel humain de la Fondation 101 Génomes » (Ref. B2022/001).

Le dossier évalué comprend les pièces suivantes :

- Cover Letter, dated March 13, 2022
- Demande d'avis du Comité d'Ethique, dated March 13, 2022
- Annexe : lien : 20220313 F101G Biobanque

Le Comité octroie, en date du 05/04/2022, un avis favorable par rapport aux activités et objectifs, tels que décrits dans le dossier de soumission

Nous vous prions d'agréer, Cher VERBOOGEN Michel, l'expression de nos meilleurs sentiments.

Pr J.M. BOEYNAEMS
Président

AFMPS

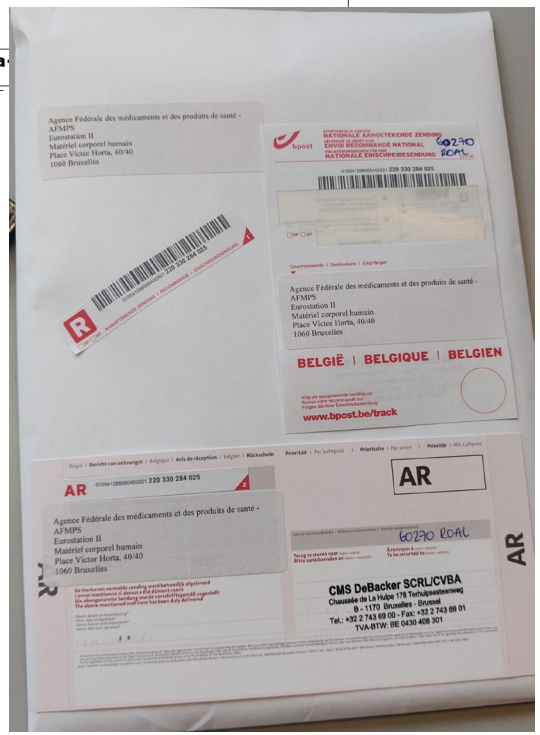
Notification (18 May 2022) & Confirmation (9 June 2022)

FORMULAIRE·DE·NOTIFICATION·DE·LA·BIOBANQUE¶

Ce·document·est·le·formulaire·de·demande·de·notification·tel·que·mentionné·dans·l'Arrêté·royal·du·09/01/2018·relatif·aux·biobanques.·Après·l'avoir·rempli·et·signé,·il·doit·être·envoyé·avec·les·annexes·par·courrier·recommandé·à·l'adresse·suivante·:¶

Agence·fédérale·des·médicaments·et·des·produits·de·santé·–·AFMPS¶
Eurostation·II¶
Matériel·corporel·humain¶
Place·Victor·Horta·40/40¶
1060·BRUXELLES¤

1°·Données·concernant·la·



afmps
agence fédérale des médicaments et des produits de santé

Cellule Matériel Corporel Humain

Philippe De Buck
Tél. : +32 2 528 40 00
e-mail : biobanks@fagg-afmps.be

Agence fédérale des médicaments et des produits de santé
Avenue Galilée 5/3
1210 Bruxelles
www.afmps.be

FIOIG Biobanque
Avenue de Sumatra 6
1180 Uccle
Belgique

Votre lettre du	Vos références	Nos références	Annexe(s)	Date
		0000	0	

Objet: Notification établissement biobanque

Madame, monsieur,

J'accuse bonne réception de votre notification concernant votre biobanque conformément à l'art. 3 de l'arrêté royal du 9 janvier 2018 relatif aux biobanques. Nous avons reçu la notification en date du **31-05-22** et nous vous confirmons que le dossier est complet et recevable.

En date du **09-06-2022** le numéro de notification **BB220008** est accordé à la biobanque sise à
FIOIG Biobanque
Avenue de Sumatra 6
1180 Belgique

L'exploitant de la biobanque est : **Fondation 101 Génomes**
le gestionnaire du matériel corporel humain au sein de la biobanque est : **Verboogen, Michel**

Ce numéro de notification vous est accordé sans préjudice de toutes consultations ou vérifications ultérieures relatives à la conformité aux dispositions de l'Arrêté Royal 9 janvier 2018 relatif aux biobanques.

Toute modification aux renseignements fournis la pour la présente notification ou toute cessation temporaire ou définitive envisagée des activités de la biobanque doit, conformément l'art. 4 l'arrêté Royal du 9 janvier 2018, immédiatement être signalée à l'Agence Fédérale des Médicaments et des Produits de Santé. Ces informations peuvent être communiquées soit par lettre soit par courriel adressée à l'adresse biobanks@fagg-afmps.be, toujours en mentionnant le numéro de notification.

Veuillez agréer, Madame, Monsieur, l'expression de nos salutations distinguées,

afmps fagg
Digitally signed by
Philippe De Buck
(Signature)
Date: 2022.06.10
17:41:24 +02'00'

Philippe De Buck,
Chef de division autorisation.

Bioinformatic storage

Microsoft Azure & Data Twin

Cloud Storage

After legal examination and regular contact at Microsoft (both at European and Belgian level), **Microsoft Azure** was chosen as the partner to host the data. Mainly because Microsoft offers the **safest and most regulatory compliant current Cloud option** for genomic storage on the market as of today.

T**he F101G opened its Cloud (Data Lake)** and since **October 2020** we have been working on the development of this facility with different consultants.

The F101G Data Lake now already allows to host and store genomic data securely in the cloud.

This solution will facilitate at a later stage access for as many researchers as possible.

Genomics in the Cloud

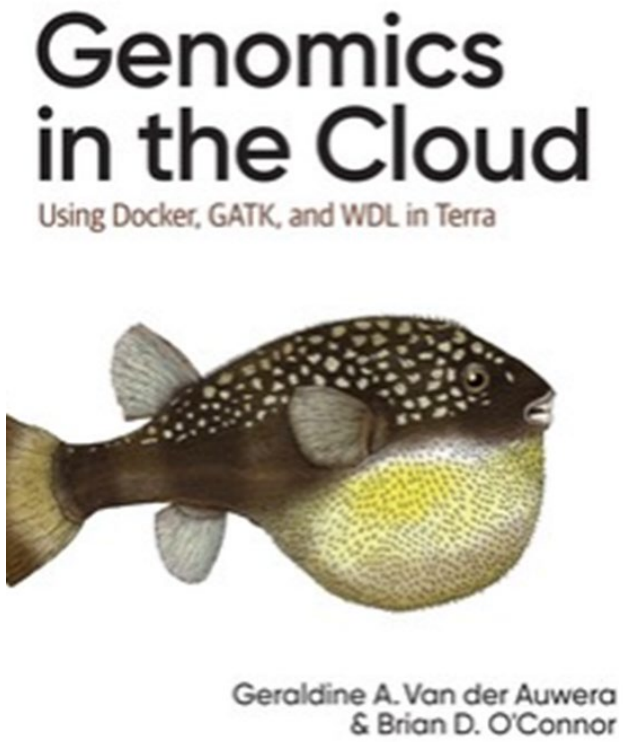
Géraldine Van Der Auwera (Broad Institute MIT/Harvard)

Géraldine Van der Auwera (Broad Institute MIT/Harvard - Author of *Genomics in the Clouds*) has accepted to be involved in the set-up of our **Genomic Cloud and its optimization**, keeping in mind the numerous interactions required for fair genomics activities.

Until now, Géraldine has mainly developed her expertise in the Google environment. She was looking for a genomic project to replicate what she did on Google Cloud Platform in the Microsoft Azure world. Our project is a perfect fit for her and she will work with us to implement our genome storage solution on Azure.

We have bi-monthly meetings with Géraldine to advance our development.

We are considering structuring our data by aligning them with ***Terra* data model**, a cloud-native platform for biomedical researchers to access data, run analysis tools, and collaborate.



Tools integration

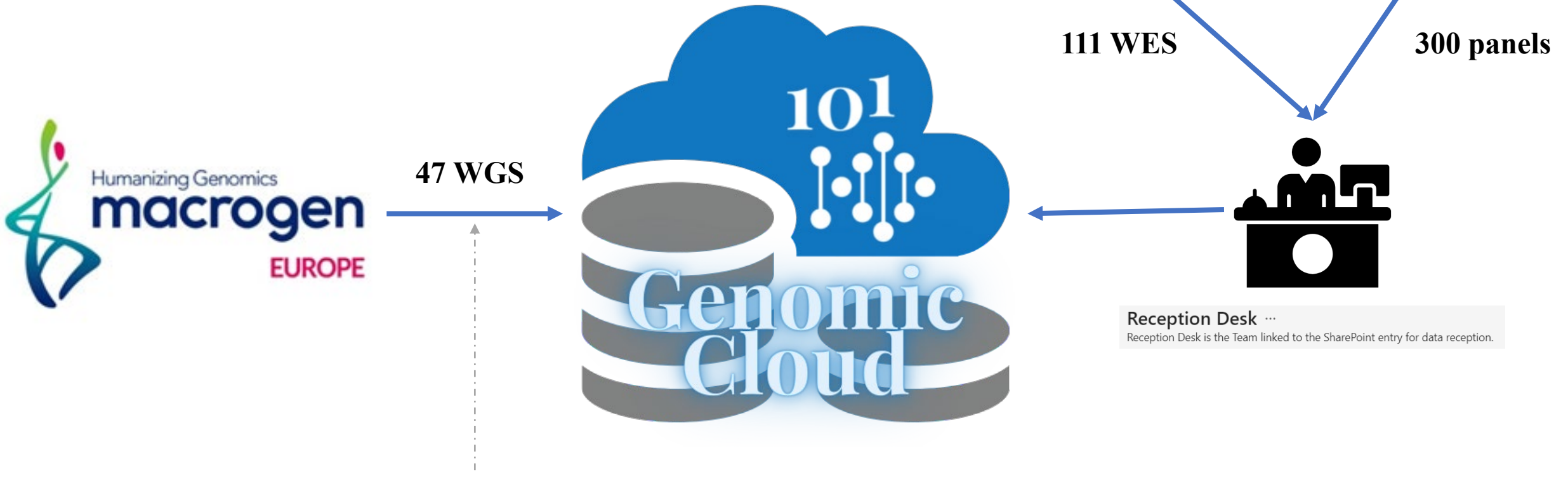
Emma Verkinderen

Bioinformatician **Emma Verkinderen**, who is engaged by Prof. Tom Lenaerts in the context of **Genome4Brussels**, has become involved with this component of the project, notably by helping to define the requirements for the hosting solution in order to ensure that the Cloud solution will allow to integrate and use AI tools developed in the Marfan context.

https://www.f101g.org/en/genome4brussels-par-emma-verkinderen/

Bioinformatic flow

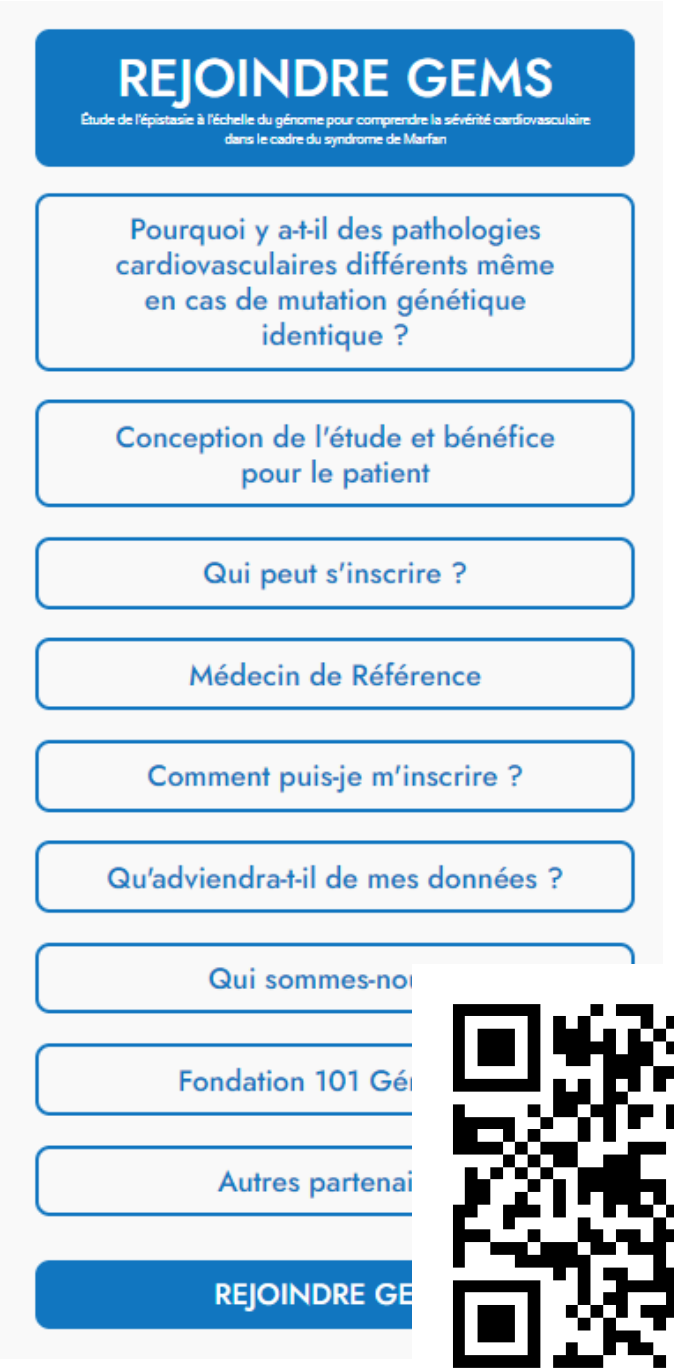
Gathering 300 panels, 111 WES & 52 WGS



First ever SFTP transfer between macrogen and Azure! Established with Data Twin

101 GEMS App

Web App for consent management
& phenotypic data collection



GEMS App

Welcome & approved

On **October 8th, 2021**, the GEMS App was **presented by Professor Bart Loeys to the entire European Marfan Syndrome research community at the annual meeting of VASCERN** (the European Reference Network dedicated to rare vascular diseases). The researchers and representatives of patient organizations (Belgian, French, Dutch, German, Spanish and Austrian) present at the event gave an **enthusiastic welcome to the GEMS App**.

On **January 10th, 2022**, the GEMS App received **approval from the UZA Ethics Committee** (Annexe 02 20220110 UZA Ethic approval).

GEMS project

Genome-wide Epistasis for cardiovascular severity in Marfan Study

Paris – october 8, 2021

For VASCERN-HTAD

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COMITE VOOR MEDISCHE ETHIEK

Prof. B. Loeys
Centrum Medische Genetica

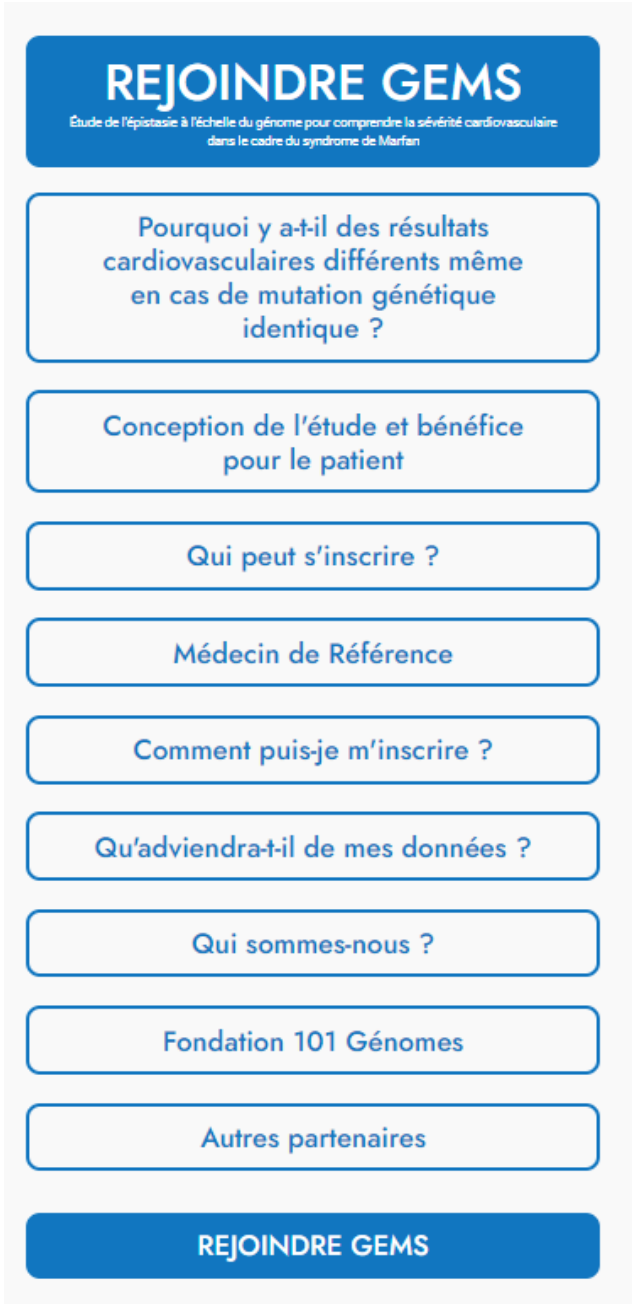
VOORZITTER
Prof. dr. Peter Michielsen

SECRETARIAAT
tel: 03 821 38 97

Genome-wide Epistasis for cardiovascular severity in Marfan Study (GEMS) to pave the road to individualized treatment protocols (EDGE 000847)

Belgisch Nummer: B3002021000292

datum	ons kenmerk	contactpersoon
10/01/2022	20/08/087	Secretariaat Ethisch Comité ethisch.comite@uza.be



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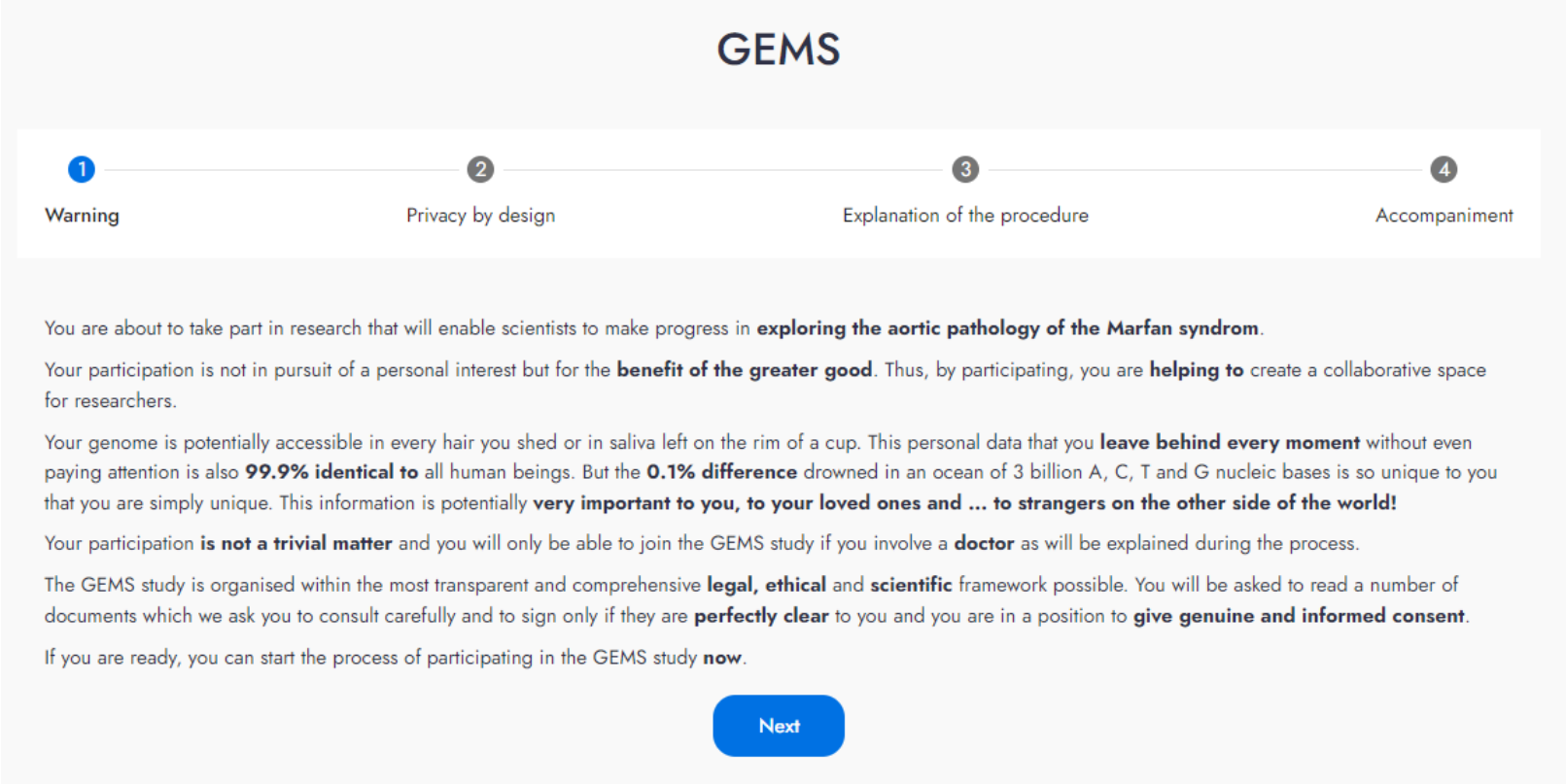

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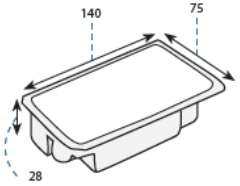
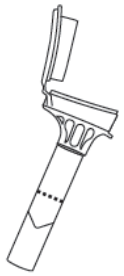
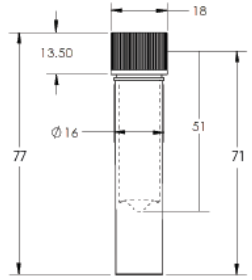
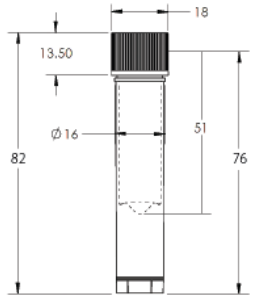
Individual saliva collection kits

DNAGenotek

DNA genotek

Oragene® 600 series product weight and dimensions

	Catalogue numbers	Saliva volume	Pre-collection: Package dimensions and contents — WEIGHT 34-38g† — Clamshell (mm)	Pre-collection: Components	Pre-collection: Collector	Post-collection: Total sample volume††	Post-collection: Tube dimensions (mm)
Without 2D bottom barcode	OG(X)-600	2 mL		 Instructions for use Cap  Sponges for assisted collection (OG(X)-675 products only)	 OR 	4 mL	
	OG(X)-675	.75 mL via sponge				1.5 mL	
	OG(X)-610	1 mL				2 mL	
	ON-600	.5 mL					
With 2D bottom barcode	OG(X)-600.S2P	2 mL				4 mL	
	OG(X)-675.S2P	.75 mL via sponge				1.5 mL	
	OG(X)-610.S2P	1 mL				2 mL	
	ON-600.S2P	.5 mL					

† Weight is inclusive of all product configurations within referenced catalogue numbers.
†† Total sample volume includes saliva and Oragene stabilization solution. May vary based on volume of saliva collected.

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Accessory pack (ACP-055) components:

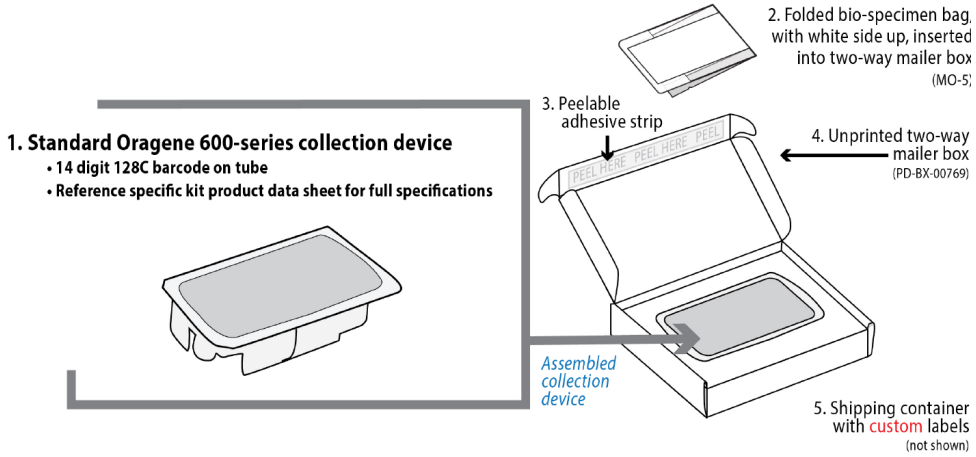


Diagram above shows kit in final assembly order.

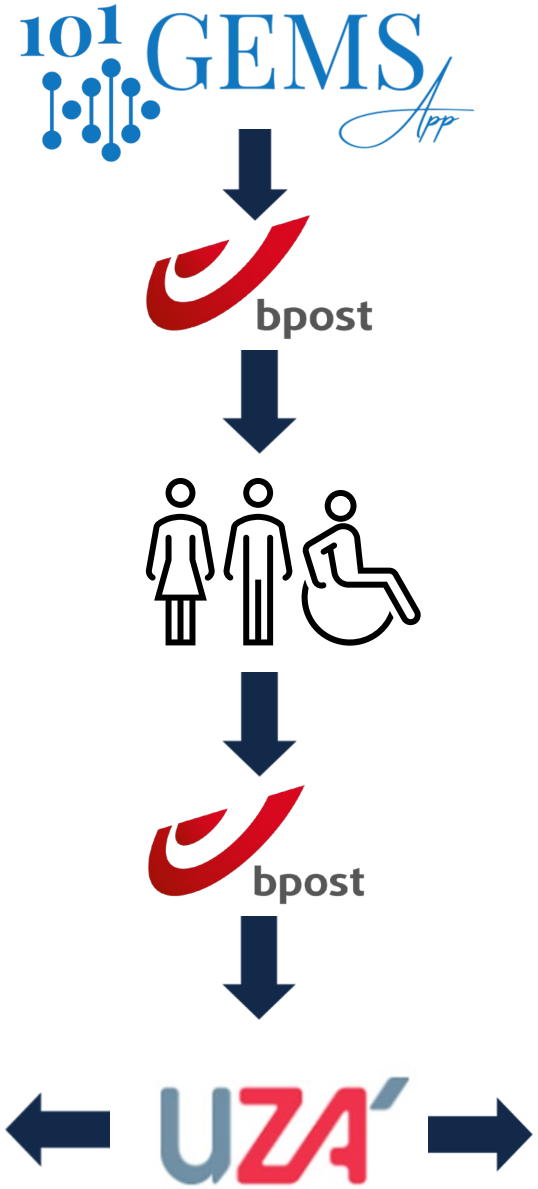
Box Dimensions: 18 cm x 13 cm x 3,5 cm

DNA genotek

Saliva kits

Bioflow

Individuals = GEMS2Patient



https://www.101gems.be/

50 lots 'Rest' are shipped for long storage in Paris (*4 DNA storage tubes*).

50 lots '500 ng' are shipped for sequencing batch to Amsterdam in the Netherlands (*1 DNA storage tube*).

100% of the form completed

Thank you for joining GEMS!

Dear GEMS participant,

We confirm that your consent has been registered and that a saliva sampling kit will be sent to the address you have provided.

The 101 Genomes Foundation and Professors Bart Loeys and Paul Coucke thank you for your trust. Your participation will help to advance the understanding of Marfan syndrome. A better understanding of Marfan syndrome and how certain genes interact with each other to prevent or aggravate the cardiovascular damage caused by this disease opens the way to better diagnosis and new therapeutic horizons.

On behalf of all those affected by Marfan syndrome and their families: THANK YOU!

Manage your profile

All the information you have provided to us and the consent documents you have signed are now available via your online profile management portal at: **https://www.101gems.be/profile**.

Through this portal, you will be able to update and complete the information you have provided at any time and to see the research and publications that have been produced thanks to your participation.

Conclusion

Conclusion

Sparkle

- Limited to 101 genomes, our initiative **is only a sparkle** in comparison with other state actions **but it can grow**.
- This sparkle is currently concentrated on Marfan syndrome **but it can be extended to other rare diseases**.
- This sparkle is a **patient driven initiative**.
- Our ambition is to provide the scientific community with **what they need to better understand rare diseases**.
- Our dream is that it could **contribute to the development of new drugs that could improve our children's lives**.
- **You can join the project today!**

You can join the project now by helping us testing the GEMS App!

101 GEMS App

https://www.101gems.be/

Conclusion

7 year old!

www.f101g.org

Aknowledgements

- **To Scientists:** Pr. Guillaume Smits, Pr. Anne De Paepe, Pr. Julie De Backer, Pr. Bart Loeys, Pr. Guillaume Jondeau, Pr. Catherine Boileau, Pr. Paul Coucke, Aline Verstraeten et Marjolijn Renard.
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- **To:** Carole Wininger, Patrice Touboulie, Lauriane Janssen et leurs familles.

www.f101g.org

Contact

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