Building genomics

genomDE : National and European initiatives

30th November 2020

DIGITAL EVENT

Supported by the European Union's Structural Reform Support Programme (SRSP) and implemented in cooperation with the European Commission's Directorate-General for Structural Reform Support (DG REFORM)

European Commission

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Genomics in the Netherlands

Han G. Brunner

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hello

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Human Genetics Nijmegen

Maastricht UMC+

Radboudumc

The Netherlands

17 Million inhabitants

1 Height 183 / 169 cm
17 Life expectancy (81.5)
8 Corruption ranking
5 World happiness ranking

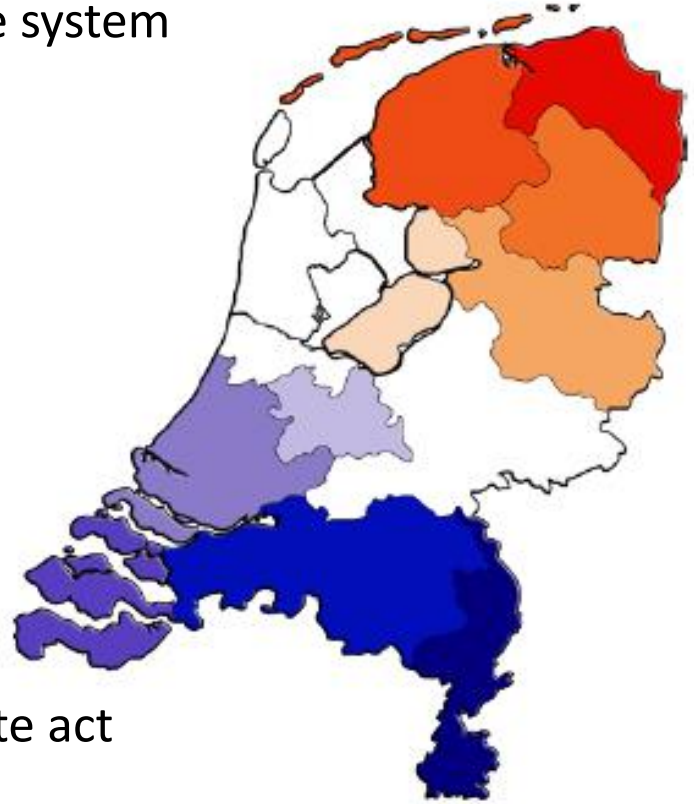
The Netherlands

Single payer (National) health care system

~180 M Euros for genetic services
~12M Euros for NIPT program
Neonatal screening program

600 PGD Procedures / yr

Genetics healthcare under separate act



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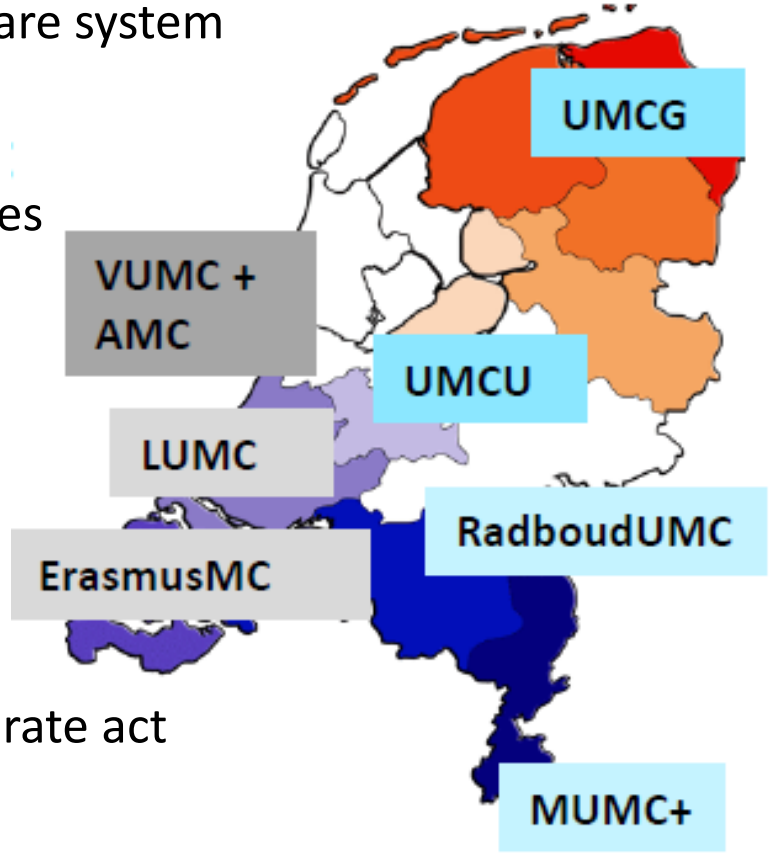


8 Clinical Genetics Centers
All are academic

No private genetics labs
No private genetics doctors

The Dutch system

Dutch Law (1983; 1991; 2007) regulates special medical services and procedures, such as kidney transplants , radiotherapy , heart surgery , brain surgery , heart lung and liver tranplantations , and neonatal intensive care.

This law stipulates that for a center to provide genetic services requires:

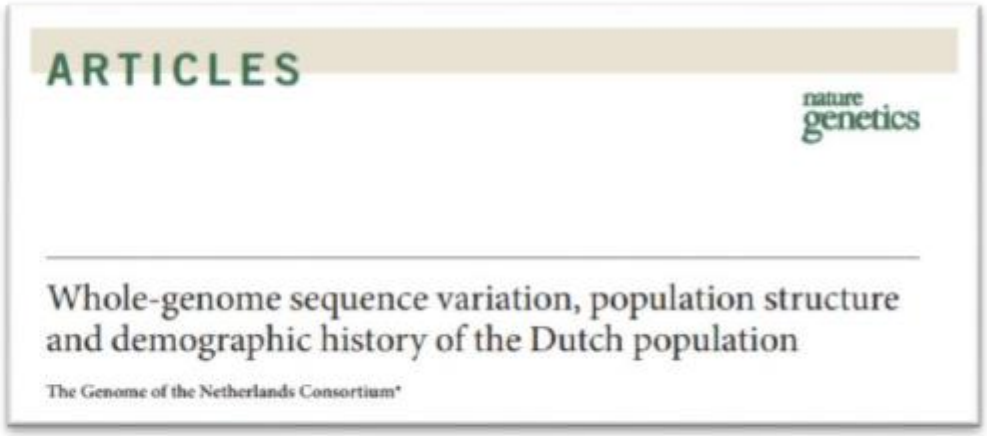
- **Proven medical and ethical expertise, and know how regarding genetic disorders, in order to provide a full and up to date spectrum of genetic diagnostic services with respect for societal and ethical values**

- **And to have access to all relevant technological expertise, <u>including innovation.</u>**

250 Whole Genome Trios

2012

2015



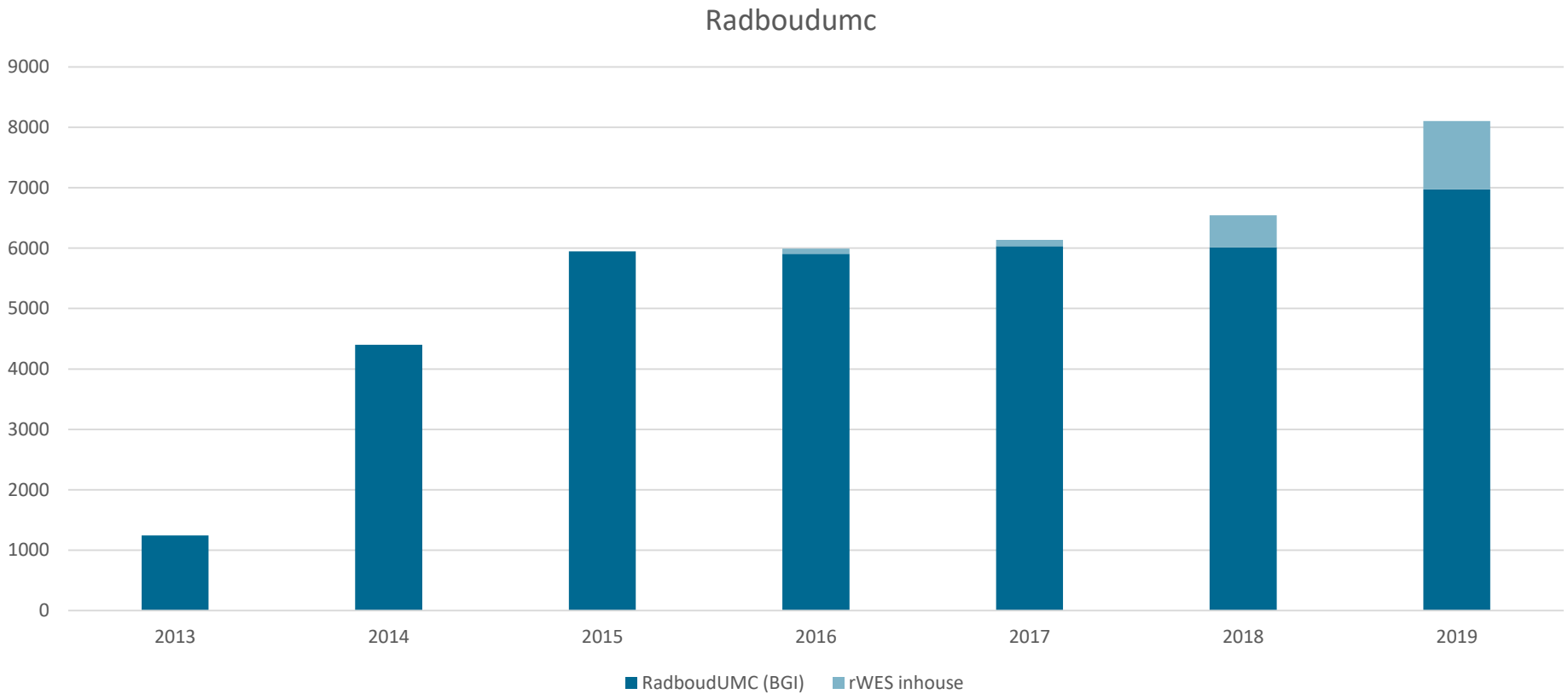
Omics measure	Technique	Number of samples
Whole Genome Sequencing	Illumina	750
Imputed genotypes	HRC	~6000
DNA Methylation	Illumina 450K	~4000
Transcriptome	Illumina RNA seq	~4000
Metabolome	Nightingale NMR	~32,000

BBMRI.nl
Biobanking and BioMolecular resources Research Infrastructure The Netherlands

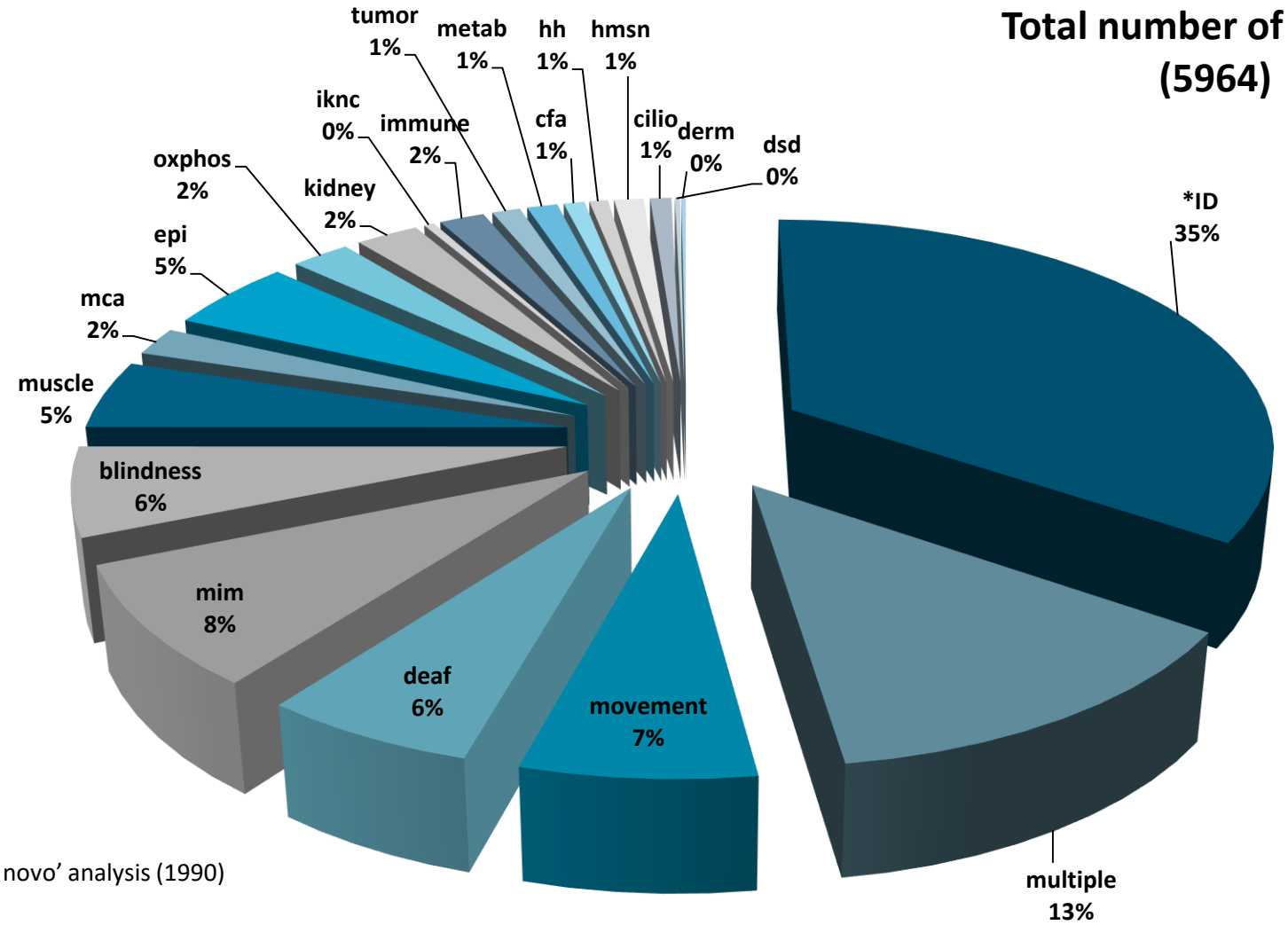
Human Genetics Nijmegen
Maastricht UMC+
Radboudumc

The Dutch experience with clinical exomes

~30.000 Exomes Netherlands



% requested clinical exomes per disease panel in 2015



*ID: majority has a trio based 'de novo' analysis (1990)

Rare diseases

8 diagnostic labs, all based at University hospitals
All use the same technology, and standards

Diagnostic variants are shared and stored in National database

High-quality Exomes are the main tool in Genome Diagnostics

Panels are used only for a limited number of (relatively common) problems with fewer than 50 genes responsible

- **Breast cancer**
- **Cardiomyopathy**
- **Cardiac Arrhythmias**

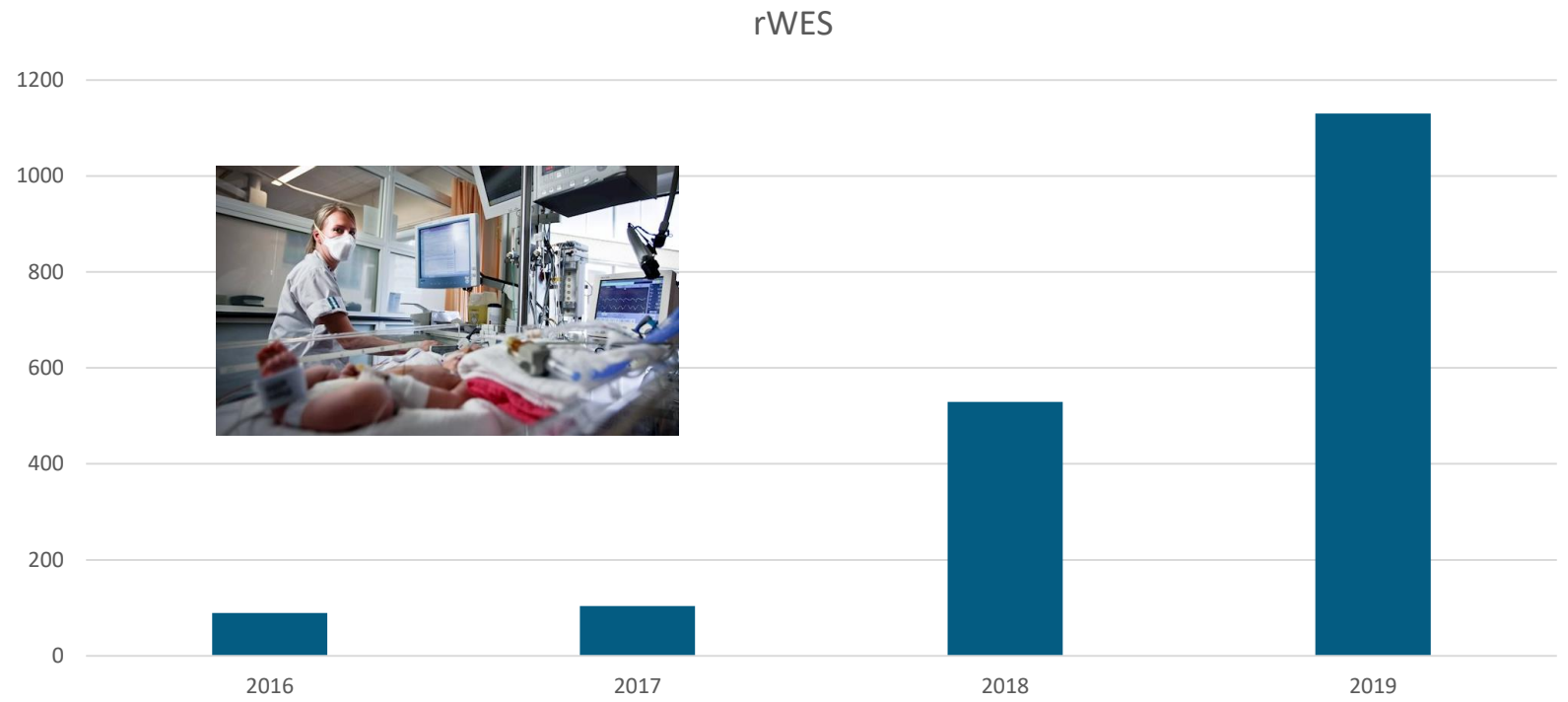
- **Genomes will be introduced as the main diagnostic test starting 2021**

Diagnosis matters

In 2011 or 2012 investigations uncovered a GRIN2a spontaneous mutation.

The mother writes:
“Truly, the day you informed us of the diagnosis, was the best day of my life.“

Rapid WES RadboudUMC



National variant sharing improves diagnosis

Received: 20 February 2019 | Revised: 5 August 2019 | Accepted: 14 August 2019
DOI: 10.1002/humu.23896

Human Mutation HGVS HUMAN GENOME VARIATION SOCIETY WILEY

DATABASES

Dutch genome diagnostic laboratories accelerated and improved variant interpretation and increased accuracy by sharing data

Ivo F. A. C. Fokkema[1*] | Kasper J. van der Velde[2*] | Mariska K. Slofstra[2] | Claudia A. L. Ruivenkamp[3] | Maartje J. Vogel[4] | Rolph Pfundt[5] | Marinus J. Blok[6] | Ronald H. Lekanne Deprez[7] | Quinten Waisfisz[8] | Kristin M. Abbott[9] | Richard J. Sinke[9] | Rubayte Rahman[10] | Isaäc J. Nijman[11] | Bart de Koning[6] | Gert Thijs[12] | Nienke Wieskamp[13] | Ruben J. G. Moritz[4] | Bart Charbon[2] | Jasper J. Saris[14] | Johan T. den Dunnen[1] | Jeroen F. J. Laros[1,3] | Morris A. Swertz[2] | Marielle E. van Gijn[9,11]

The nine Dutch labs publicly share variant classifications.
Variant classifications of nearly 100,000 unique variants in centralized database.

Variants labeled as “consensus” when classifications agreed between labs, and shared internationally with LOVD and ClinVar.

Different populations carry different disease alleles

The landscape of autosomal-recessive pathogenic variants in European populations reveals phenotype-specific effects

Hila Fridman[1,2,3], Helger G. Yntema[4], Reedik Mägi[5], Reidar Andreson[5], Andres Metspalu[5], Massimo Mezzavila[6], Chris Tyler-Smith[7], Yali Xue[7], Shai Carmi[1], Ephrat Levy-Lahad[2,3,*], Christian Gilissen[4,*] and Han G. Brunner[4,8,*]

Cold Spring Harbor Laboratory
bioRχiv
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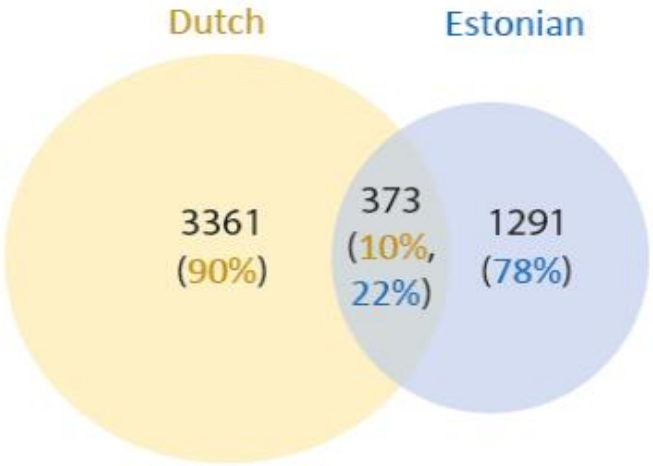
Figure 2. PLP variants in the Dutch and Estonian cohorts- variant classification.



Genomics changes medicine

Official journal of the American College of Medical Genetics and Genomics **ORIGINAL RESEARCH ARTICLE** Genetics inMedicine

Open

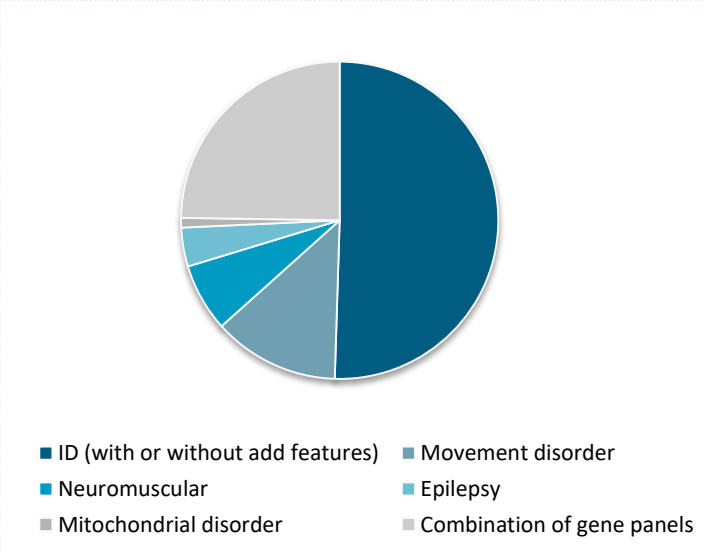
A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology

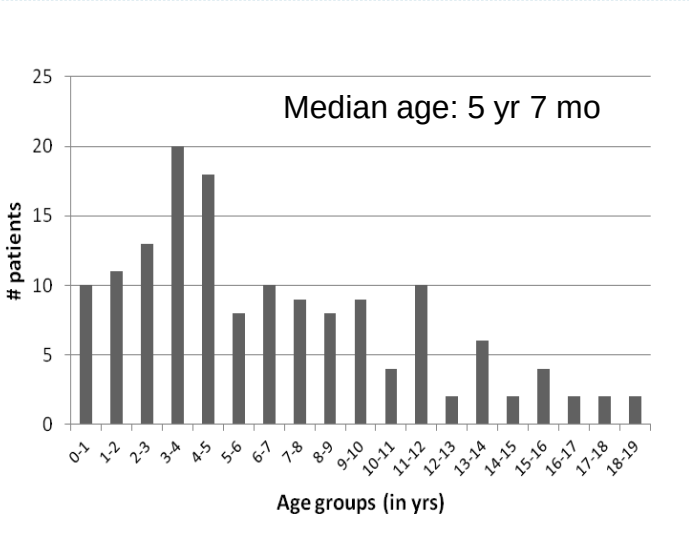
Lisenka E.L.M. Vissers, PhD[1], Kirsten J.M. van Nimwegen, MSc[2], Jolanda H. Schieving, MD[3], Erik-Jan Kamsteeg, PhD[1], Tjitske Kleefstra, MD, PhD[1], Helger G. Yntema, PhD[1], Rolph Pfundt, PhD[1], Gert Jan van der Wilt, PhD[2], Lotte Krabbenborg, PhD[4,5], Han G. Brunner, MD, PhD[1,6], Simone van der Burg, PhD[4], Janneke Grutters, PhD[2], Joris A. Veltman, PhD[1,6] and Michèl A.A.P. Willemsen, MD, PhD[3]

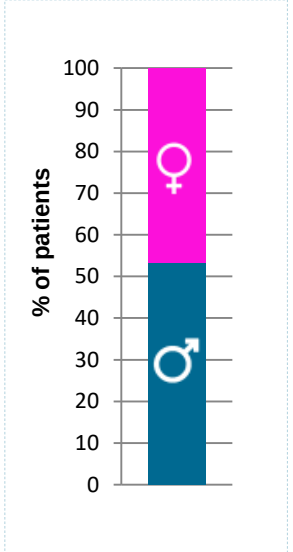
Genetics in Medicine 2017

Pediatric neurology cohort description

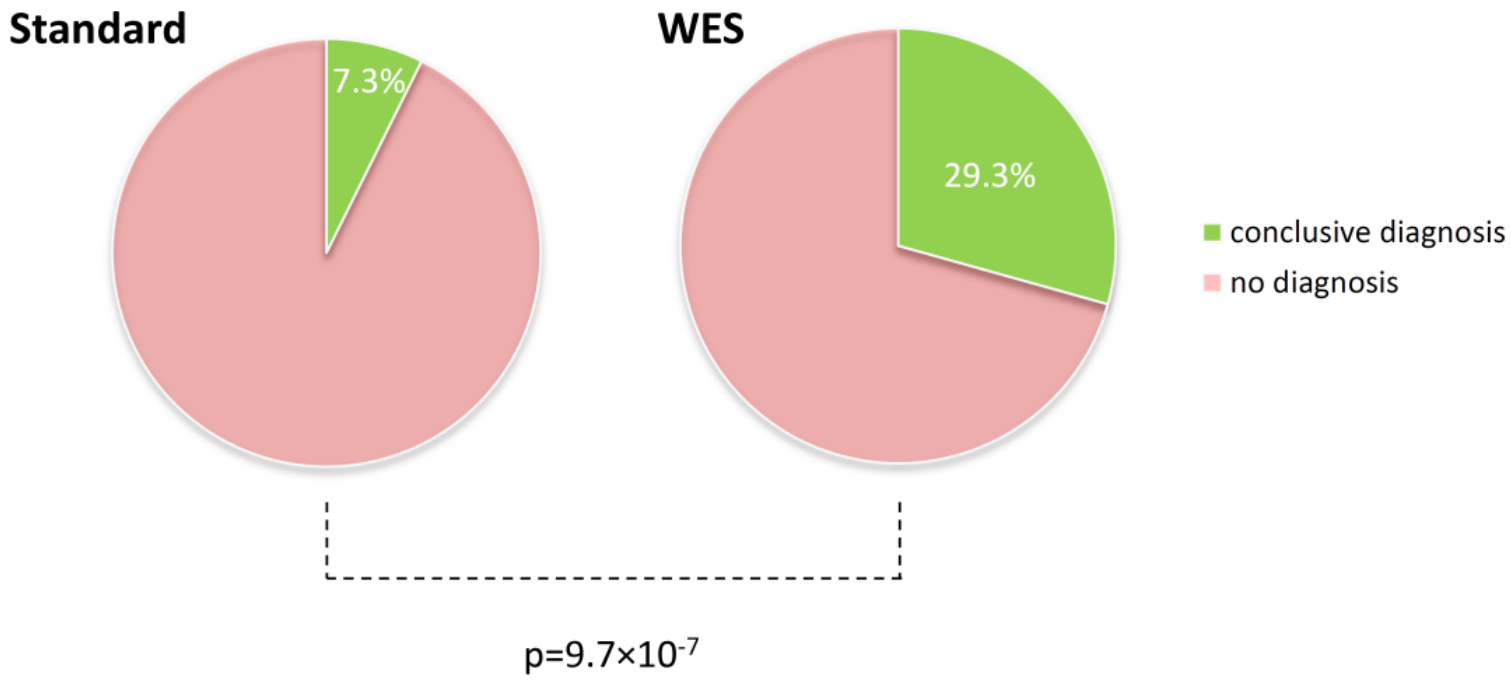
- 150 consecutive patients recruited between Nov 2011 and Jan 2015
- Represents ‘every day practice’ in tertiary pediatric neurology clinic



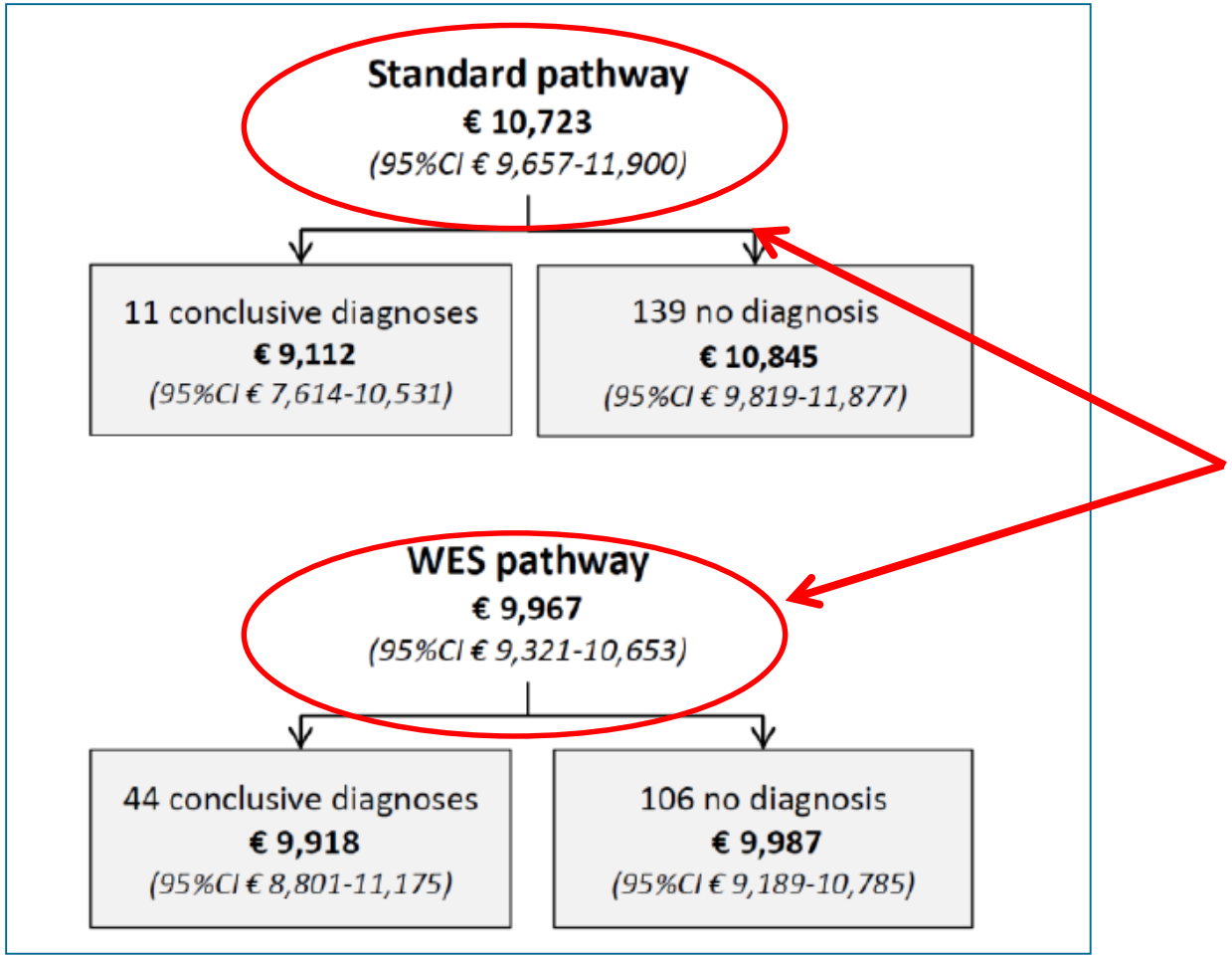




WES provides significantly more diagnoses

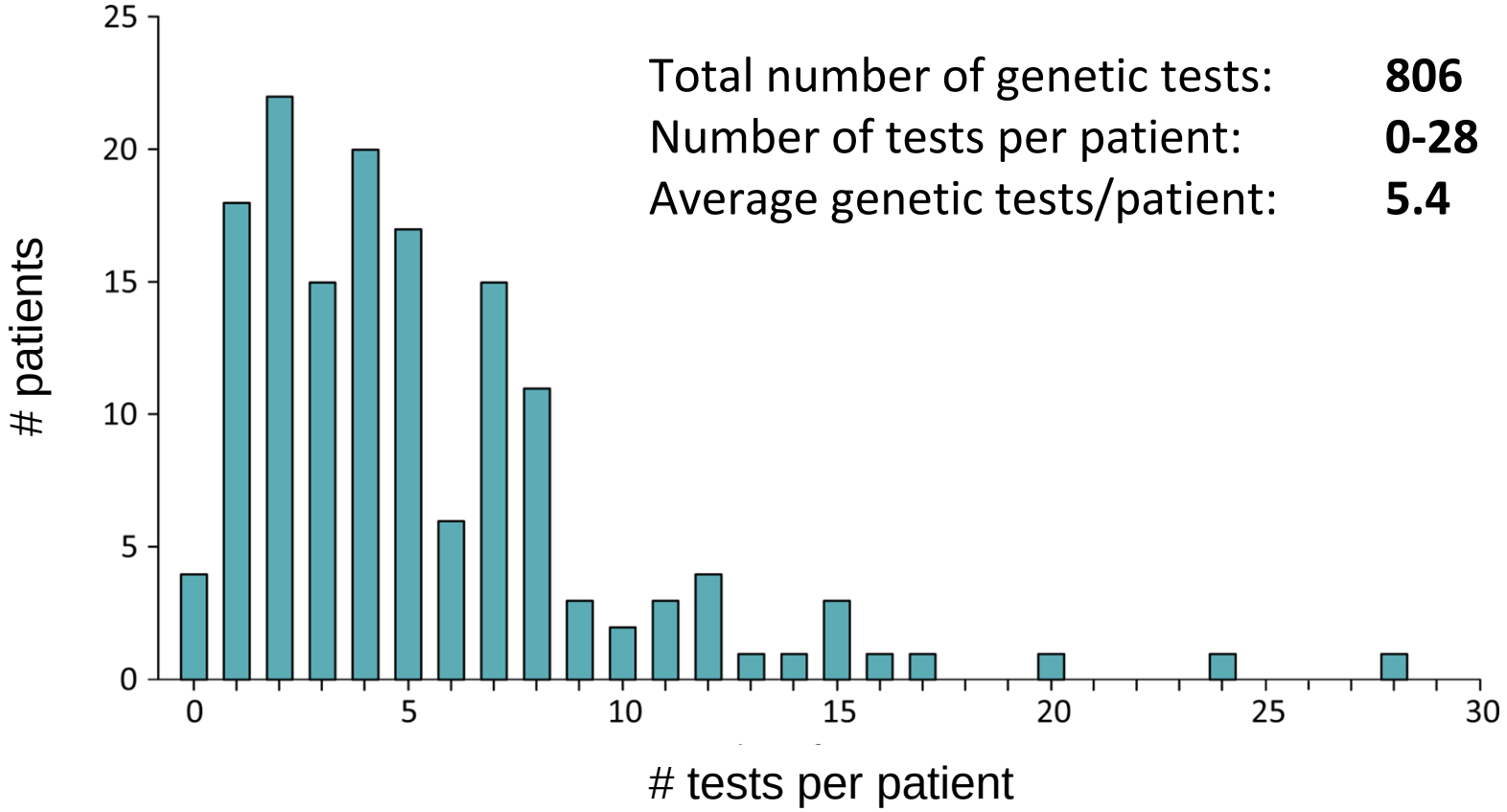


150 Pediatric Neurology patients



Lisenka Vissers, et al. Genetics in Medicine 2017

Number of genetic tests per patient



Total number of genetic tests: **806**
Number of tests per patient: **0-28**
Average genetic tests/patient: **5.4**

An inconvenient truth

The hit rate of diagnostic exome sequencing (including CNVs)

Clearly Exceeds

The current diagnostic standard of clinician driven investigation

How clinicians see themselves

Test

How things mostly work out

Screening Test

- **Doctors are great**

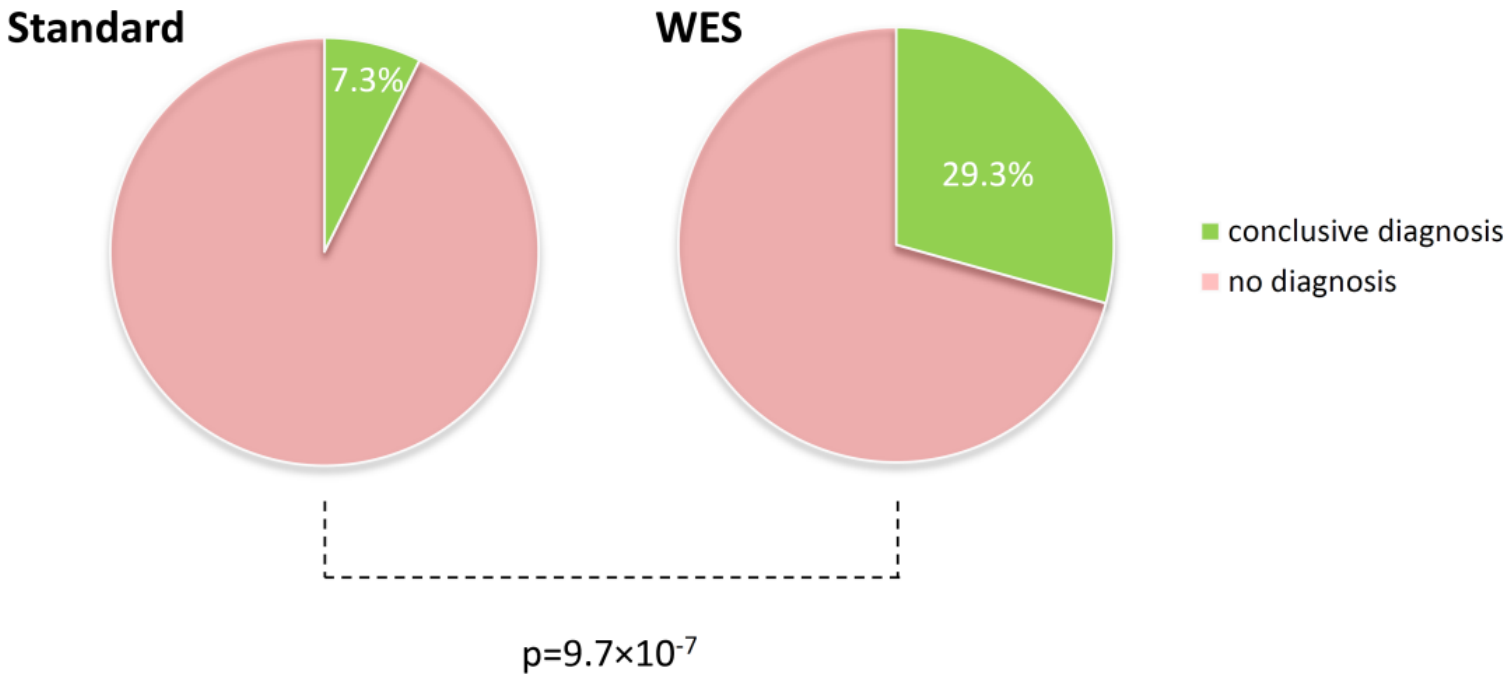
BUT

- **Exomes are better**

Vissers, van Nimwegen, Schieving et al. Genetics in Medicine 2017

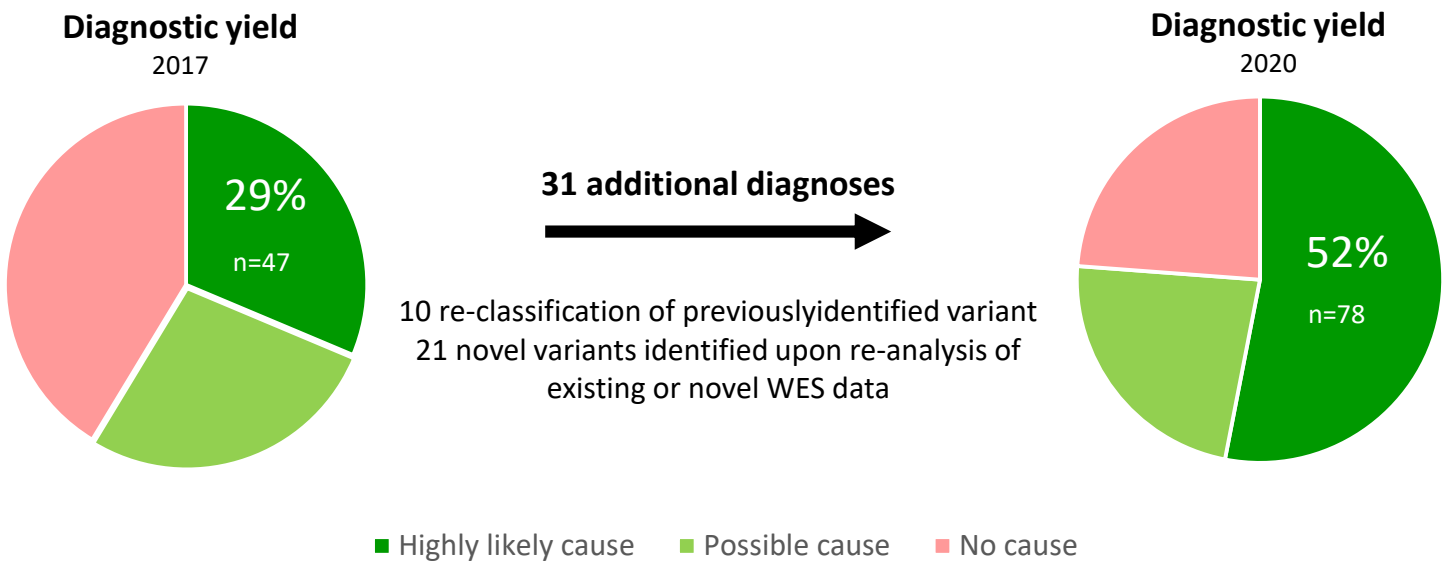
WES provides significantly more diagnoses

2017



Storing the data and systematic re-evaluation

2020



Vissers et al. GiM 2017; Schobers et al. Manuscript in preparation

What this means

For rare diseases, most diagnoses reside in the exome

Exome-first is cost-effective compared to traditional clinician-driven diagnosis

National variant curation and collection is helpful

Storage allows Reanalysis and Re-interpretation

Academic embedding drives innovation, and reduces cost.

Thank you

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