Genomics Changes Medicine

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Why Genetics Matters

Everything is genetic (a bit)

AND

We now have the technology to measure and diagnose (almost) all genetic conditions

AND

We have more and more therapies that need genetics first

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Why Genetics Matters

Rare is not Rare

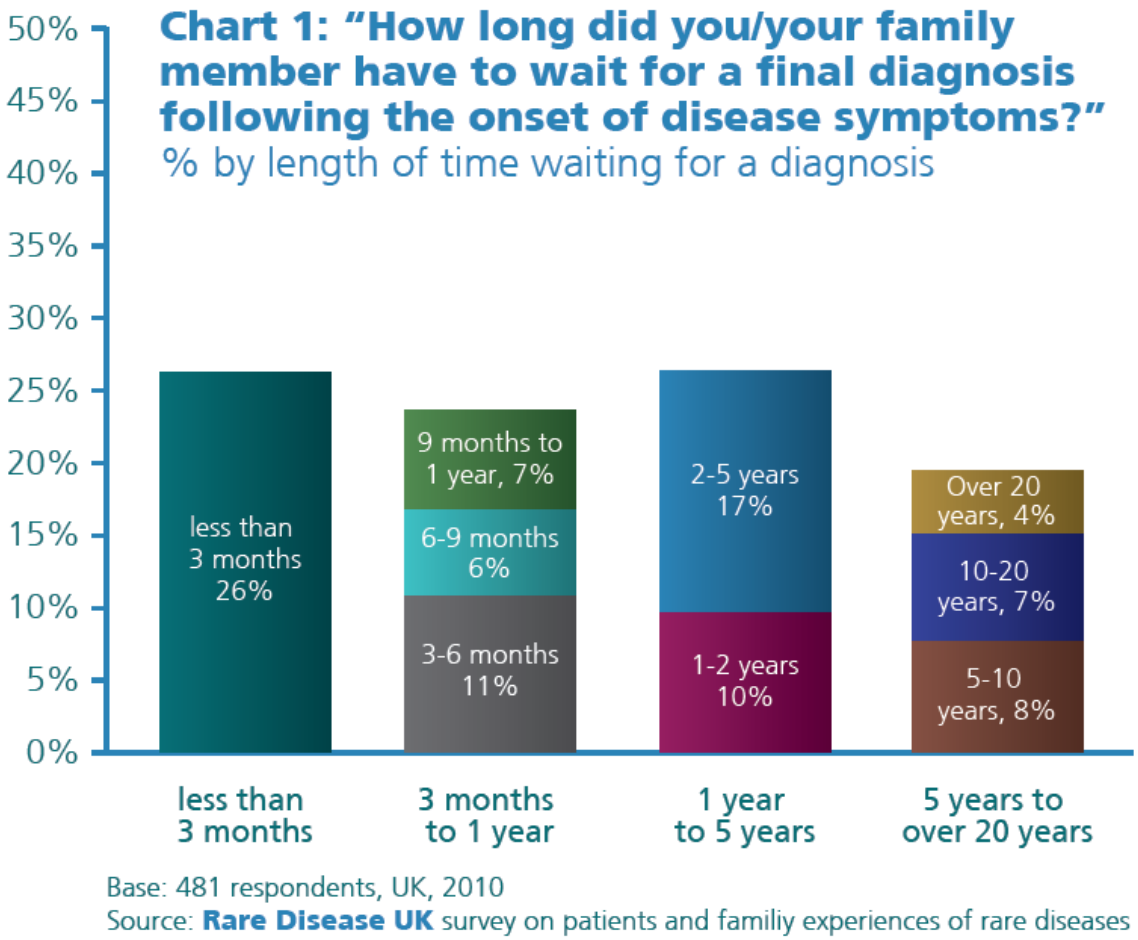
Medicine is becoming more Personalized

Medicine is becoming more Genetic

How clinicians see themselves

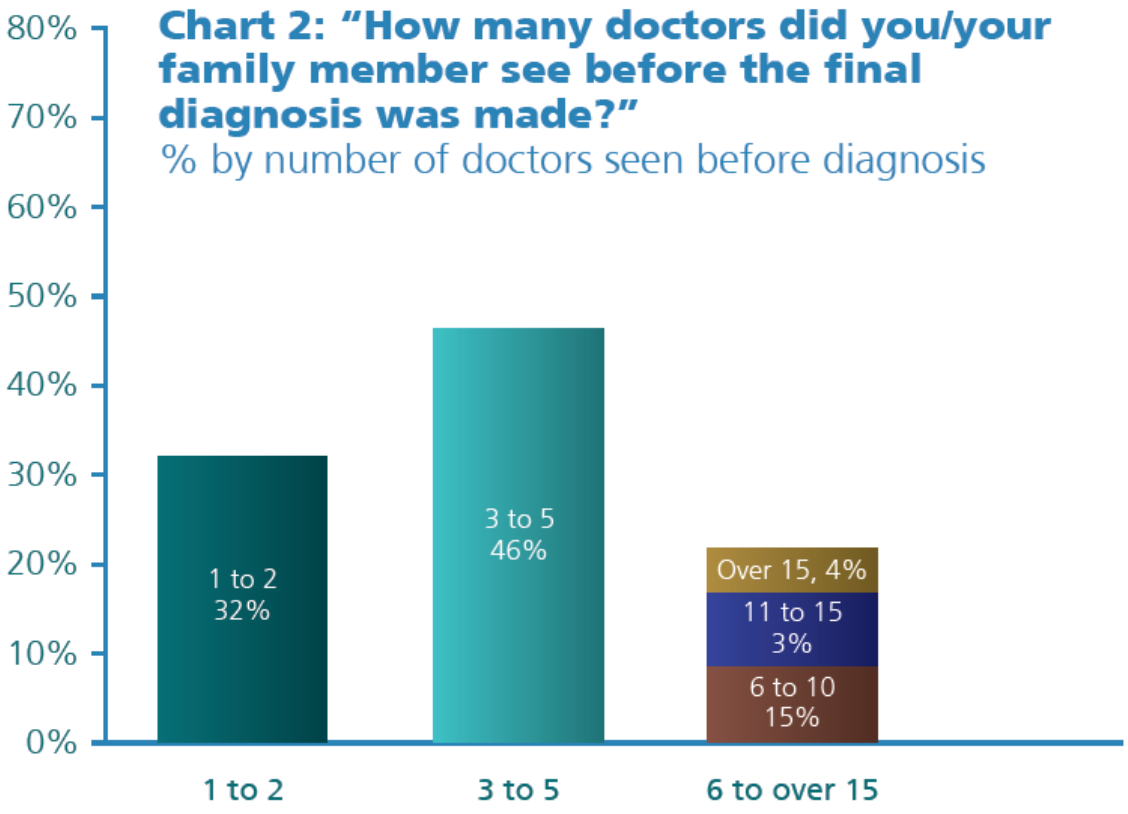
Test

Rare diseases are often not diagnosed



Source: Rare Disease UK Survey

Rare diseases are often not diagnosed



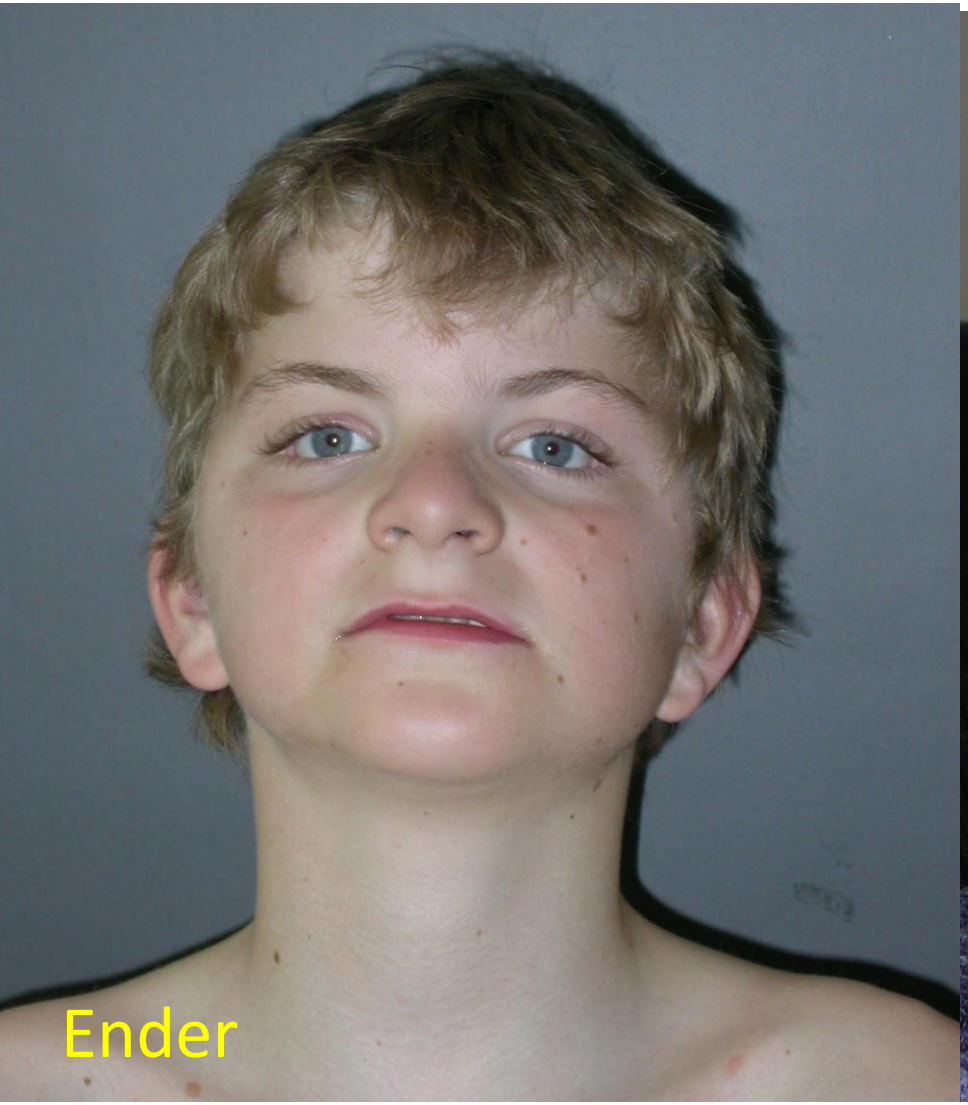
Base: 495 respondents, UK, 2010
Source: **Rare Disease UK** survey on patients and familiy experiences of rare diseases

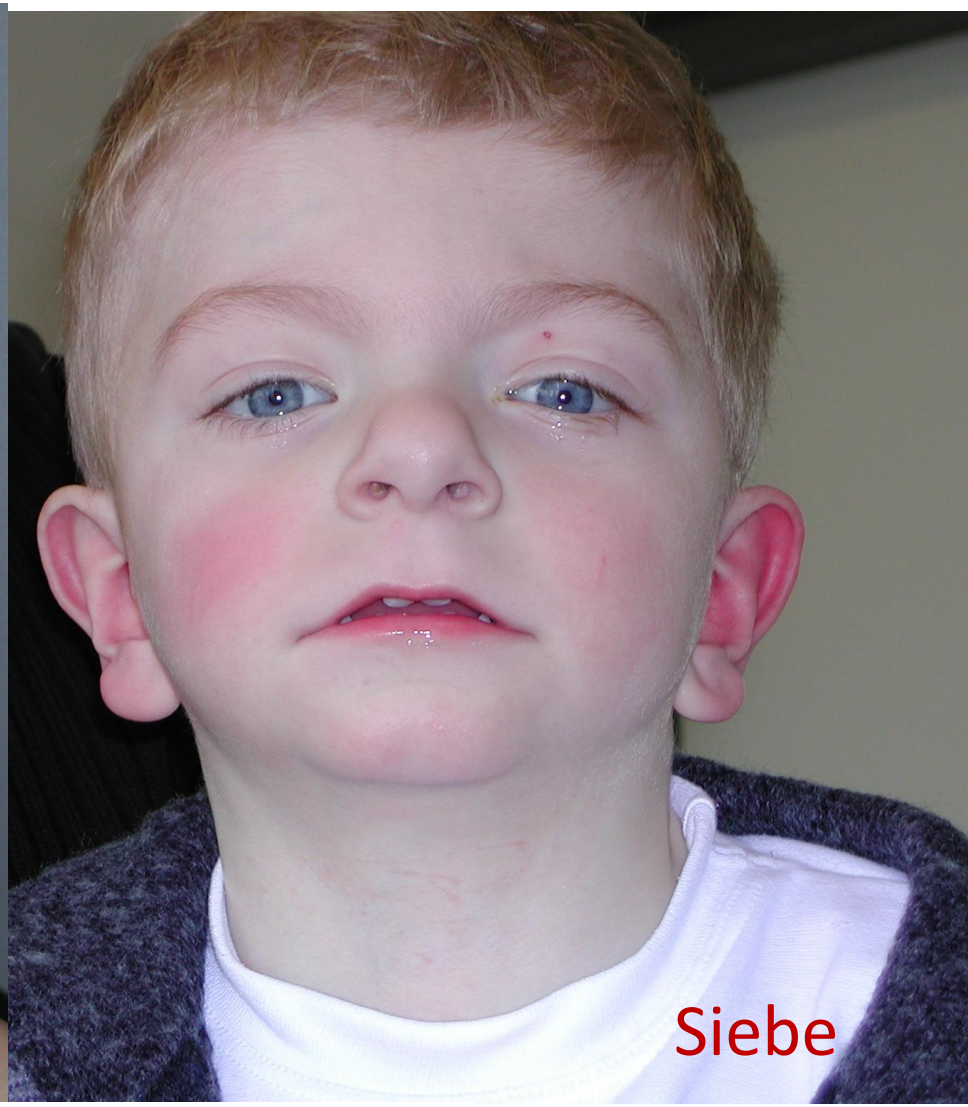
Source: Rare Disease UK Survey

How things mostly work out

Genome sequencing

Exome sequencing discovers a new rare disease



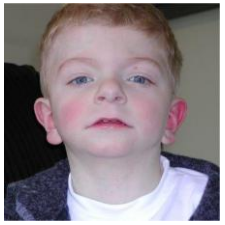


Exome sequencing 20.000 genes of Ender and his parents

Shows that **Ender** has just 1 de novo mutation.
This mutation is in the PACS1 gene

And they have **the same** **PACS1** mutation

Exome sequencing 20.000 genes of Siebe and his parents



Shows that **Siebe** has just 2 de novo mutations.
One mutation is in the PACS1 gene

What this means for Siebe's parents:

- The end of a journey: Clarity
- Exoneration of guilt
- Low recurrence risk
- Confusion after ten years
- Hope

Neonatal volvulus

extensive resection > Short bowel

 Normal growth

At 10 years: *Growth retardation*:

- ~~Syndrome~~?

  OR

- Short bowel?

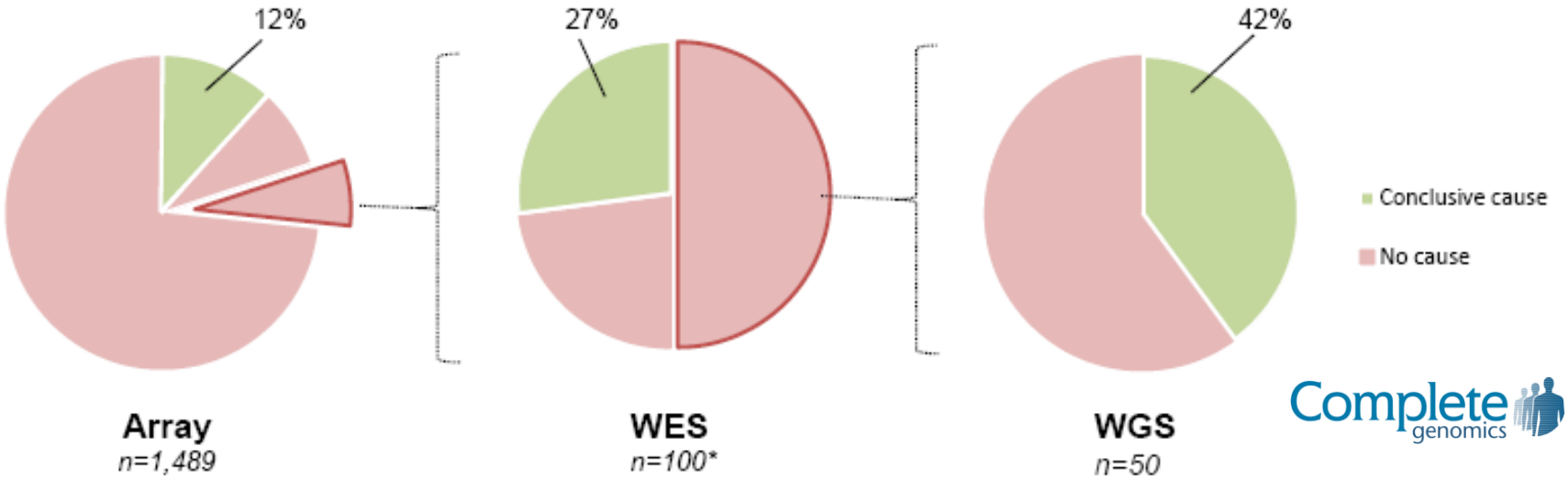
Now 18 patients with PACS1 Arg203Trp mutation

Some through Matchmaking by
DDD – Decipher / other clinicians

Most matches through mother's Facebook page !

` Schuurs-Hoeijmakers et al. Am J Med Genet, 2016

New GeneticTechnologies elucidate Intellectual Disability



De Vries et al. American Journal Human Genetics 2006

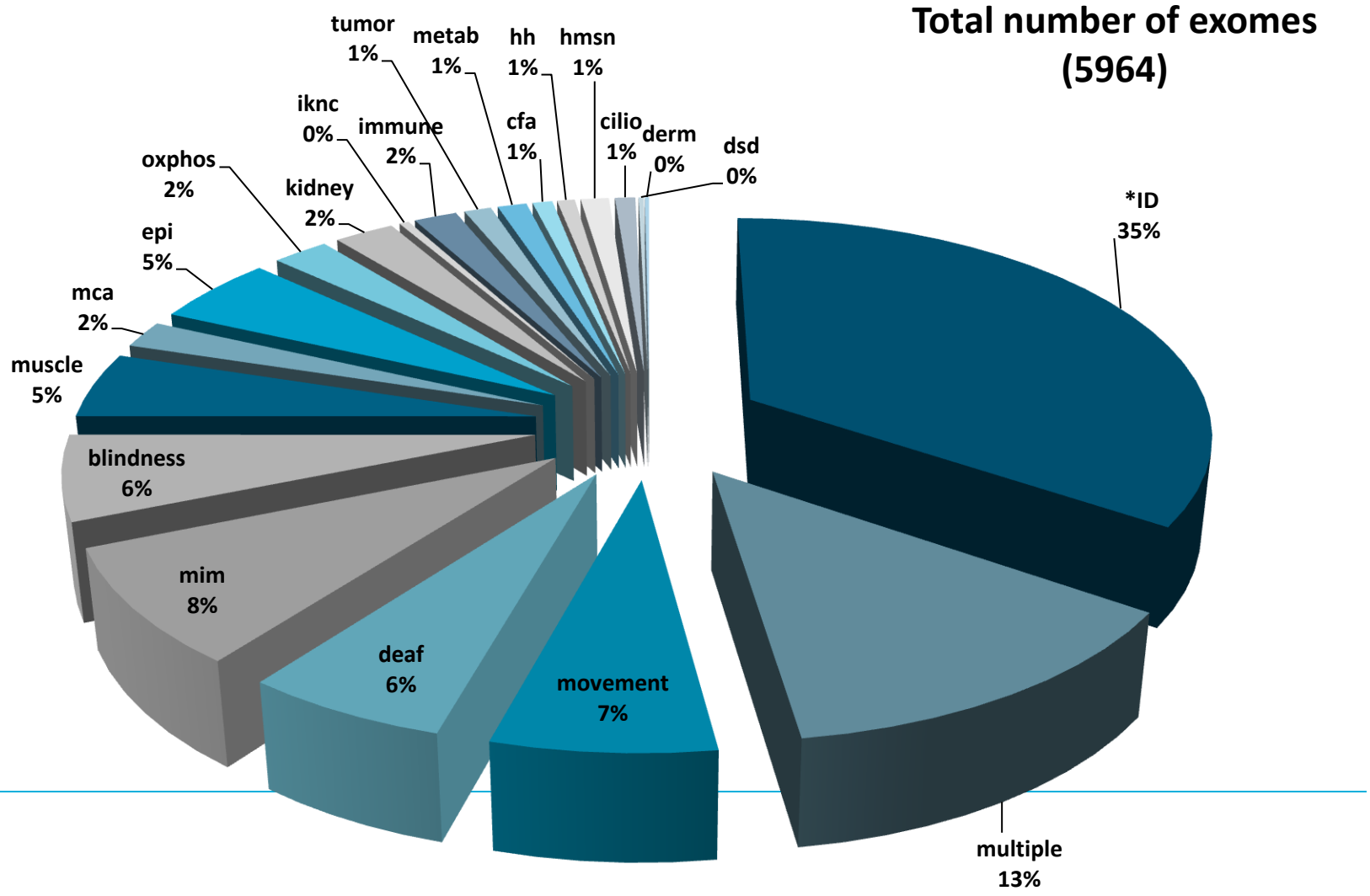
De Ligt et al. New England Journal of Medicine 2012

Gilissen et al. Nature 2014

At Radboudumc, we see ~ 8.000 patients / year

And we run ~ 6000 exomes / year
On people with various (genetic) developmental problems

% requested clinical exomes per disease panel in 2015



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

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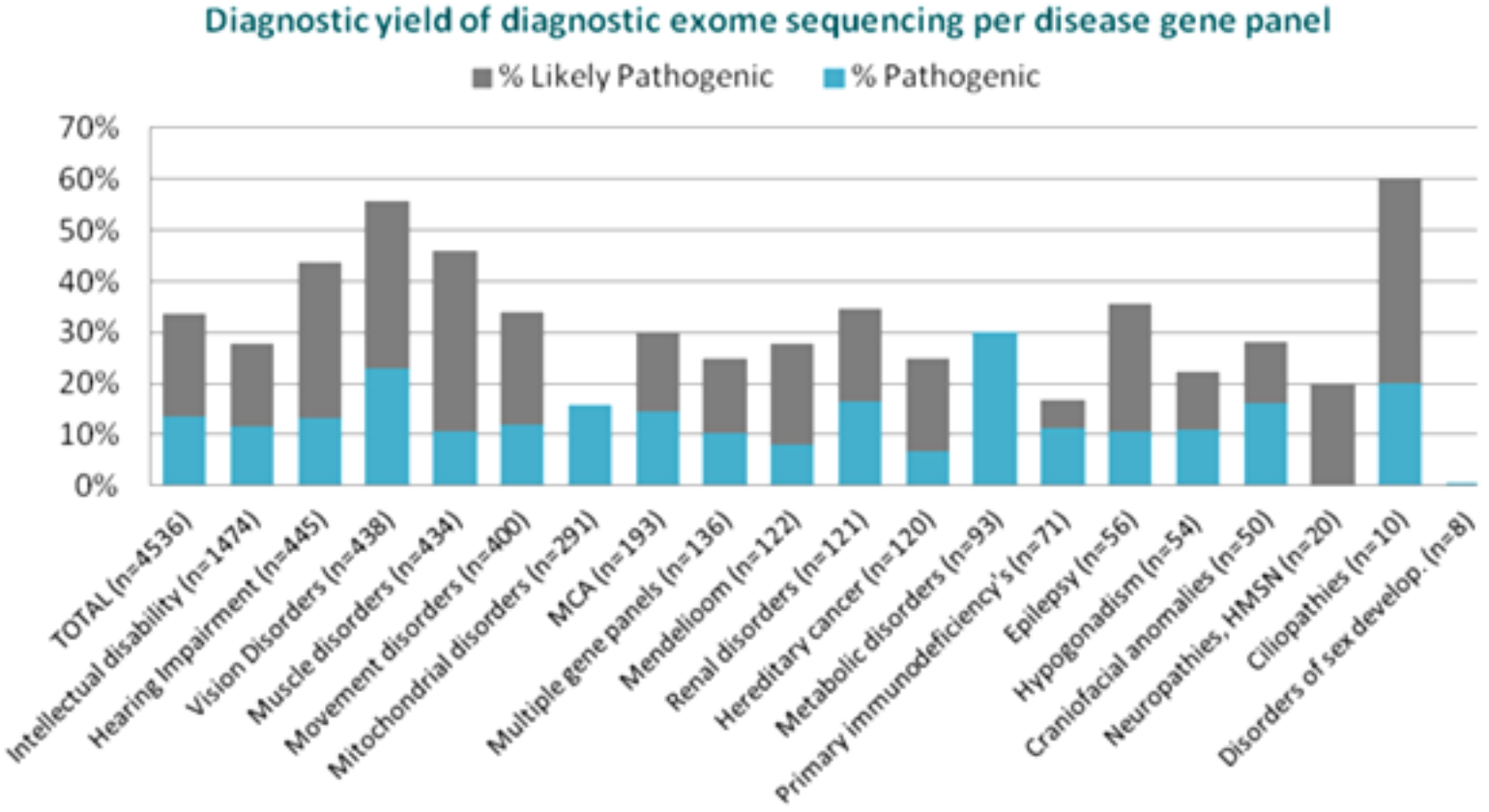
Diagnostic yield of diagnostic exome sequencing per disease gene panel
% Likely Pathogenic
% Pathogenic
70%
60%
50%
40%
30%
20%
10%
0%
TOTAL (n=4536)
Intellectual disability (n=1474)
Hearing Impairment (n=445)
Vision Disorders (n=438)
Muscle disorders (n=434)
Movement disorders (n=400)
Mitochondrial disorders (n=291)
MCA (n=193)
Multiple gene panels (n=136)
Mendelioom (n=122)
Renal disorders (n=121)
Hereditary cancer (n=120)
Metabolic disorders (n=93)
Primary immunodeficiency's (n=71)
Epilepsy (n=56)
Hypogonadism (n=54)
Craniofacial anomalies (n=50)
Neuropathies, HMSN (n=20)
Ciliopathies (n=10)
Disorders of sex develop. (n=8)

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Is next generation sequencing costly?

~1500 Euros

Is next generation sequencing costly?

~1500 Euros

But the sequencing is the *smallest* part of cost

Is next generation sequencing costly?

~1500 Euros

But the sequencing is the smallest part of cost

If done at scale

2017

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

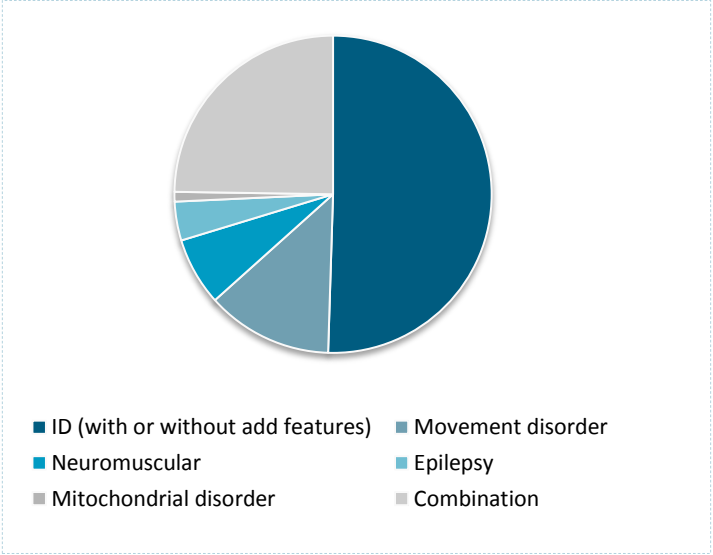
Open

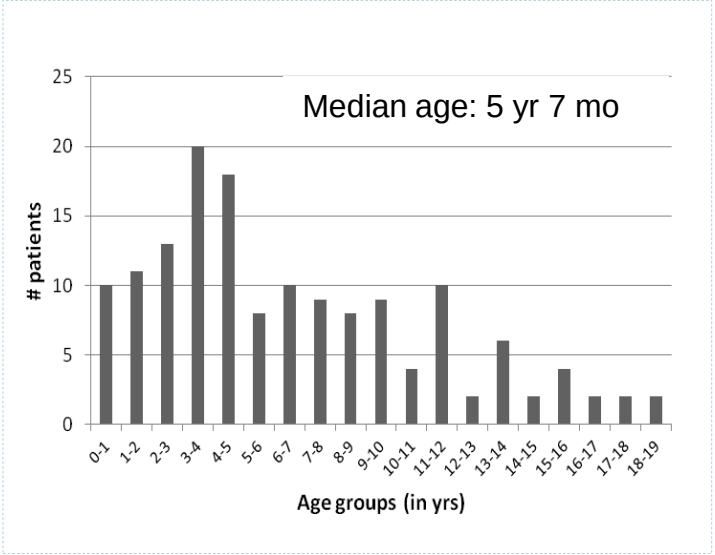
A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology

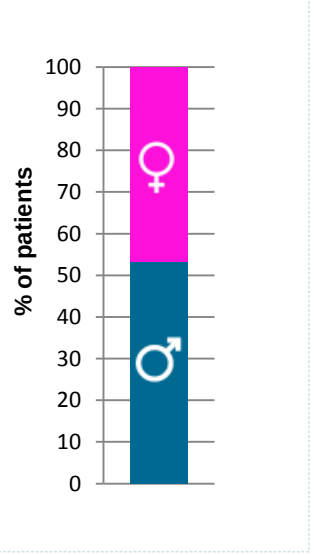
Lisenka E.L.M. Vissers, PhD[1], Kirsten J.M. van Nimwegen, MSc[2], Jolanda H. Schieving, MD[3], Erik-Jan Kamsteeg, PhD[1], Tjitske Kleefstra, MD, PhD[1], Helger G. Yntema, PhD[1], Rolph Pfundt, PhD[1], Gert Jan van der Wilt, PhD[2], Lotte Krabbenborg, PhD[4,5], Han G. Brunner, MD, PhD[1,6], Simone van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

Pediatric neurology cohort description

- 150 patients Nov 2011 - Jan 2015
- Representing ‘every day practice’ in tertiary pediatric neurology clinic
- Mixture of new patient referrals (n=66) and patients ‘somewhere’ in the diagnostic trajectory (n=84)







Last resort or First tier test?

150 consecutive patients consulted in clinical practice of pediatric neurology with a phenotype of presumed genetic origin

Patient Perspective

Interviews
assessing expectations and experience of diagnostic process so far

Interviews
assessing experience of diagnostic process and obtained diagnosis
(IQ Health care)

Conventional process

- MRI
- Blood draw
- Gene test 1
- Lumbar Puncture
- Gene test 2
- Genomic array
- Gene test 3
- ...
- Diagnosis?

Whole Exome Sequencing

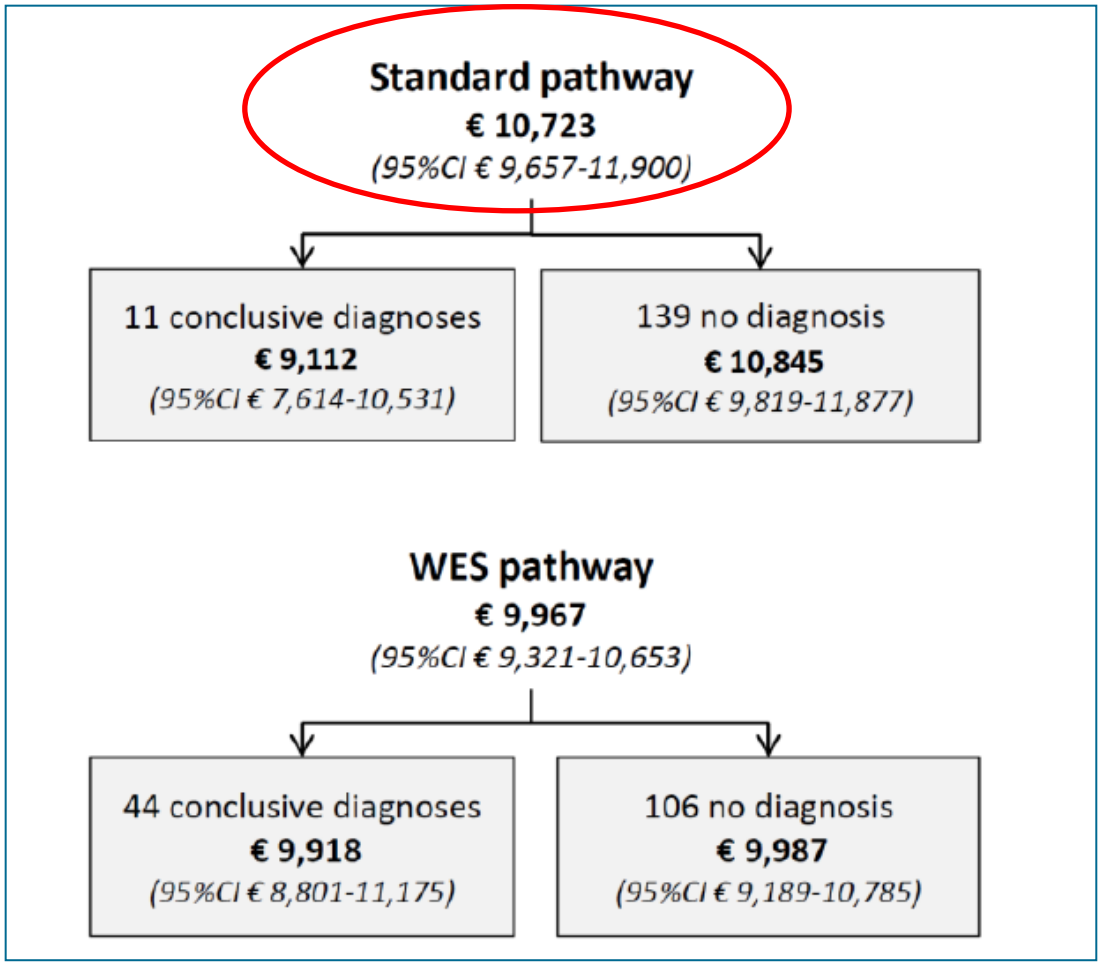
- Blood draw
- Exome sequencing
- Diagnosis?

Compare diagnostic yield of both trajectories
(Human Genetics/ Pediatric Neurology)

Cost effectiveness *(HTA)*

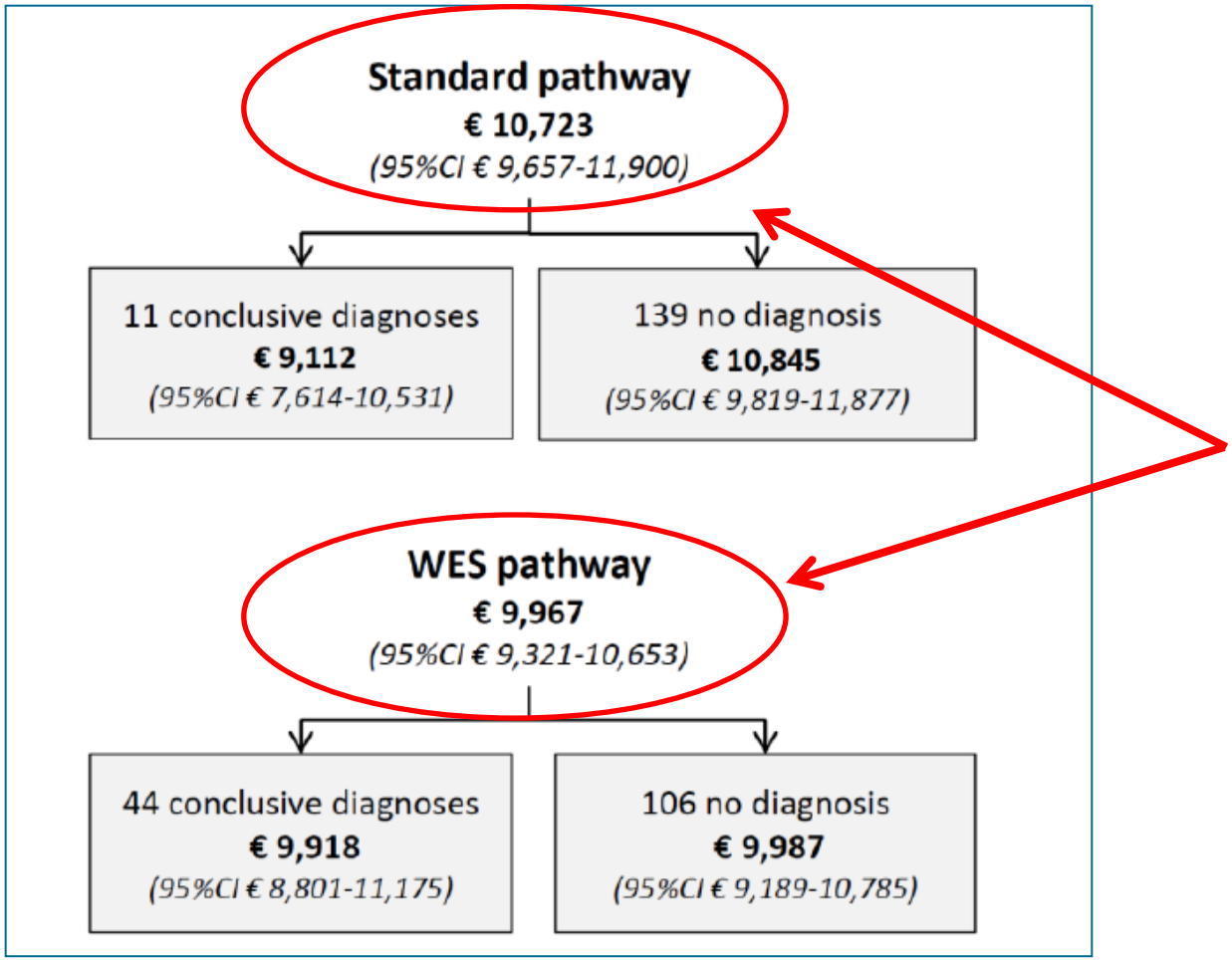
Project support: ZonMW Doelmatigheidsonderzoek (40-41200-98-9131)

150 patients admitted to pediatric neurology



Lisenka Vissers, et al. Genetics in Medicine 2017

150 patiënten voor de kinderneuroloog



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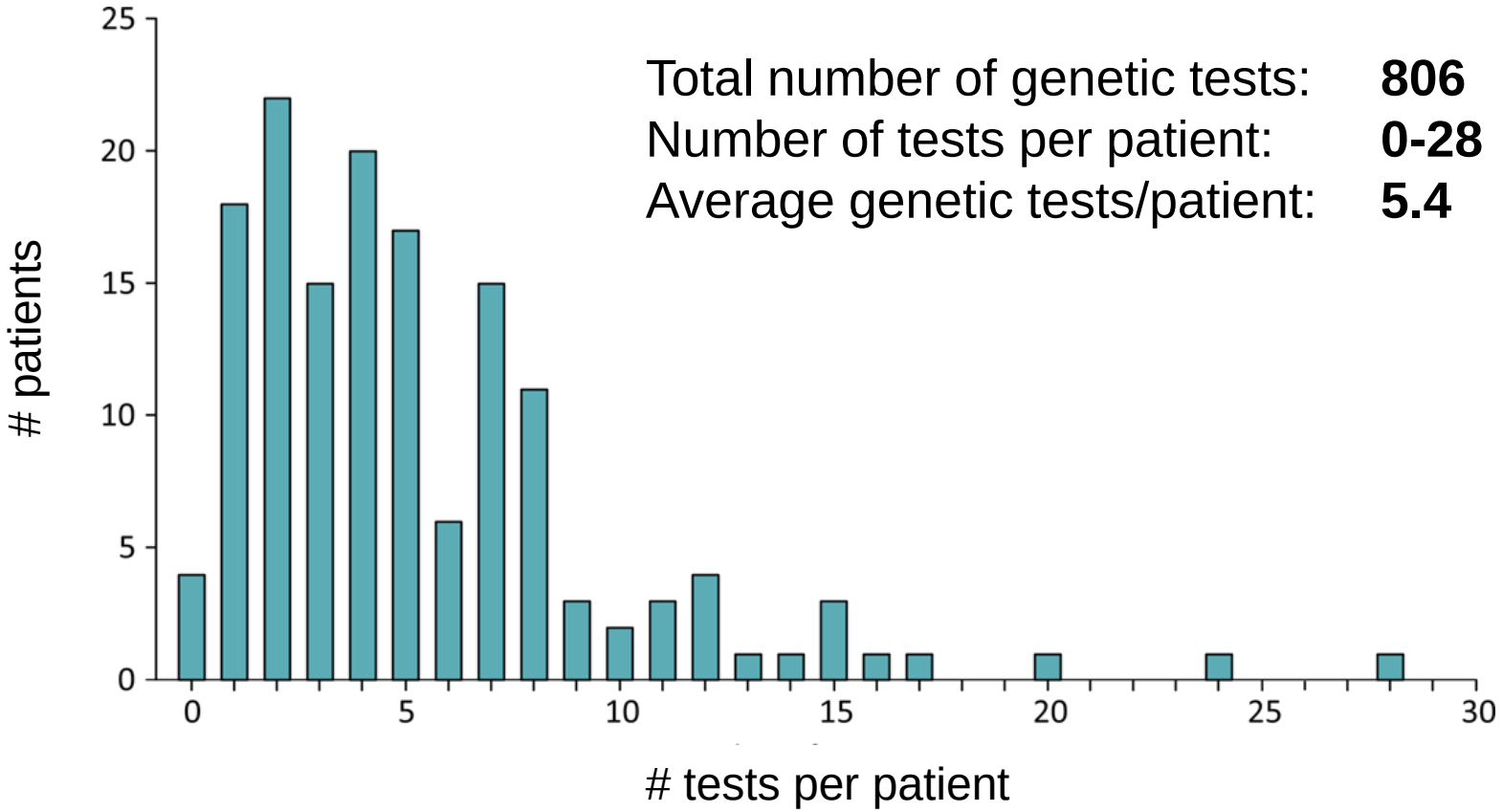
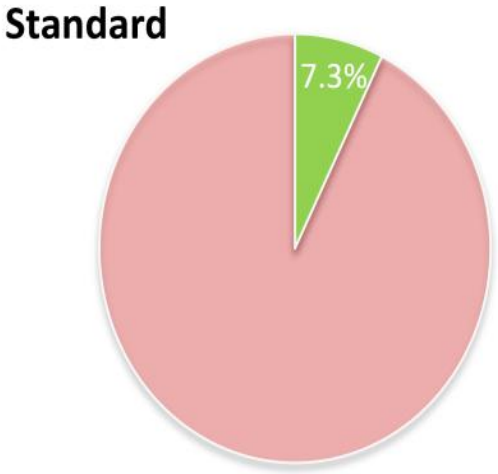
Number of genetic tests per patient



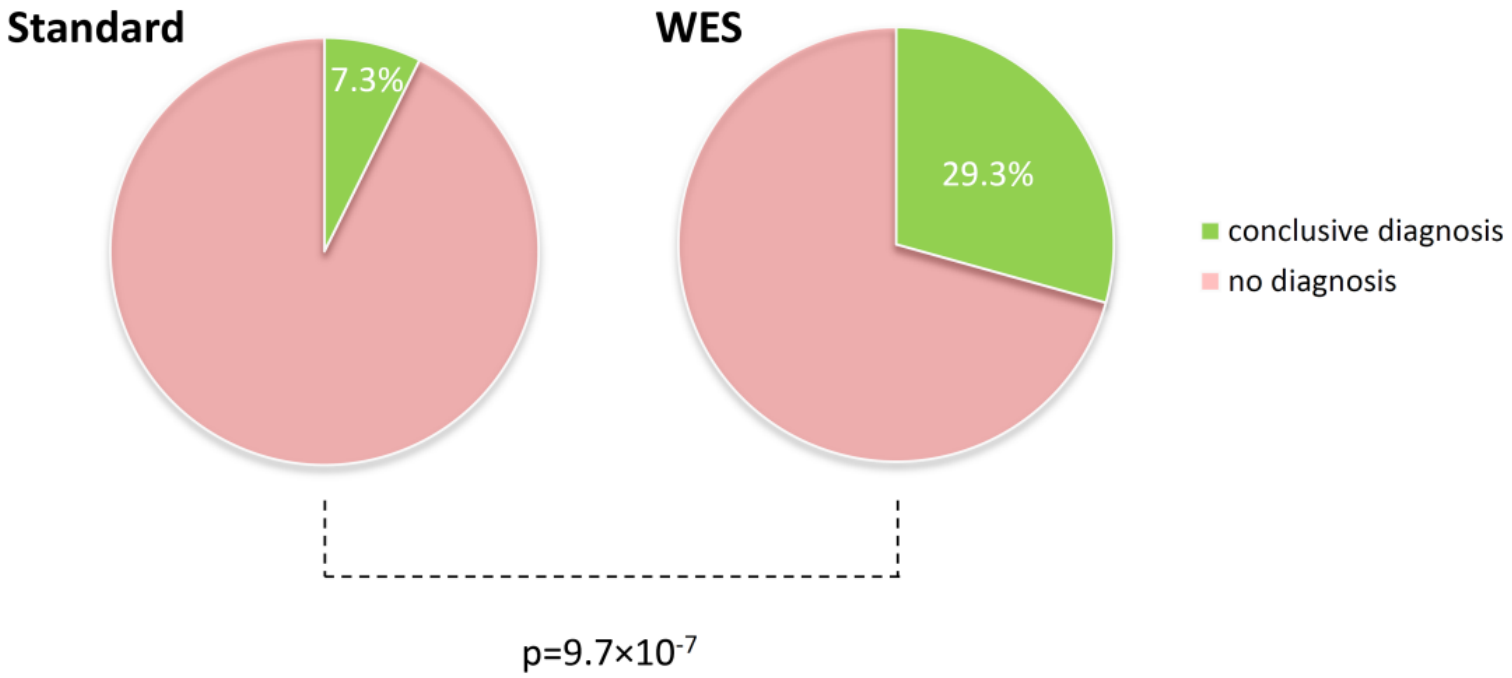
Total number of genetic tests: **806**
Number of tests per patient: **0-28**
Average genetic tests/patient: **5.4**

WES provides significantly more diagnoses

Neurologist



WES provides significantly more diagnoses

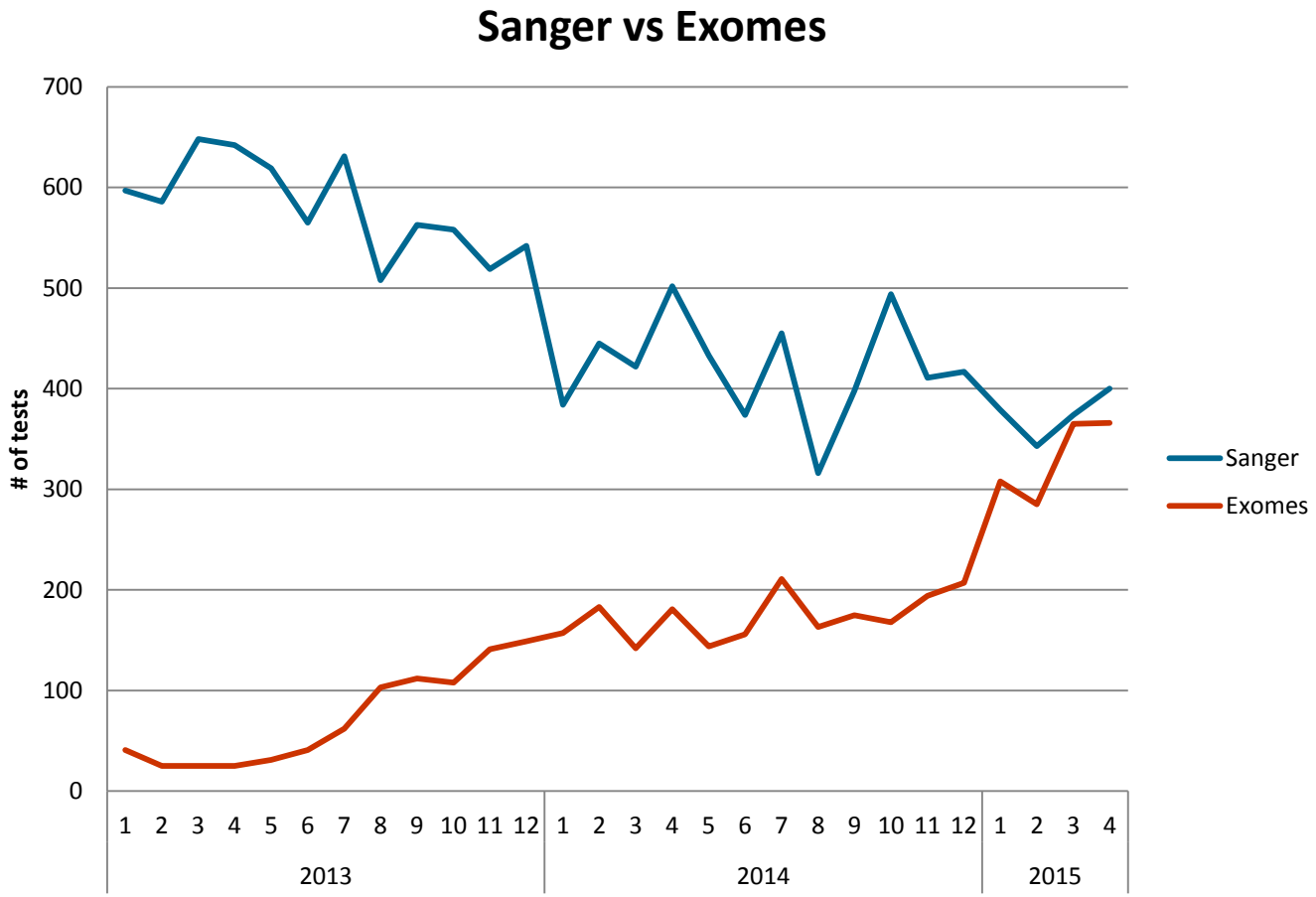


Our experience with clinical exomes

Conclusions clinical exome sequencing:

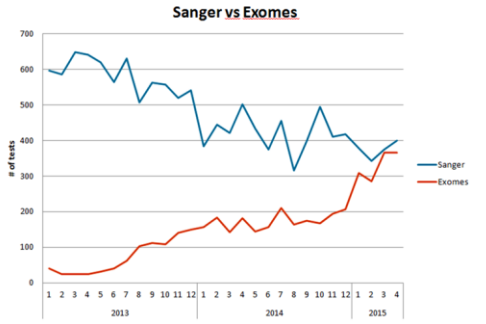
- **Diagnostic yield of WES significantly exceeds standard of care genetic testing for patients seen in pediatric neurology**

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


Sanger vs Exomes
# of tests
700
600
500
400
300
200
100
0
1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4
2013
2014
2015
Sanger
Exomes

Is next generation sequencing costly?

~1500 Euros



The *extra* cost of Genome sequencing (+ interpretation) is largely compensated by savings on conventional diagnostics

Conclusions clinical exome sequencing:

- Diagnostic yield of WES significantly exceeds standard of care genetic testing for patients seen in pediatric neurology
- **Doctors are great, but Genomes (exomes) are better**

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

Main Points

~6% of people will have a rare disease during their lifetimes. Most of these diseases are genetic

Next Generation Sequencing is an *effective diagnostic* strategy for diagnosing rare diseases

Next Generation Sequencing is a *cost-effective* strategy for diagnosing rare diseass

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Next Generation Sequencing is an effective diagnostic strategy for diagnosing rare diseases

Next Generation Sequencing is a cost-effective strategy for diagnosing rare diseases

More and more new therapies are developed based on our understanding of diease genetics and biology

Every patient has the right to a correct diagnosis

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