Genomics Changes Medicine

Han G. Brunner

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Human Genetics Nijmegen

Maastricht UMC+

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university medical center

The first whole genomes

James Watson

Craig Venter

The Diploid Genome Sequence of an Individual Human

PloS Biology 2007

Marjolein Kriek

Jim Lupski

The complete genome of an individual by massively parallel DNA sequencing

Nature 2008

The diploid genome sequence of an Asian individual

Nature 2008

Ozzy Osbourne

DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome

Nature 2008

Ozzy Osbourne
genome sequencing project

TEDMED 2010

Ozzy Osbourne
genome
sequencing project

WHAT WILL THE UNVEILING OF A FULL OSBOURNE GENOME REVEAL?

TEDMED2010

An independent event. TED logo used under license from Ted Conferences, LLC.

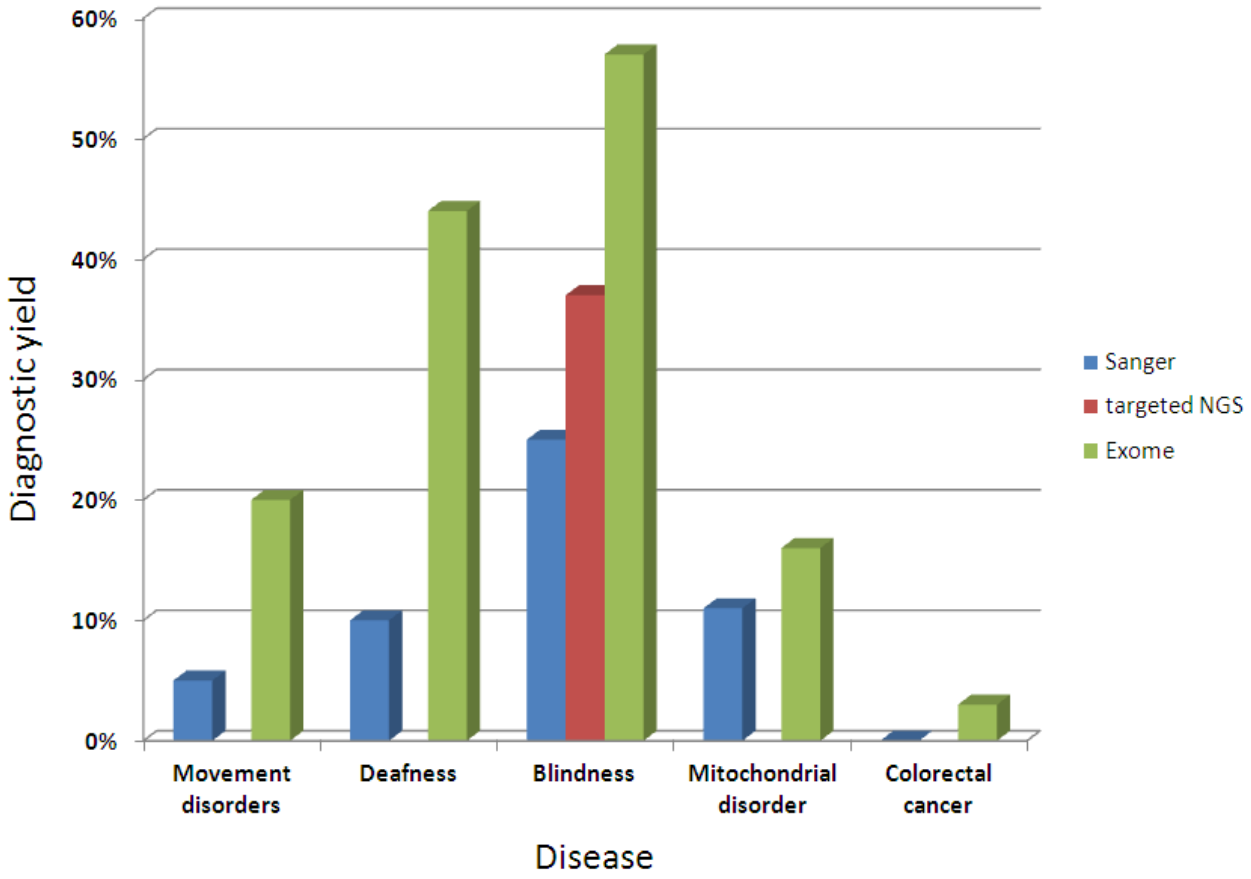
"Given the swimming pools of booze I've guzzled over the years–not to mention all of the cocaine, morphine, sleeping pills, cough syrup, LSD, Rohypnol…you name it–there's really no plausible medical reason why I should still be alive," he said in the Times.

"Maybe my DNA could say why."

The results of Osbourne's genome sequencing project will be presented in full detail Friday at the TEDMED 2010 meeting in San Diego, Calif.


SOLiD 4 Analyzer

2012: 186 Diagnostic exomes across 5 diagnostic groups



Compare with clinical diagnostic practice 2011

Genomics Changes Medicine

* Pharmacogenomics
* Innovative therapies
* Diagnosis

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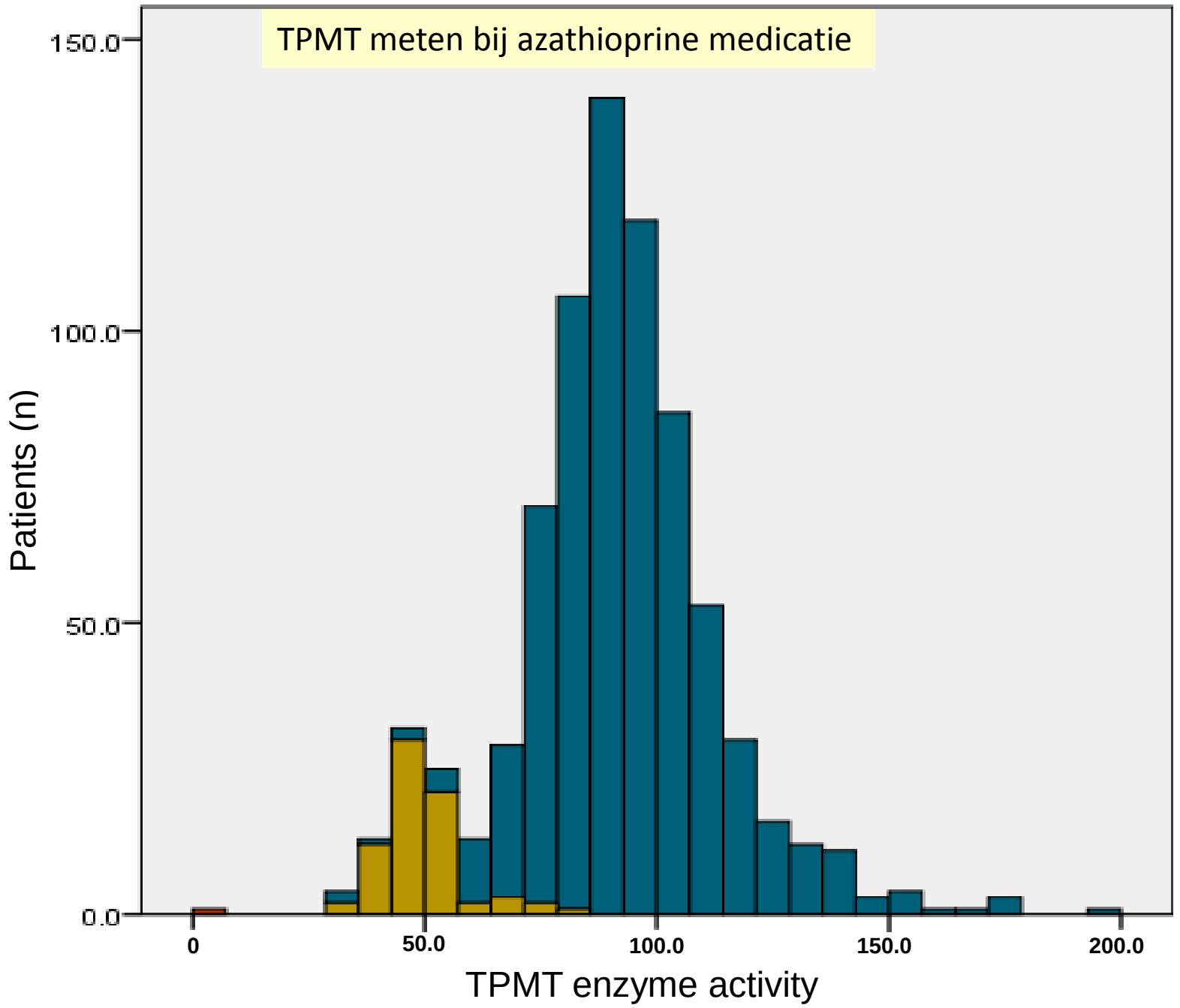
Farmacogenetica (PGx)

Hoe genetische variatie de respons van een individu op medicatie kan beïnvloeden

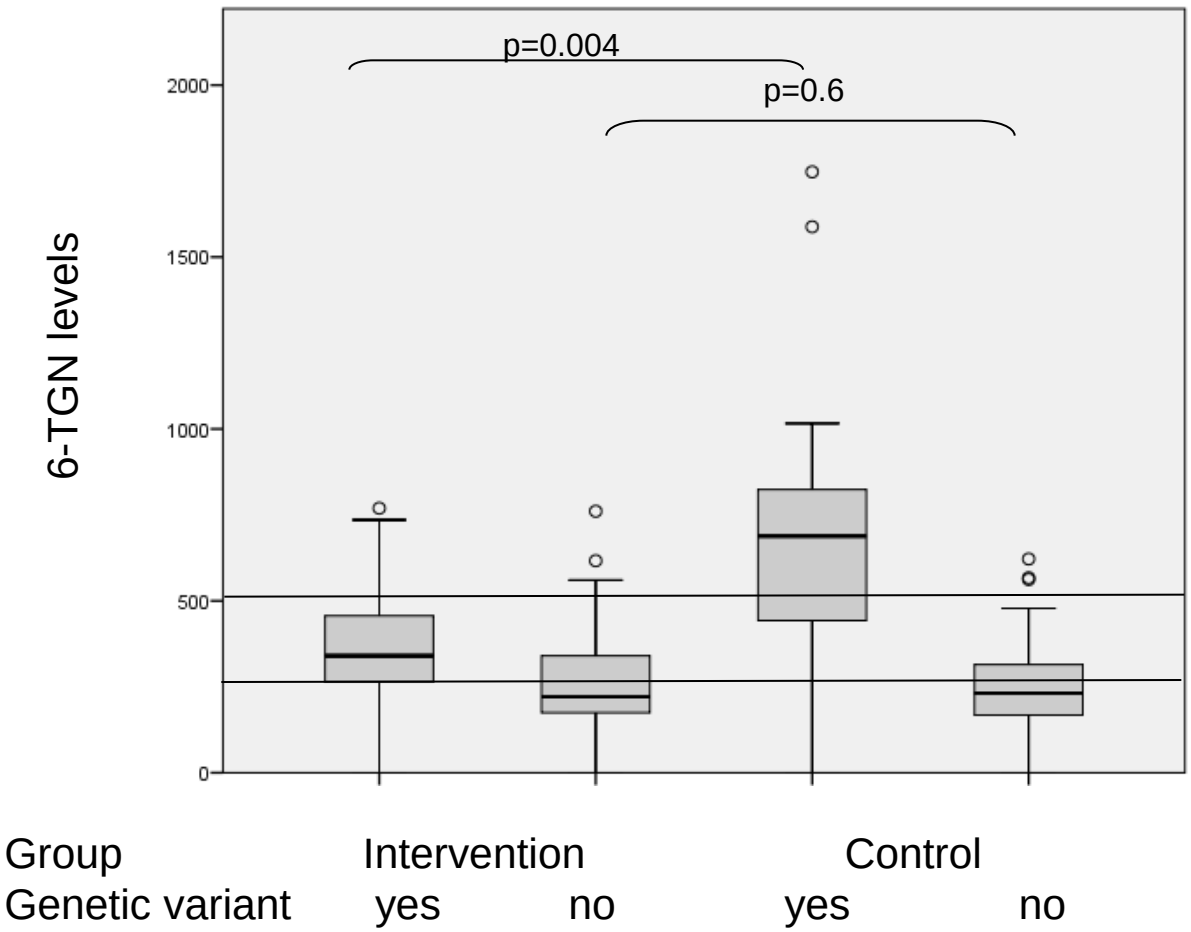
Optimaliseren therapeutisch effect

Juiste dosis bepalen

Vermijden bijwerkingen


TPMT meten bij azathioprine medicatie
150.0
100.0
50.0
0.0
Patients (n)
0
50.0
100.0
150.0
200.0
TPMT enzyme activity

Patients treated with an adjusted dose achieve normal levels of the active metabolite



Marieke Coenen

Dosering op basis van het *TPMT* genotype resulteert in minder hematologische bijwerkingen in de groep met een variant

	Interventie	Controle	RR (95%CI)
Totaal (n)	399	370	
Hematologische bijwerking	29 (7,2%)	29 (7,8%)	
TMPT variant	1 / 39 (2,6%)	8 / 35 (22,9%)	0,11 (0,01-0,85)
Geen *TPMT* variant	29 / 360 (8,1%)	22 / 335 (6,6%)	1,2 (0,72-2,09)

Human Genetics Nijmegen

De interventie groep maakt lagere kosten

Marieke Coenen

	Interventie (n=238)	Controle (n=216)	p-waarde
Gezondheidszorgperspectief	2297 ± 3123	2440 ± 4456	0,683
Maatschappelijk perspectief (inclusief gezondheidszorgkosten)	4433 ± 6175	6150 ± 10859	0,023

Human Genetics Nijmegen

KNMP guidelines

REPORTS

nature publishing group

Pharmacogenetics: From Bench to Byte—An Update of Guidelines

JJ Swen[1], M Nijenhuis[2], A de Boer[3], L Grandia[2], AH Maitland-van der Zee[3], H Mulder[3,4], GAPJM Rongen[5,6,7], RHN van Schaik[8], T Schalekamp[3], DJ Touw[9], J van der Weide[10], B Wilffert[11], VHM Deneer[12] and H-J Guchelaar[1]

Voorbeeld richtlijnen KNMP

CYP2D6

Drug	Subjects (*N*)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene–drug interaction	Therapeutic (dose) recommendation	References
Nortriptyline	270	PM	3	C	Yes	Reduce dose by 60% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	122–127
		IM	4	C	Yes	Reduce dose by 40% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	122–124, 126, 128–132
		UM	3	C	Yes	Select alternative drug (e.g., citalopram, sertraline) or increase dose by 60% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	39, 123, 124, 128
Codeine	453	PM	4	B	Yes	Analgesia: select alternative drug (e.g., acetaminophen, NSAID, morphine—not tramadol or oxycodone) or be alert to symptoms of insufficient pain relief Cough: no	45–55
		IM	3	A	Yes	Analgesia: select alternative drug (e.g., acetaminophen, NSAID, morphine—not tramadol or oxycodone) or be alert to symptoms of insufficient pain relief Cough: no	46, 56
		UM	3	F	Yes	Analgesia: select alternative drug (e.g., acetaminophen, NSAID, morphine—not tramadol or oxycodone) or be alert to ADE Cough: be extra alert to ADEs due to increased morphine plasma concentration	45, 57–60

Children's codeine deaths prompt warning

Kids given standard doses of painkiller after tonsil surgery

CBC News Posted: Apr 09, 2012 4:47 PM ET | Last Updated: Apr 09, 2012 8:56 PM ET

Codeine can kill 2:14

Two more children's deaths and a near fatality have been linked to standard doses of codeine after tonsil surgery, leading researchers to suggest reconsidering the painkiller's use.

Dagelijkse praktijk

- PGx wordt nauwelijks gebruikt
  - Onbekendheid:
    het komt maar weinig voor dat het rampzalig mis gaat
  - Genetische test voorspelt niet *altijd* het fenotype
  - Men denkt dat het lang duurt voordat uitslag bekend is
  - Kosten niet in DBC

- Als het al gebruikt wordt, vaak pas na start behandeling

Het standaard invoeren van enkele gevalideerde farmacogenetica testen

dient nu voortvarend opgepakt te worden door ziekenhuisapothekers

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Genomics Changes Medicine

* Pharmacogenomics

* Innovative therapies

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Genomics just got personal

Wat als we elke kanker zouden sequencen?

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International Cancer Genome Consortium

The CANCER GENOME challenge

CPCT Center for Personalized Cancer Treatment

De missie van het CPCT
"Het is onze missie is om elke patiënt een gepersonaliseerde behandeling tegen kanker aan te kunnen bieden, welke gebaseerd is op de genetische eigenschappen van de tumor van de patiënt, …."

‘’Personalised medicine is the **most exciting change** in cancer treatment since the invention of chemotherapy’’
Professor Peter Johnson, Chief Clinician, Cancer Research UK

CANCER RESEARCH UK

ARTICLE

doi:10.1038/nature11412

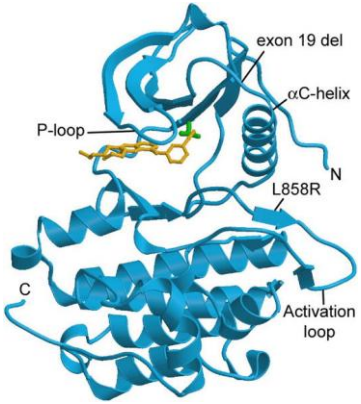
Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

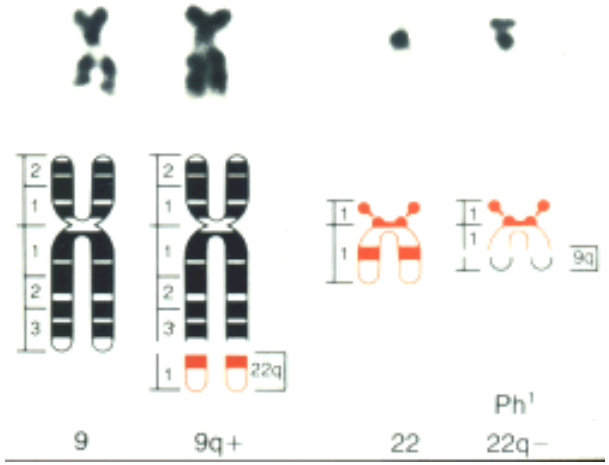
The New York Times September 24, 2012

"This is the road map for how we might cure breast cancer in the future," said Dr. Matthew Ellis of Washington University, a researcher for the study.

Magic bullets



BCR-ABL	CML	Imatinib
PDGFR-alpha	Hyper-eosinofiel syndroom	Imatinib
KIT	Gastro-intestinale stromal tumor	Imatinib
EGFR	Niet-kleincellig longkanker	Gefitinib



Philadelphia chromosoom

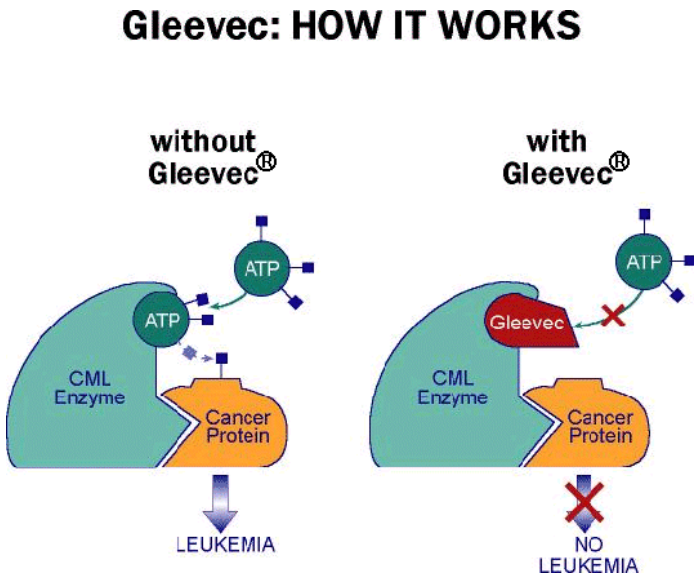
Bij

Chronische Myeloiede Leukemie

Moleculair Mechanisme:

Geactiveerd kinase

Imatinib

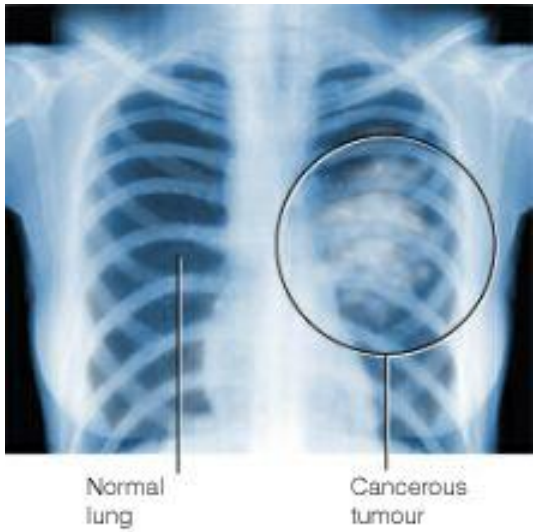


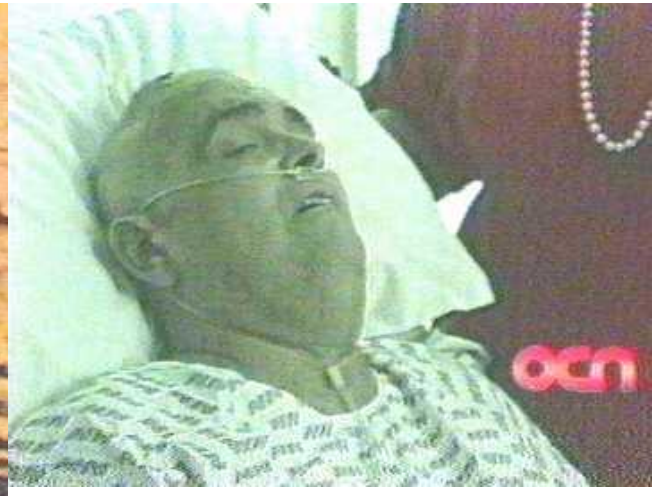
geneesmiddel

Lung cancer

Small cell lung cancer

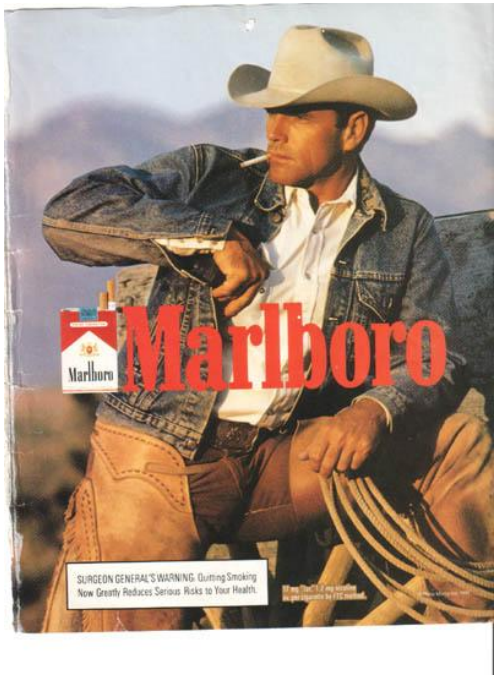
Non-Smal Cell lung cancer

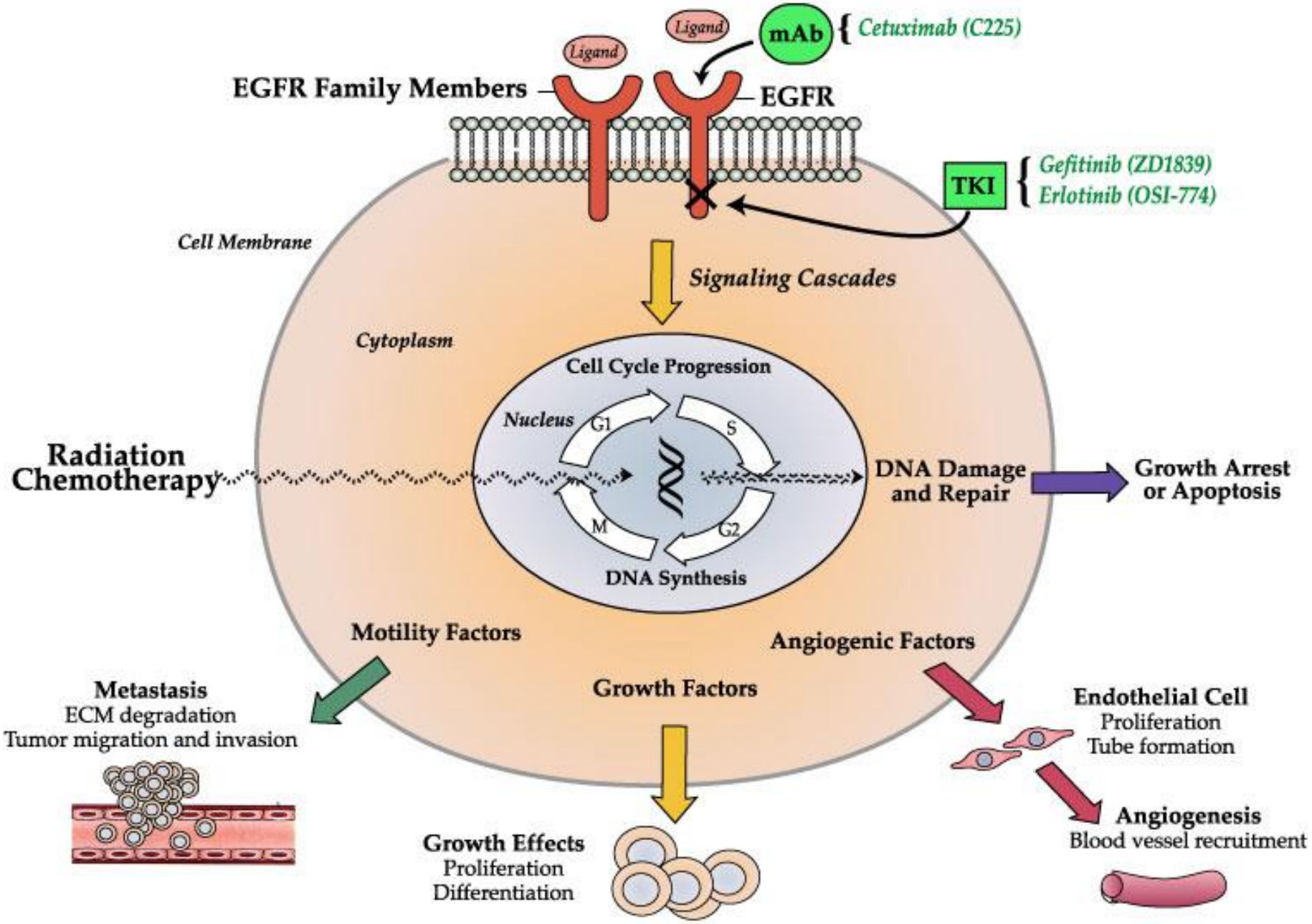




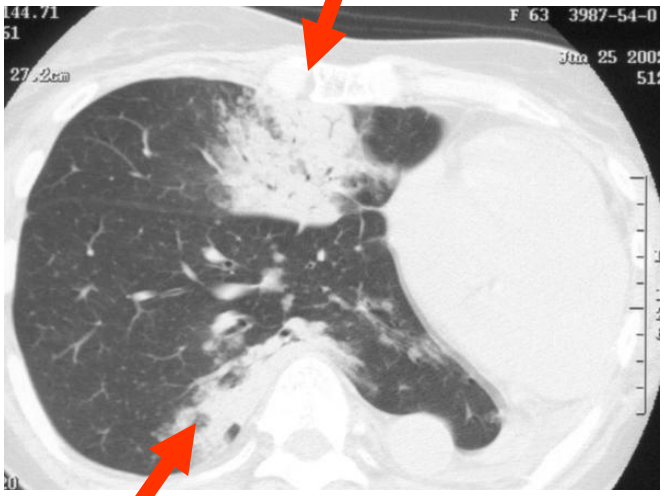
The main cause of lung cancer is smoking

The influence of genetic factors is **small**

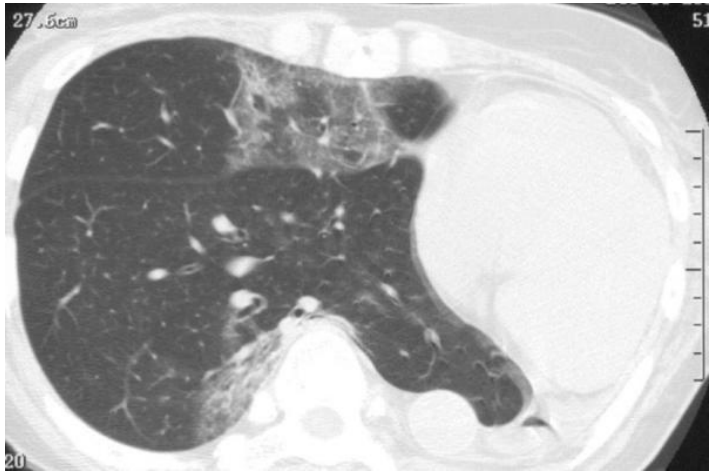



Ligand
Ligand
mAb
Cetuximab (C225)
EGFR Family Members
EGFR
TKI
Gefitinib (ZD1839)
Erlotinib (OSI-774)
Cell Membrane
Signaling Cascades
Cytoplasm
Cell Cycle Progression
Nucleus
G1
S
M
G2
DNA Synthesis
Radiation
Chemotherapy
DNA Damage
and Repair
Growth Arrest
or Apoptosis
Motility Factors
Angiogenic Factors
Growth Factors
Metastasis
ECM degradation
Tumor migration and invasion
Endothelial Cell
Proliferation
Tube formation
Angiogenesis
Blood vessel recruitment
Growth Effects
Proliferation
Differentiation

10% van niet-kleincellig longca.



Before treatment



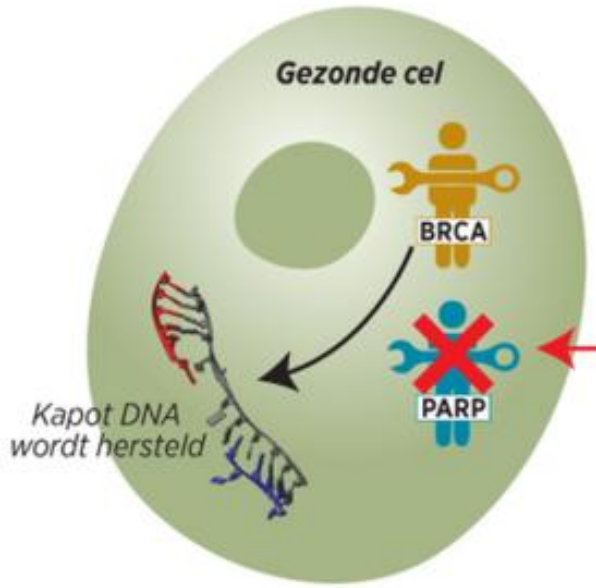
After 8 weeks Gefitinib

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

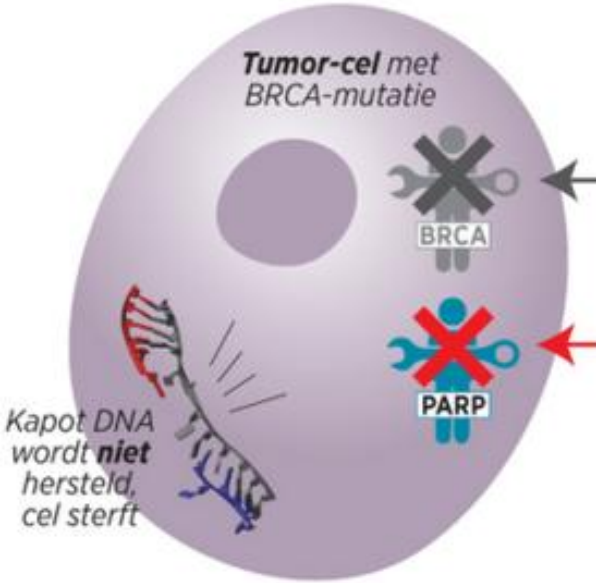
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

REMSTOF DOODT TUMORCEL, GEZONDE CEL BLIJFT LEVEN



Als in een gezonde cel een dna-breuk optreedt, zijn er twee 'monteurs' (reparatie-eiwitten) die dat kunnen repareren: BRCA en PARP.

Bij gebruik van een PARP-remmer (een kankermedicijn) blijft de BRCA-monteur over om het kapotte dna te repareren.



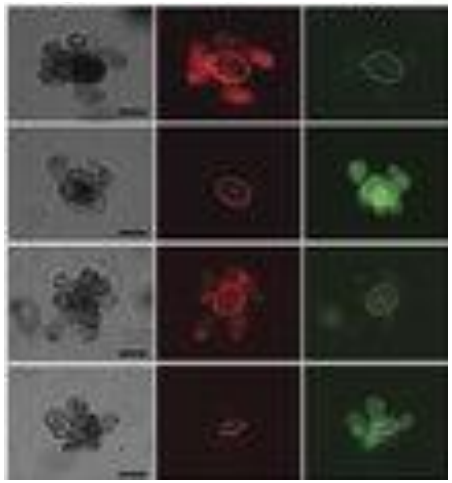
In een tumor-cel met BRCA-mutatie ontbreekt de BRCA-'monteur'.

Afwezig door mutatie.

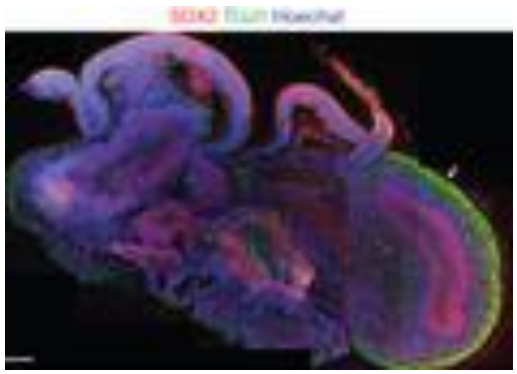
Bij gebruik van een PARP-remmer is er geen enkele monteur over om het DNA te repareren zodat de tumorcel sterft.

Hans Clevers

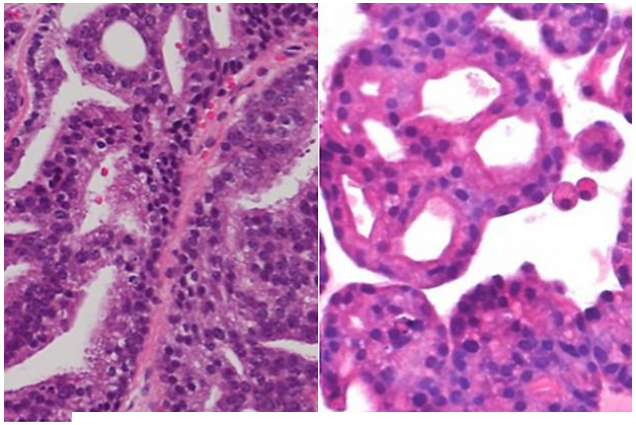
Intestine



Organoids



Brain



Prostate cancer

> Retouradres Postbus 20350 2500 EJ Den Haag

Ministerie van Volksgezondheid,
Welzijn en Sport

De Voorzitter van de Tweede Kamer
der Staten-Generaal
Postbus 20018
2500 EA DEN HAAG

Datum 10 juni 2014
Betreft Voorwaardelijke toelating tot het basispakket

Door middel van deze brief wil ik u informeren over de verdere ontwikkeling en vormgeving van het instrument voorwaardelijke toelating, de uitbreiding van voorwaardelijke toelating naar de extramurale hulpmiddelensector en over de interventies die ik als potentiële kandidaat zie voor voorwaardelijke toelating in 2014 en 2015.

Financiële middelen en dekking

Voor de financiering van het instrument voorwaardelijke toelating heb ik in het budgettair kader zorg (BKZ) middelen gereserveerd van € 15,5 miljoen in 2014 oplopend naar structureel € 99 miljoen in 2018. Voorwaardelijke toelating van interventies vindt plaats binnen deze budgettaire reeks. Dekking van deze middelen is beschikbaar door lager dan geraamde uitgaven op het kader geneesmiddelen. Het grootste deel van de gereserveerde middelen (€ 12,5

Het vinden van een genetische verandering in kanker moet

* ***onmiddelijk***
* ***pas na adequate RCTs***

tot aanpassing van de behandeling leiden

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Genomics Changes Medicine

* Pharmacogenomics
* Innovative therapies
* Diagnosis

Human Genetics Nijmegen

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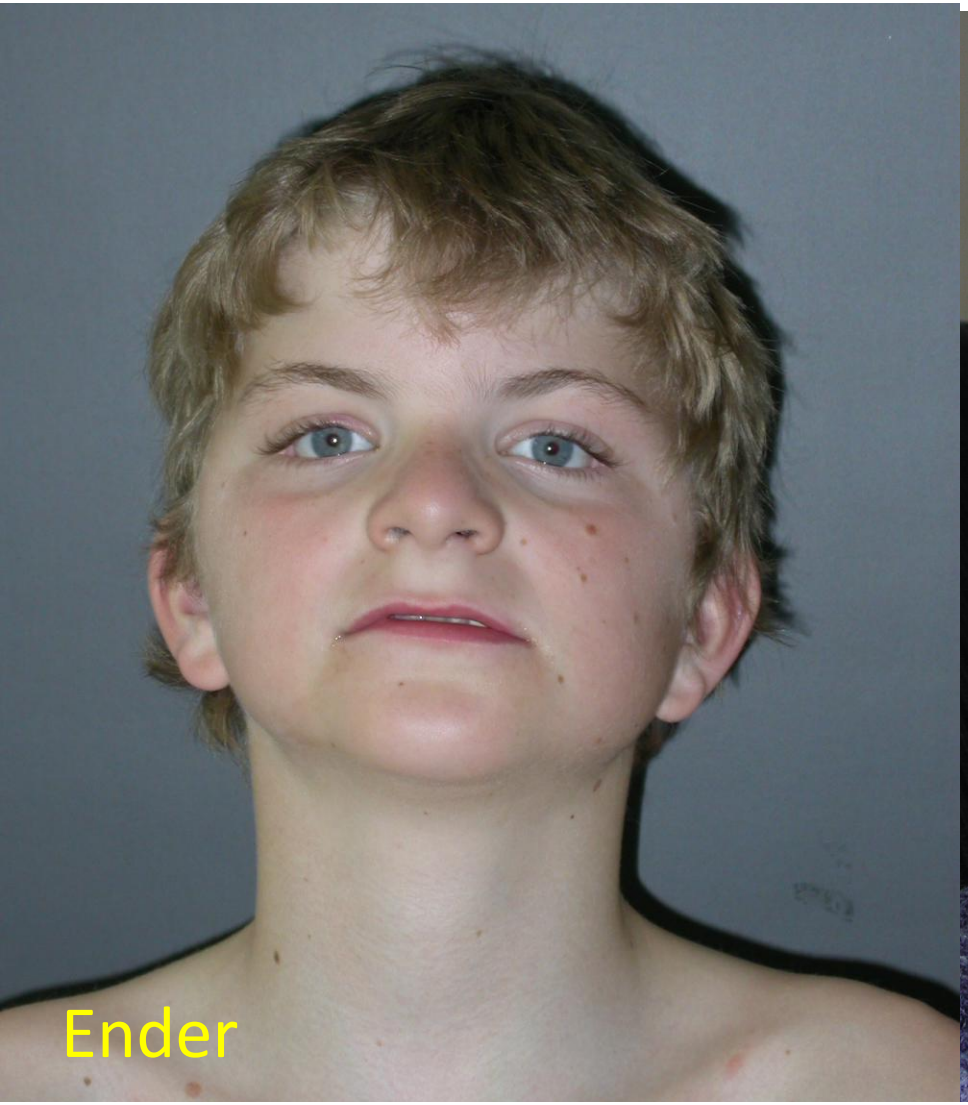
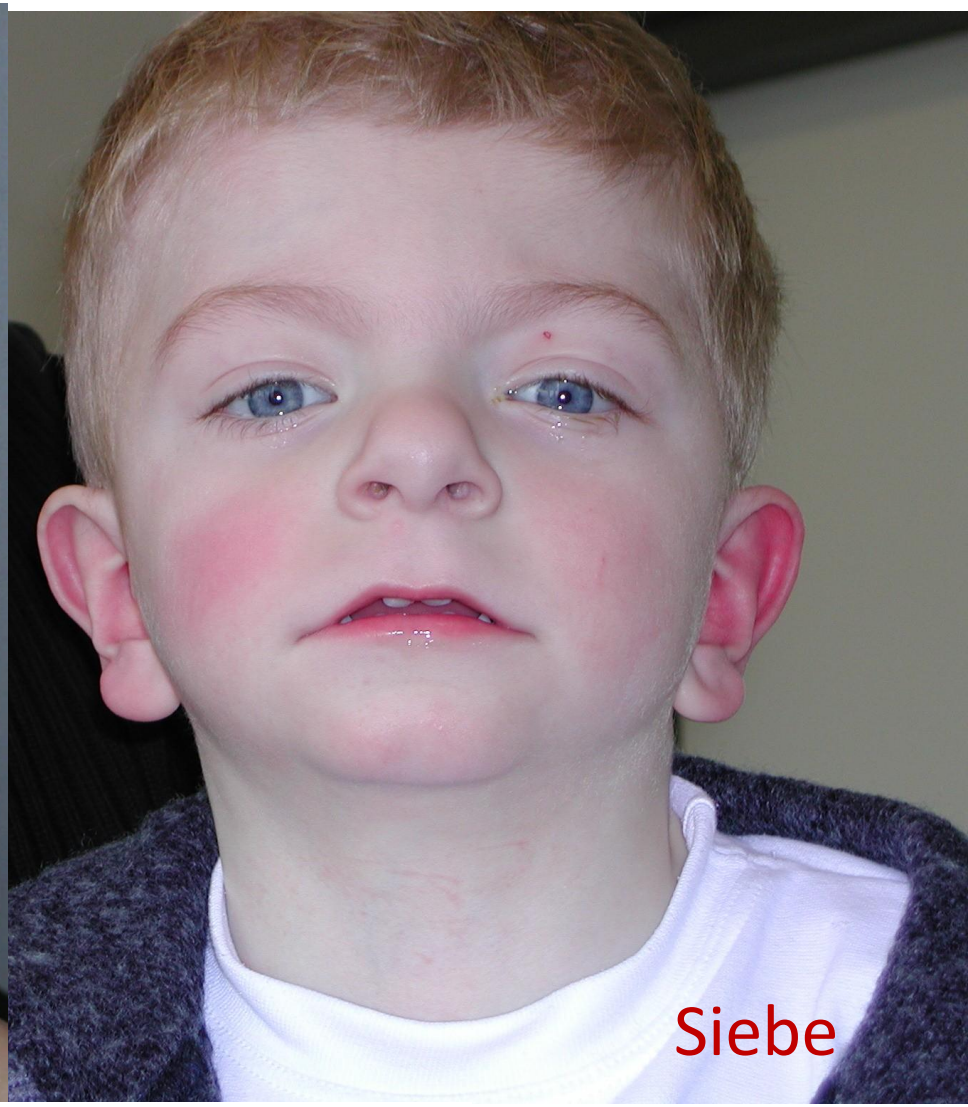
Our experience with clinical exomes

Exome sequencing discovers a new rare disease





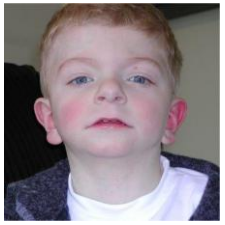
Exome sequencing 20.000 genes of Ender and his parents

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

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

Exome sequencing 20.000 genes of Siebe and his parents



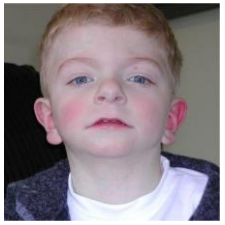
Shows that **Siebe** has just 2 de novo mutations.
One mutation is in the PACS1 gene

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

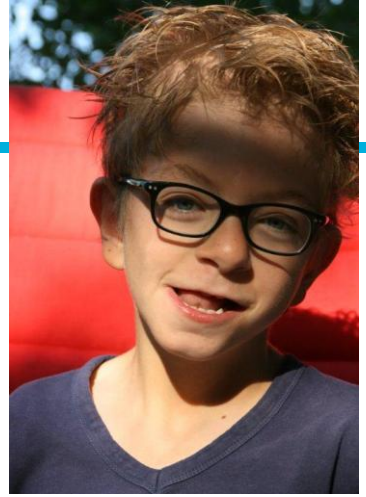
Exome sequencing 20.000 genes of Siebe and his parents



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

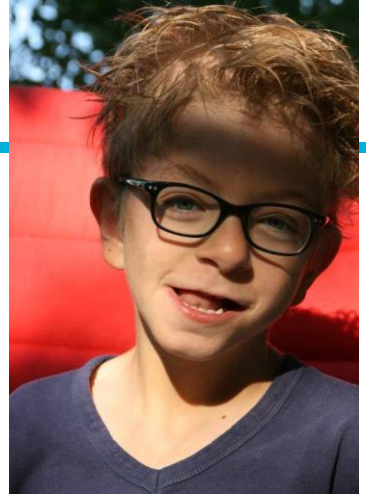
extensive resection > Short bowel

At 10 years: *Growth retardation:*

- Syndrome?

  OR

- Short bowel?


Neonatal volvulus

extensive resection > Short bowel

Normal growth

At 10 years: *Growth retardation*:

- ~~Syndrome~~?

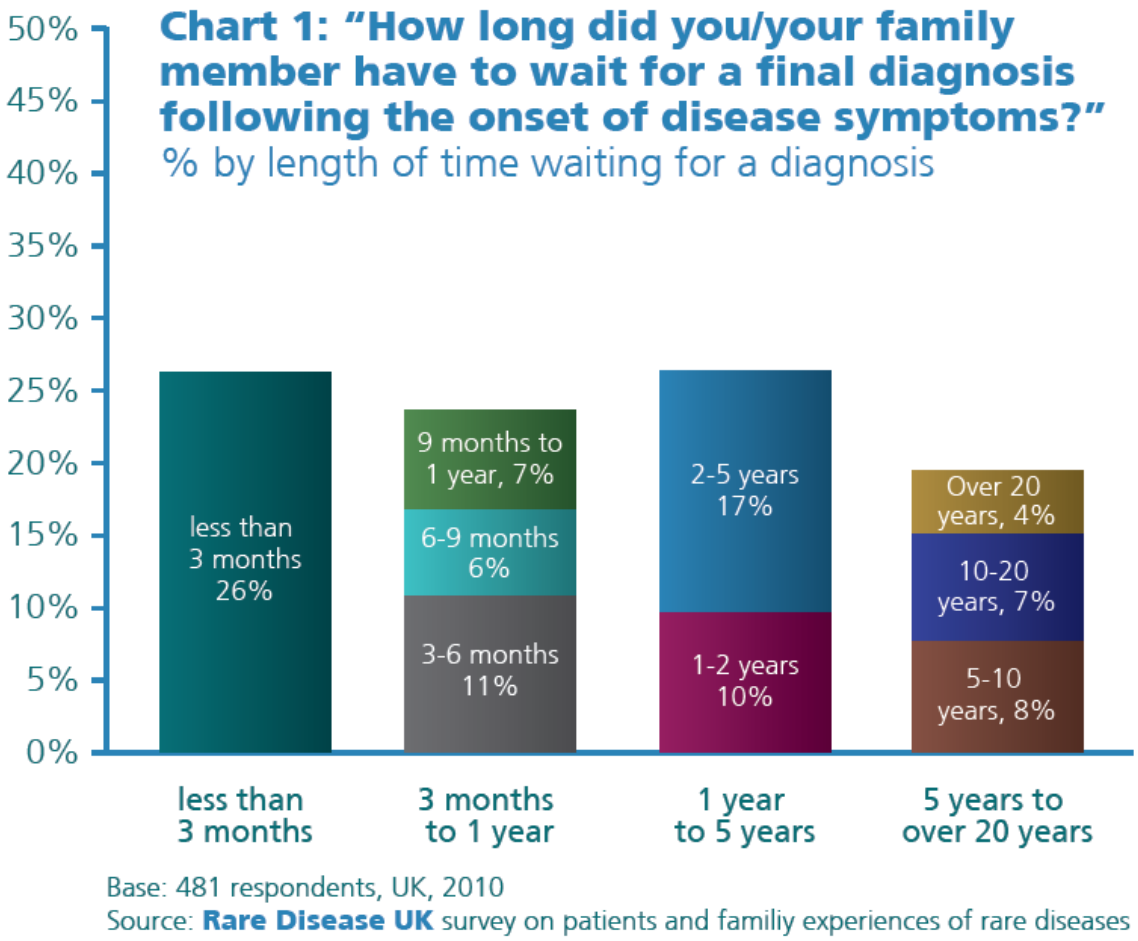
  OR

- Short bowel?

Is exome sequencing costly?

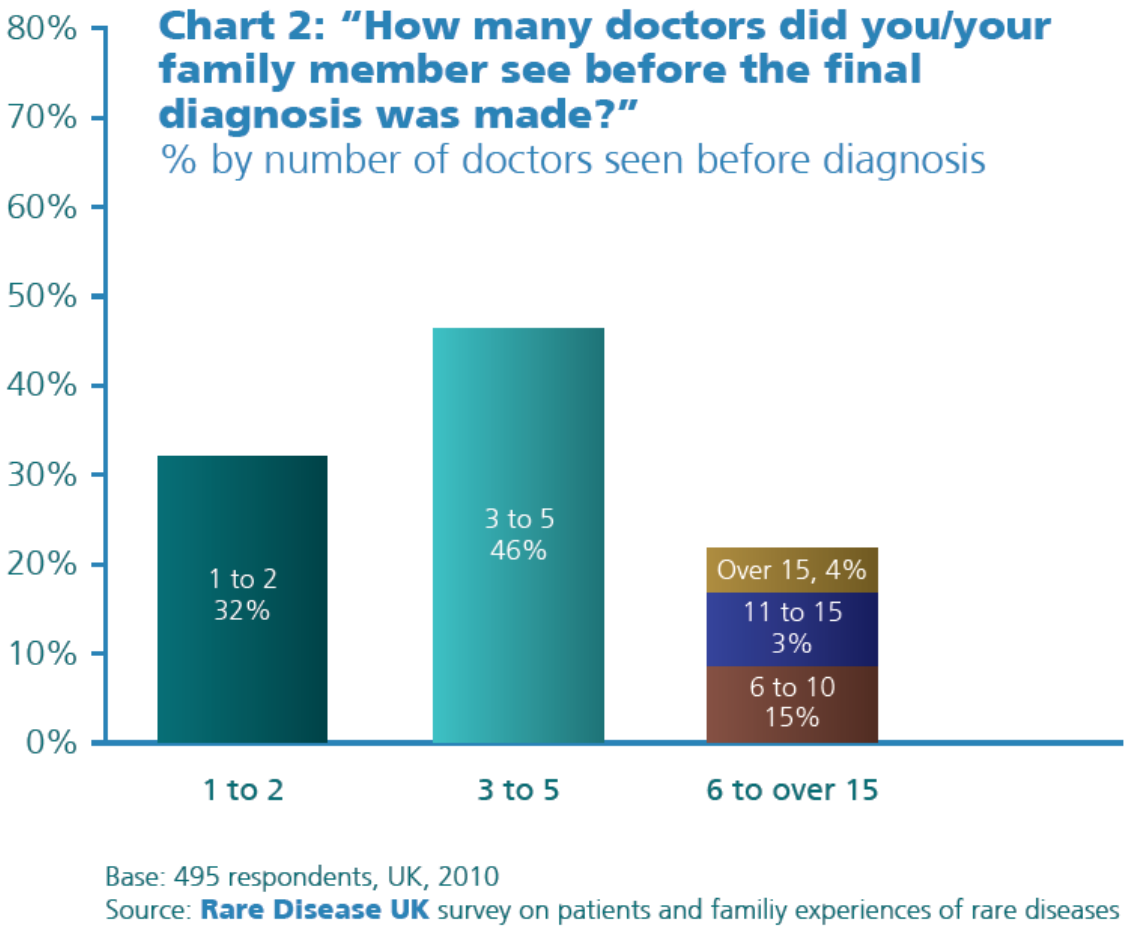
~1500 Euros

Rare diseases are often not diagnosed

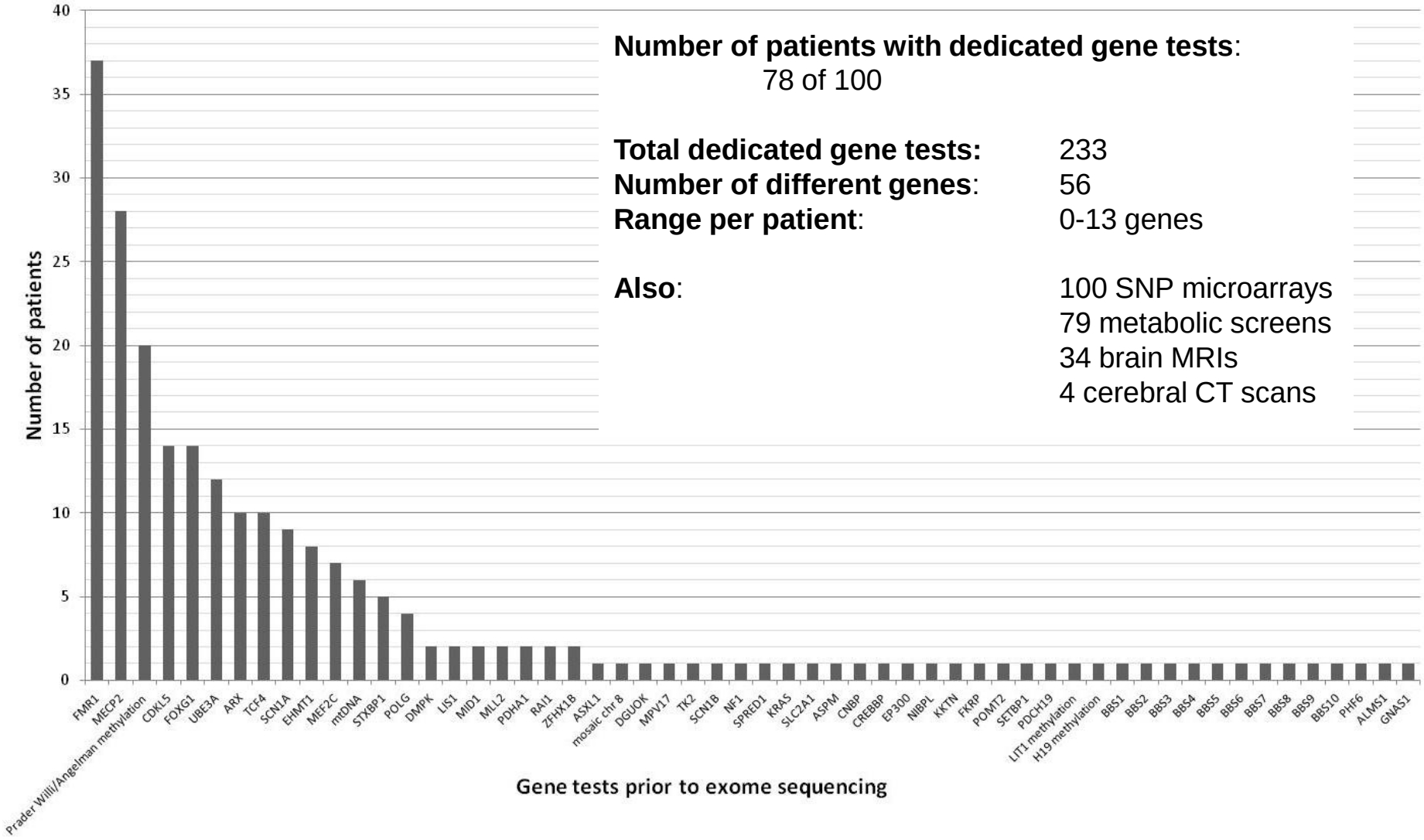


Source: Rare Disease UK Survey

Rare diseases are often not diagnosed



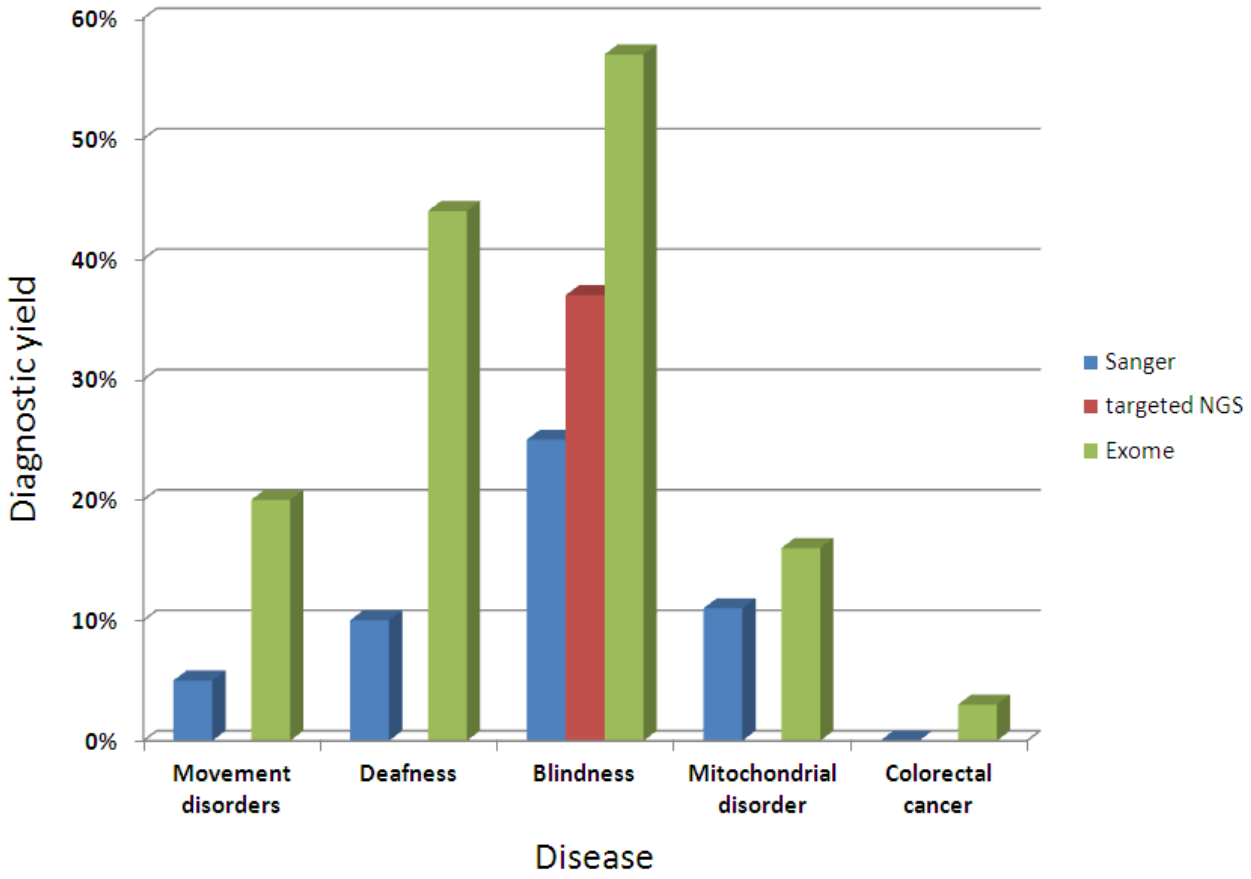
Source: Rare Disease UK Survey



Human Genetics Nijmegen

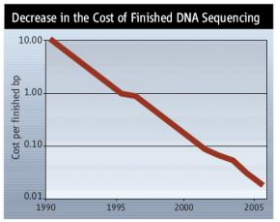
186 Diagnostic exomes across 5 diagnostic groups

targeted analysis



Compare with clinical diagnostic practice 2011

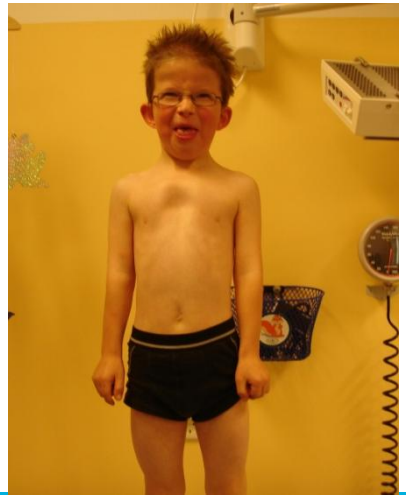
Three reasons why Diagnostic Next Generation Sequencing of all genes (exome) is becoming part of mainstream medicine:

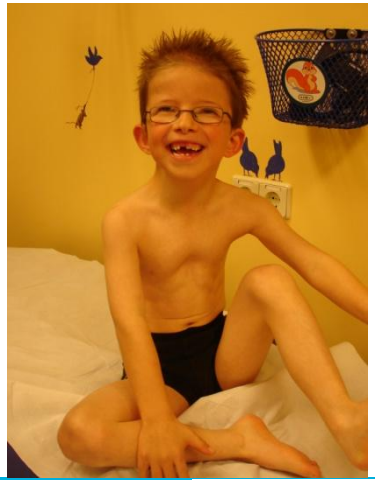


•1500 Euros is not prohibitive, *and it will be less soon*

• We are not as good at clinical diagnosis as we would like to think

• NGS can suggest a molecular diagnosis even in *a single patient* without prior hypothesis





De beste reactie op alle nieuwe en verfijnde genetische diagnoses met whole genome sequencing is

“so what”!

Want: Als er geen behandeling is dan boeit het niet

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Genomics Changes Medicine

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azM | Maastricht University

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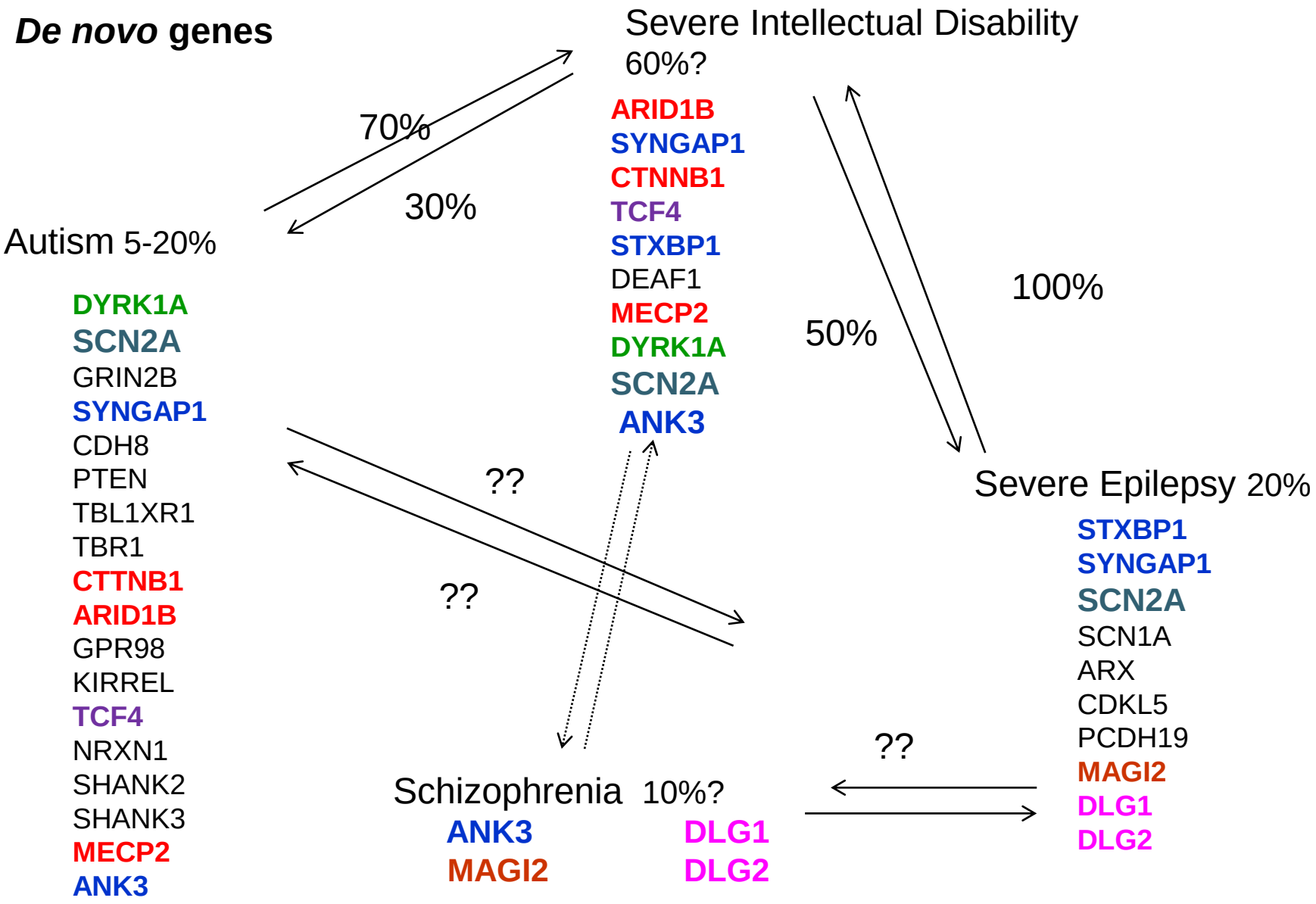
An inconvenient truth:

Genes do not respect diagnostic boundaries



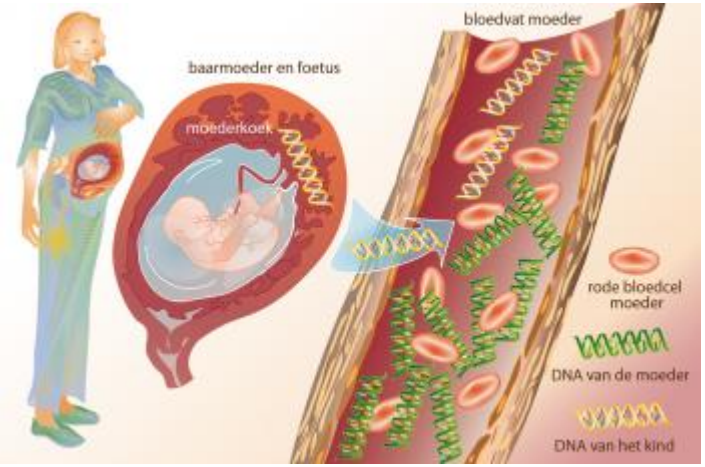
Another inconvenient truth

We cannot prevent *de novo* mutations

An inconvenient truth

We cannot prevent *de novo* mutations

So should we offer prenatal testing to everyone?

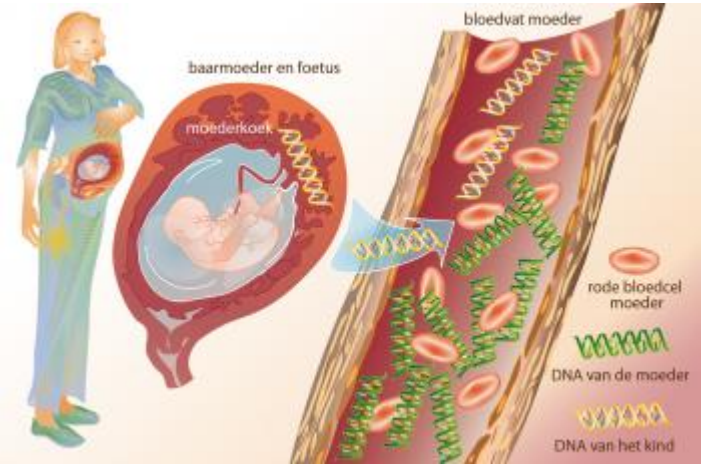


Non invasive prenatal testing NIPT

An inconvenient truth

We cannot prevent *de novo* mutations

So should we offer prenatal testing to everyone?



Non invasive prenatal testing NIPT

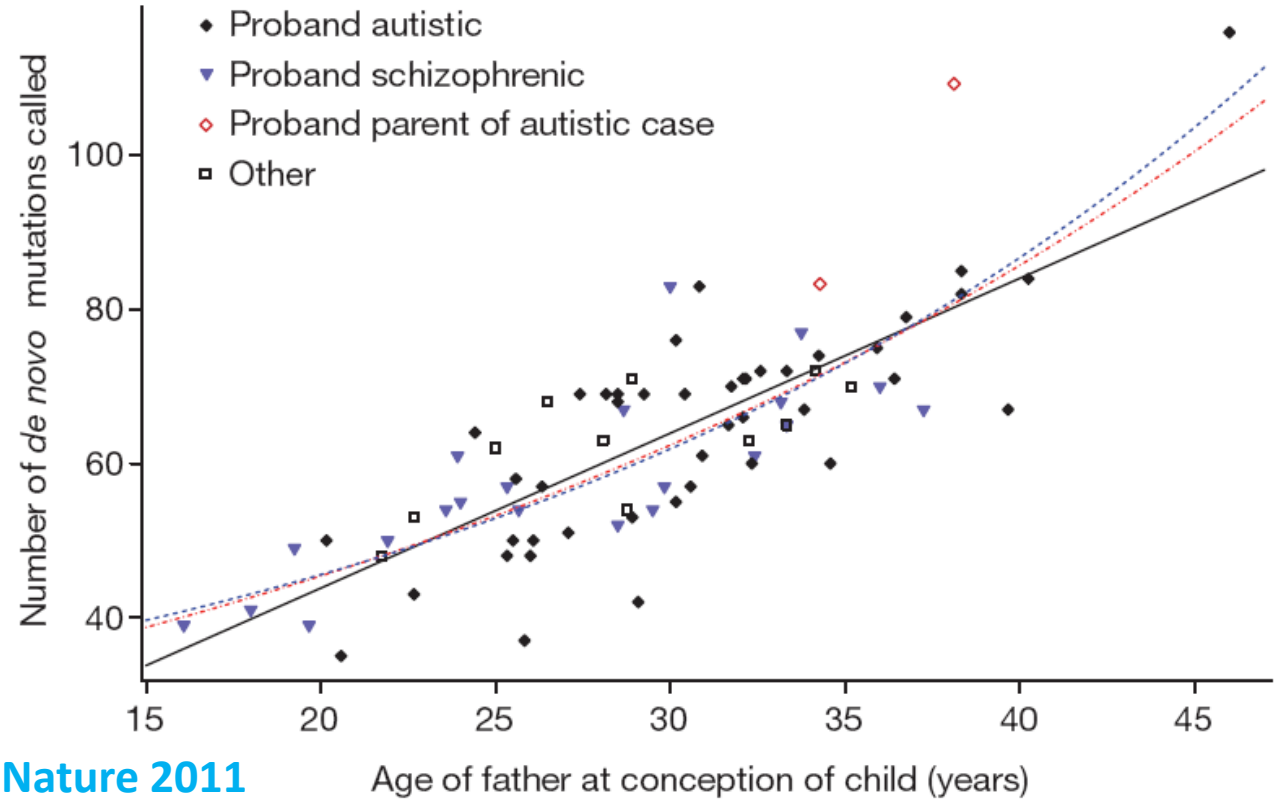
Why offer this for Down syndrome (risk 1/1000) and not for other forms of ID (risk 5/1000)?

Another inconvenient truth

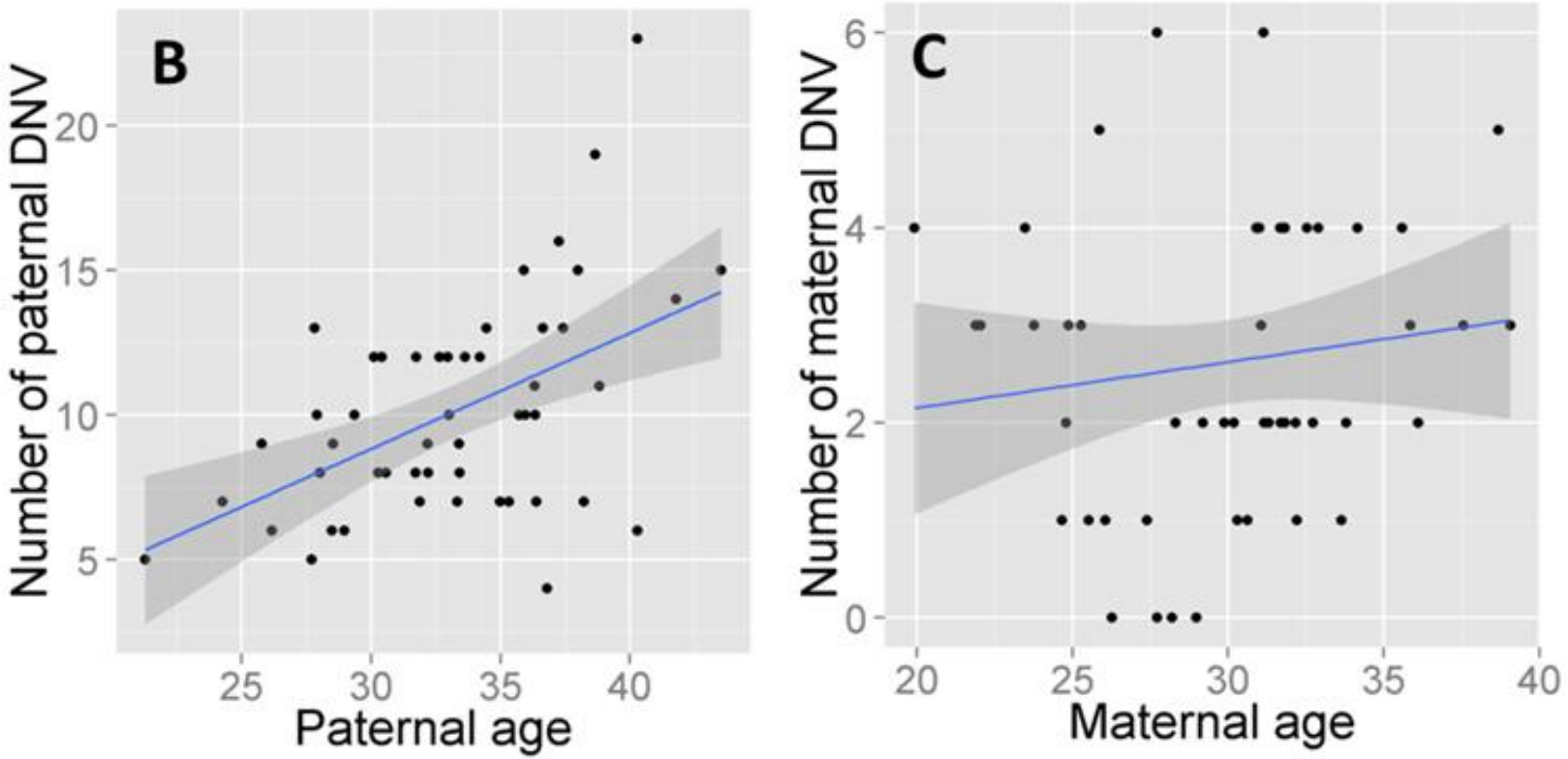
There is one known risk factor for *de novo* mutations

Rate of *de novo* mutations and the importance of father's age to disease risk

Augustine Kong[1], Michael L. Frigge[1], Gisli Masson[1], Soren Besenbacher[1,2], Patrick Sulem[1], Gisli Magnusson[1],



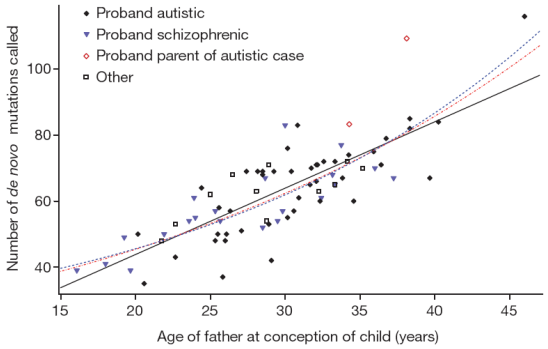
Kong et al. Nature 2011



Gilissen *et al*. Nature, 17 July 2014

A question to ponder

- Should we offer prenatal diagnosis to everyone?
- Should boys freeze their sperm at 17?



Conclusions

- For sporadic ID *de novo* mutations are the most frequent cause in first world countries.

- About 1000 genes cause ID by *de novo* mutation
  - 500 established
  - 500 candidate genes

- X-linked ID accounts for ~5%. → Most genes are known

- In consanguineous populations *recessive ID* may be frequent

Acknowledgements

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Human Genetics

Christian Gilissen
Jayne Hehir-Kwa
Joep de Ligt
Alex Hoischen
Djie Tjwan Thung
Maartje van de Vorst
Petra de Vries
Michael Kwint
Irene Janssen
Marloes Steehouwer
Tan Bo
Joris Veltman
Willy Nillesen
Dorien Lugtenberg
Helger Ijntema
Rolph Pfundt
Marjolein Willemsen
Bregje van Bon
Tjitske Kleefstra
Bert de Vries
Lisenka Vissers
Charlotte Ockeloen
Tjitske Kleefstra
Anneke Vulto – van Silfhout

Complete Genomics

Rick Tearle
Robert Klein
Richard Leach

Many clinical collaborators

Washington University, Seattle

Heather Mefford, Gemma Carvill
Evan Eichler, Bradley Coe

European Research Council

TECHGENE

SEUVADIS CONSORTIUM

AnEUploidy

NWO

On the origins of Intellectual Disability

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