

Future developments

course
based on



VEPTC | 27 - 30 Aug. 2018

NUMed, Johor, Malaysia

Johan den Dunnen



Your genome

who knows his genome sequence ?

who had a DNA test ?

...future !?

...your grand children will not believe you dared to live without knowing your genome,

...nor your partner's genome



*maybe good to start
trying to understand what
info your DNA contains*

**Eerst een DNA-test, dan pas
bevruchten**

Geneeskunde

Een baby zonder ernstige erfelijke ziekte. Stellen die dat willen, kunnen hun DNA op tientallen ziekten laten testen. Nog vóór ze het kind maken.

⌚ Wim Köhler ⌚ 23 september 2016



nrc.nl >

...future !?

*nowadays nobody would start surgery
without an X-ray,*

*why do we start treatment without
knowing the genome ?*

Olaf Rieß

... for the hospital

...a patient will not be treated when the basics, the DNA, is not known

*...why risk undesired effects from treatment,
when these can be determined beforehand ?*

*...why risk treating a problem for which the origin
lies elsewhere (has a genetic component) ?*

Your genome

"preventive medicine"

 European Journal of
Human Genetics

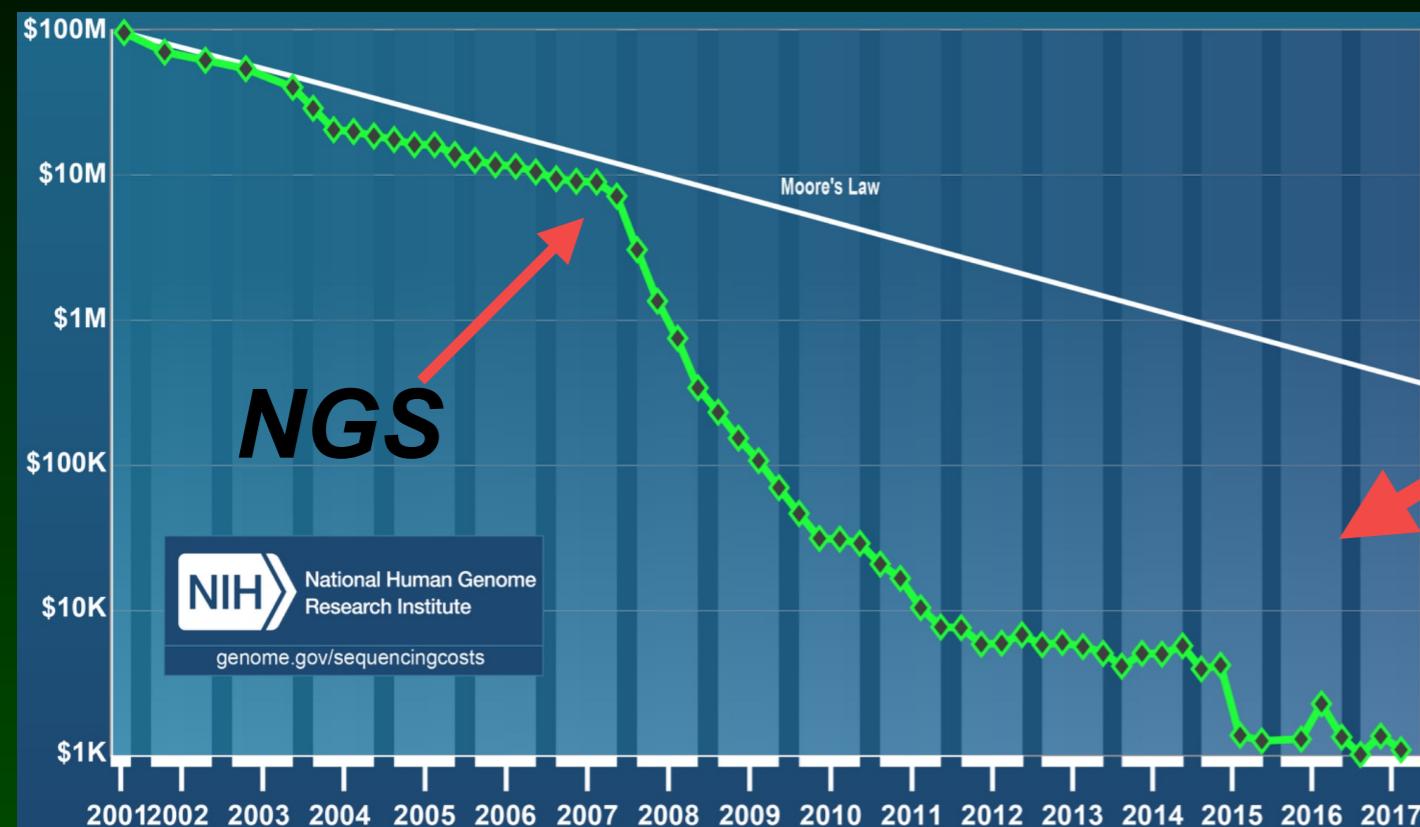
Article | Published: 05 October 2018

1 in 38 individuals at risk of a dominant
medically actionable disease

Lonneke Haer-Wigman, Vyne van der Schoot, Ilse Feenstra, Anneke T. Vulto-van Silfhout, Christian
Gilissen, Han G. Brunner, Lisenka E. L. M. Vissers & Helger G. Yntema 

*...and from pharmacogenetic information
to fun (bitter taste, m/paternal origin, ...)*

Sequencing revolution



to a €1000 genome

now a reality !



*more sequence
longer reads
faster
cheaper*



```
ACAAGTTACCCTAGGGATAAACAGGCCCAATCTTATTCTAGAGTCATATCAACAAATAGGCTTA  
TCTATCTACNTTCAAATTCTCCCTGTACCGAAAAGGACAAAGAGAATATAGGCTACTTCACAAAG  
GTCAGAGGTTCAATTCTCTTCTTAAACAAACATACCCATGCCAACCTCTACTCTCTTCTTCTA  
TGACCCCATAAAACCTCTCACCAGGAGGCCCTAAACCCGCCACATCTACCCATCACCTCTA  
GCTTAGCCGTTTACTCTCATCTCTGATCAGCGTGAACGATCAAACTCAAACTACGCCCCTGATCG  
GAACACCTCTGATTACTCTCTGCACATGACCCCTGGGCAATAATGATTATCTCCACACTA  
AAACATTATTATAATAAAACACCCCTCACCACTNCAATCTCTAGGAACAAACATATGACCCACT  
TATGAAAAAAACTCCCTACCTCACTCCATTACTTATATGATATGATCTCCATACCCATTAA  
CATCCCTGAGAATCAGAAATTCTCCGTGCCACCTATCACACCCCCATCTAAAGTCAAGGTCA  
GGCTTAAGCTCGCACTGATTTTTACCTGAGTAGGCCTAGAATAAACATGCTAGCTTATT  
CTCGGACAATGAACCATAAACCAATAACTTACCAATCAACTCATCATTAAATCAATAAGC  
CAATCATATAACCAAAATCTCCCTCCTAAACGTAAGCCTCTCCCTACTCTCAATTCTTAT  
ATAACCATCTTAAATTAAACTTATATTCTAACTACTACCGCATTCTACTACTCAAC  
CTTTTGCCAAATGGGCCATTATCGAGAAGAATTCAACAAAAAAACATAGGCTCATCATTCC  
ATACAAACCCCCCCTTCCCTCCCACTCATGCCCTTACCGCT&gt;CTCTACCTATCT  
CACTCTGATCAGTGAACGAAATCAGGCCACTTTAAAGCTAAGGCTTACCGCCTAGAAC  
GCTCTTGAATTTCGAAATTCAATAATGAAATCACCTCGAGGTGGTAAAGAGGCGCTAAC  
TATTATGGCGCATGAGCTGGAGCTCTAGGCACAGCCTTAAGGCTCTTATTCGAGCCGAGC  
AACTGACTAGTTCCCTAAATAATCGTGGCCGGATATGGCTTCCCTGATAAACACACATA  
TGGAGCCTCCGGTAGACCTAAACCATCTCTTACACCTAGCCAGGTGTCTCTATCTTACG  
TCCCAGCTCTAGCTGGCTGGCATCACTATACTACTAACACAGCCAACCTCAACACCACCT  
ACTACTACTCCGGAAAAAGAACCTATTGGATACATAGCTATGGCTGAGCTATGATATCA  
CAAAGTATTAGCTGACTCGCCACACTCACGGAAAGCAATATGAAATCTGCTGAGCT  
ACTATGCTCTATCAATAAGCAGCTGTATTGCGCATACATGGAGGCTTCACTCTGATTC  
CGACGTACTCGGACTACCCGATGCGATACACCCACATGGAAACATCTCATCTGAGGTCA  
ATGCCCCCACCTACCCACATTEGAGAAGGCTGATACATAAAATCTGAGCAGAAAGGA  
CTATATACTTAAATGCGACATGCGCGCAAGTAGCTCAAAAGACGCTACTTCCCTATCAT
```

*...single molecule
...label-free*

World record



Kingsmore Has Done it Again: Rady Children's Set Guinness World Record for Genetic Diagnosis

Front Line
Genomics
Unzipping genes for the good of humanity

19.5 h
incl. diagnosis

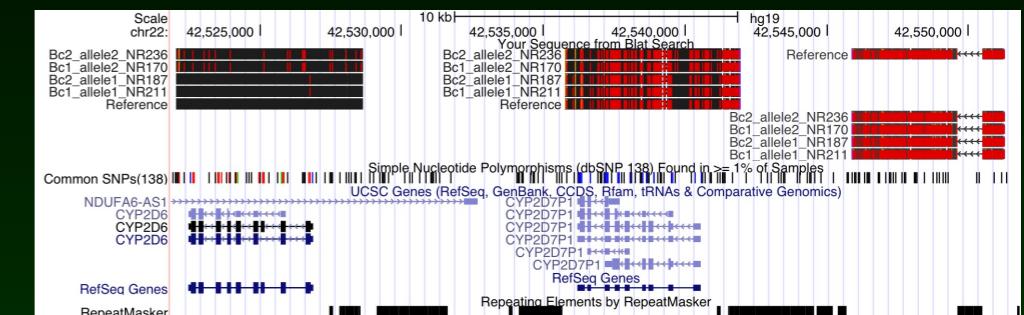


Long-read seq

(phasing)

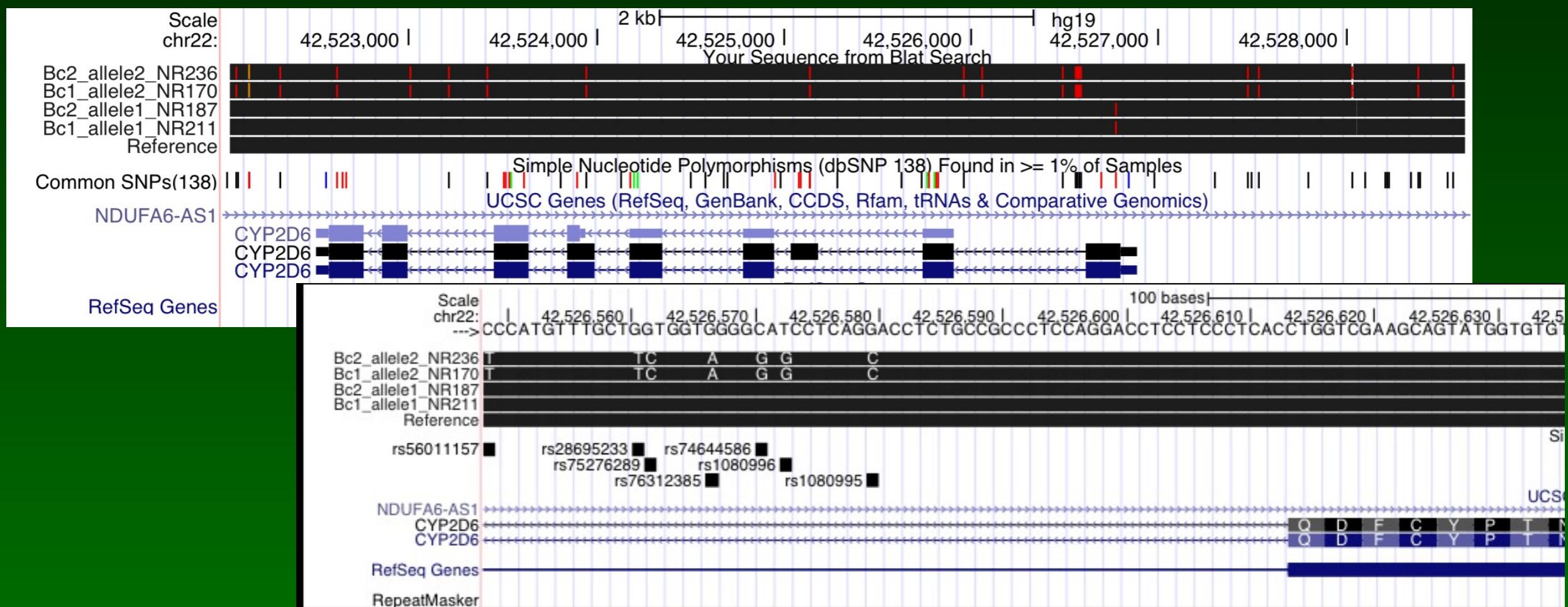
- **CYP2D6**

*long-range PCR > PacBio seq
2 alleles clearly separated*



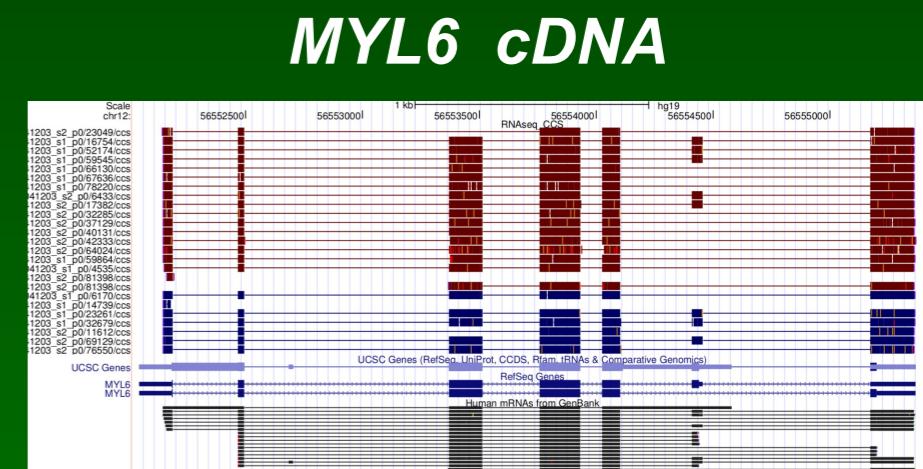
CYP2D6

CYP2D6-like



PacBio allele-seq

- PKD1 gene
 - unique 3' end, repetitive 5' end*
 - long-range PCR far into repetitive region*
- PMS2 gene
 - several pseudogenes*
 - specific long-range PCR and/or discriminate based on sequence*
 - get & load long molecules*
- ...other genes
 - CYP-genes*
 - discriminate maternal/paternal*
 - long-range cDNA-seq*



Single molecule sequencing

Oxford
NANOPOR
Technologies



nanopore technology

STRATOS genomics inc. [HOME](#) [TECHNOLOGY](#) [NEWS](#) [BLOG](#) [ABOUT](#) [CAREERS](#) [CONTACT](#)

STRATOS GENOMICS
BRINGS YOU THE
BASES OF LIFE™

[learn more >>](#)

ZSGenetics

[Home](#) [3G Sequencing](#) [Technology](#) [About ZS Genetics](#) [Contact Us](#)



genia

TECHNOLOGY

About Us
genia information

Technology
technology overview

Careers
join the team

Contact
reach out



Nabsys

Whole Genome Mapping, now in HD

Technolog

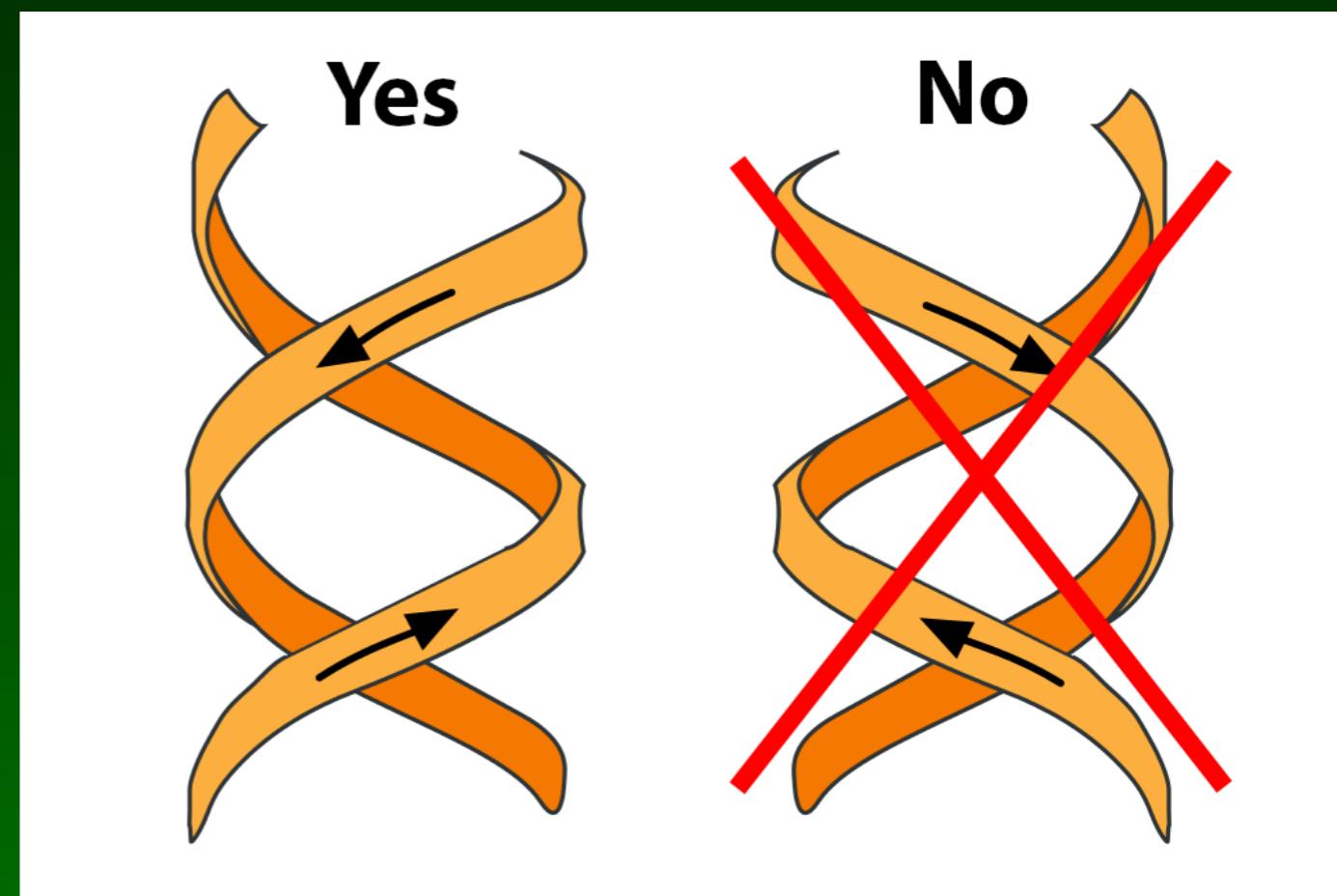
See the whole story with high
definition whole genome mapping
using **solid-state nanodetectors**

DNA



will the system work?

*...YOU did pay
attention at school*



Future technology

The image shows a screenshot of the TwoPoreGuys website. At the top, there is a navigation bar with links for HOME, TECHNOLOGY, ABOUT, CONTACT, and CAREERS. The main content area features a large image of a handheld biosensor device with a digital display screen. The screen shows the TwoPoreGuys logo and the text "INFLUENZA A". Below this, it displays "30" and "5%" with the label "# Detected" and "Concentration". The device is shown against a background of a city skyline at night. A text overlay on the left side of the image reads "As easy to use as a glucometer".

twoPoreGuys

Meet the Guys...



..and then



SmidgION

*sequence
@home*

Rare cases ?

- maybe, ...but
 - we go for the simple & obvious*
 - many options not even considered*
 - many not detected using exome sequencing*
 - rare cases difficult to proof*
 - may require additional experiments and functional proof*
- recent publications
 - intellectual disability, >2100 WES trios*
 - used statistics to find proof of causality*
 - several new genes/variants implicated*

Rare cases ?

- many mono-genic diseases solved

***where are the di-genic diseases ??
I would expect many more***

NATURE GENETICS VOLUME 44 | NUMBER 12 | DECEMBER 2012

Digenic inheritance of an *SMCHD1* mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2

Richard J L F Lemmers^{1,13}, Rabi Tawil^{2,13}, Lisa M Petek³, Judit Balog¹, Gregory J Block³, Gijs W E Santen⁴, Amanda M Amell³, Patrick J van der Vliet¹, Rowida Almomani⁴, Kirsten R Straasheim¹, Yvonne D Krom¹, Rinse Klooster¹, Yu Sun¹, Johan T den Dunnen^{1,4}, Quinta Helmer⁵, Colleen M Donlin-Smith², George W Padberg⁶, Bazi G M van Engelen⁶, Jessica C de Greef^{1,12}, Annemieke M Aartsma-Rus¹, Rune R Frants¹, Marianne de Visser⁷, Claude Desnuelle^{8,9}, Sabrina Sacconi^{8,9}, Galina N Filippova¹⁰, Bert Bakker⁴, Michael J Bamshad^{3,11}, Stephen J Tapscott¹⁰, Daniel G Miller^{3,11} & Silvère M van der Maarel¹

***clear phenotype
unsolved FSHD cases***

***WES analysis several families
shared SMCHD1 variants***



Genes

- 20,000 protein coding
60,000 total
- which gene should be in a specific panel
- which transcript to use
preferred reference transcript



New rare disease gene tool launched
PanelApp

standards for analysis, agreement on what to analyse

RNA, it exists !

..the neglected molecule

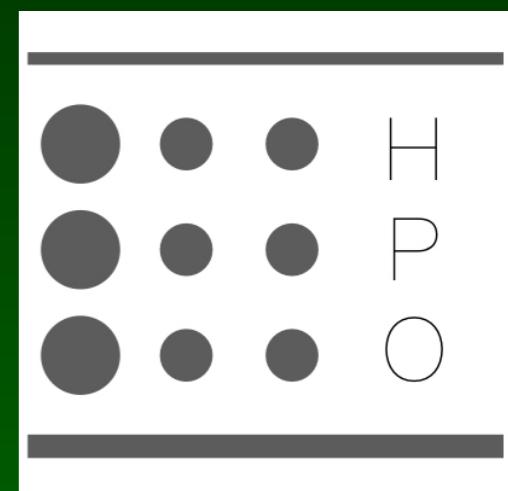
under-appreciated

most go blindly DNA > protein

..there is much more

Standards

- annoying, ...but
we need them
..and use without errors
- variants
HGVS nomenclature
- phenotypes
Human Phenotype Ontology (HPO)
- classification
ACMG



Variant classification

standards for classification

*ACMG recommendations
labs start sharing classifications*

ACMG:
"beware of variants that may impact splicing"



The screenshot shows the Variant Annotation Integrator (VAI) web application. At the top, there's a navigation bar with links for 'Genomes', 'Genome Browser', 'Tools', and 'Mirrors'. Below this is a section titled 'Variant Annotation Integrator' with a sub-section 'Select Genome Assembly and Region'. It includes dropdown menus for 'clade' (Mammal), 'genome' (Human), and 'assembly' (Feb. 2009 (GRCh37/hg19)). A 'region to annotate' dropdown is set to 'genome'. A large, stylized watermark 'Ve!P' is overlaid across the bottom half of the interface.



The screenshot shows the Varsome website. At the top right, there's a logo with a green checkmark icon and the word 'varsome'. Below it, a 'Verdict' section says 'Likely Pathogenic'. Underneath, there's a 'Rules' section containing a 4x8 grid of colored boxes representing ACMG classification rules. The grid includes columns for PVS1 through PM3 and rows for PM4 through BP7, each with a color-coded background (e.g., red for PM5, yellow for BA1).

PVS1	PS1	PS2	PS3	PS4	PM1	PM2	PM3
✓ ?	✓ ?	✓ ?	✓ ?	?	✓ ?	✓ ?	?
PM4	PM5	PM6	PP1	PP2	PP3	PP4	PP5
✓ ?	✓ ?	✓ ?	✓ ?	✓ ?	✓ ?	?	✓ ?
BA1	BS1	BS2	BS3	BS4	BP1	BP2	BP3
✓ ?	?	?	✓ ?	✓ ?	✓ ?	?	✓ ?
BP4	BP5	BP6	BP7	BP8	BP9	BP10	BP11
✓ ?	?	✓ ?	✓ ?	?	✓ ?	✓ ?	✓ ?

Databases

...all these databases

DNA diagnostics is based on:

SHARING what we know on the *relation*
between **variants in genes** & **phenotypes**

without sharing, no DNA diagnostics

Variant of Unsufficient Sharing
(VUS)





Global Alliance
for Genomics & Health



brcaexchange.org

BRCA Challenge

The BRCA Challenge aims to advance understanding of the genetic basis of breast and other cancers using data from around the world.



BRCA Exchange

Expert Reviewed

HOME VARIANTS COMMUNITY

search for "c.1105G>A", "brca1" or "IVS7+1037T>C"

brcaexchange app

Search	
search for "c.1105G>A" or "brc..."	
20644 variants	
Gene	HGVS Nucleotide
BRCA1	c.4358-2692G>A
BRCA2	c.775delA
BRCA1	c.117T>A
BRCA2	c.7341T>C
BRCA1	c.134+1508G>A
BRCA2	c.7544C>T
BRCA1	c.825_828delCAC...
BRCA2	c.9118-1G>A
BRCA1	c.5333-18T>G



©Johan vd Leij



Search

[Advanced Search Preferences](#)

Web [Show options...](#)

Did you mean: [c.62G>A loved](#)

[Search unique variants - LOVD - Leiden Open Variation Database ...](#)

02, c.62G>A, -, r.(?) p.(Arg21Gln), ARG1_00001, -, -, Mitchell 2009, DNA, HRMA ... Powered by LOVD v.2.0 Build 18. Enabled modules: showmaxdbid, chromium.liacs.nl/LOVD2/variants.php?select_db=ARG1&a unique&search_pathogenic_= - 28k - [Cached](#) - [Similar pages](#)

[View unique variants - LOVD - Leiden Open](#)

01, 1-62G>A (Reported 10 times), -, -, GCK_00037, Leu20Pro, GCK_00063, -. 02, 106C>T (Reported 2 ti chromium.liacs.nl/LOVD2/variants.php?action=view_ [Cached](#) - [Similar pages](#)
[More results from chromium.liacs.nl »](#)

[Variants - NGRL, Manchester LOVD - Leiden Open](#)

NGRL, Manchester LOVD. ubiquitin protein ligase E3A (UBE3A) RNA change. Protein, p.Cys21Tyr (predicted) ... ngrl.man.ac.uk/lovd2/variants.php?select_db=UBE3A&acti 0000082%2C0000082%2C21 - [Similar pages](#)



c.1A>G LOVD

ALL

IMAGES

VIDEOS

SHOPPING

NEWS

MAPS

BOOKS

Did you mean: [c.1A>G LOVE](#)

HBB:c.1A>G - bx.psu.edu).

<https://lovd.bx.psu.edu> › variants › DNA...



LOVD homepage View unique variants Public list of submitters Submit new data
View unique variants · Search unique ... LOVD - Variant listings for HBB. Unhide

transcript variants in gene FANCA - Global Variome shared LOVD
[https://databases.lovd.nl/shared/FANCA](http://databases.lovd.nl/shared/FANCA)

Adopt a gene !

become a
foster parent
database curator



*claim your child at
gene.LOVD.nl*



***essential on your CV
...only ~15,000 available***

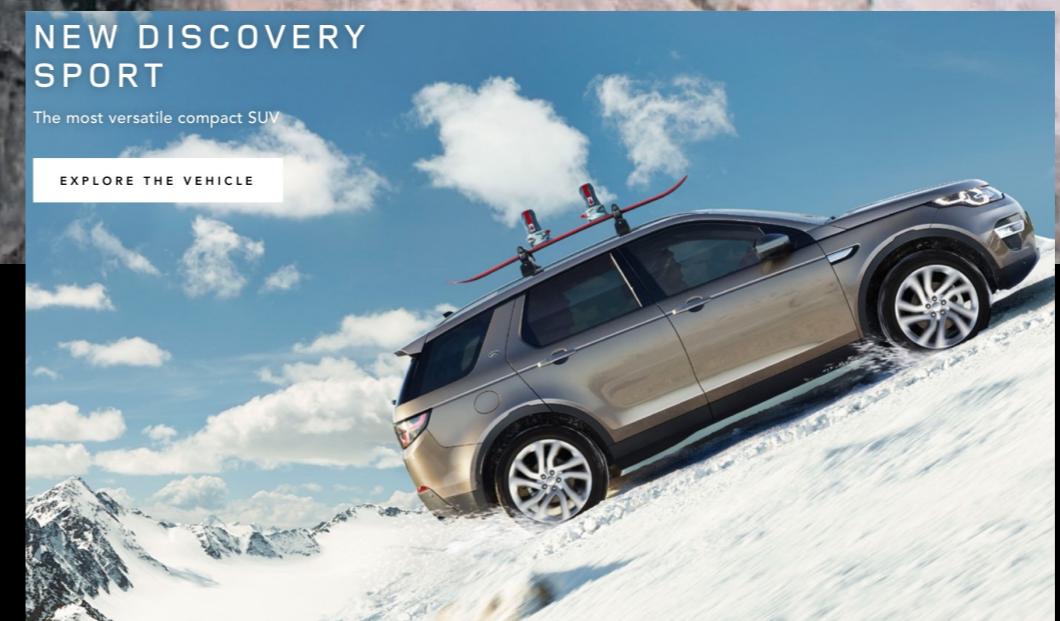


***with 7,000,000,000 people
chance 1/400,000***

Do you have the DRD4 7R gene ?

*1 in 4 has the
DRD4 7R gene*

The image shows the official Land Rover website homepage. At the top, there's a navigation bar with links for 'FIND A DEALERSHIP', 'BUILD YOUR OWN', 'DOWNLOAD A BROCHURE', and 'CONTACT US'. Below the navigation is a dark banner with the Land Rover logo and menu items: 'VEHICLES ▾', 'APPROVED PRE-OWNED', 'FLEET & BUSINESS', 'OWNERSHIP', 'EXPERIENCES', and 'ABOVE AND BEYOND'. Underneath this is another banner with links: 'ABOVE AND BEYOND OVERVIEW', 'RESPONSIBILITY', 'UNSTOPPABLE SPIRIT', '25 YEARS OF DISCOVERY', and 'CELEBRATE DEFENDER'. The main content area features a large blue DNA helix graphic. Overlaid on the DNA is the text 'THE ADVENTURE GENE' in white, bold, sans-serif font. Below this, a smaller line of text reads 'Are you hard-wired to go Above and Beyond?'. At the bottom of this section is a white button labeled 'WATCH THE FILM'.



Commercial DNA test

The image shows a composite of three parts. On the left is a screenshot of a website for 'dante labs'. It features a logo with blue and red intertwined bands, the text 'dante labs' in a serif font, and a slogan 'Never worry again' at the bottom, all within a white header bar. Below this is a large photograph of a man carrying a child on his shoulders, with another child walking alongside them in a scenic outdoor setting. Overlaid on this image is the text 'Analyze 100% of Your DNA' and 'For Your Health, Longevity and More'. A red oval highlights the slogan 'Never worry again'. At the bottom right of the image is a teal button labeled 'SHOP NOW'. Above the main image are navigation links: 'OUR TESTS', 'ABOUT US', 'BLOG', and 'CONTACT'. To the right of the main image are two white boxes. The top box, with a pink circular icon containing a DNA helix, offers 'Whole Genome Sequencing (WGS) - Full DNA Analysis' for £399. The bottom box, with a blue circular icon containing a DNA helix, offers 'Whole Exome Sequencing (WES) - Sequence all Your Genes' for £299.

Never worry again

OUR TESTS ABOUT US BLOG CONTACT

Analyze 100% of Your DNA

For Your Health, Longevity and More

SHOP NOW

Whole Genome Sequencing (WGS) - Full DNA Analysis
£399

Whole Exome Sequencing (WES) - Sequence all Your Genes
£299

2017

Special offer



HALLOWEEN SPECIAL: €399 WHOLE
GENOME SEQUENCING

FOR OCTOBER 30 AND 31 ONLY

SPECIAL OFFER →

*maybe offer on Halloween
because it is a scary thing to do ?*

Halloween Special

SALE



Whole Genome Sequencing (WGS) - Full DNA Analysis

€399.00 €850.00

YOU SAVE €451.00



Whole Exome Sequencing (WES)
- Sequence all Your Genes

€299.00 €549.00

YOU SAVE €250.00

Test the baby



A cartoon illustration of a white stork with orange legs and beak, carrying a baby wrapped in a blue blanket. The baby has a surprised expression. They are flying through a white space with colorful circles (yellow, blue, green) scattered around them.

Het leukste en meest originele kraamcadeau!

Vijf leuke weetjes over je baby op basis van zijn of haar DNA in een gepersonaliseerde animatievideo.



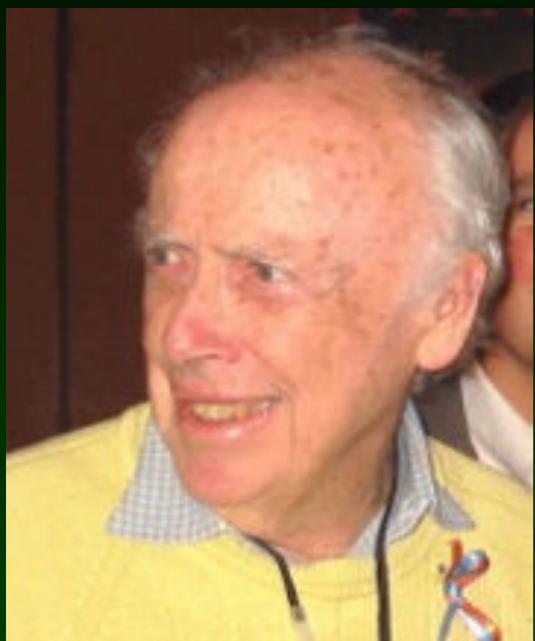
Dna-test voor baby's voorlopig van de markt

© VRIJDAG, 17:33 BINNENLAND

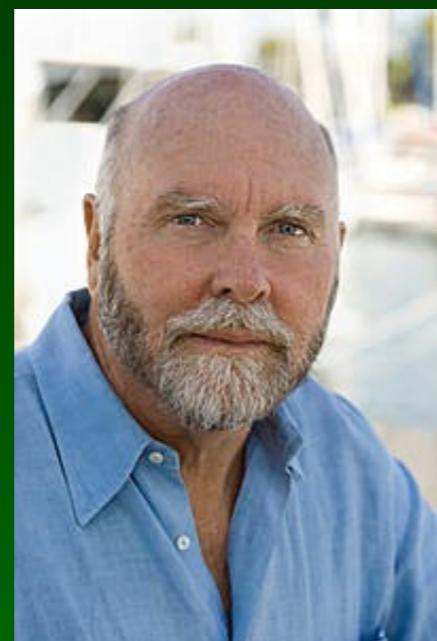


Focus on disease

(*individual genomes sequenced*)



James Watson



Craig Venter

JLupsky, Kim,
GChurch, DTutu, JFlattery,
MSnyder,
....

Marjolein Kriek





TCCAGGATTCAATTGA TTTTGAAGG
CTCAAGAGTGTTCCCAAATATCCTT
GCTCAAAAATGTCCCTTCCACAGATC
ATCAAGGGATATTCCTTTTCATGA
TTTAACTCTGTGAGATGAATGCACAC
AAC TGCTTAACTCAAAGAAAGGTTA
ACACCAAAAGCAATGGCAACAAAAA
TTAATTTTTAACATAGGCCTCTGTA
AGAATGTGGATWCAGGTAACCTTGC
CCGATTTACCCAAAAGAGTGT
ATGAATCCACAGATCACAGGC
TGCAATTGAGTTCAATTCTTGGAT
TGCACCTGCTGGAACT
CTGGGAAGCTGTCTTTAGCTGT
ATGATGTTAGCTGGTTATTTGCTC
CTGTGGTAAAAGGGAAATTCTTC
GTTTGGAAAACAACGTTTCTAGA
GTTTGGAAAACAACGTTTCTAGA
GTTTGGAAAACAACGTTTCTAGA

A rumour

female DNA finally sequenced



"here the defective gene for parking a car backwards"

From: **Pastafarian ®**

Subject: **re: Scientists claim to understand women**

Nobel Prize for them

27/05/2008 3:15:32 PM

post id: 3604572

The Advertiser | Sunday Mail

News **Sport** **Business** **Money** **Entertainment** **Travel** **Lifestyle**

[Homepage](#) [Breaking News](#) [South Australia](#) [National](#) [World](#) [Technology](#)

Scientists crack women's DNA code

FINALLY, men may be able to understand women,
it seems. Dutch scientists said they have mapped
the full genetic sequence of an individual
woman's DNA for the first time.

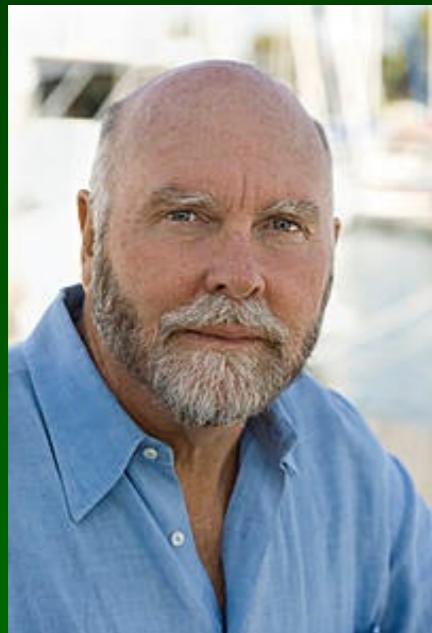
Researchers at Leiden University Medical Centre said they had sequenced the genome of one of their researchers, geneticist Marjolein Kriek, and plan to publish it after review.

Focus on disease

(*individual genomes sequenced*)



James Watson



Craig Venter

JLupsky, Kim,
GChurch, DTutu, JFlattery,
MSnyder,
....

Marjolein Kriek



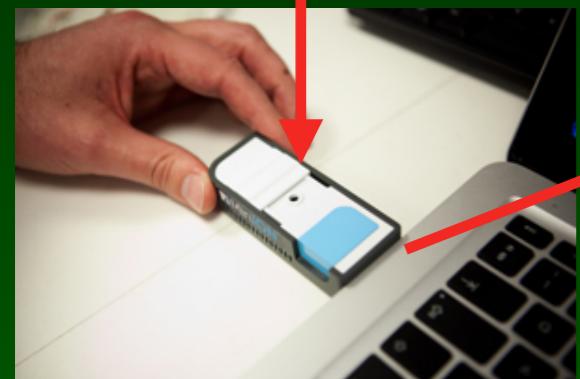
**conclusion 'sick' much
easier then 'healthy'**

Predictions

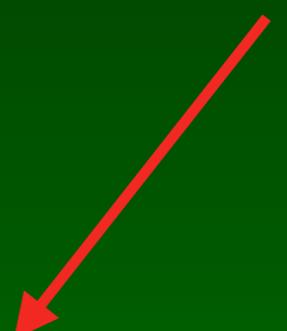
...it is good we can not yet trust predictions

(dangerous tools, eventually they will take over your job)

Future VEP



FINAL
Ve!P



GENOME REPORT

(complete error free)

Evaluation

- how was the course ?
- topics missing ?
- format ?
*length
demos*

Acknowledgement

Presentation prepared by:

Johan den Dunnen



*Human Genetics & Clinical Genetics
Leiden University Medical Center
Leiden, Nederland*



lieven sheire

date: April 2019