Snelle ontwikkelingen rond DNA en de gevolgen voor de screeningen

Derde landelijke conferentie pre- en neonatale screeningen

Doorn

17 april 2012

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Quality of Care

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EMGO Institute for Health and Care Research

Centre for Medical Systems Biology

CSG CENTRE FOR SOCIETY AND THE LIFE SCIENCES

VU university medical center

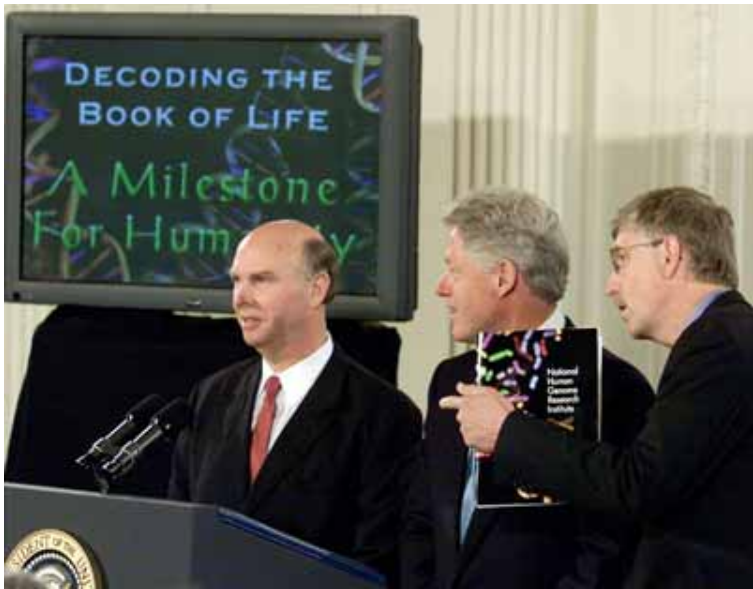
VU University Amsterdam

EMGO+ Institute for Health and Care Research

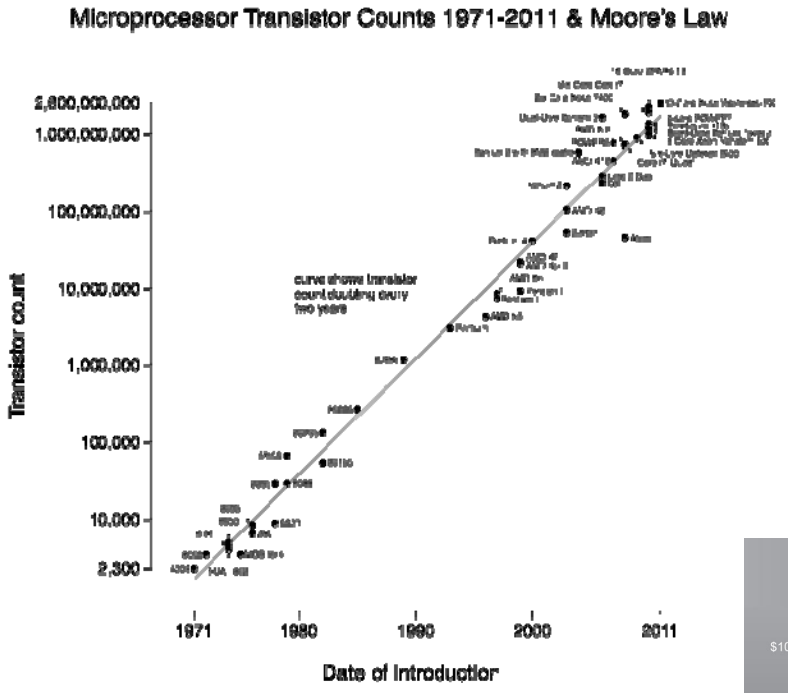
2000: Humane genoom in kaart

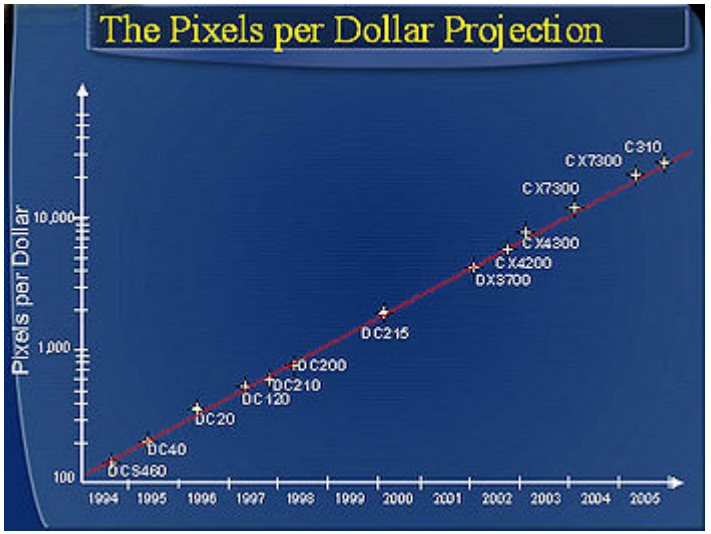
- Without a doubt, this is the most important, most wondrous map ever produced by humankind.
- With this profound new knowledge, humankind is on the verge of gaining immense, new power to heal. Genome science will have a real impact on all our lives -- and even more, on the lives of our children. It will revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases.

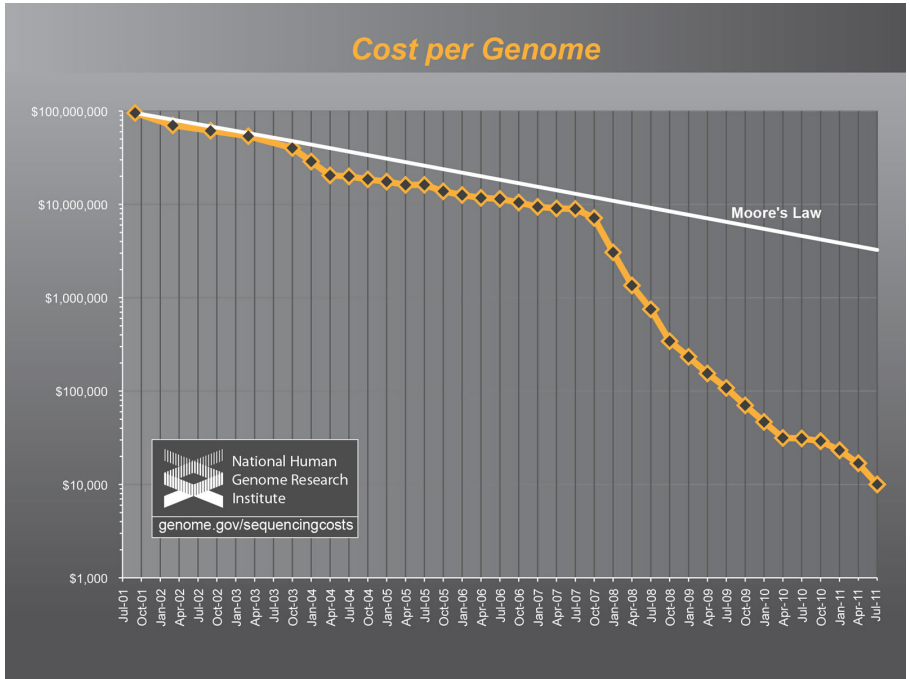
Human genome project 2000



Prijs genoomdata daalt sneller dan in ICT







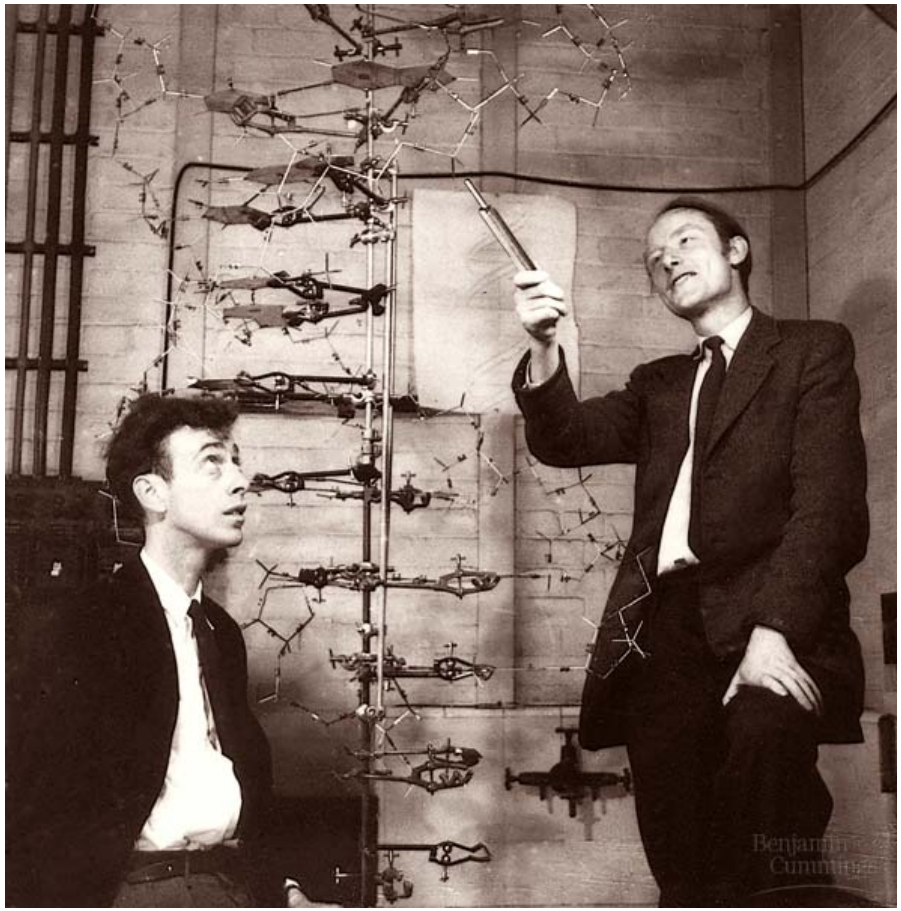
Bron: wikipedia

Pasgeborenen?

- Kan bij pasgeborenen het hele genoom, of de gedeeltes van het genoom waarin tussen mensen verschillen bestaan, worden onderzocht?
- Human Genetics Commission Verenigd Koninkrijk 2005: Afgewezen vanwege ethische, juridische en maatschappelijke bezwaren.
- Gezondheidsraad, Neonatale Screening, 2005: Eveneens afgewezen. Het zou onbehandelbare aandoeningen aan het licht brengen, en aandoeningen die zich pas op latere leeftijd voordoen.

Genetica: “theorie” of “praktijk”?

Wetenschap of gezondheidszorg?

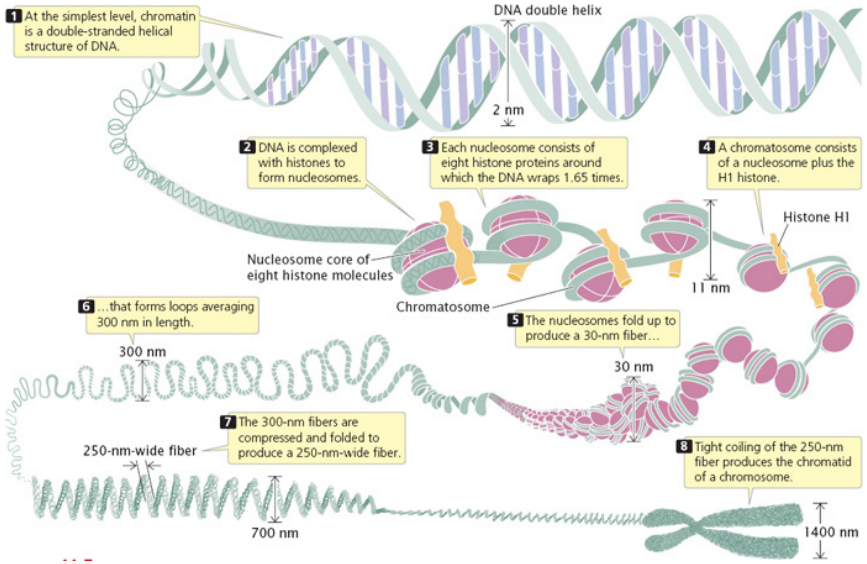


Links: Watson & Crick beschrijven de structuur van DNA

Boven: Breuning legt de consequenties uit

>10 jaar na het in kaart brengen genoom …

- Resultaten in gezondheidszorg bescheiden
- Genetische varianten die afgelopen 10 jaar werden onderzocht (SNPs) verklaren slechts minderheid van interindividuele verschillen
- Het menselijke moleculaire systeem is complexer dan verwacht.



Levensfasen & genetische screening

- Preconceptioneel
- Antenataal
- Neonataal
- Later in het leven

USA ziekten in de hielprik 2011

Additional Conditions/Abbreviations and Names

BIO	Biotinidase	**CF**	Cystic fibrosis	**GALT**	Transferase deficient galactosemia (Classical)	**HB S/C**	Sickle – C disease	~~**HEAR**~~	Hearing screening
CAH	Congenital adrenal hyperplasia	**CH**	Congenital hypothyroidism	**HB S/S**	Sickle cell anemia	**HB S/A**	S-βeta thalassemia	**SCID**	Severe Combined Immunodeficiency

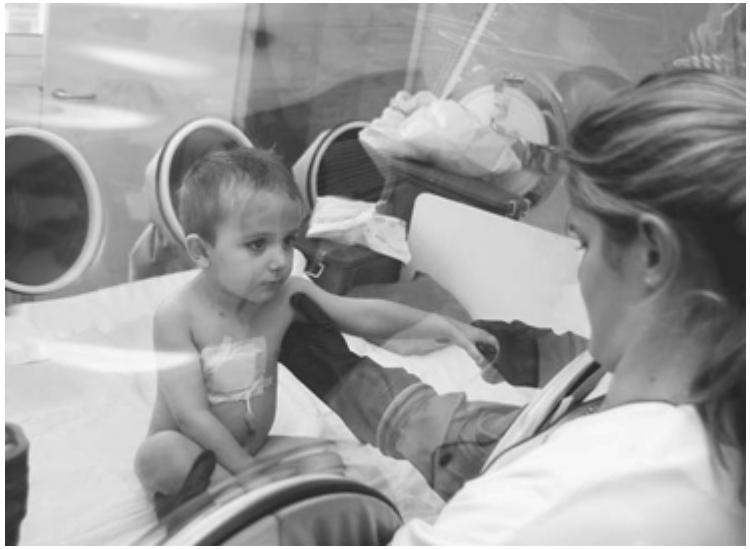
Other Disorders

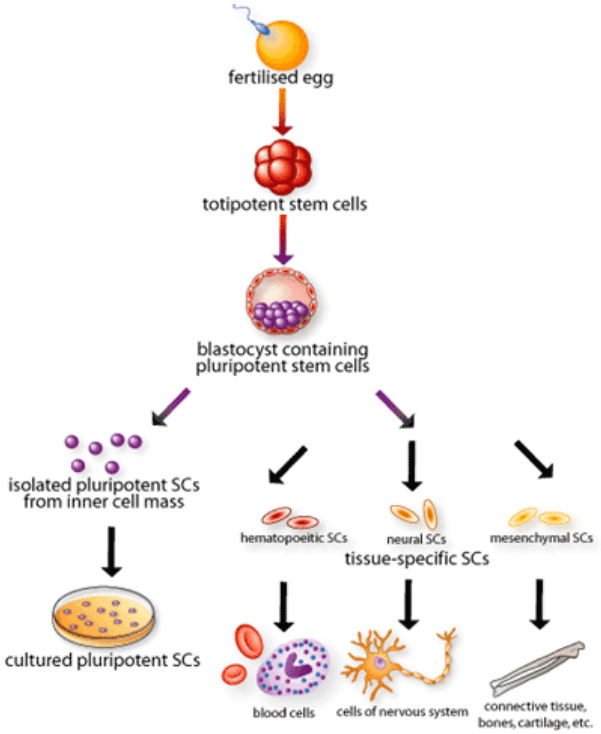
5-OXO	5-oxoprolinuria (pyroglutamic aciduria)	**G6PD**	Glucose 6 phosphate dehydrogenase	**NKH**	Nonketotic hyperglycinemia
CPS	Carbamoylphosphate synthetase	**HHH**	Hyperammonemia/ornithinemia/ citrullinemia (Ornithine transporter defect)	**PRO**	Prolinemia
EMA	Ethylmalonic encephalopathy	**HIV**	Human immunodeficiency virus	**TOXO**	Toxoplasmosis

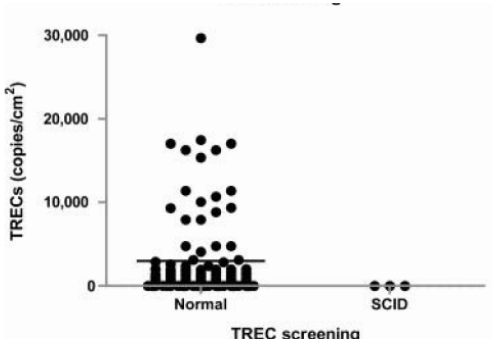
3-MCC	3-Methylcrotonyl-CoA carboxylase	**CUD**	Carnitine uptake defect (Carnitine transport defect)	**LCHAD**	Long-chain L-3- hydroxyacyl-CoA dehydrogenase	**PKU**	Phenylketonuria/ hyperphenylalaninemia
ASA	Argininosuccinate aciduria	**GA-1**	Glutaric acidemia type 1	**MCAD**	Medium-chain acyl-CoA dehydrogenase	**PROP**	Propionic acidemia (Propionyl-CoA carboxylase)
BKT	Beta ketothiolase (mitochondrial acetoacetyl-CoA thiolase ; short-chain ketoacyl thiolase; T2)	**HCY**	Homocystinuria (cystathionine beta synthase)	**MCD**	Multiple carboxylase (Holocarboxylase synthetase)	**TFP**	Trifunctional protein deficiency
CBL A,B	Methylmalonic acidemia (Vitamin B12 Disorders)	**HMG**	3-Hydroxy 3 - methylglutaric aciduria (3-Hydroxy 3-methylglutaryl-CoA lyase)	**MSUD**	Maple syrup urine disease (branched-chain ketoacid dehydrogenase)	**TYR-1**	Tyrosinemia Type 1
CIT I	Citrullinemia type I (Argininosuccinate synthetase)	**IVA**	Isovaleric acidemia (Isovaleryl-CoA dehydrogenase)	**MUT**	Methylmalonic Acidemia (methylmalonyl-CoA mutase)	**VLCAD**	Very long-chain acyl-CoA dehydrogenase

2M3HBA	2-Methyl-3-hydroxy butyric aciduria	**CACT**	Carnitine acylcarnitine translocase	**GA-II**	Glutaric acidemia Type II	**MAL**	Malonic acidemia (Malonyl-CoA decarboxylase)
2MBG	2-Methylbutyryl-CoA dehydrogenase	**CBL-C,D**	Methylmalonic acidemia (Cbl C,D)	**GALE**	Galactose epimerase	**MCKAT**	Medium-chain ketoacyl-CoA thiolase
3MGA	3-Methylglutaconic aciduria	**CIT-II**	Citrullinemia type II	**GALK**	Galactokinase	**MET**	Hypermethioninemia
ARG	Argininemia (Arginase deficiency)	**CPT-Ia**	Carnitine palmitoyltransferase I	**H-PHE**	Benign hyperphenylalaninemia	**SCAD**	Short-chain acyl-CoA dehydrogenase
BIOPT-BS	Defects of biopterin cofactor biosynthesis	**CPT-II**	Carnitine palmitoyltransferase II	**IBG**	Isobutyryl-CoA dehydrogenase	**TYR-II**	Tyrosinemia type II
BIOPT-REG	Defects of biopterin cofactor regeneration	**De-Red**	Dienoyl-CoA reductase	**M/SCHAD**	Medium/Short chain L-3-hydroxy acyl-CoA dehydrogenase	**TYR-III**	Tyrosinemia type III

SCID: immuun deficientie; stamcellen!







McGhee 2005

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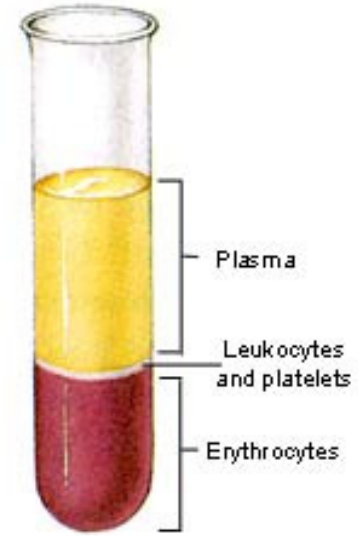
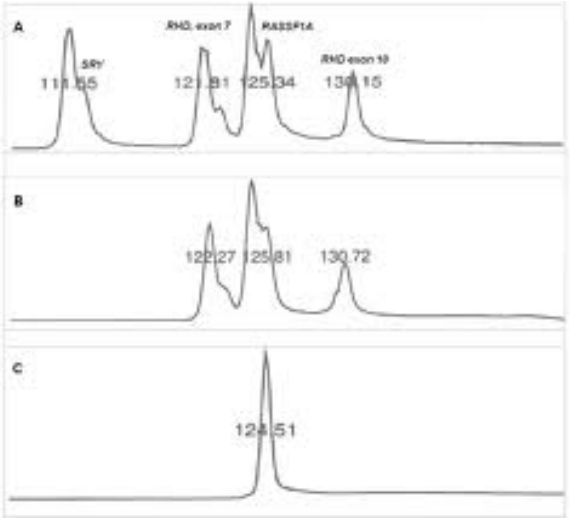
Non-invasieve prenatale testen

- Van het DNA in moederlijk plasma is ~10% afkomstig van foetus *(Chiu et al. BMJ 2011)*
- RhD+ DNA in bloed van RhD- moeder, is dus van foetus!
- Ook trisomie 21 (18, 13)?

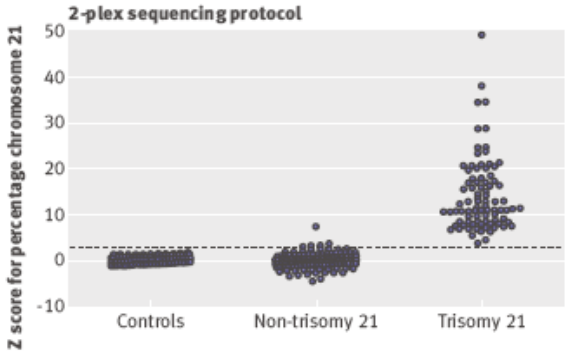




Man RhD+

Vrouw RhD+

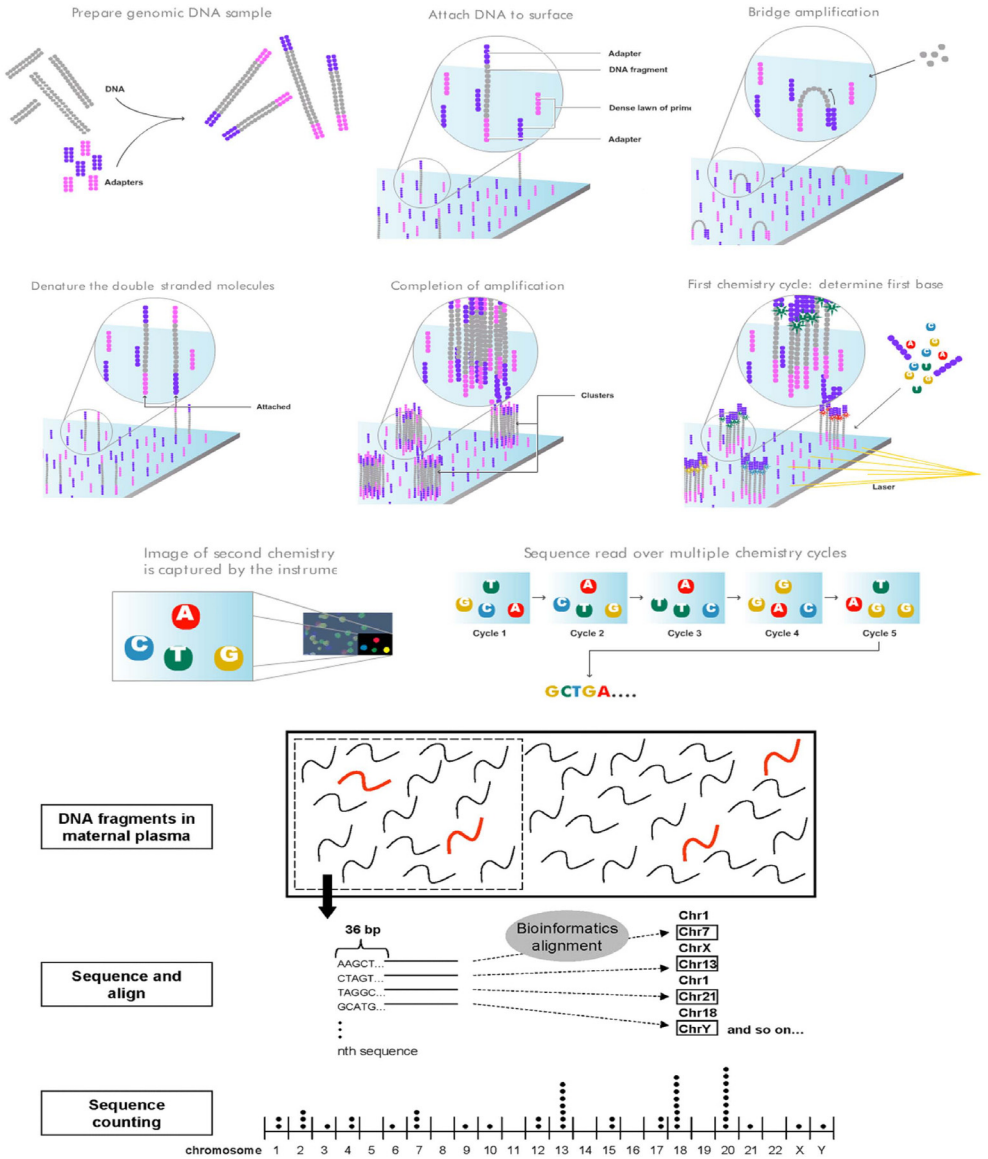
Vrouw RhD-

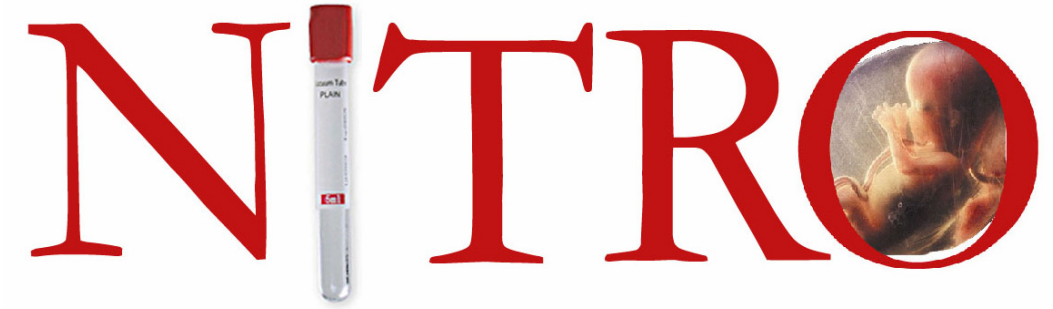


BMJ 2011: trisomie 21
PLoS One 2011: ook tris 13&18

Massively parallel genomic sequencing

This technique can identify and quantify millions of DNA fragments in a span of days





Landelijk consortium werkt aan een toekomstverkenning, gevolgen als NIPD voor trisomiedetectie ingevoerd wordt. Verschillende scenarios doorgerekend:

- **Uitslag veel grotere mate van zekerheid**:
  "overall sensitivity 125/125 (100%, 95% CI 97.5-100%) specificity 552/556 (99.3%, 95% CI 98.7-99.3%)".
- **Veel minder vruchtwaterpuncties nodig**

LUMC:

Dick Oepkes, Joanne Verweij

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Patient Login | Medical Login

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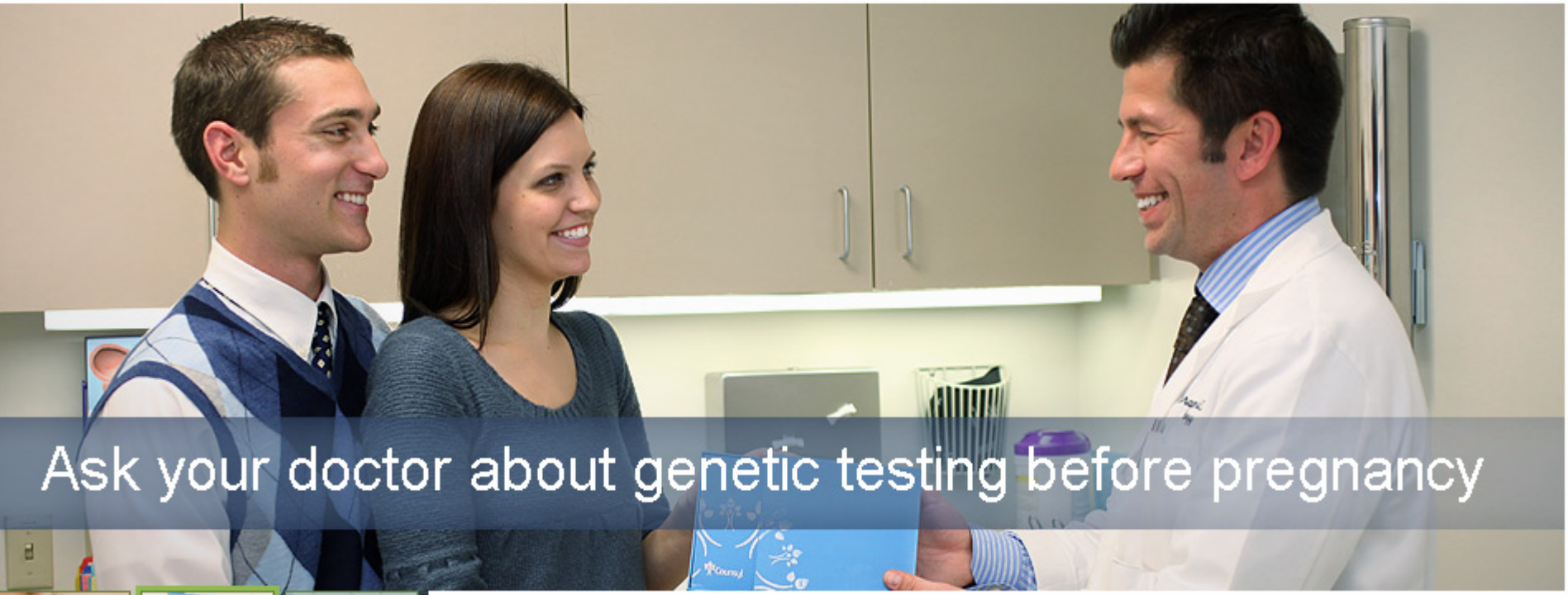

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—Professor Pasquale Patrizio, MD
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Prevent Genetic Disease before Pregnancy with a DNA Test - Counsyl - Windows Internet Explorer

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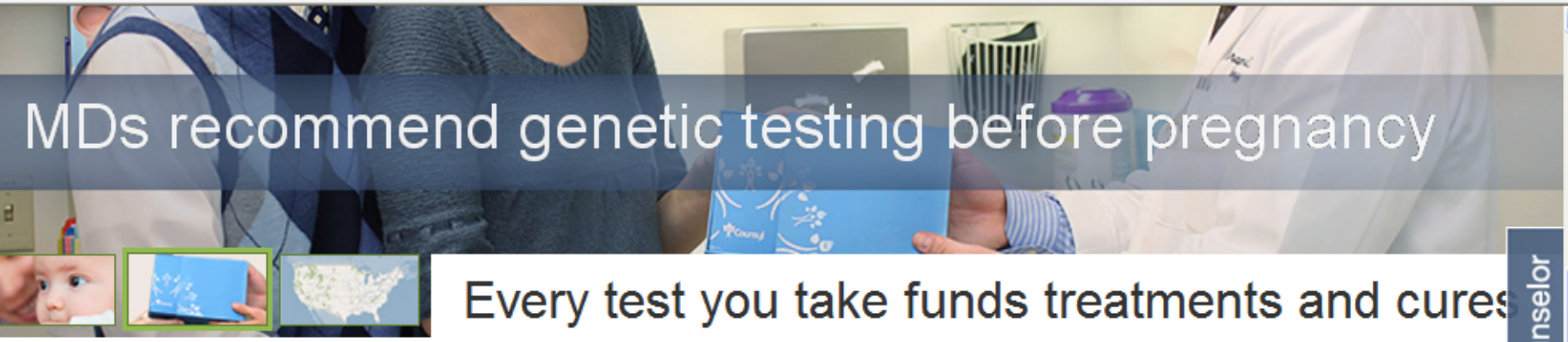
Bing

tand Bewerken Beeld Favorieten Extra Help

Favorieten

Prevent Genetic Disease before Pregnancy with a DN...

Pagina Beveiliging Extra



Ask a Counselor

Every test you take funds treatments and cures for children living with genetic disease. Learn More

"Every adult of reproductive age needs the Counsyl test."

—Professor Pasquale Patrizio, MD
Director, Yale Fertility Center

"Universal genetic testing can drastically reduce the incidence of genetic diseases, and may very well eliminate many of them."

—Professor Steven Pinker, PhD
Harvard University

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Our Values

We believe that genetic testing is a human right, not a luxury.

We believe children deserve healthy lives, free from genetic disease.

And we believe in universal access, especially for those most in need.

Learn More

ed

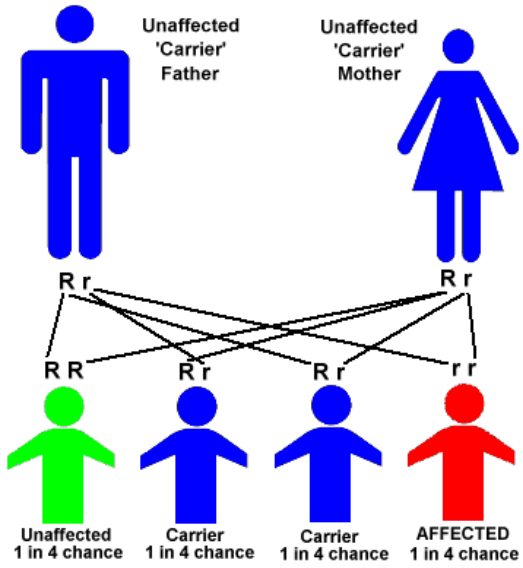
Internet

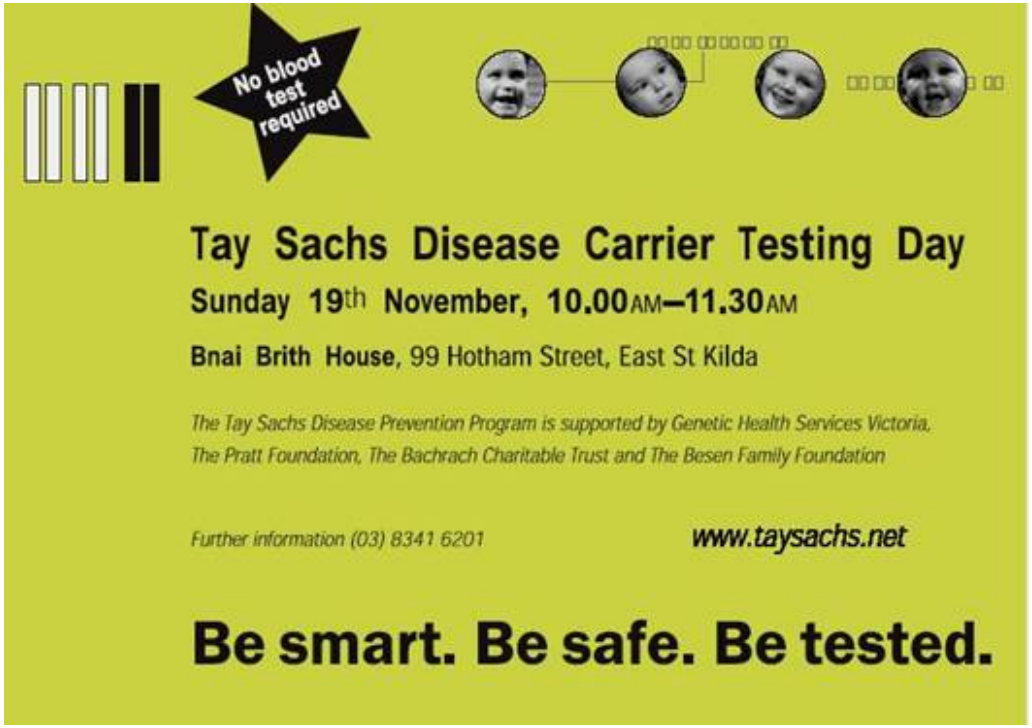
110%

Genetische screening voor Tay Sachs in USA

- Rond 1970 ontstaan in orthodox joodse gemeenschap, waar huwelijken gearrangeerd werden.
- Prenatale diagnostiek en selectieve abortus werden onaanvaardbaar geacht.
- Huwelijkskandidaten screenen, informatie aan de “matchmaker” doorgeven, en dragerparen vermijden was in die cultuur passende èn effectieve aanpak.

Genetic screening for Tay Sachs in USA





Het hele genoom?

Offered in 2009

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Knome in the media

Knome CEO Named Top Innovator
Technology Review, August 18, 2009

The Business of Personal Genomes
Technology Review, July 23, 2009

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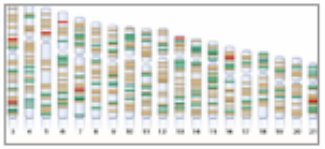

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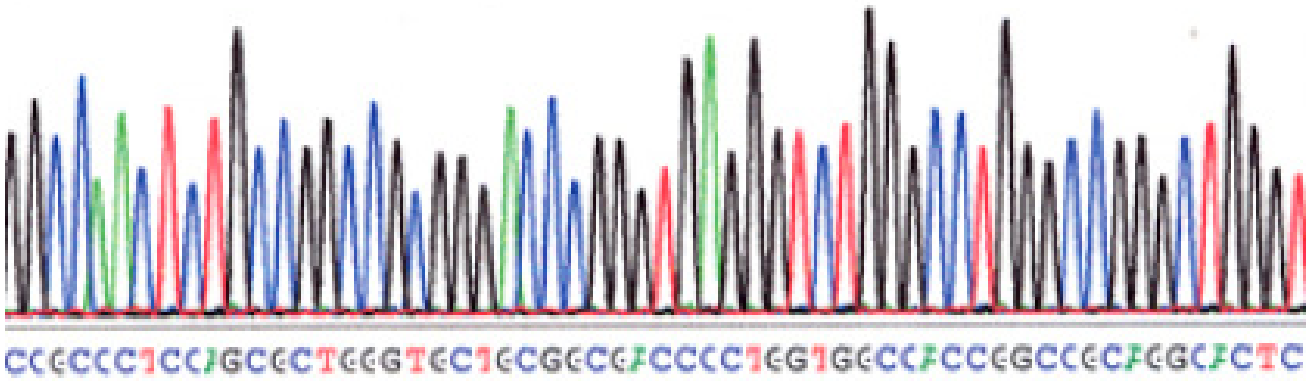
A window into your genes.

GenomeKey™

“Sequence” of “analyse”?

- Sequence:



- Analyse=interpretatie
  - Mutaties in genen betrokken bij acute hartdood
  - CF drager
  - Farmacologische varianten

Ashley et al. Clinical assessment incorporating a personal genome. Lancet 2010

Data steeds goedkoper; analyse nog lastig…

Year	Cost	Personal genomes sequenced	Company	Source
2003	$3,000,000,000	1	Various	
2009	$48,000	100	Illumina	[11]
2010	$19,500	1000+	Illumina	[12]
2011	$19,500 to $4,000	?	Illumina	[17]

Source: wikipedia

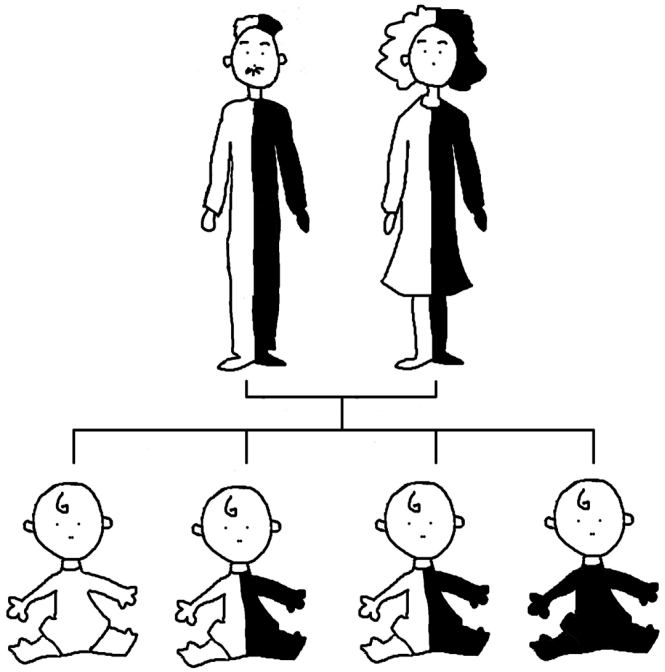
Samenvattend

- Wetenschap: snelle ontwikkelingen
- Gezondheidszorg: toch ook interessante uitdagingen
  - Neonataal: tientallen kansen
  - Prenataal: niet invasieve testen
  - Preconceptioneel: internetaanbod
  - Analyse hele genoom: niet op grote schaal

Bedankt voor uw aandacht

Autosomaal recessieve ziekten

- Ieder mens heeft in zijn genen een aantal afwijkingen.
- Zolang een afwijking alleen in één van de 2 genen van een paar zit, heeft deze persoon geen zogenaamde autosomaal recessieve aandoening. Hij 'draagt' alleen de afwijking met zich mee, maar is gezond.
- De ziekte ontstaat pas op het moment dat er twee genen met dezelfde afwijking zijn, omdat de zieke persoon zowel van zijn vader als van zijn moeder dit afwijkende gen heeft geërfd.
- Als de ouders beide drager zijn, is de kans dat ze dit afwijkende gen doorgeven 1 op 4, ofwel 25%.



Dragerschap en de hielprik

	A	a
A	AA	Aa
a	Aa	aa

	A	?
A	AA	
a	Aa	

Als kind drager is, is één van de ouders ook drager. Als de andere ouder voorouders uit zelfde regio heeft, is kans op dragerpaar verhoogd, dus kans op ernstige vorm van hemoglobinopathie bij volgende zwangerschap is verhoogd.