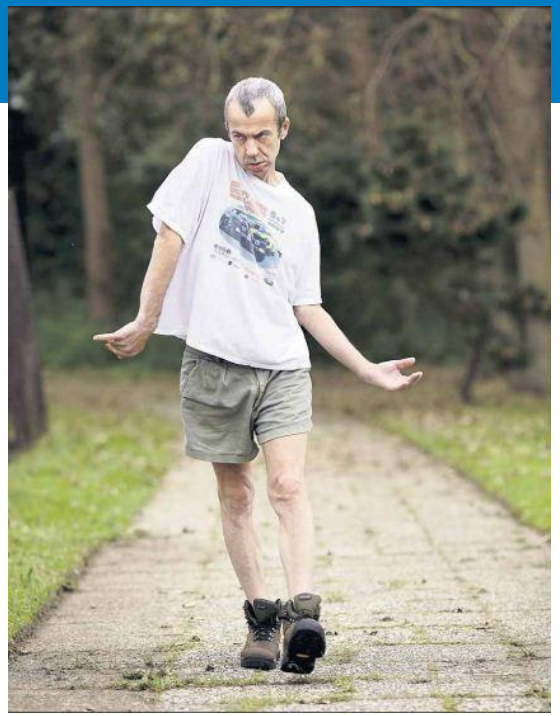
Leids Universitair
Medisch Centrum

Nieuwe onderzoeksontwikkelingen bij de Ziekte van Huntington



HD café Overduin
5 juni 2019

S.T. de Bot, neuroloog

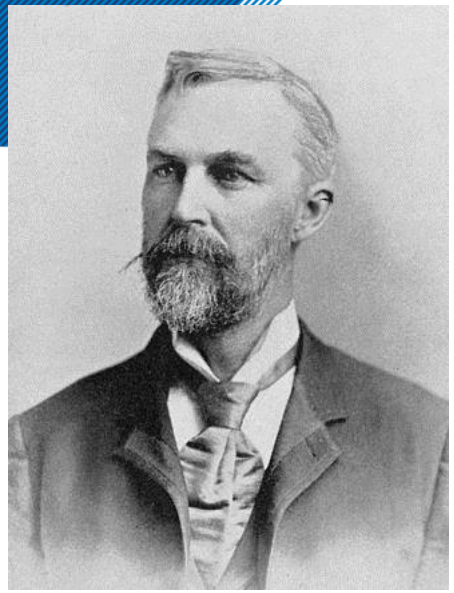
Afdeling Neurologie

LEIDS UNIVERSITAIR MEDISCH CENTRUM

Overzicht

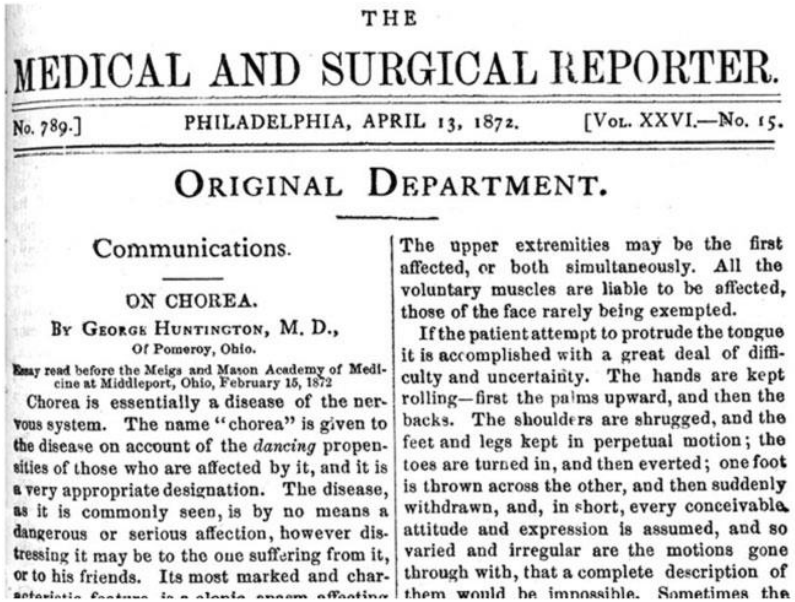
- Historisch overzicht en introductie
- Pathofysiologie & pathologie
- Recent en huidig onderzoek
- Toekomstig onderzoek

ZvH: introductie en voorkomen



- ZvH voor het eerst beschreven in 1872
- Is een erfelijke neurodegeneratieve ziekte
- Vóórkomen (prevalentie): 1/10,000-1/20,000

- Gemiddelde beginleeftijd: 30-50 jr
- Maar varieert tussen: 2-85 jaar
- Ziekteduur gemiddeld 17-20 jaar



THE

MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

By George Huntington, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and char-

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of them would be impossible. Sometimes the

Huntington's disease: a clinical review. Roos RA. Orphanet J Rare Dis. 2010 Dec 20;5:40. Review.

THE

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The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of them would be impossible. Sometimes the

Cell, Vol. 72, 971–983, March 26, 1993, Copyright © 1993 by Cell Press

A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington's Disease Chromosomes

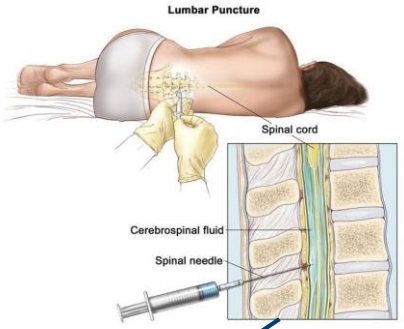
The Huntington's Disease Collaborative Research Group*

Summary

The Huntington's disease (HD) gene has been mapped in 4p16.3 but has eluded identification. We have used haplotype analysis of linkage disequilibrium to spotlight a small segment of 4p16.3 as the likely location of the defect. A new gene, IT15, isolated using cloned trapped exons from the target area contains a polymorphic trinucleotide repeat that is expanded and unstable on *HD* chromosomes. A $(CAG)_n$ repeat longer than the normal range was observed on *HD* chromosomes from all 75 disease families examined, comprising a variety of ethnic backgrounds and 4p16.3 haplotypes. The $(CAG)_n$ repeat appears to be located within the coding sequence of a predicted ~348 kd

Introduction

Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by motor disturbance, cognitive loss, and psychiatric manifestations (Martin and Gusella, 1986). It is inherited in an autosomal dominant fashion and affects ~ 1 in 10,000 individuals in most populations of European origin (Harper et al., 1991). The hallmark of HD is a distinctive choreic movement disorder that typically has a subtle, insidious onset in the fourth to fifth decade of life and gradually worsens over a course of 10 to 20 years until death. Occasionally, HD is expressed in juveniles, typically manifesting with more severe symptoms including rigidity and a more rapid course. Juvenile onset of HD is associated with a preponderance of paternal transmission of the disease allele. The neuropathology of HD also displays a distinctive pattern, with selective loss of neurons that is most severe in the caudate and putamen. The biochemical basis for neuronal death



1872


George Huntington


Americo Negrette


Nancy Wexler

1972

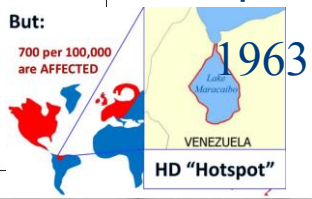
1993

2015


James Gusella


Nancy Wexler with a Choreic child in her arms

But:

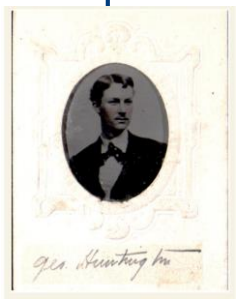


1963

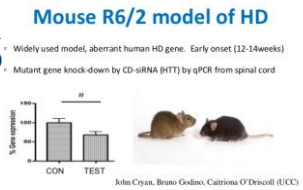
1983
HD locus

2017
IONIS HttR/
Phase 1b/2a

2005
Htt lowering therapy proven in animal model



1996

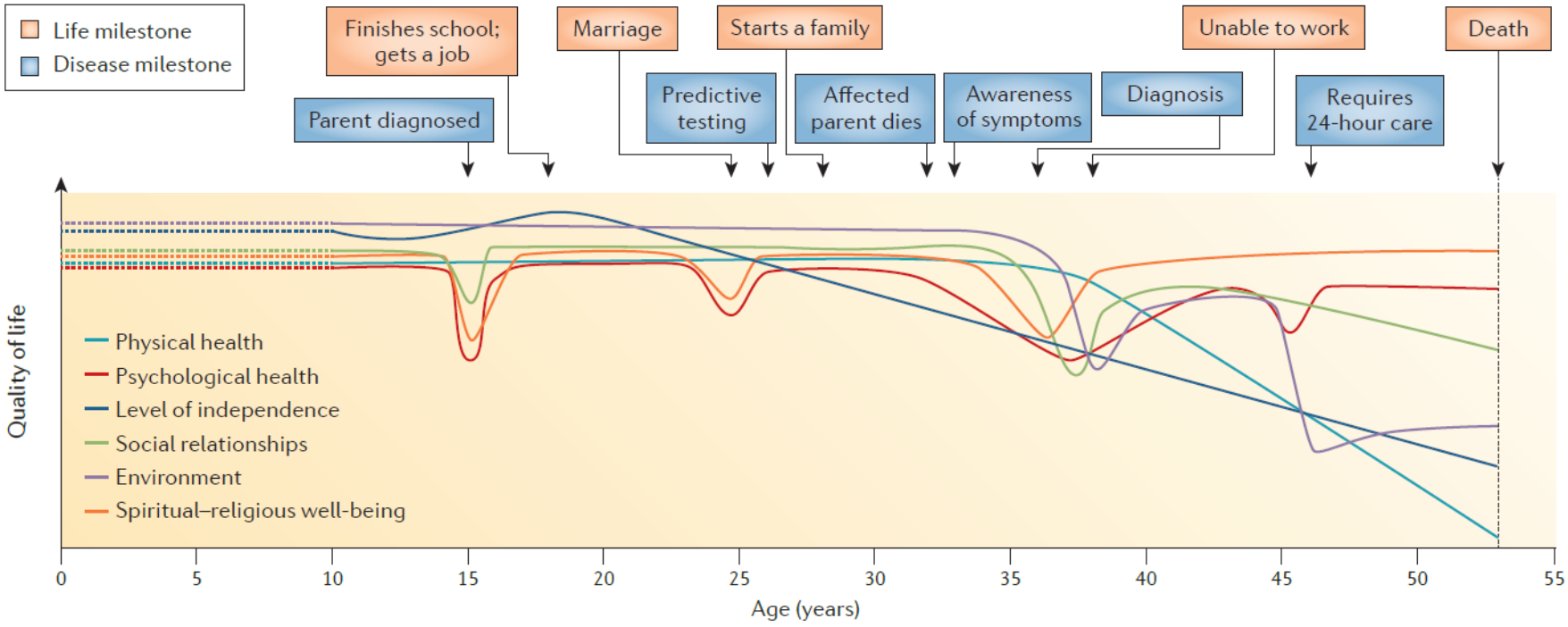


A. Wexler et al. George Huntington: a legacy of inquiry, empathy and hope. Brain 2016

Symptomen en kenmerken

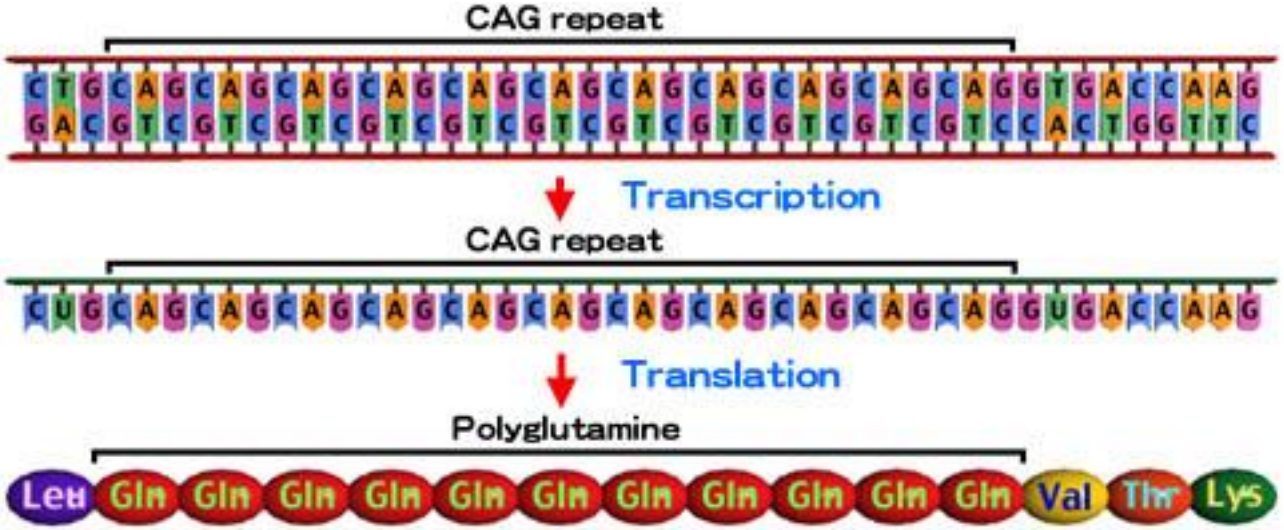
Bewegingsstoornis:	hyperkinesie: chorea
	hypokinesie: “parkinsonisme”
	andere problemen met de motoriek: gestoorde oog-bewegingen, spraak- en slikproblemen, loop- en balansproblemen
Psychiatrisch/gedragsverandering	depressie en angst
	apathie
	prikkelbaarheid/agressie
Cognitieve veranderingen (denken)	dementie (planning ed.)

De mogelijke impact van verschillende levenfasen op ziekte mijlpalen op kwaliteit van leven



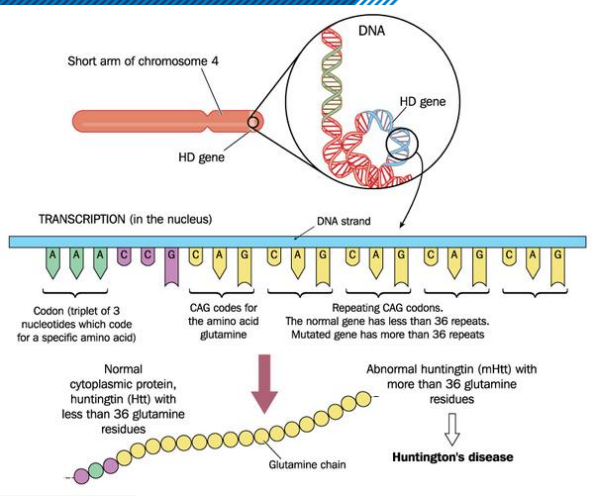
Onderliggende fout op het DNA

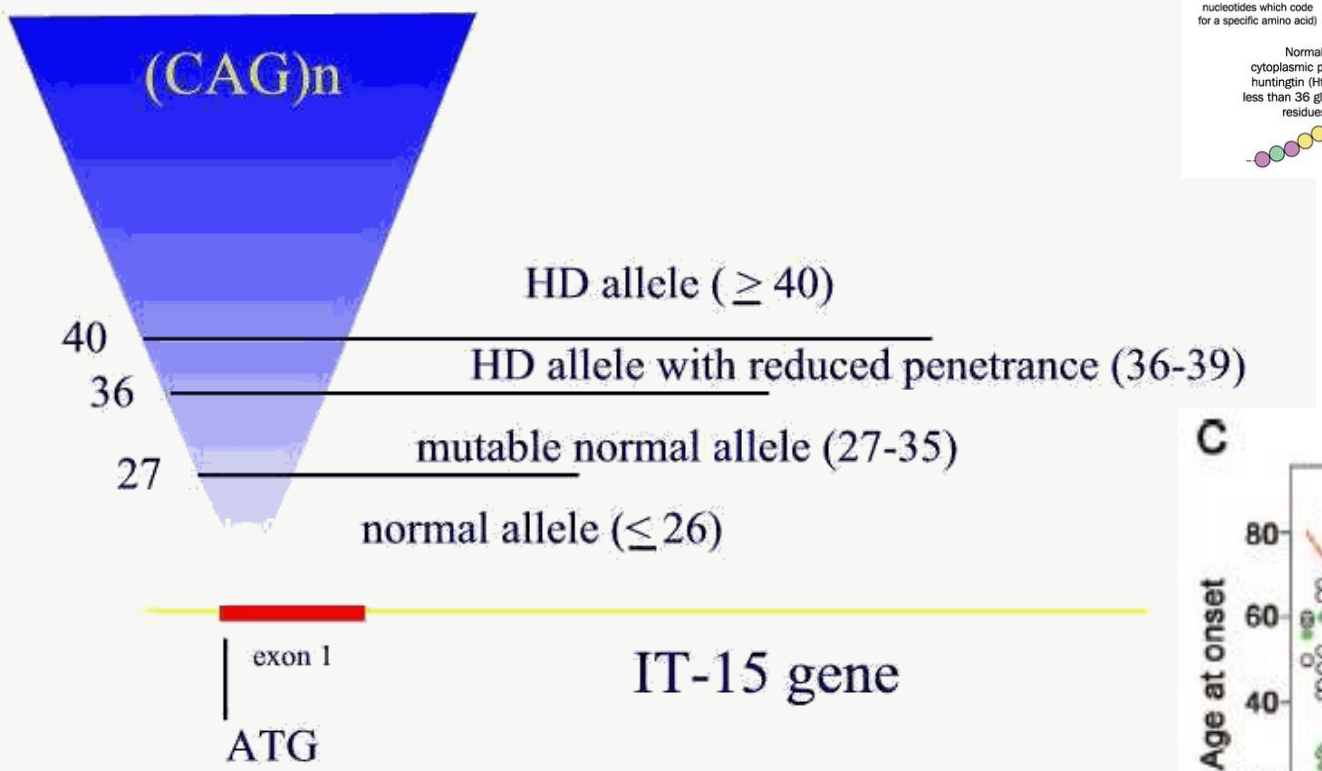
DNA	CAG repeat (herhaling)
CAG coding	Glutamine
Protein	Huntingtine met polyglutamine staart

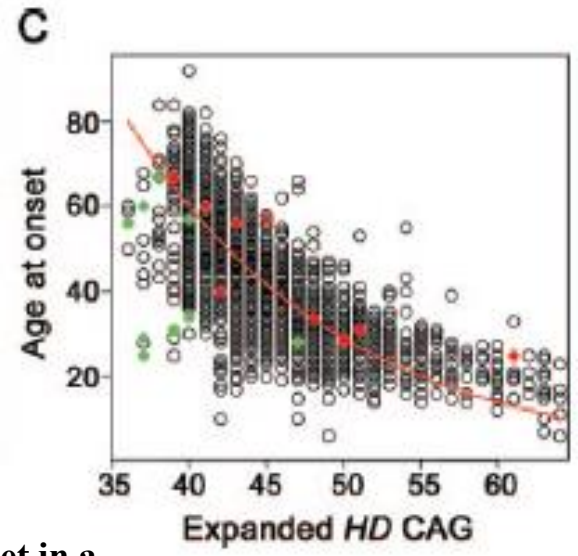


In de ZvH is een verminderde expressie van normaal huntingtine en een toename van een toxisch effect van het mutante huntingtine (met te lange polyglutamine staart)

CAG repeat grenzen

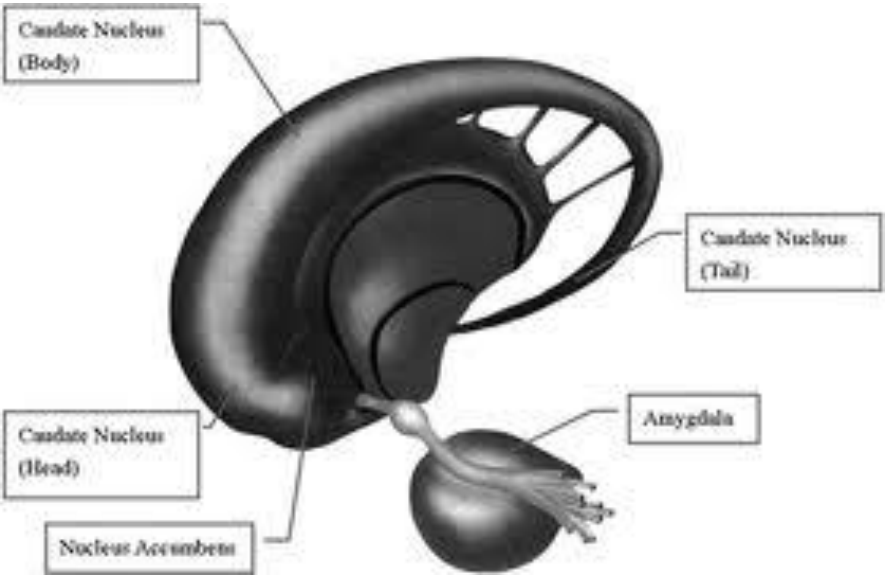


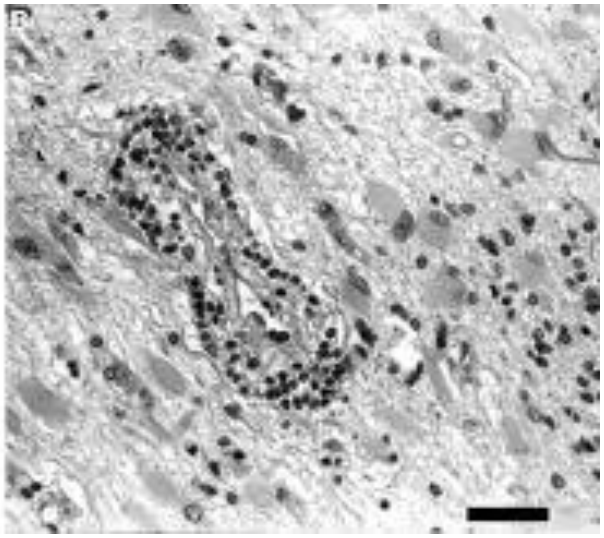


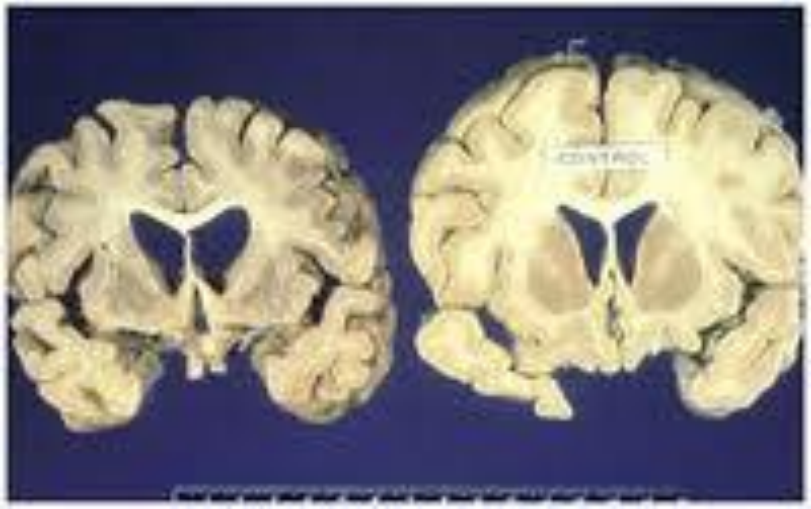


CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion J.M. Lee et al . Neurology 2012 Mar 6;78(10):690-5

Pathologie: nucleus caudatus atrofie



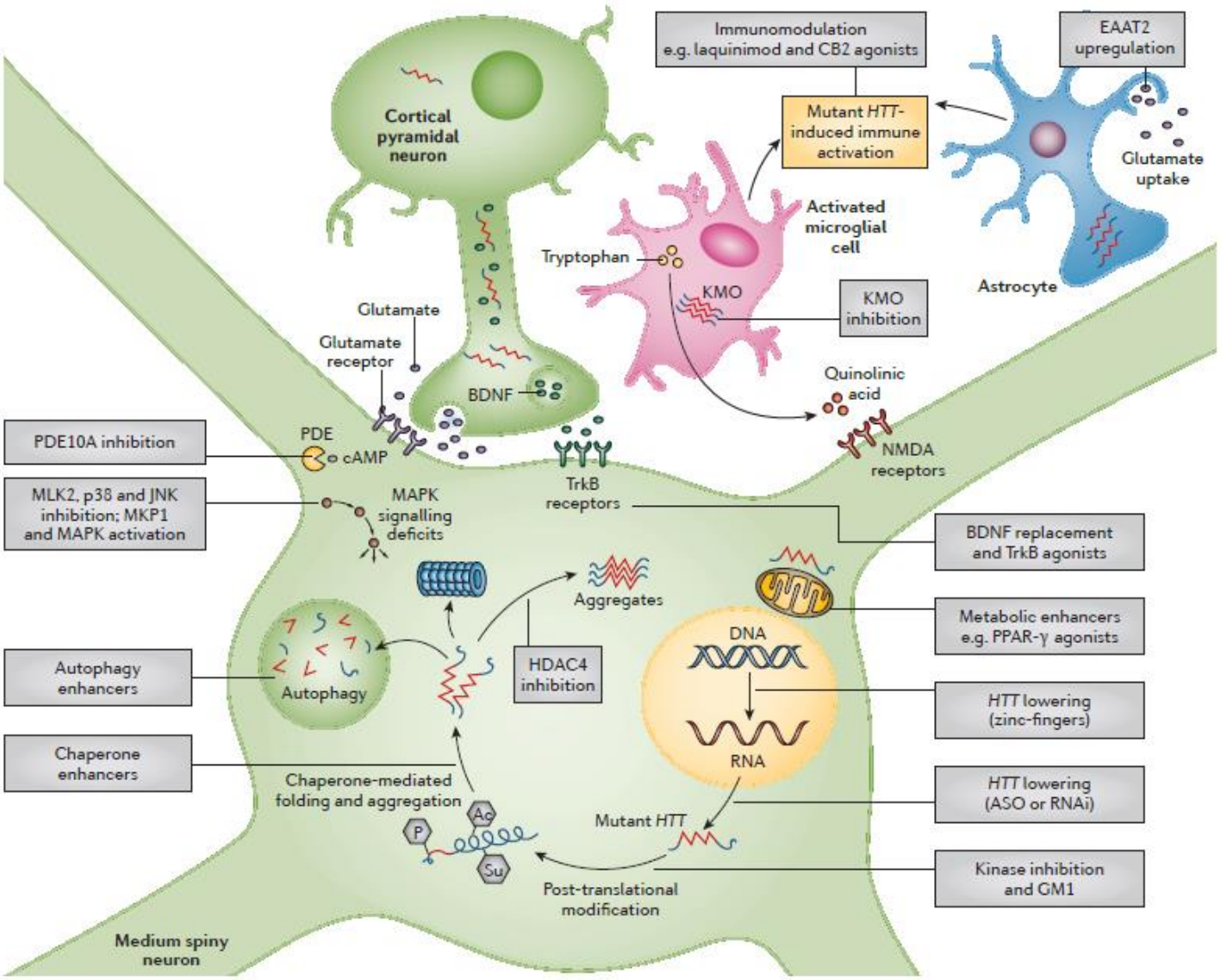




Maar daarnaast ook:

- Ernstige hersenatrofie
  (meeste in basale kernen)
- Verlies van zenuwcellen en steuncellen
- Inclusies van stoffen in de celkernen

Recent en huidig onderzoek



Als eerste: natuurlijk beloop studies:

EHDN EUROPEAN HUNTINGTON'S DISEASE NETWORK

Advancing Research, Conducting Trials, Improving Care

HUNTINGTON STUDY GROUP

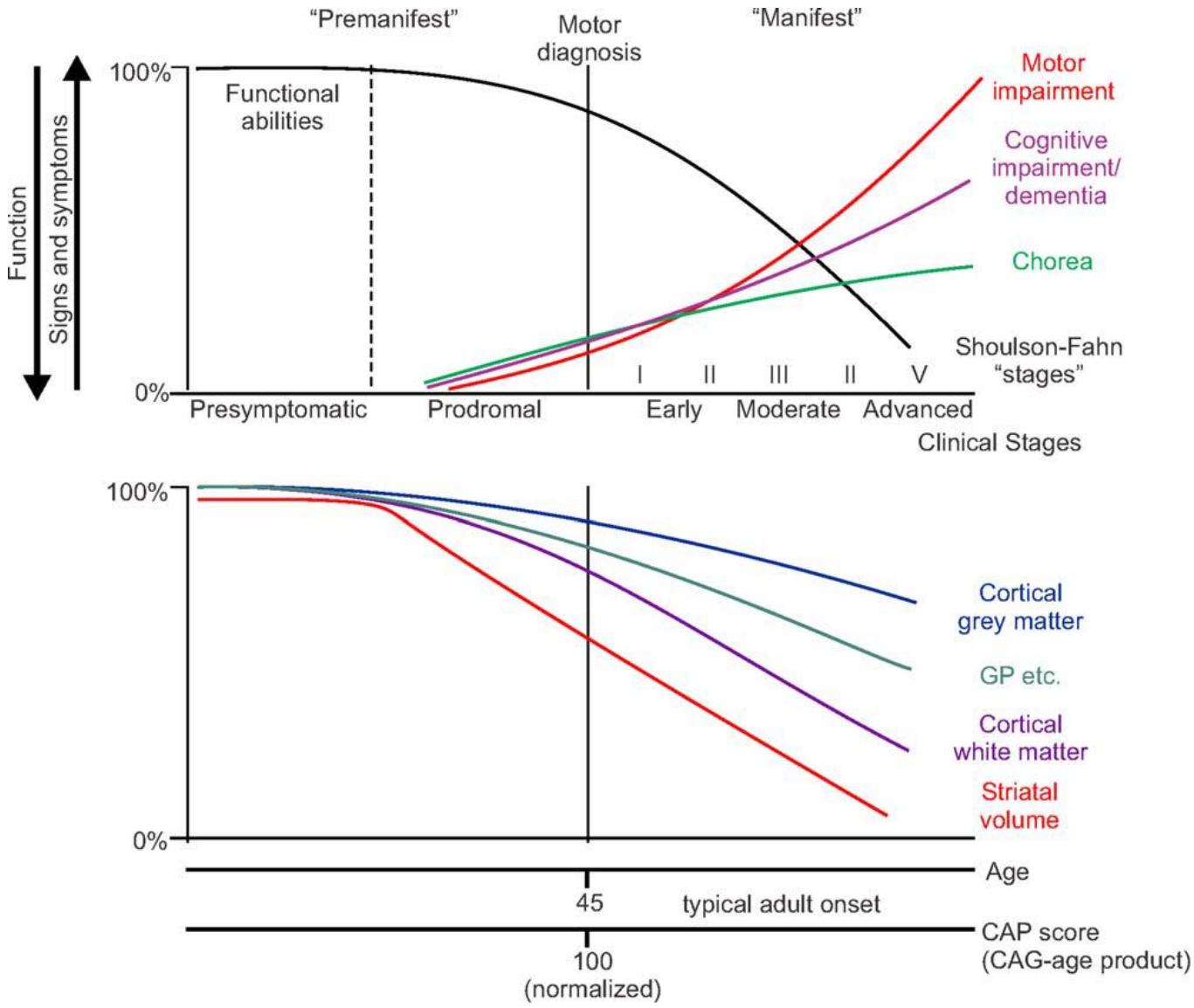
seeking treatments that make a difference

Enroll-HD

A worldwide observational study for Huntington's Disease families

18.479 Actieve deelnemers (405 in Leiden)
174 deelnemende klinieken wereldwijd
19 deelnemende landen

(nieuwe) Diagnostische Criteria voor de ziekte van Huntington gebaseerd op natuurlijk beloop studies

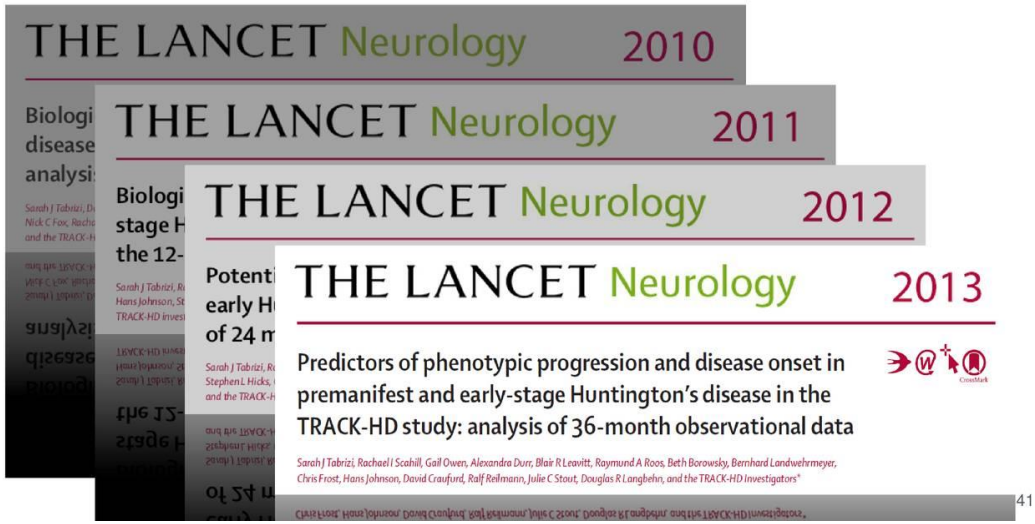


Reilmann, Leavitt and Ross, Movement Disorders 2014

Leiden, Londen, Parijs, Vancouver

TRACK-HD

- Insights into Huntington's disease natural history pre- and post-symptom-onset
- TRACK-HD battery now used in current global clinical trials



41

Table 2 | **Overview of potential biomarkers in Huntington disease**

Biomarker	Measure	Change	Ref.
Clinical			
Speeded tap interval	Q-motor	Increased	120
Grip force	Q-motor	Increased variability	120
HD-CAB	Cognitive	Increased score	175
Imaging			
Caudate volume	MRI	Decreased	129
Fractional anisotropy	Diffusion imaging	Decreased	257
Mean diffusivity		Increased	
Thalamic FDG activity	PET	Increased	193
Putaminal *N*-acetyleaspartate	MRS	Decreased	192
Putaminal myoinositol		Increased	
Electrophysiological			
Cortical activity	EEG	Decreased α-signal	183
Biochemical			
Neurofilament	CSF	Increased levels	258
Clusterin	Plasma	Increased levels	180
	CSF	Increased levels	
24-hydroxycholesterol	Plasma	Decreased levels	259
Pharmacodynamic			
Mutant huntingtin levels	CSF	Treatment response	187

Predicting Clinical Diagnosis in Huntington's Disease: An Imaging Polymarker

Sarah L. Mason, PhD,[1]* Richard E. Daws, Msc,[3]* Eyal Soreq, MA,[3]
Eileanoir B. Johnson,[4] Rachael I. Scahill, PhD,[4] Sarah J. Tabrizi, PhD,[4]
Roger A. Barker, MRCP, PhD,[1,2] and Adam Hampshire, PhD[3]

Objective: Huntington's disease (HD) gene carriers can be identified before clinical diagnosis; however, statistical models for predicting when overt motor symptoms will manifest are too imprecise to be useful at the level of the individual. Perfecting this prediction is integral to the search for disease modifying therapies. This study aimed to identify an imaging marker capable of reliably predicting real-life clinical diagnosis in HD.
Method: A multivariate machine learning approach was applied to resting-state and structural magnetic resonance imaging scans from 19 premanifest HD gene carriers (preHD, 8 of whom developed clinical disease in the 5 years postscanning) and 21 healthy controls. A classification model was developed using cross-group comparisons between preHD and controls, and within the preHD group in relation to "estimated" and "actual" proximity to disease onset. Imaging measures were modeled individually, and combined, and permutation modeling robustly tested classification accuracy.
Results: Classification performance for preHDs versus controls was greatest when all measures were combined. The resulting polymarker predicted converters with high accuracy, including those who were not expected to manifest in that time scale based on the currently adopted statistical models.
Interpretation: We propose that a holistic multivariate machine learning treatment of brain abnormalities in the pre-manifest phase can be used to accurately identify those patients within 5 years of developing motor features of HD, with implications for prognostication and preclinical trials.

ANN NEUROL 2018;83:532–543

Recent onderzoek LUMC





TRF Expertise centrum voor de ZvH


- **HD-Neurology**
  - **Observational**
    - **Enroll-HD** *(n = ∞)*
    - **PET** *(n = 12)*
      - **Cross-sectional (finished)**
      - **Longitudinal** *(n = 10; finished)*
  - **Clinical trials**
    - **Legato-HD** *(n = 10)*
    - **Trihep-3** *(n = 50)*
      - **cohort 1** *(n = 25)*
        - **rct (finished)**
        - **open label** (n = 9)
      - **cohort 2** *(n = 25)*
    - **Pride-HD** *(n = 17)*
      - **rct (finished)**
      - **open label** *(n = 10 finished)*
  - **PhD projects**
    - **Drive-HD** *(n = 90)*
    - **HDvisual** *(n = 60)*
    - **UHDRS-FAP** *(n = 50)*




Toekomstig Onderzoek: 3 strategieen

1. **Medicatie eerder voor een andere neurodegeneratieve ziekte ontwikkeld**, zoals MS of Parkinson, vb: Pridopidine (Parkinson).
Laquinimod (MS)

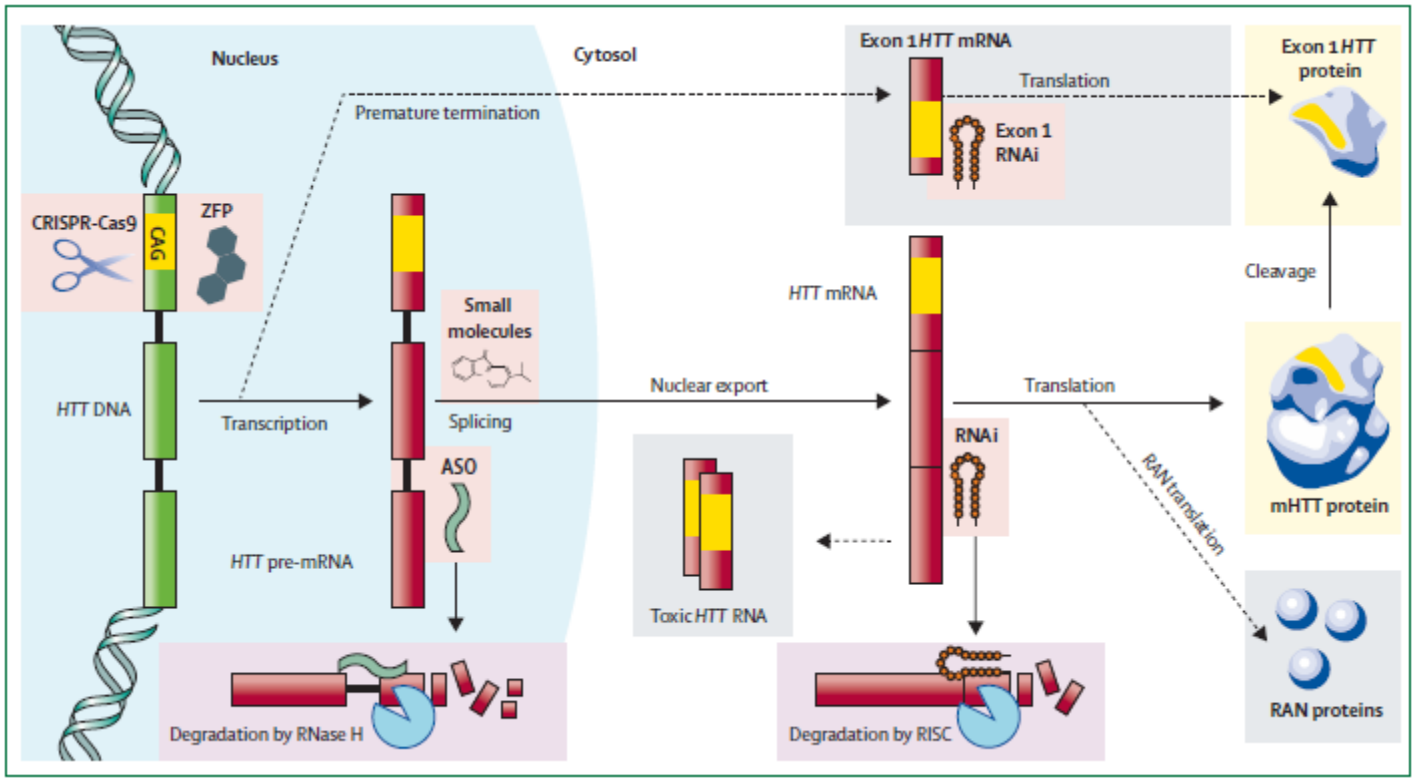
2. **Celvervangende therapie: vb:** stamceltherapie, (van embryo's of IPS cellen)

Postmortem (na overlijden) studies-> veel cellen sterven af

3. **Gen (gerichte) therapie**: meest hoopgevende benadering
mogelijk zenuwcel beschermend (neuroprotectief)
gericht op aanpassen/verlagen van het mutante huntingtine gen/eiwit
=Huntingtine verlagende therapie

Huntington's disease: Current and future therapeutic prospects.
Kieburctz K, **Reilmann** R, Olanow CW. Mov Disord. 2018 Jul;33(7):1033-1041

Huntingtine verlagende strategieen



Therapies targeting DNA and RNA in Huntington's disease:..
Wild EJ, Tabrizi SJ. Lancet Neurol. 2017;16: 837-47.

Huntingtin-lowering programs targeting mRNA

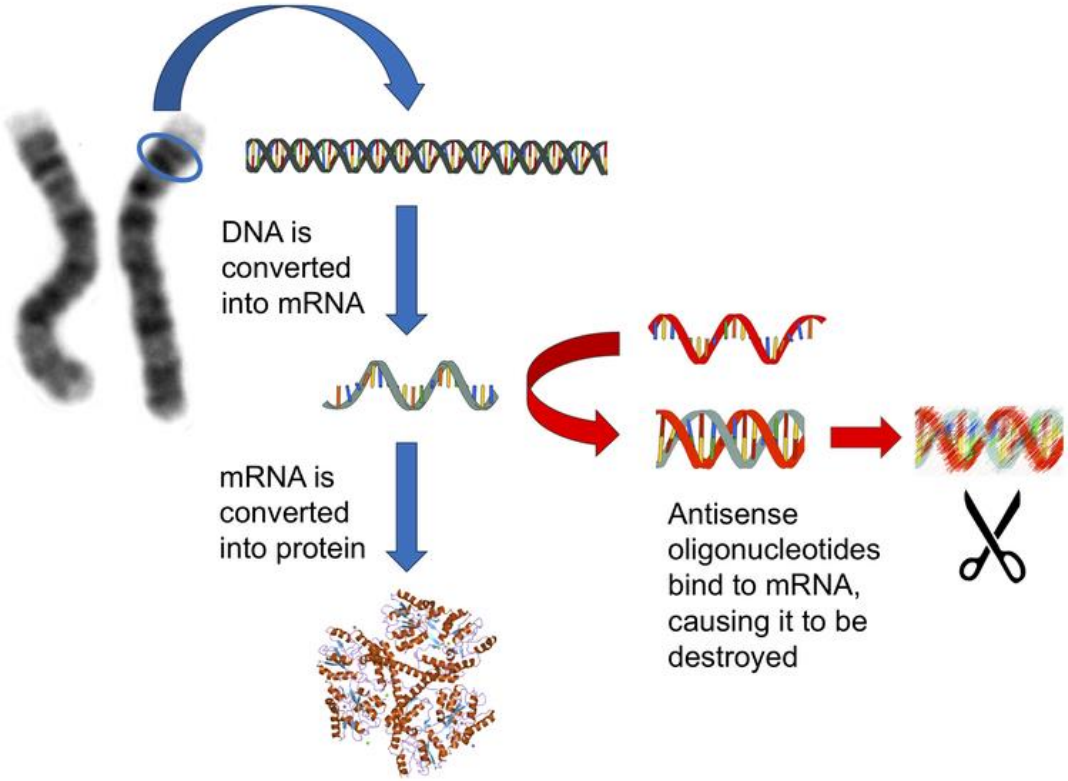
	Allele selectivity	Delivery	Vector	Sponsor	Key advantages	Key disadvantages	References
Antisense oligonucleotides							
Pre-mRNA degradation	None	Intrathecal	None	Ionis Pharmaceuticals (Carlsbad, CA, USA)	Single drug for all carriers of the Huntington's disease mutation	Theoretical risk from reducing wild-type HTT	Bennett, 2010;[25] Kordasiewicz, 2012;[26] Leavitt, 2016;[27] NCT02519036
Pre-mRNA degradation	SNP-targeted	Intrathecal	None	Wave Life Sciences (Cambridge, MA, USA)	Selective silencing of mutant allele	Several drugs required to treat most patients; SNP targeting limits choice of RNA-binding sequences	Hersch, 2017;[28] Butler, 2015[29]
Pre-mRNA degradation	CAG repeat	Intrathecal	None	Biomarin (Leiden, Netherlands)	Selective silencing of mutant allele with a single drug for all mutation carriers	Reduced expression of other important CAG-containing genes, risking off-target effects	Datson, 2017[30]
RNA interference compounds							
mRNA degradation	None	Intracranial	AAV2	Spark (Philadelphia, PA, USA)	Single treatment provides sustained HTT reduction	Invasive delivery; limited treatment volume; cannot be reversed if adverse events occur	Harper, 2005;[15] Franich, 2008;[16] McBride, 2011[17]
mRNA degradation	None	Intracranial	AAV1	Voyager (Cambridge MA, USA)	As above	As above	Stanek, 2015[31]
mRNA degradation	None	Intracranial	AAV5	UniQure NV (Amsterdam, Netherlands)	As above	As above	Miniarikova, 2016;[32] Samaranch, 2017[33]
Small molecules							
Screening programme*	Unknown	Potentially oral	None	CHDI Foundation (New York, NY, USA)	Potentially highly accessible route of delivery; potentially readily reversible	More difficult to achieve selectivity for *HTT* than with nucleotide approaches	Doherty, 2017[34]

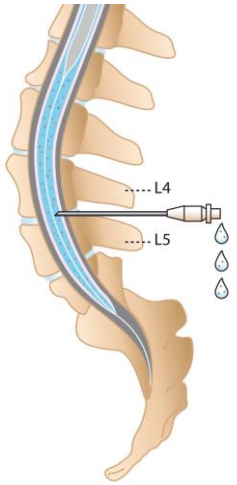
SNP=single nucleotide polymorphism. AAV1, 2, and 5=adeno-associated virus 1, 2, and 5. HTT=huntingtin protein. *The mechanisms of action, route of delivery, and advantages and disadvantages of the small molecules being investigated by CHDI Foundation remain to be determined because the programme is currently at the phenotypic screen stage.

Therapies targeting DNA and RNA in Huntington's disease:..
Wild EJ, Tabrizi SJ. Lancet Neurol. 2017;16: 837-47.

Antisense oligonucleotiden (ASO's)

kleine stukjes synthetisch DNA die individuele boodschapper-RNA-moleculen kunnen herkennen en markeren voor vernietiging.





Kan alleen via herhaalde toediening rechtstreeks in het hersenvocht: LP's

IONIS/ROCHE: RG6042

fase 1b/2a in nov 2017 afgerond:

46 HD patiënten

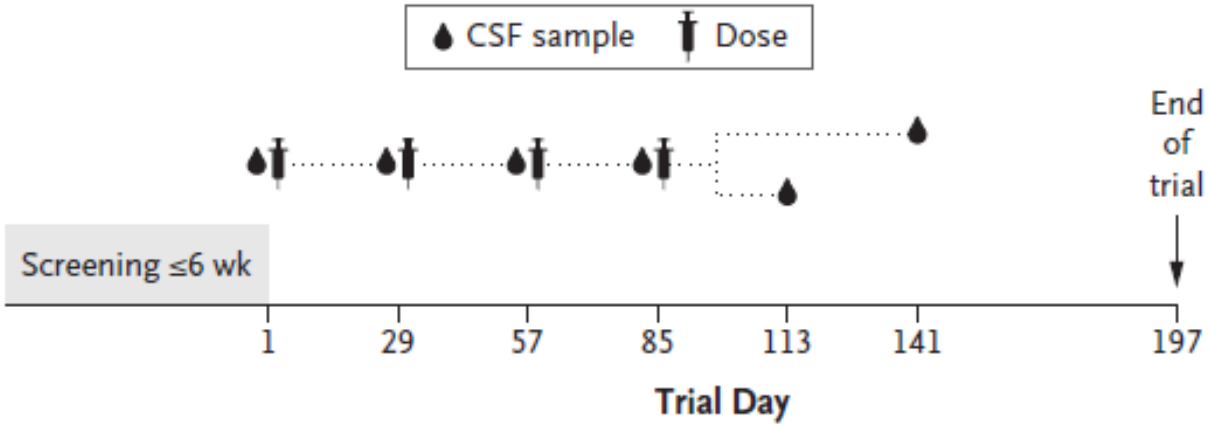
in 3 landen: UK, Duitsland, Canada

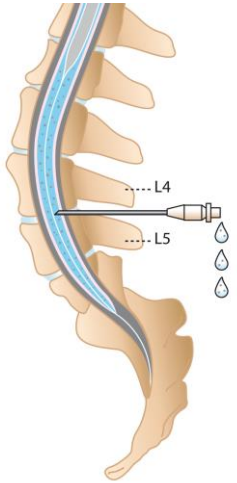
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting Huntingtin Expression in Patients with Huntington's Disease

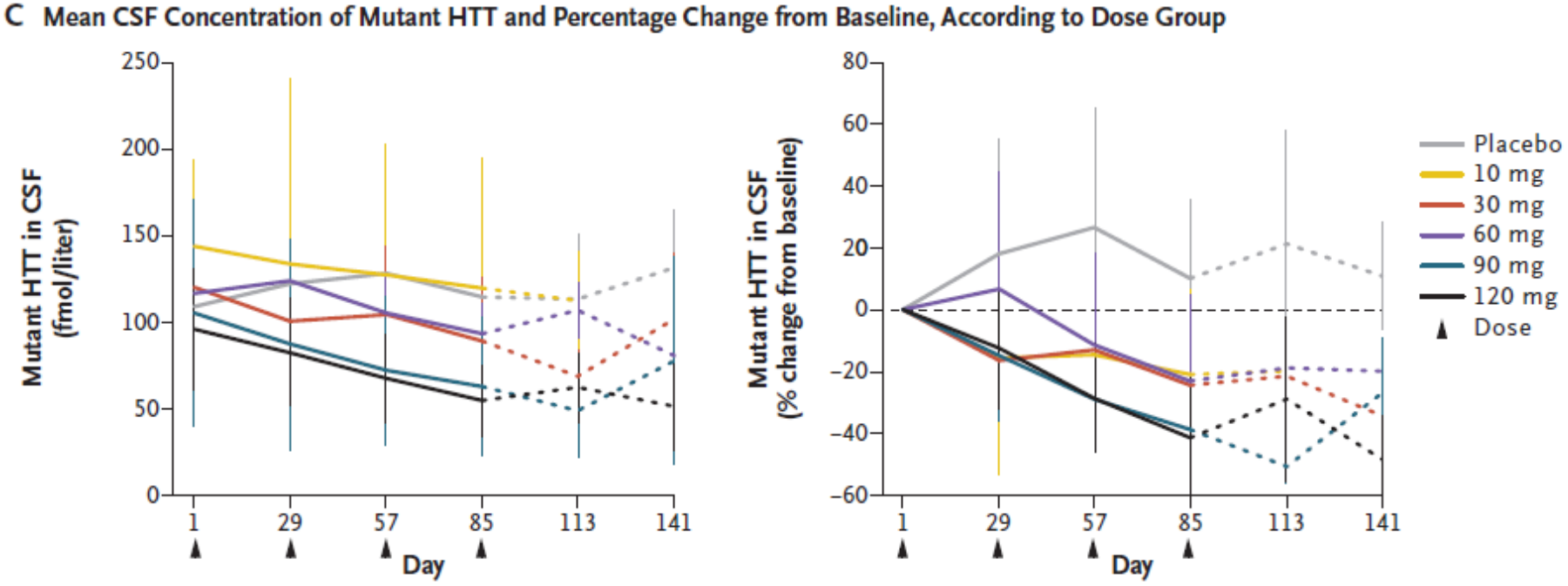
Sarah J. Tabrizi, M.B., Ch.B., Ph.D., Blair R. Leavitt, M.D., C.M., G. Bernhard Landwehrmeyer, M.D., Edward J. Wild, M.B., B.Chir., Ph.D., Carsten Saft, M.D., Roger A. Barker, M.R.C.P., Ph.D., Nick F. Blair, M.B., B.S.,* David Craufurd, M.B., B.S., Josef Priller, M.D., Hugh Rickards, M.D., Anne Rosser, M.B., B.Chir., Ph.D., Holly B. Kordasiewicz, Ph.D., Christian Czech, Ph.D., Eric E. Swayze, Ph.D., Daniel A. Norris, Ph.D., Tiffany Baumann, B.S., Irene Gerlach, Ph.D., Scott A. Schobel, M.D., Erika Paz, B.S., Anne V. Smith, Ph.D., C. Frank Bennett, Ph.D., and Roger M. Lane, M.D.





Vervolg IONIS/ROCHE: RG6042

Veiligheid bewezen én verlaging van concentraties mutant Huntingtine eiwit



Binnenkort start fase 3 (GENERATION-HD1) met 2 jaar lang 2-maandelijkse injecties (120 mg)

Wave Life Sciences

Ook een antisense oligonucleotide, echter….

de benadering van Wave richt zich op kleine genetische verschillen (SNP's) tussen de gezonde en de mutante ZvH-genen, die buiten de ziekteverwerkkende CAG-herhaling liggen

Bij ongeveer 70% van de Huntingonpatiënten aanwezig

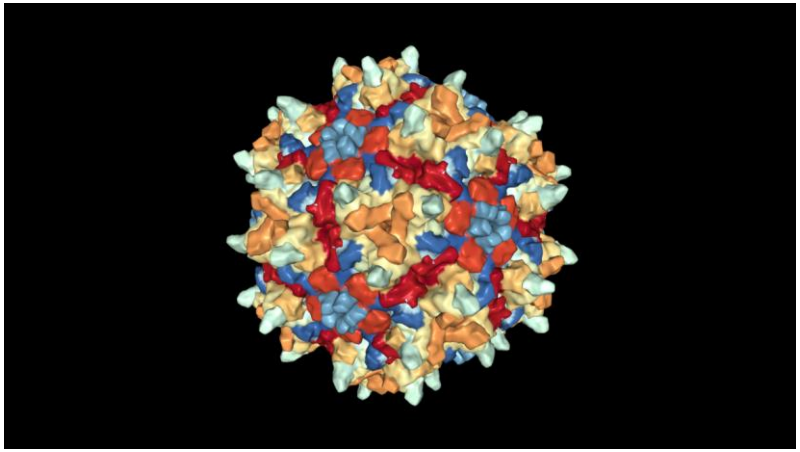
Zo richten deze 2 geneesmiddelen (ASO's) zich specifiek op het mutante gen en blijven weg van de normale kopie

PRECISION-HD1 en 2: 2x 50 beginnende ZvH patiënten, gestart in Canada

UniQure: gentherapie middels micro-RNA: AMT-130

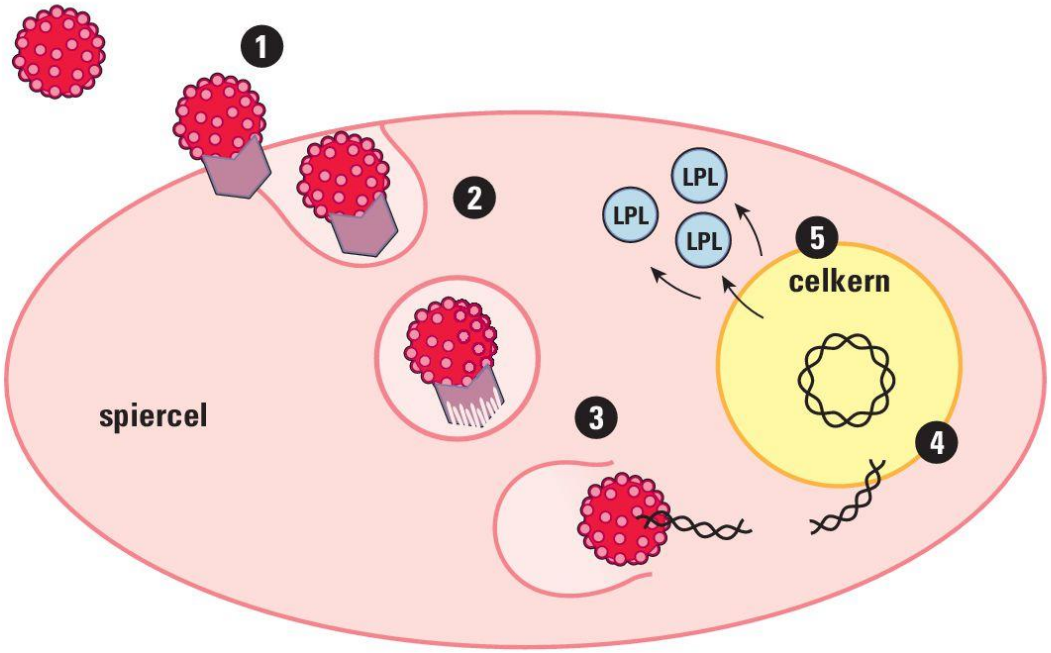
1. door de cellen een **extra gen** te geven dat een klein stukje RNA produceert: **micro- RNA** dat het vastplakt aan het huntingtine- RNA.
2. Wanneer de cel de twee stukjes RNA aan elkaar ziet plakken, activeert het zijn eigen RNA-vernietigingsmachine om ze allebei te vernietigen

Hoe komt dit extra gen in de celkern?: middels een een klein, ongevaarlijk virus dat bekend staat als **adeno-geassocieerd virus** of AAV.



AVV mechanisme

Virus loodst therapeutisch gen de cel binnen



1 Het virus bindt aan receptoreiwit in het celmembraan.
2 Het virus wordt opgenomen door de cel, en in een celblaasje (endosoom) getransporteerd.
3 Het virus ontsnapt uit het celblaasje en verliest zijn eiwitmantel.
4 Het virale DNA, met werkende kopie van het LPL-gen, komt de celkern. binnen en vormt een minichromosoom.
5 Het minichromosoom wordt afgelezen. De cel produceert nu werkende LPL-enzymen.

NRC 210712 / RvS / Bron: Scielo

Hoog risico, maar ook kans op hoge opbrengst

Nadeel: virus kan alleen in neuronen komen door directe injectie in de hersenen, middels een hersenoperatie dus:

Hoeft meer éénmalig met hoog risico op een hoge opbrengst, maar ook op blijvende bijwerkingen

Fase I/II onderzoek start mogelijk al eind van dit jaar (in de VS)

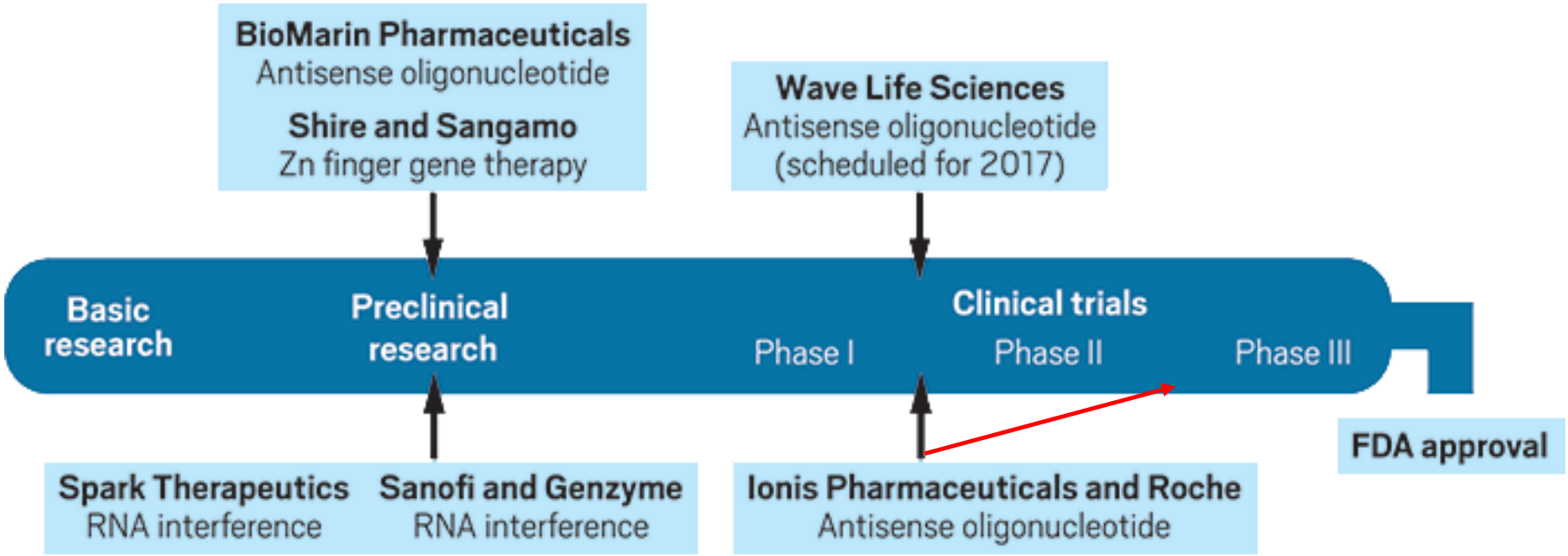
Huntingtin-lowering programs targeting DNA

	Allele selectivity	Delivery	Vector	Sponsor	Key advantages	Key disadvantages	References
Zinc finger transcription factor							
Transcriptional repression	CAG repeat	Intracranial	AAV	Shire (Dublin, Republic of Ireland)	Single drug for all carriers of the Huntington's disease mutation; single administration to provide long-term treatment; targeting transcription should ameliorate all pathogenic pathways	Invasive; cannot be deactivated; small treatment volumes; risk of inflammation from non-host repressor proteins	Zeitler, 2014[66]
Transcriptional repression	CAG repeat	Intracranial	AAV	Imperial College London (London, UK)	As above, plus use of host-species proteins reduces inflammatory effects	Use of human proteins in clinical candidate compound might limit utility of animal work	Garriga-Canut, 2012;[67] Agustín-Pavón, 2016[68]
CRISPR-Cas9							
Genome editing	SNP-targeted	Direct to fibroblasts	None	Harvard University (Cambridge, MA, USA)	Permanent removal of genetic cause; highly specific and targeted	Very early work in model systems only; irreversible; shares delivery problems with other virally delivered approaches; ethical concerns for germline manipulation; bacterial proteins might be immunogenic	Shin, 2016[69]
Genome editing	Nonselective HTT depletion by polyglutamine domain deletion	Intracranial	AAV	Emory University (Atlanta, GA, USA)	As above	As above	Yang, 2017[70]

AAV=adeno-associated virus. CRISPR-Cas9=clustered regularly interspaced short palindromic repeats-CRISPR-associated system. SNP=single nucleotide polymorphism.

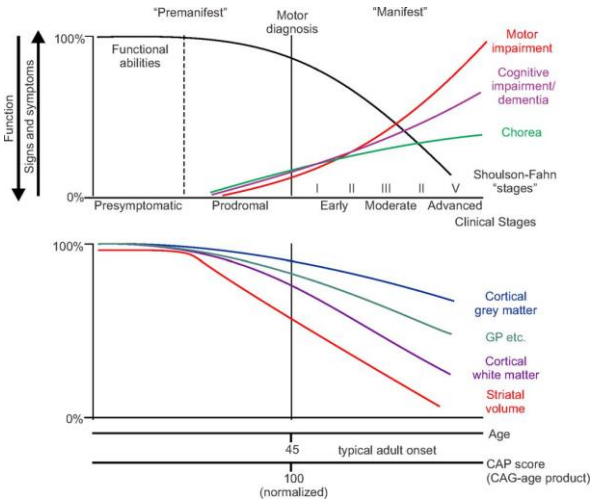
Therapies targeting DNA and RNA in Huntington's disease:..
Wild EJ, Tabrizi SJ. Lancet Neurol. 2017;16: 837-47.

Waar staan we nu?



Nieuwe dilemma's

Als één van deze HTT verlagende therapieen werkt:

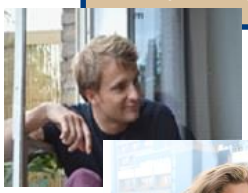


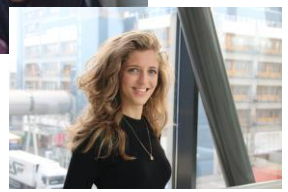
- Wanneer starten? Premanifest, prodromaal, hoe moet je dit precies vaststellen, kortom met welke ‘biomarker’?
- (2-)Maandelijkse injecties middels ruggenprik gedurende >20-40 jaar?
- Kosten/vergoeding?

Huidig en toekomstig onderzoek in LUMC

HD-Neurologie

- **Observationeel**
  - **7T-mri** *(n = 60)*
  - **Enroll-HD** *(n = ∞)*
    - **Serumstudie** *(n = 20)*
- **Clinical trials**
  - **Generation-HD1** *(n = 10)*
  - **Trihep-3** *(n = 49)*
    - **cohort 1** *(n = 25)*
      - **rct (afgerond)**
      - **open label (afgerond)**
    - **cohort 2** *(n = 24)*
      - **rct (afgerond)**
      - **open label**
- **Promotie onderzoek**
  - **HD-work** *(n = 170)*
  - **PGx** *(n = ?)*
  - **Pain-HD** *(n = ?)*





HD-work: veranderingen in het werk bij mutatiedragers

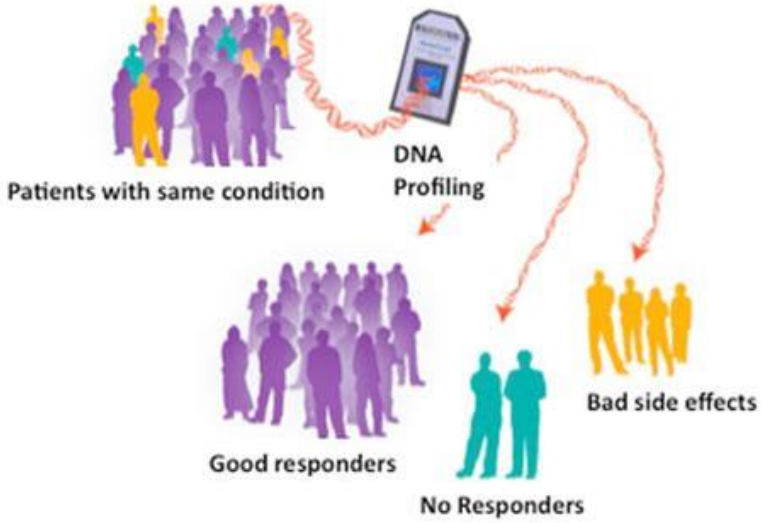
- 65% meldt als eerste veranderingen bij de ZvH, veranderingen gerelateerd aan werk
- Bijvoorbeeld: klachten die lijken op een burn-out.

- <u>Doel:</u> uit te zoeken welke ziekteverschijnselen van de ziekte van Huntington verantwoordelijk zijn voor de veranderingen op het werk.
- Dit onderzoek is gestart in voorjaar 2019
- Beoogd aantal deelnemers: 170

Farmacogenetica

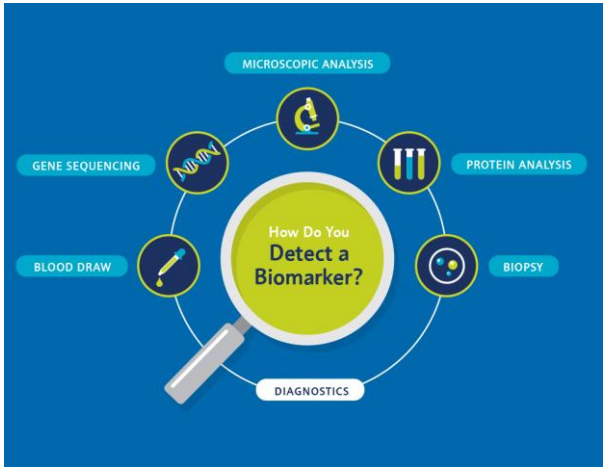
- Medicijn starten ‘op proef’
- Regelmatig bijwerkingen
  - bijvoorbeeld: overmatige slaperigheid
- Doel: Bij de individuele patient kunnen voorspellen of dit medicijn zal aanslaan en/of ernstige bijwerkingen zal gaan geven
- Beoogde startdatum: najaar 2019
- Beoogd aantal deelnemers: 230

LNPT
Leiden Network for Personalised Therapeutics



biomarkers in young-onset HD

- Als straks gerichte therapie beschikbaar, wanneer starten?
- Juveniele ZvH (JHD) gedraagt zich anders dan ZvH die op volwassen leeftijd start, wat zijn de grote verschillen?



- Biomarker onderzoek is daarom belangrijk, zeker ook in JHD

- Middels: herhaaldelijke metingen in bloed en hersenvocht, scans
- Middels: hersenonderzoek na overlijden (hersendonatie)
- Beoogde startdatum begin 2020

Meer info

https://www.lumc.nl/patientenzorg/ziektebeelden/huntington/research/

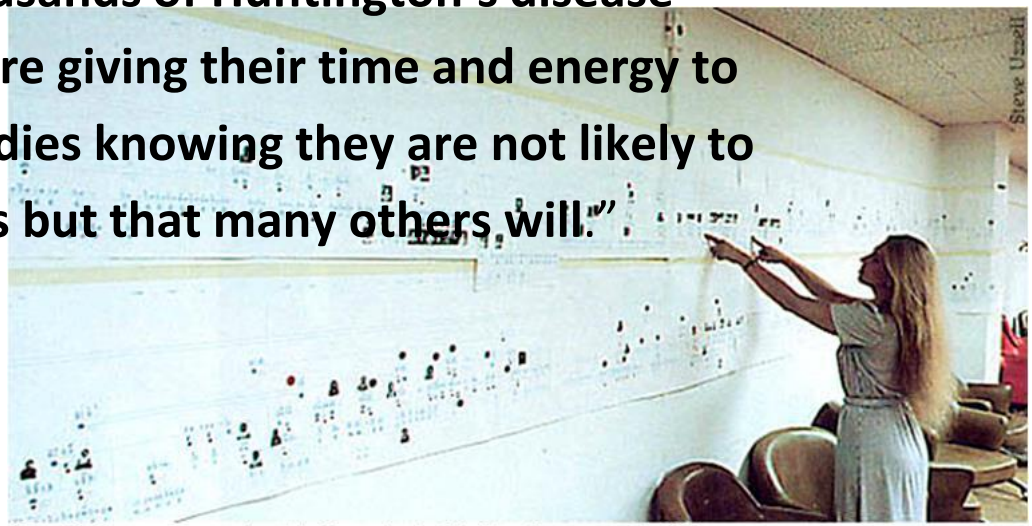
https://nl.hdbuzz.net/

https://www.enroll-hd.org/

Vragen over onderzoek in LUMC: huntingtononderzoek@lumc.nl

"Whatever the outcome of this first tentative step, the 'third age' of Huntington's disease—the age of rationally-developed therapeutics targeting the cause and known pathobiology of Huntington's disease—is now at hand."

""Crucially, the ASO trial and its successors are empowered by biomarkers and outcome measures **established and validated by thousands of Huntington's disease family volunteers who are giving their time and energy to observational cohort studies knowing they are not likely to benefit themselves but that many others will."**



Nancy Wexler examines a section of the Venezuelan family's HD pedigree on a wall at NIH. The family tree now includes nearly 10,000 persons and is over 100 feet long.

Wexler et al. George Huntington: a legacy of inquiry, empathy and hope. Brain 2016

Leids Universitair Medisch Centrum

Literatuur

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2. CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion. J.M. Lee et al Neurology. 2012 Mar 6;78(10):690-5

3. Huntington's disease: Current and future therapeutic prospects. Kieburtz K, Reilmann R, Olanow CW. Mov Disord. 2018 Jul;33(7):1033-1041

4. Therapies targeting DNA and RNA in Huntington's disease: Wild EJ, Tabrizi SJ. Lancet Neurol. 2017;16: 837-47

5. George Huntington: a legacy of inquiry, empathy and hope. Wexler A, Wild EJ, Tabrizi SJ. Brain. 2016 Aug;139(Pt 8):2326-33. doi: 10.1093/brain/aww165.