Ricerca clinica e nuove prospettive terapeutiche per la malattia di Huntington

Torino, 08/11/2019

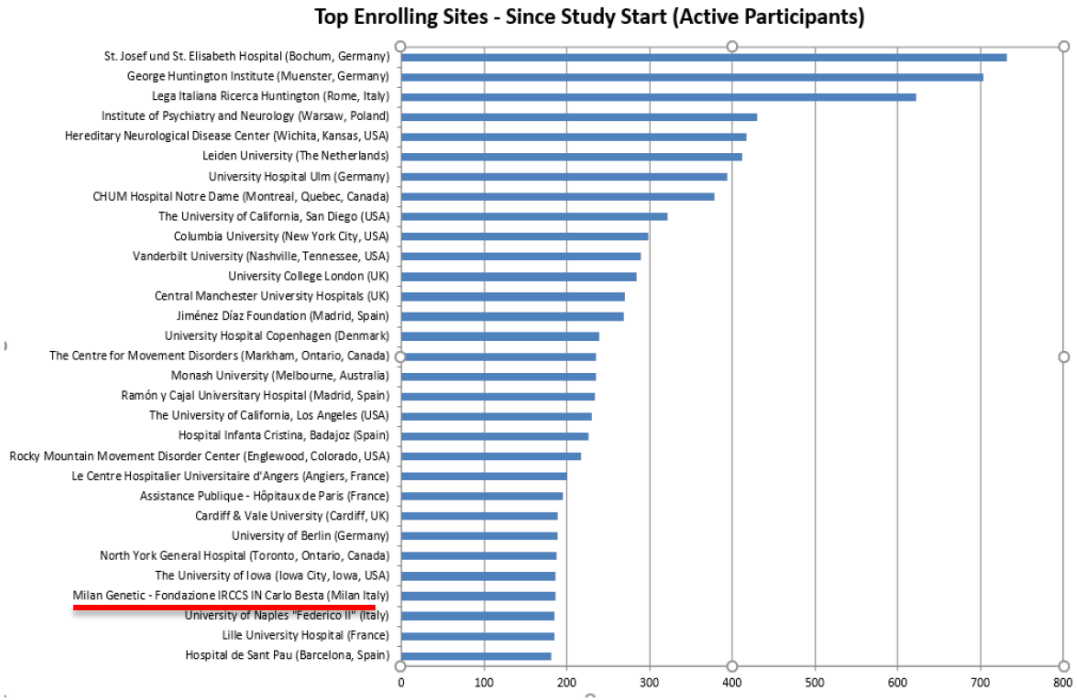
Dr Lorenzo Nanetti
UO Genetica Medica e Neurogenetica

Fondazione I.R.C.C.S.
Istituto Neurologico Carlo Besta

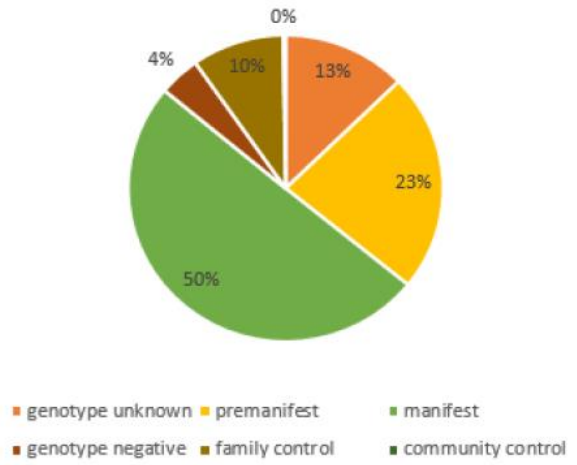
Sistema Socio Sanitario
Regione Lombardia

Studi osservazionali per caratterizzare la storia naturale della malattia di Huntington

Enroll-HD



>20000 soggetti arruolati nel mondo



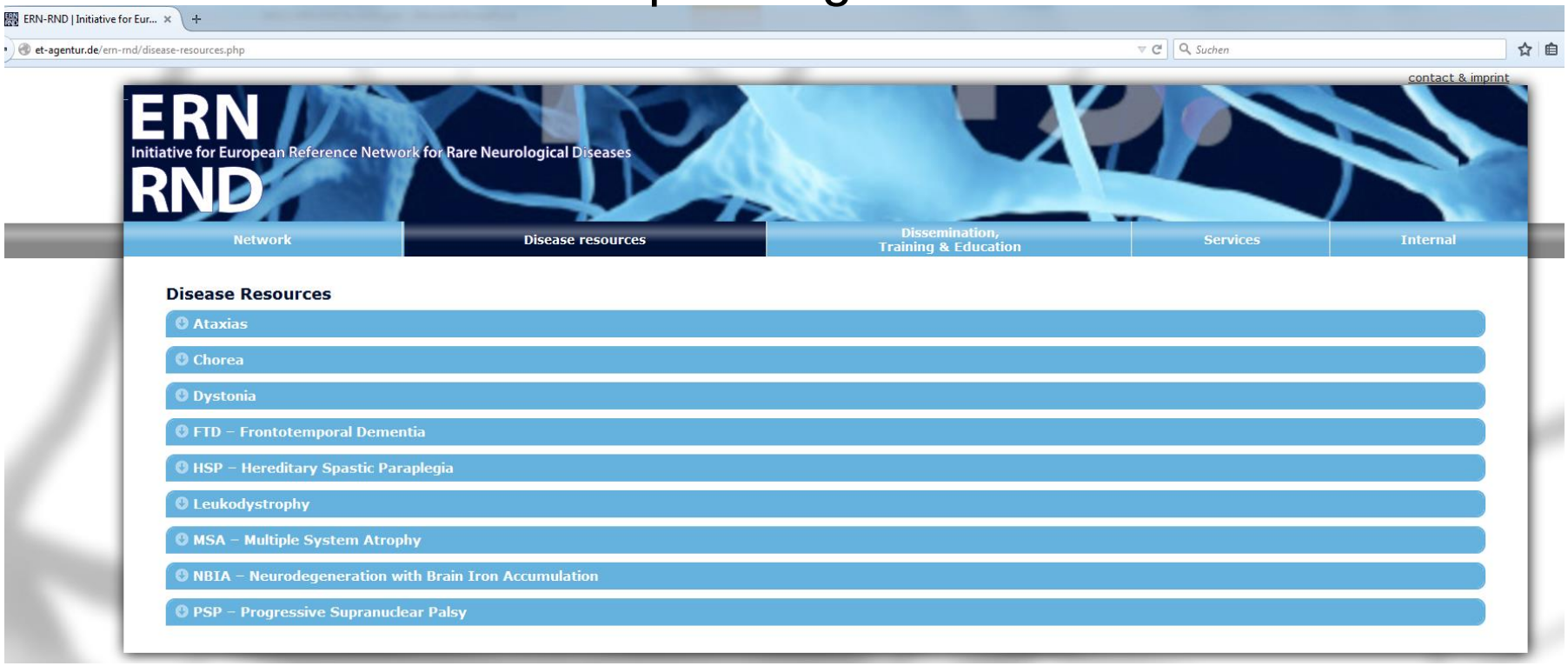
European Reference Network for Rare Neurological Diseases

- **25 Centres from 14 EU countries**

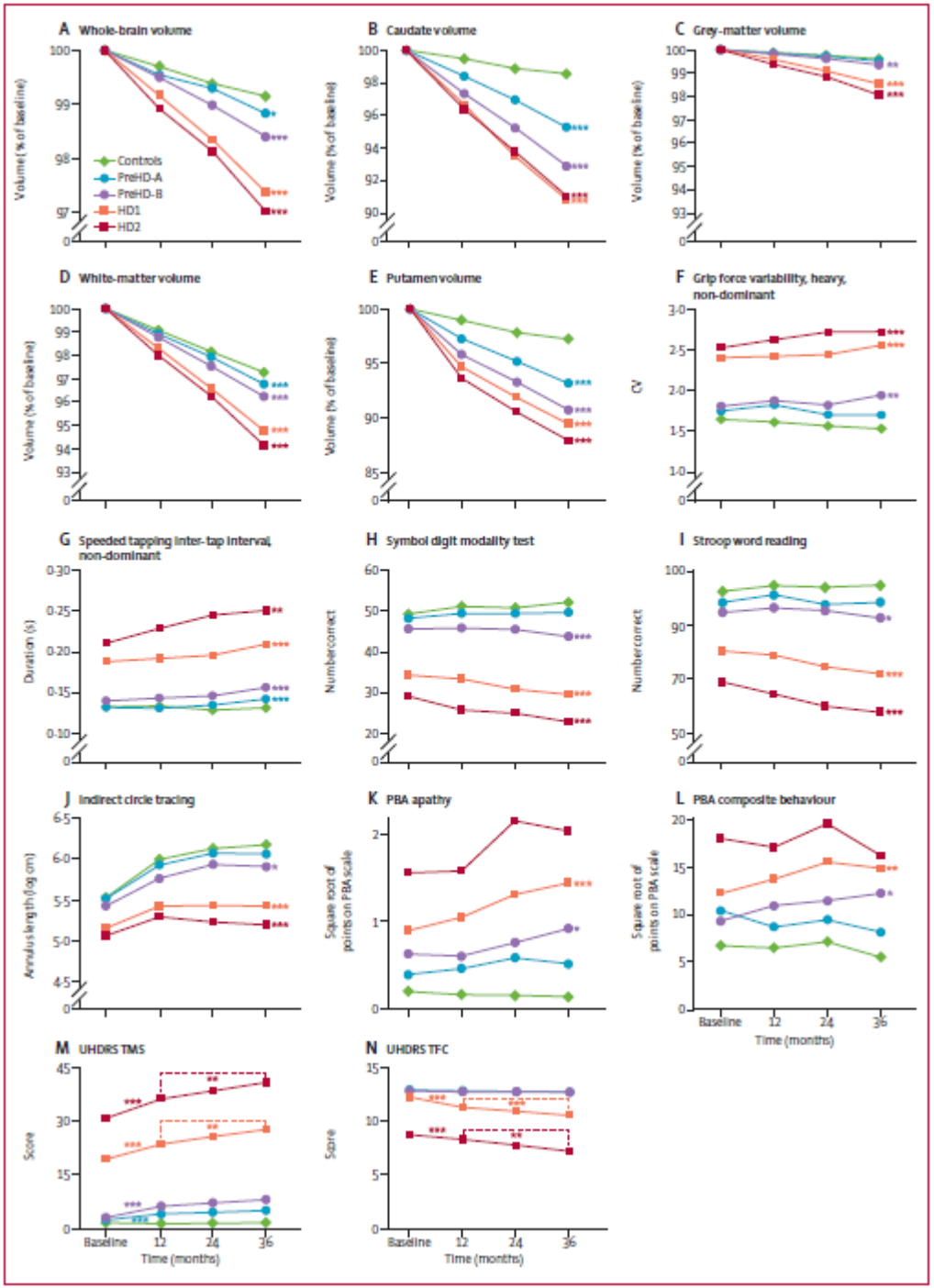
  Innsbruck, Milan, Brescia, Siena, Roma, Nijmegen, Amsterdam, Groningen, Paris, Bordeaux, Brussels, Budapest, Pecs, Athens, Tübingen, Bonn, Ulm, Lübeck, Munich, Prague, London, Aarhus, Oslo, Ljubljana, Barcelona

- **Disease focus on rare movement and cognitive disordes**
  - •Ataxias/Hereditary Spastic Paraplegias
  - •Frontotemporal degeneration
  - •Dystonia / Paroxysmal (non-epileptic)/ NBIA
  - •Leukodystrophies and neurometabolic movement disorders
  - •Huntington and Choreas
  - •Rare and atypical Parkinson (including MSA, PSP)

Web site: http://et-agentur.de/ern-rnd/



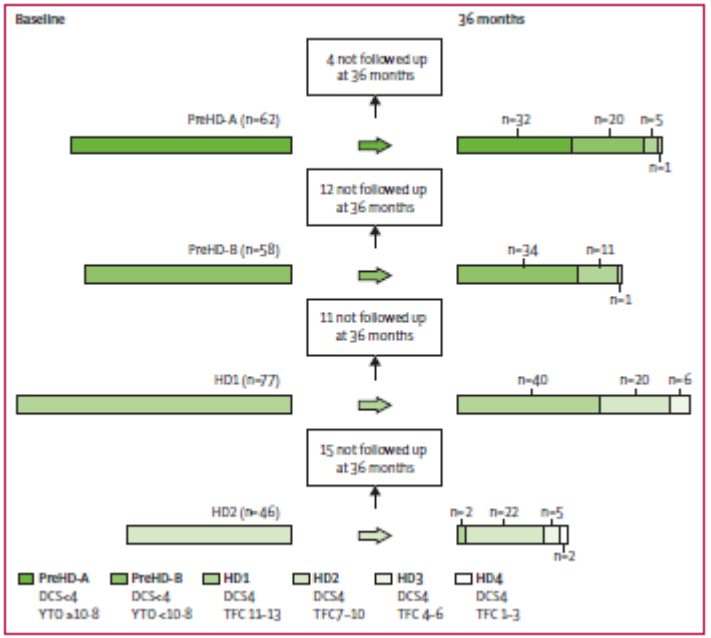
- European Network for the Study of Dystonia Syndromes,
- Leukotreat,
- SPATAX Network: Clinical and Genetic Analysis of Spastic paraplegia and Ataxia,
- European MSA Study Group
- Brain-Team - French RD network focused on brain diseases,
- Ataxia Study Group,
- European Huntington Disease Network, EHDN
- German Ataxia / HSP Network /
- Genetic FTD Initiative,
- Progressive supranuclear palsy (PSP) study group
- NBIA network (TIRCON)



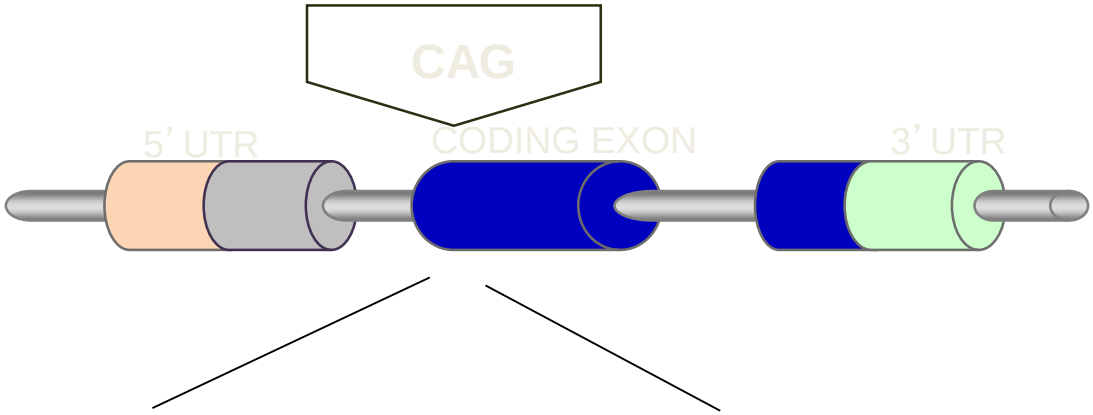
Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data

*Sarah J Tabrizi, Rachael I Scahill, Gail Owen, Alexandra Durr, Blair R Leavitt, Raymund A Roos, Beth Borowsky, Bernhard Landwehrmeyer, Chris Frost, Hans Johnson, David Craufurd, Ralf Reilmann, Julie C Stout, Douglas R Langbehn, and the TRACK-HD Investigators**

Lancet Neurol 2013



Huntington Disease: Expansion of triplet repeat CAG

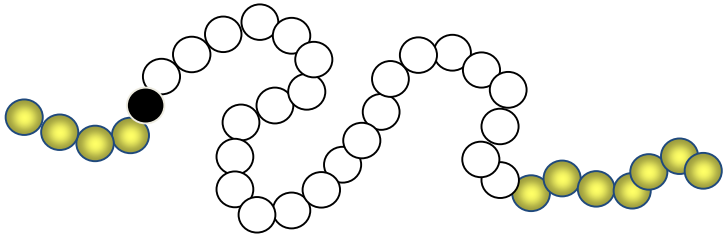


DNA: Normal allele: ≤ 26 CAG

GTTTTC **CAG...CAG** CAACAG

mRNA: Normal messanger RNA

Normal (wild type) protein



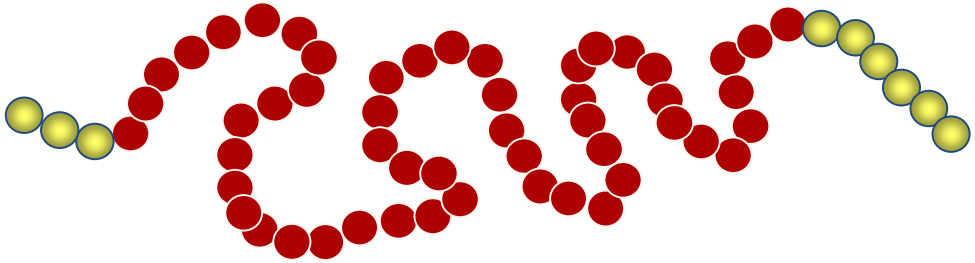
≤ 26 glutamine (Q)

Mutated Allele: ≥40 CAG expansion

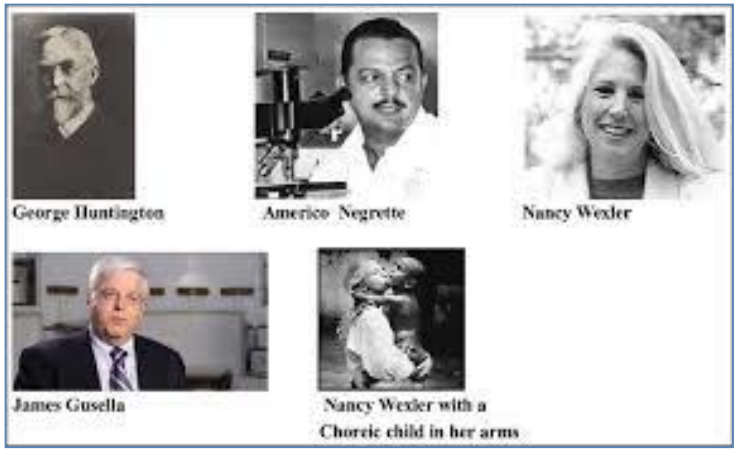
GTTTTC **CAGCAGCAG.....CAGCAG** CAACAG

mRNA: mutated messanger RNA

Mutated protein



Expanded Poly-Q



PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Abstract

Cell. 1993 Mar 26;72(6):971-83.

A novel gene containing a trinucleotide repeat that is expanded chromosomes. The Huntington's Disease Collaborative Researc

[No authors listed]

Abstract

The Huntington's disease (HD) gene has been mapped in 4p16.3 but has eluded ide disequilibrium to spotlight a small segment of 4p16.3 as the likely location of the defe from the target area contains a polymorphic trinucleotide repeat that is expanded an the normal range was observed on HD chromosomes from all 75 disease families ex 4p16.3 haplotypes. The (CAG)n repeat appears to be located within the coding sequ expressed but unrelated to any known gene. Thus, the HD mutation involves an unst syndrome, spino-bulbar muscular atrophy, and myotonic dystrophy, acting in the con

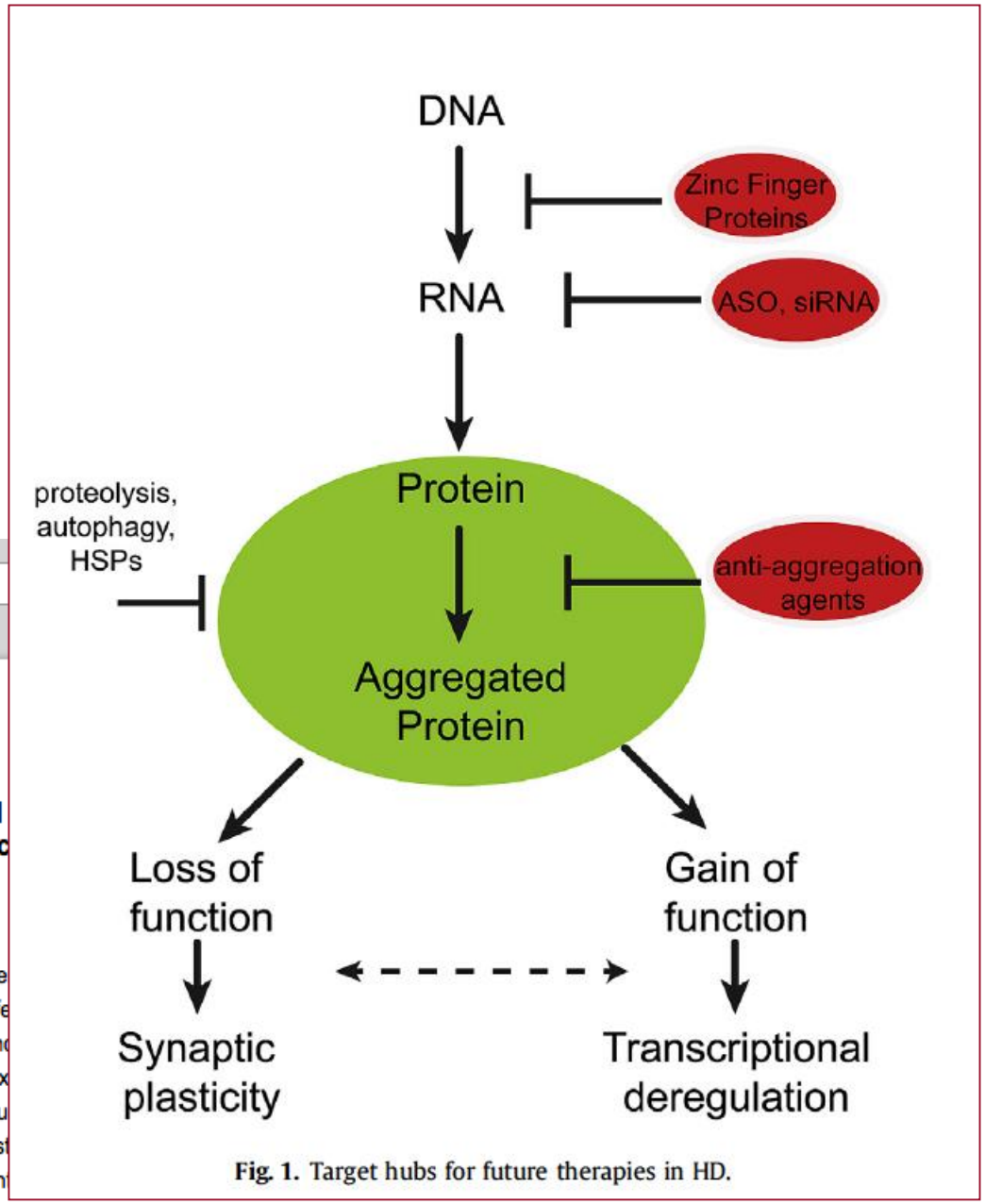
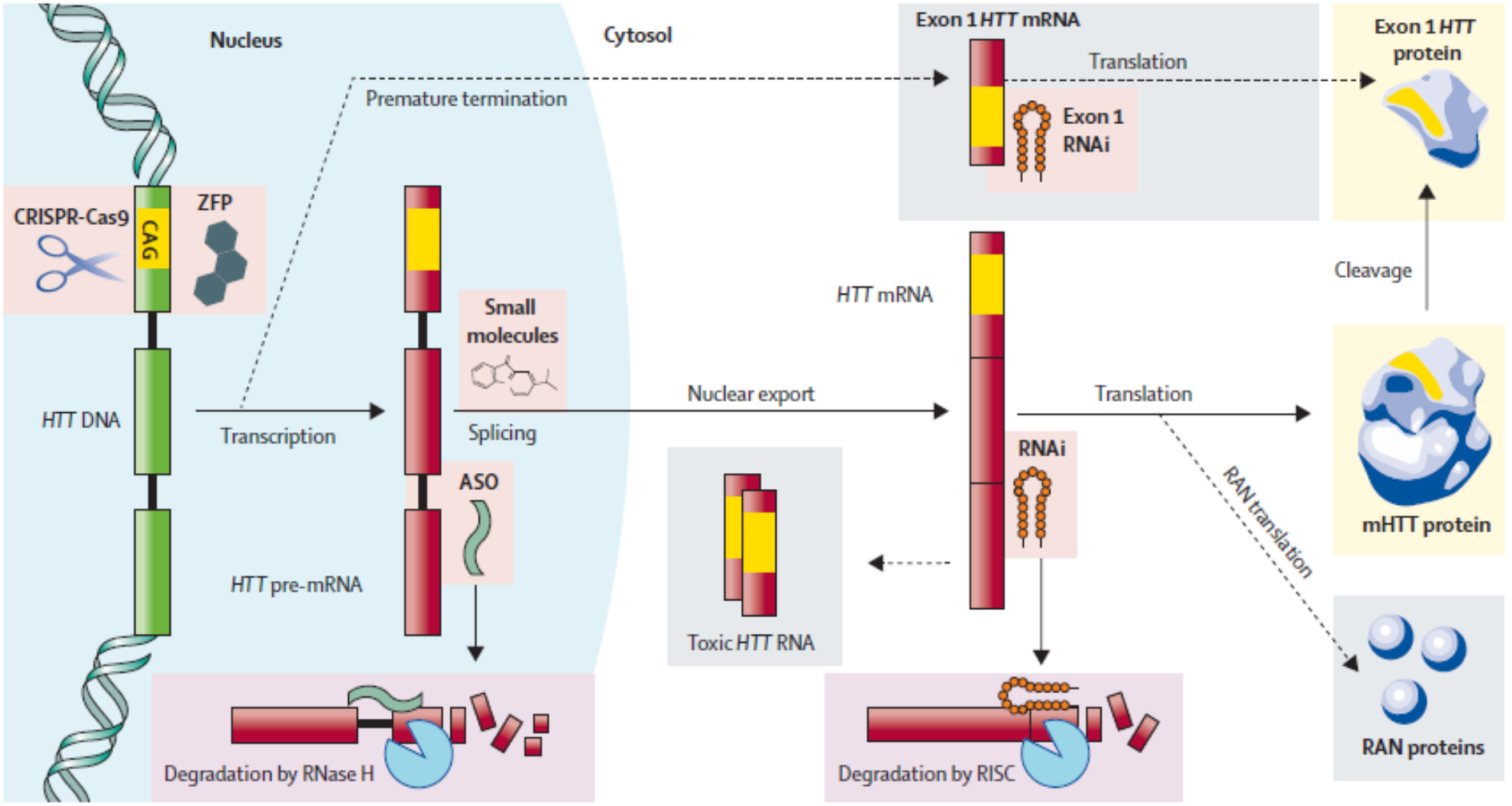


Fig. 1. Target hubs for future therapies in HD.

Parkinsonism and Related Disorders (2015)



Tabrizi et al. Lancet Neurol 2017

The Nobel Prize in Physiology or Medicine 2006

"for their discovery of RNA interference - gene silencing by double-stranded RNA"

Photo: L. Cicero/Stanford

Andrew Z. Fire

Photo: R. Carlin/UMMAS

Craig C. Mello

Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*

Andrew Fire*, SiQun Xu*, Mary K. Montgomery*, Steven A. Kostas*†, Samuel E. Driver‡ & Craig C. Mello‡

** Carnegie Institution of Washington, Department of Embryology, 115 West University Parkway, Baltimore, Maryland 21210, USA*
† Biology Graduate Program, Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218, USA
‡ Program in Molecular Medicine, Department of Cell Biology, University of Massachusetts Cancer Center, Two Biotech Suite 213, 373 Plantation Street, Worcester, Massachusetts 01605, USA

Experimental introduction of RNA into cells can be used in certain biological systems to interfere with the function of an endogenous gene[1,2]. Such effects have been proposed to result from a simple antisense mechanism that depends on hybridization between the injected RNA and endogenous messenger RNA transcripts. RNA interference has been used in the nematode *Caenorhabditis elegans* to manipulate gene expression[3,4]. Here we investigate the requirements for structure and delivery of the interfering RNA. To our surprise, we found that double-stranded RNA was substantially more effective at producing interference than was either strand individually. After injection into adult animals, purified single strands had at most a modest effect, whereas double-stranded mixtures caused potent and specific interference. The effects of this interference were evident in both the injected animals and their progeny. Only a few molecules of injected double-stranded RNA were required per affected cell, arguing against stochiometric interference with endogenous

an Publishers Ltd 1998

NATURE | VOL 391 | 19 FEBRUARY 1998

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group*

2017

	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.

***Table 1*: Huntingtin-lowering programmes targeting mRNA, by class and mechanism**

Tabrizi et al. Lancet Neurol 2017

The NEW ENGLAND JOURNAL of MEDICINE

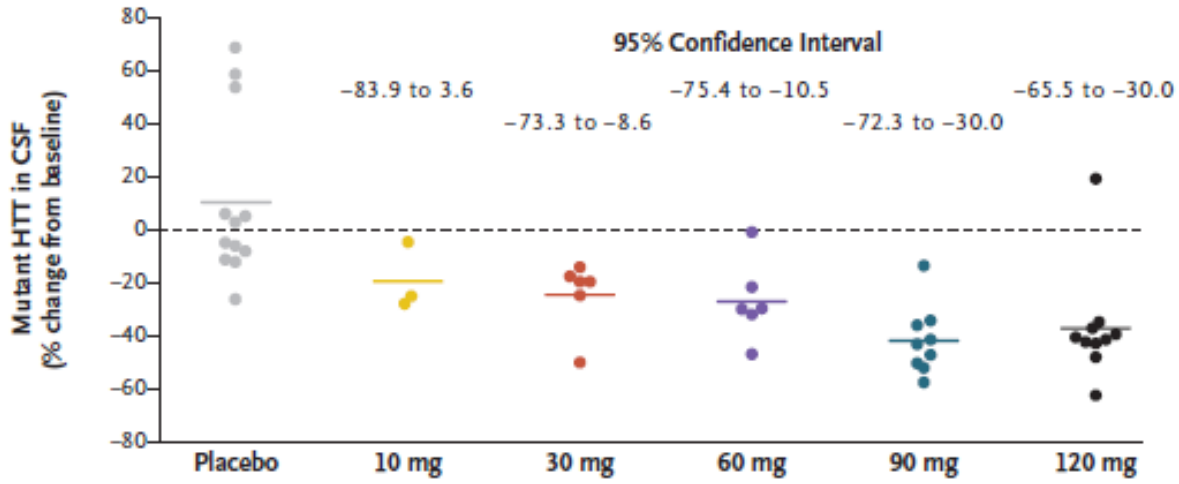
ORIGINAL ARTICLE

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., for the Phase 1–2a IONIS-HTT$_{Rx}$ Study Site Teams†

- ✓ **Fase I-II**
- ✓ **46 pazienti in doppio cieco (3:1)**
- ✓ **somministrazione intratecale**
- ✓ **4 dosi a cadenza mensile**

B Percentage Change in CSF Concentration of Mutant HTT, According to Dose Group



Non-allele-selective ASO selected for clinical development

Data from RG6042 to date suggest the non-allele-specific approach is well tolerated and has the broadest patient eligibility

- Non-allele-specific approach preferentially developed due to:
  - broad eligibility for all HD patients irrespective of individual SNP
  - ability to screen the entire *HTT* gene to identify a highly potent ASO with favorable safety profile

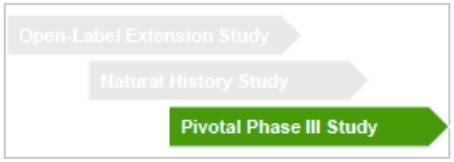
Preclinical safety	Preclinical efficacy	Pharmacology
• Lowering of total HTT in the CNS with irreversible (e.g. siRNA) or reversible (e.g. ASO) approaches appear safe in normal animals[1–3]	• Non-allele-specific ASOs have demonstrated efficacy in transgenic animal models, similar to allele selective approaches[1,2,4,5]	• RG6042 results in the dose-titratable, partial and reversible reduction of HTT • Approach appears well tolerated in Phase I/IIa and OLE • >200 doses of RG6042 have been administered in the OLE study to date

RG6042 (previously known as IONIS-HTTRx) is an investigational medicine and has not yet received regulatory approval in any country.
ASO, antisense oligonucleotide; HD, Huntington's disease; *HTT,* Huntingtin gene; HTT, Huntingtin protein; OLE, open-label extension; siRNA, small interfering RNA; SNP, single nucleotide polymorphism.
1. Kordasiewicz HB, *et al. Neuron* 2012; 74:1031–1044; 2. Drouet V, *et al. Ann Neurol.* 2009; 65:276–285; 3. Stiles DK, *et al. Exp Neurol.* 2012; 233:463–471; 4. Stanek LM, *et al. Hum Gene Ther.* 2014; 25:461–474; 5. Boudreau RL, *et al. Mol Ther.* 2009; 17:1053–1063. For further details see poster J03: Leavitt B, *et al.* Partial lowering of total huntingtin levels to treat adults with HD: Potential benefits and theoretical risks from human studies and animal models.

GENERATION HD1 Study | Global sites

GENERATION HD1 – RG6042 Pivotal Phase III study design

Objective: Evaluate efficacy and safety of intrathecally-administered RG6042 in adult patients with manifest HD



Study launch planned for end of 2018 with patients enrolling by early 2019

Countries: ~15 countries worldwide (80–90 sites)

Randomised, multicenter, double-blind, placebo-controlled study

Key inclusion criteria

- Clinically diagnosed manifest HD (DCL=4)
- Aged 25–65 years
- CAP >400
- Independence scale > or equal to 70
- Ambulatory, verbal

n=660

R 1:1:1

RG6042 120mg monthly (Q4W) (n=220)
(Q4W IT bolus)

RG6042 120mg bimonthly (Q8W) (n=220)
(Q4W RG6042 120mg for doses 1–2, thereafter, RG6042 120mg alternating with placebo Q4W IT bolus)

Placebo monthly (Q4W) (n=220)
(Q4W IT bolus)

25 months (plus follow-up)

Open-label extension RG6042 monthly or bimonthly (optional)*

Inclusion criteria for pivotal study are broader than OLE and HD NHS studies†

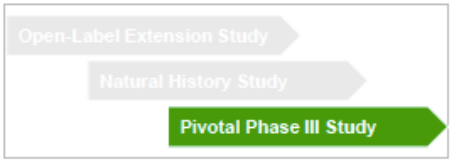
*Provided participants meet eligibility criteria, the data for RG6042 support continued development and the study is approved by Authorities and Ethics Committees/Investigational Review Boards.
†Pivotal Phase III study protocol is pending approval by Health Authorities, Investigational Review Boards and Ethics Committees.
CAP, CAG-age product; DCL, diagnostic confidence level; GENERATION HD1, Global EvaluatioN of Efficacy and Safety of Roche/Genentech AnTIsense OligoNucleotide for Huntington's Disease; HD, Huntington's disease; IT, intrathecal; NHS, Natural History Study, OLE, open-label extension; Q4W, once-a-month.

CRITERI DI INCLUSIONE

- Età compresa tra i 25-65 anni
- Segni manifesti di malattia (non soggetti presintomatici portatori della mutazione genetica)
- Discrete capacità funzionali in base ad una scala detta «Indipendence Scale», ovvero pazienti almeno in grado di vestirsi, lavarsi da soli, cucinare ed usare le posate
- Peso di almeno 40 kg
- Per le donne in età fertile necessaria adeguata contraccezione (assunzione pillola estroprogestinica ecc..)
- Presenza di altre malattie croniche (HIV, HCV, epatopatia, insufficienza renale ecc..)
- Assunzione di sostanze stupefacenti (cannabis ecc..)
- Consigliata la presenza di un caregiver (familiare/amico) disponibile ad accompagnare il paziente a tutte le visite ed eseguire alcuni compiti/questionari al domicilio (smart-phone)

Decision on primary endpoint for global Phase III study

UHDRS clinical measures are well positioned to demonstrate clinically meaningful efficacy across disease domains



- **cUHDRS** will be the global primary endpoint
  - Best tracks multidomain decline
  - Related to biology and function
  - Supported by EMA
- **The TFC** will be the primary endpoint in US only
  - A component of the cUHDRS
  - Tracks unilateral functional decline well when measured over longer time periods, and consistency of decline is helped by CAP score
  - Required measure of daily function by FDA

Consistency of effect anticipated between cUHDRS and TFC

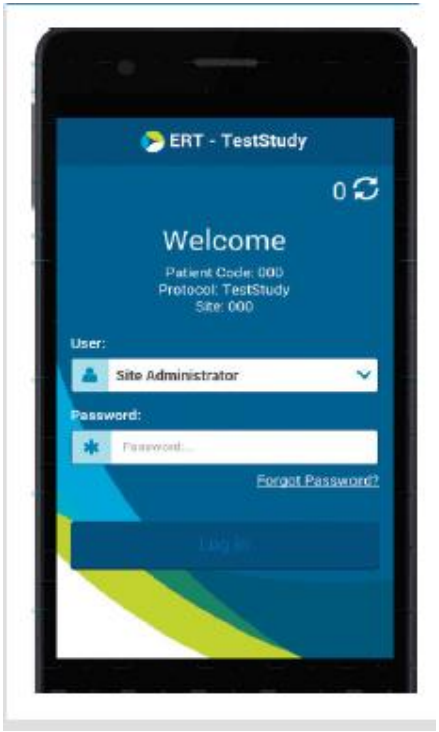
FDA requires the primary endpoint to measure daily functional abilities, so TFC will be primary endpoint in US only
CAP, CAG-age product; cUHDRS, composite UHDRS; EMA, European Medicines Association; FDA, Food and Drug Administration; HD, Huntington's disease; HTT, Huntingtin protein; TFC, Total Functional Capacity; UHDRS, Unified Huntington's Disease Rating Scale.

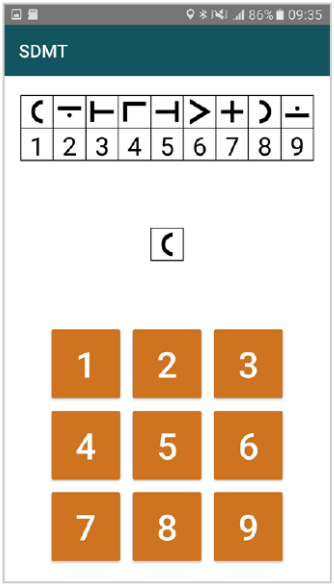
Dispositivi da utilizzare durante lo studio

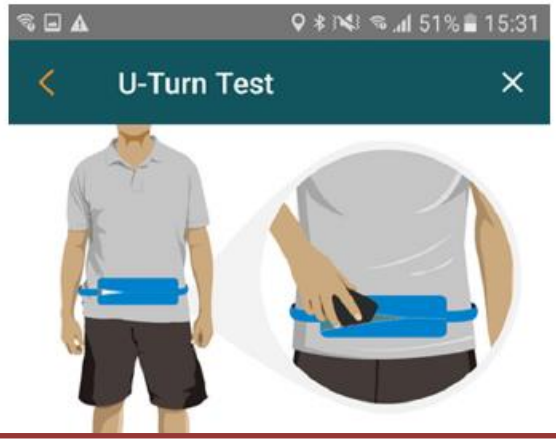
Orologio

Permette registrazione continuativa dei movimenti del paziente durante la giornata

Smart-phone

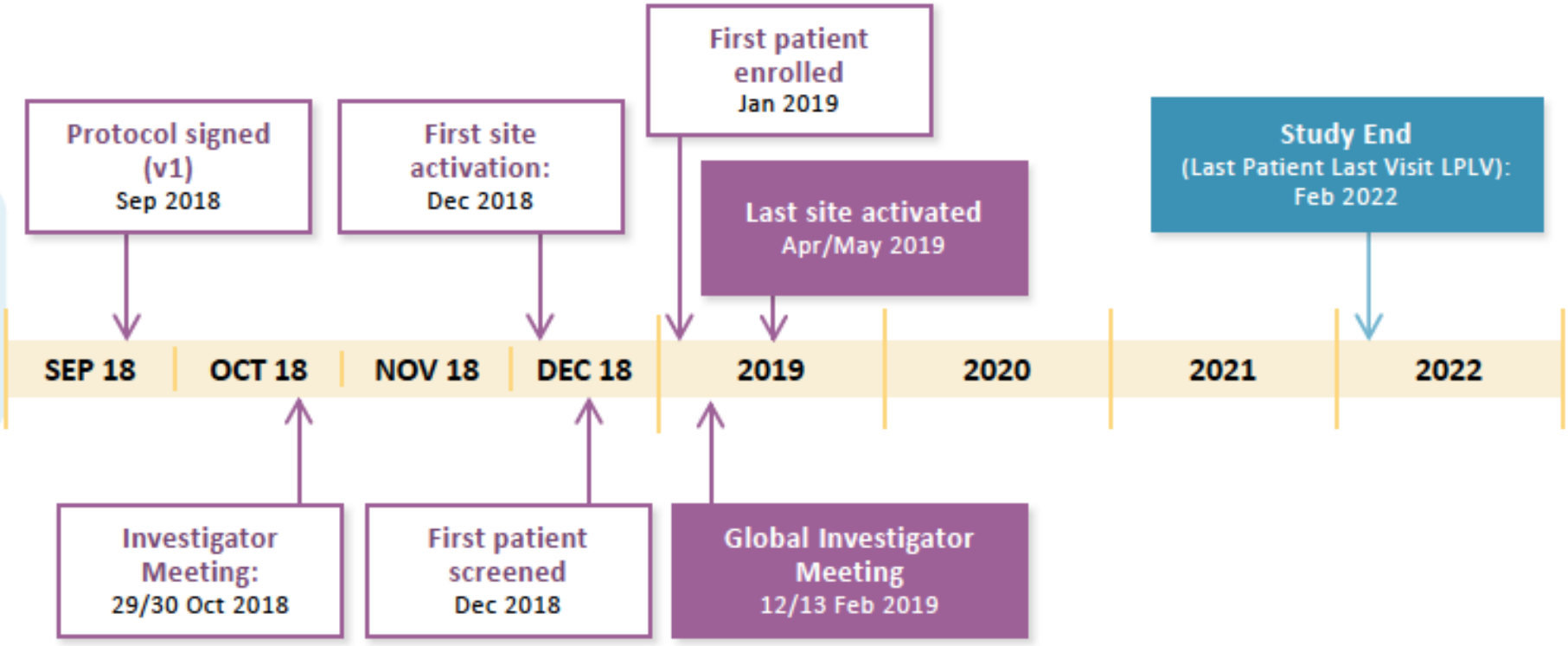


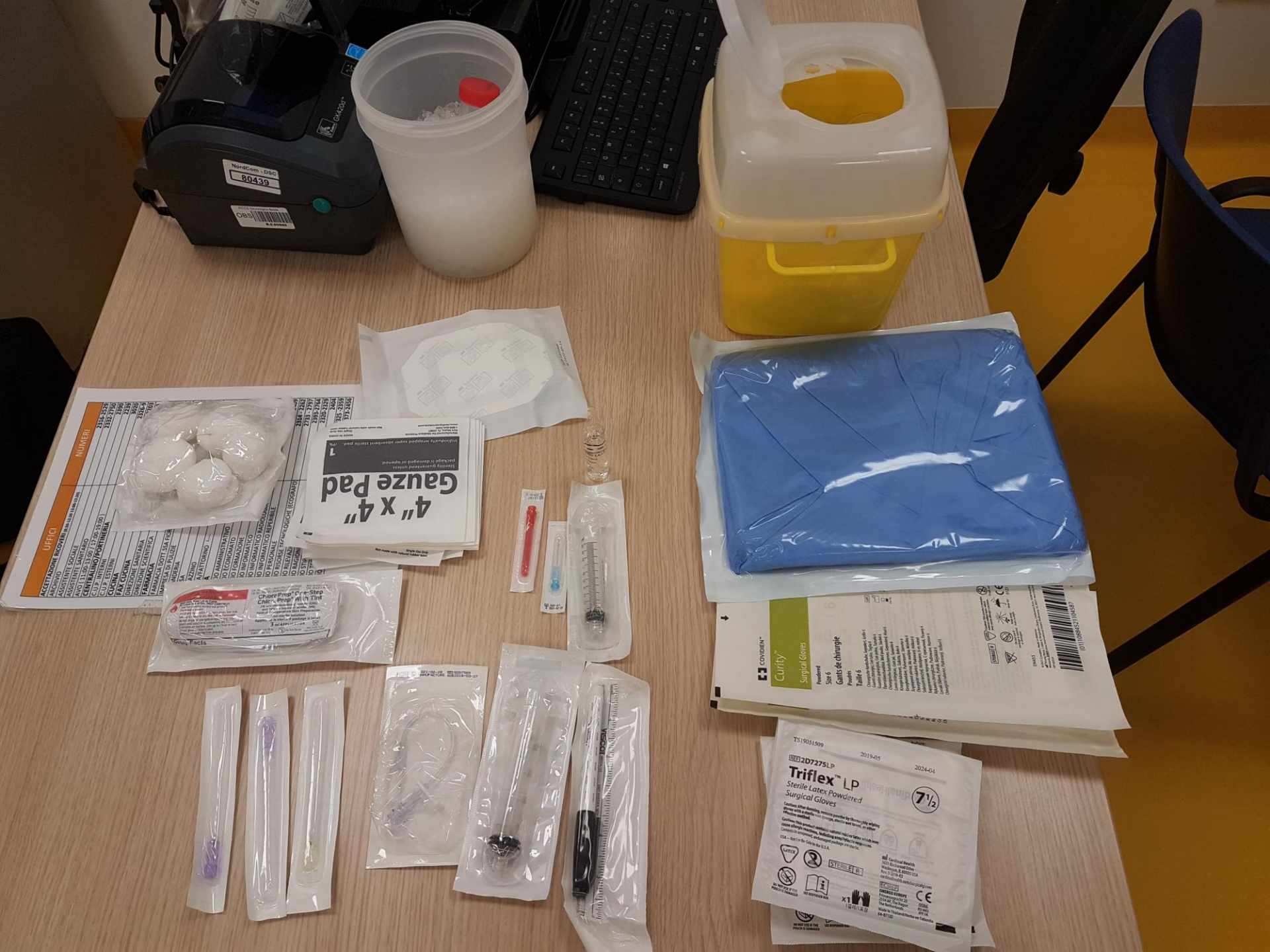




Da utilizzare al domicilio per eseguire test cognitivi e motori

GENERATION HD1 Study Start-up Timelines




NordCom DSC
80439
4" x 4"
Gauze Pad
Curity
Surgical Gloves
Triflex LP
Sterile Latex Powdered
Surgical Gloves
7½


USED BY 2021-02-28
DATE OF MANUFACTURE 2018-03-27
8057589

	Allele selectivity	Delivery	Vector	Sponsor	Key advantages	Key disadvantages	References
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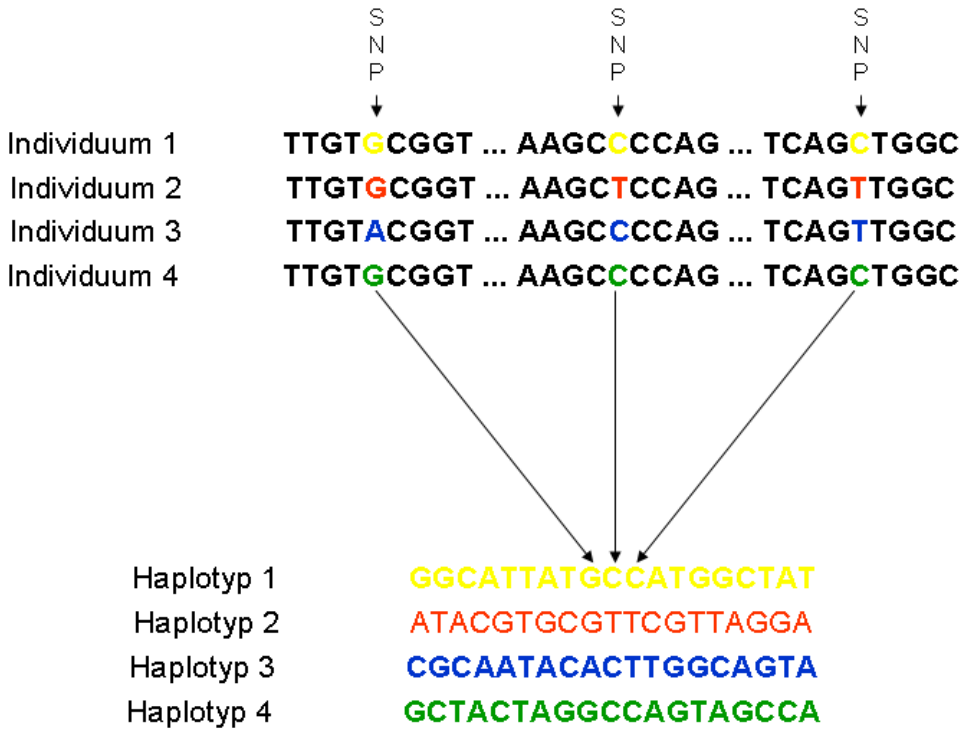
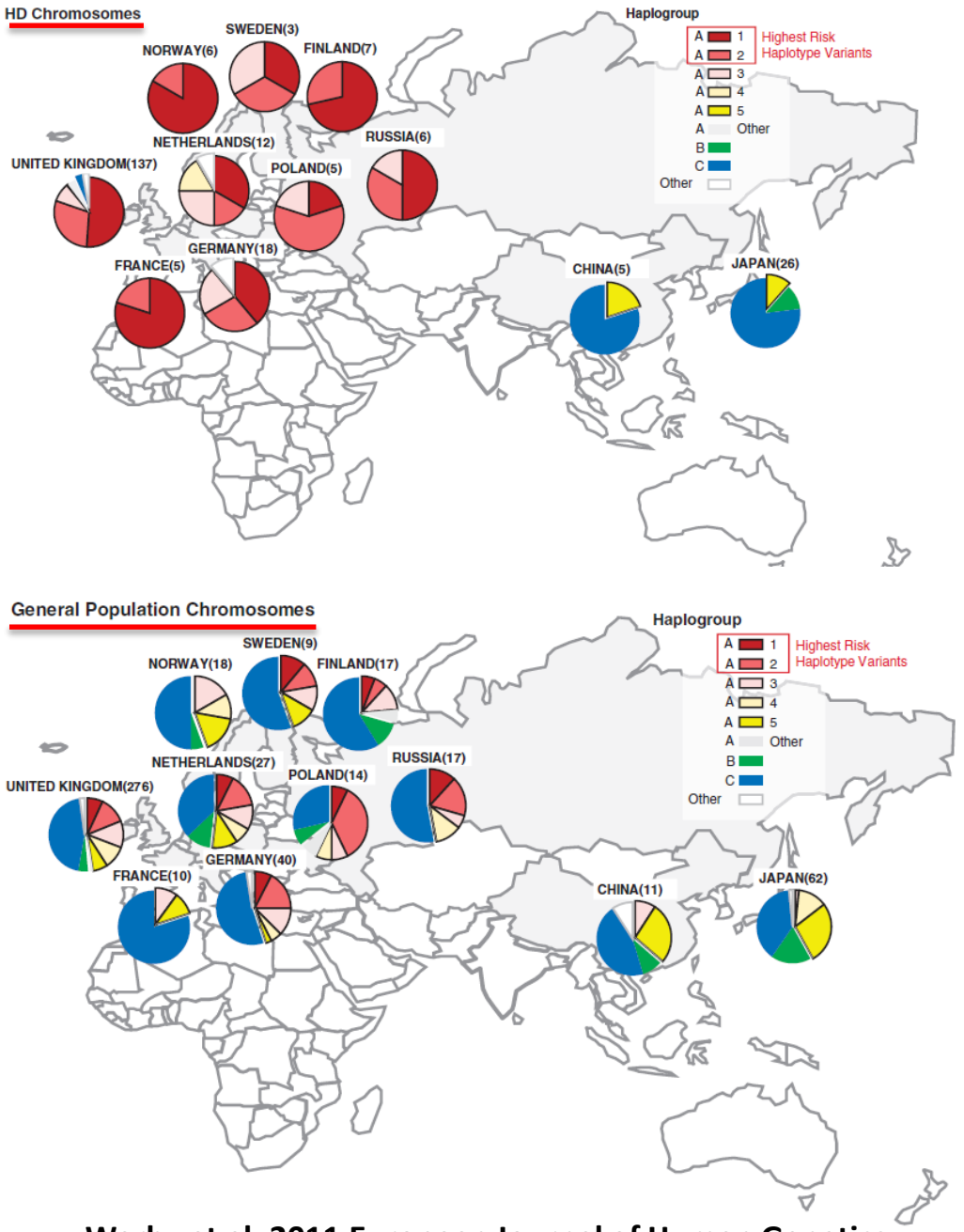
Tabrizi et al. Lancet Neurol 2017



Polimorfismo a singolo nucleotide (single-nucleotide polymorphism o SNP): variazione del materiale genico a carico di un unico nucleotide presente nella popolazione in una proporzione superiore all'1%

Aplotipo: combinazione di varianti alleliche (SNP o mutazioni genetiche) lungo un segmento cromosomico contenente loci in «linkage disequilibrium» (strettamente associati e trasmessi insieme alla progenie)

Espansione di triplette CAG nel gene *huntingtina* è in linkage disequilibrium (strettamente associato e trasmesso insieme alla progenie) con alcuni SNP. Tali SNP variano a seconda della popolazione di riferimento.



Warby et al. 2011 European Journal of Human Genetics

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	TARGET	MECHANISM	DISCOVERY	CANDIDATE	CLINICAL	TRIAL PHASE	WAVE'S COMMERCIAL RIGHTS	PARTNER
CNS								
Huntington's disease	mHTT SNP1	A	●	●	●	Phase 1b/2a	50% Global	Takeda
Huntington's disease	mHTT SNP2	A	●	●	●	Phase 1b/2a	50% Global	Takeda
Amyotrophic lateral sclerosis	C9orf72	A	●	●	○		50% Global	Takeda
Frontotemporal dementia	C9orf72	A	●	●	○		50% Global	Takeda
Spinocerebellar ataxia 3	ATXN3	S	●	○	○		50% Global	Takeda
CNS diseases	Multiple*	○	●	○	○		Milestones & Royalties	Takeda
MUSCLE								
Duchenne muscular dystrophy	Exon 51	E	●	●	●	Phase 1/OLE	100% Global	—
Duchenne muscular dystrophy	Exon 53	E	●	●	○		100% Global	—
Duchenne muscular dystrophy	Exons 44, 45, 52, 54, 55	E	●	○	○		100% Global	—
Neuromuscular diseases	Multiple	○	●	○	○		100% Global	—
OPHTHALMOLOGY								
Retinal diseases	RHO, USH2A, ABCA4, CEP290	○	●	○	○		100% Global	—
HEPATIC								
Metabolic liver diseases	APOC3 and Multiple (4)‡	S	●	○	○		Milestones & Royalties	Pfizer

S = silencing. A = allele-specific silencing. E = exon skipping. OLE = Open label extension.

*During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.
‡Pfizer has nominated four undisclosed targets in addition to APOC3.

PRECISION-HD1 and HD2

- Trattamento con ASO allele-specifico con somministrazione intratecale (non viene silenziato l'allele sano)
- ASO hanno come «target» 2 diversi SNP presenti nel 70% dei pazienti con malattia di Huntington
- 2 studi randomizzati in doppio cieco fase I-II (50 pazienti per studio)
- Risultati attesi per la fine del 2019

	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.

***Table 1*: Huntingtin-lowering programmes targeting mRNA, by class and mechanism**

Tabrizi et al. Lancet Neurol 2017

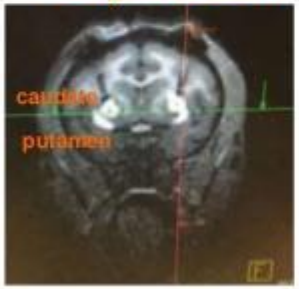
uniQure

Extensive huntingtin protein lowering in the brain of HD minipigs proves efficacy of AMT-130

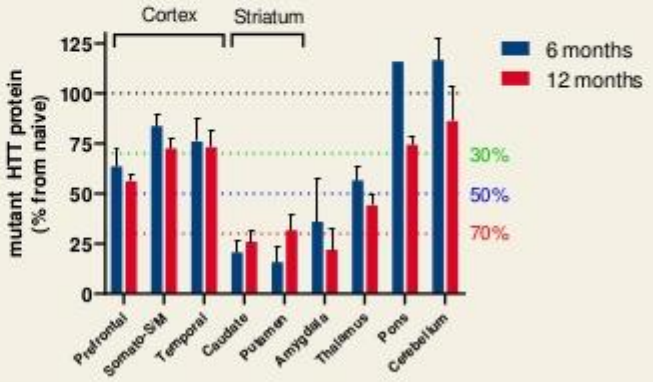
Libechov transgenic (tgHD) minipigs:

- Life-span: 12-20 years
- Body weight: 50-140 kg
- Brain weight: 90-100 g
- Extra copy of human mutant HTT gene

MRI-guided CED



Comparable mutant huntingtin protein knockdown at 6 and 12 months post-injection



Bars represent average ± SEM of n=3-4 animals/group

uniQure

First clinical study in HD patients with AMT-130

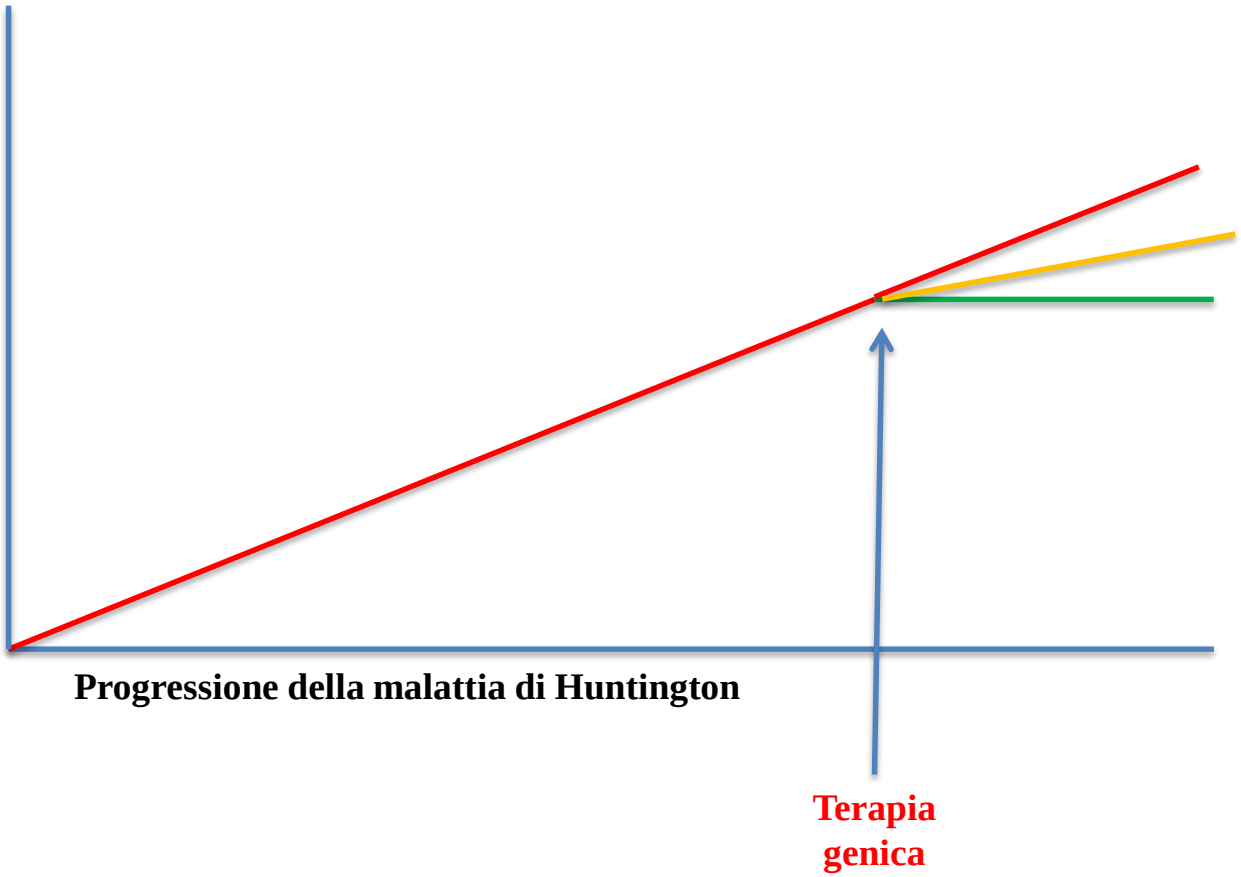
- Phase 1/2a clinical study:
  - Objective is to test **safety** of AMT-130
  - This will be tested in **adult HD patients**
  - The first study will take place in the **US**
- *More information over details of the study coming soon in ClinicalTrials.gov and through patient organisations*
  http://uniqure.com/patients/overview-contact-us.php

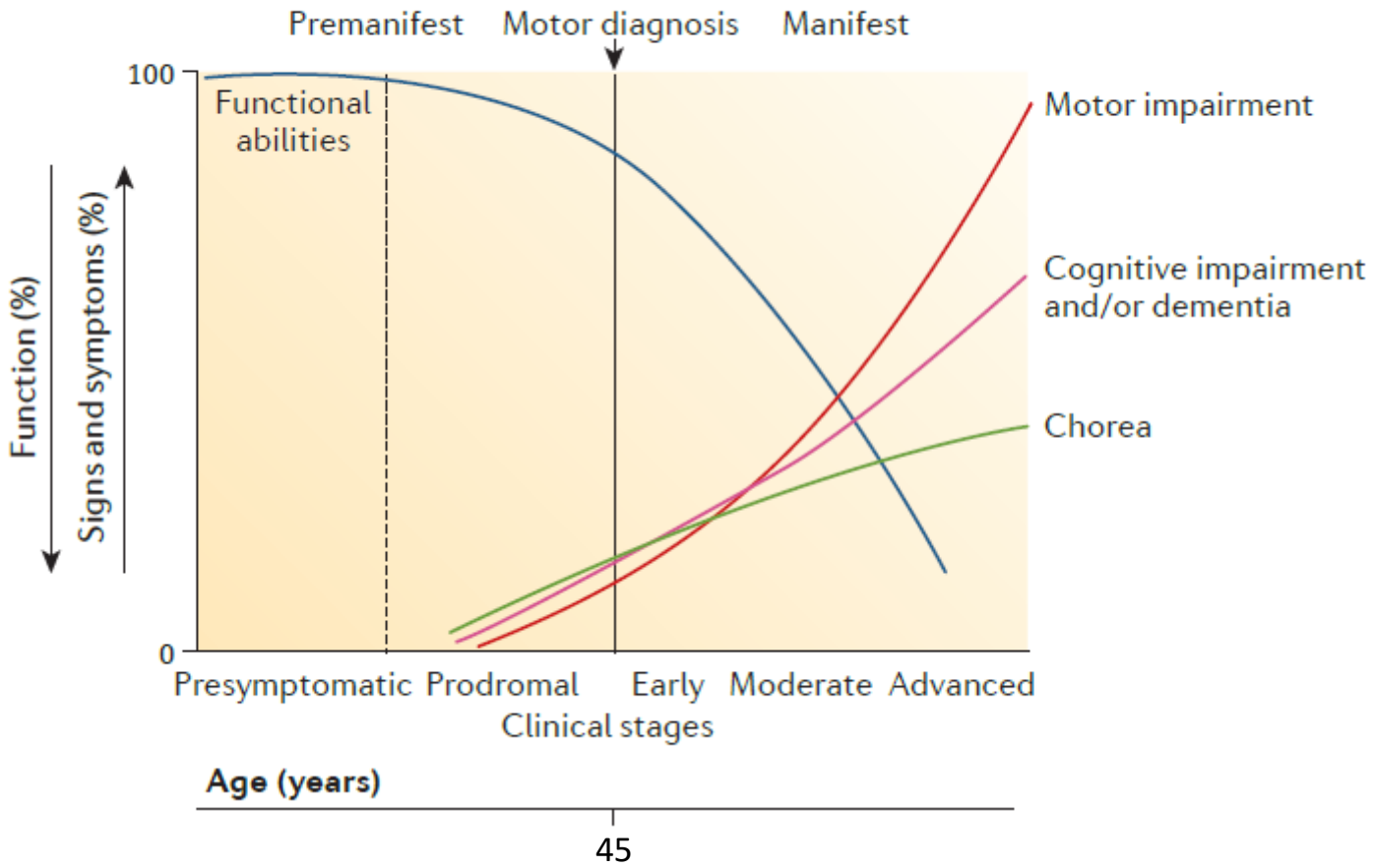
For patients:
Daniel Leonard, *Director of Global Patient Advocacy*
Patients@uniQure.com

NIH U.S. National Library of Medicine
ClinicalTrials.gov

- Inizio sperimentazione ad ottobre 2019
- 26 pazienti seguiti per 5 anni (studio randomizzato in doppio cieco)
- Somministrazione intrastriatale

Cosa ci aspettiamo come risultato delle sperimentazioni in corso?




Premanifest
Motor diagnosis
Manifest
100
Functional abilities
Motor impairment
Cognitive impairment and/or dementia
Chorea
Function (%)
Signs and symptoms (%)
0
Presymptomatic
Prodromal
Early
Moderate
Advanced
Clinical stages
Age (years)


Grazie dell’attenzione