Understanding Huntington's disease (HD)

This series of infographics are designed as a tool to aid discussions with your patients and as a teaching guide

These materials focus on enhancing the understanding of key areas of research in HD, from the mechanism of disease in HD and the role of the non-mutated, wild-type huntingtin protein, to how disease progression is currently measured and how new digital tools can be used to improve these measurements

1. What causes HD?

2. What is the role of wild-type huntingtin protein in Huntington's disease (HD)?

3. How can progression of HD be measured?

4. Digital monitoring platforms in HD

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What causes Huntington’s disease (HD)?

HD is an illness of the nervous system caused by a defective gene and has a broad impact on a person's functional abilities[1], usually impacting how a person:

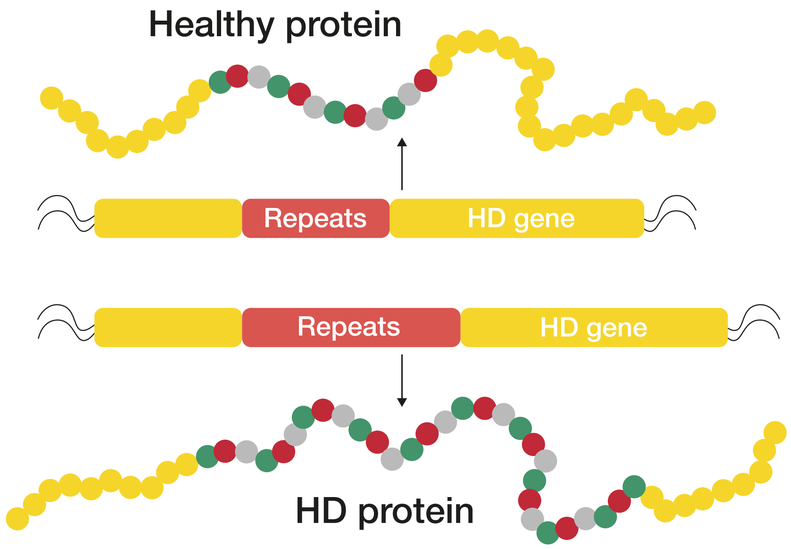
Thinks

Behaves

Moves

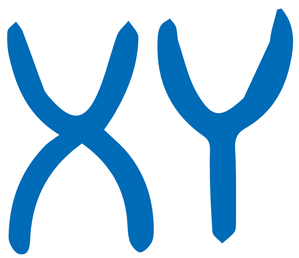
In HD, the gene that determines the structure of the huntingtin protein is affected[1–3]

The DNA of this gene is faulty, with an expanded repeating genetic sequence of three nucleotides, cytosine-adenine-guanine (**CAG**)[1–3]



The mutant huntingtin protein (mHTT) created from the faulty gene has an abnormally long structure compared with the healthy, wild-type protein (wtHTT), and is toxic to the brain and nervous system[1,3,4]

The more repetitions of CAG in the huntingtin gene, the earlier the clinical onset of HD[1]

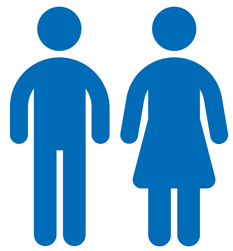


Everyone inherits two copies of the huntingtin gene from their parents – one on each chromosome – but only one chromosome needs to have a mutated huntingtin gene to cause HD[1]

Each child of an affected parent has a

50:50

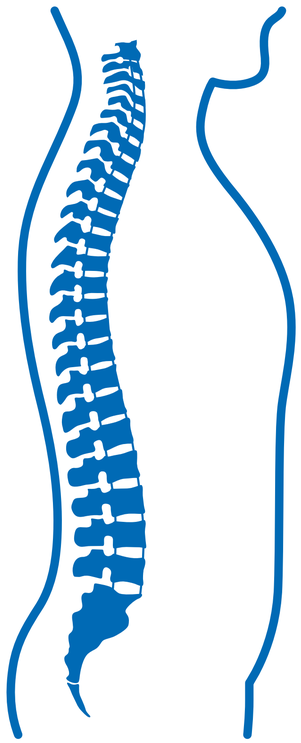
chance of inheriting the genetic mutation that causes HD[1]



Men and women are equally likely to inherit the mutation[1]

The severity of a patient's HD symptoms is dependent on the amount of mHTT protein[9]

The concentration of this mutant protein can be measured in cerebrospinal fluid (CSF)[10]



Reductions in mHTT protein levels in CSF may be associated with therapeutic benefits in people with HD[10]

1. Bates GP, et al. Nat Rev Dis Primers 2015;1:15005; 2. The Huntington's Disease Collaborative Research Group. Cell 1993;72:971–83; 3. Lee JM, et al. Neurology 2012;78:690–5;
4. Li H, et al. J Neurosci 2001;21:8473–81; 5. Moumne L, et al. Front Neurol 2013;4:127; 6. Labbadia J, Morimoto RI. Trends Biochem Sci 2013;38:378–85;
7. Ross CA, et al. Nat Rev Neurol 2014;10:204–16; 8. Morfini GA, et al. Nat Neurosci 2009;12:864–71; 9. Mangiarini L, et al. Cell 1996;87:493–506;
10. Fodale V et al. J Huntingtons Dis 2017;6(4):349–61.

What is the role of wild-type huntingtin protein in Huntington's disease (HD)?

Everyone inherits two copies of the huntingtin gene from their parents, one on each chromosome, but only one chromosome needs to have a mutated huntingtin gene (*mHTT*) to cause HD[1]

Even if a person has a non-mutated or wild-type huntingtin gene (*wtHTT*) on their second chromosome, they will still develop HD[2–4]

Huntingtin (HTT) protein has many functions, and has an essential role in healthy development of the body and brain before birth[5–7]

The mHTT protein appears to not impair neurological developmental milestones before adulthood[8–11]

Animal models indicate that symptoms of HD develop because of an accumulation of the toxic, mutated form of huntingtin protein, rather than a reduction in levels of wtHTT protein[12]

Therapies designed to lower the amount of mHTT protein in HD are not always specific, and therefore may also reduce the level of wtHTT protein as well as the mutant form[13]

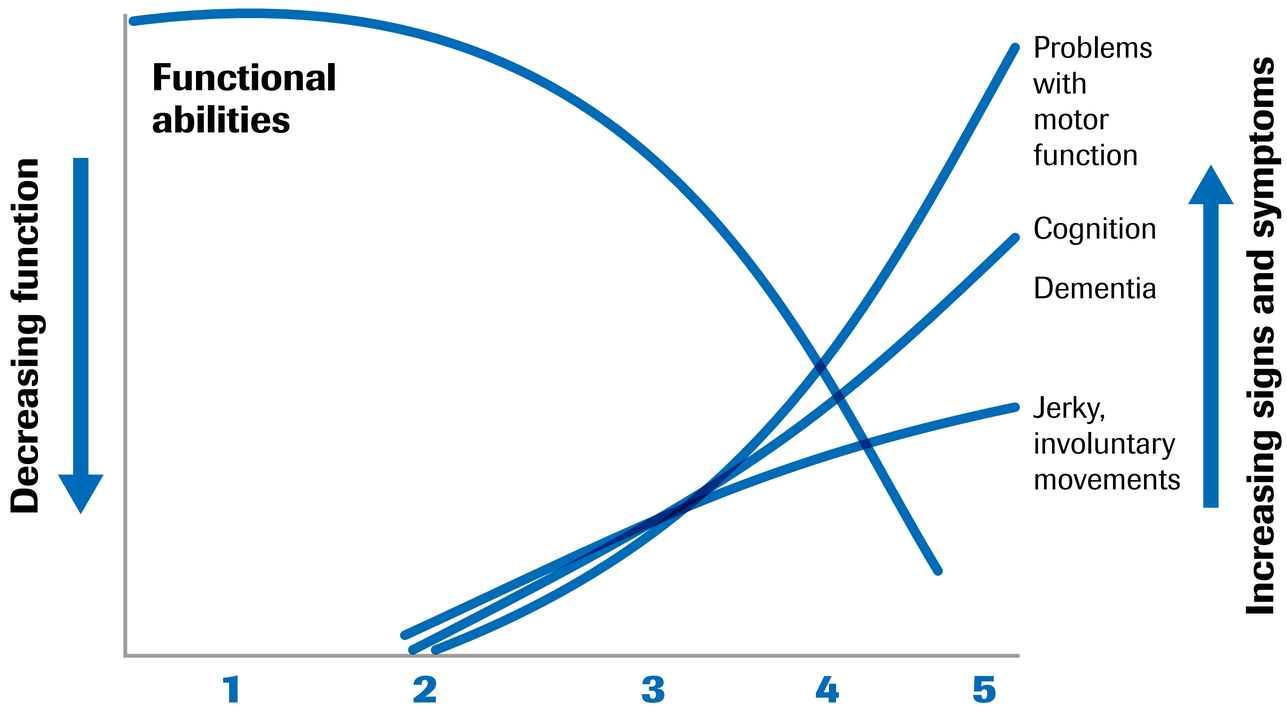
Studies in humans indicate that reduced wtHTT levels are not detrimental and do not cause HD[14]

1. Bates GP, et al. Nat Rev Dis Primers 2015;1:15005; 2. The Huntington's Disease Collaborative Research Group. Cell 1993;72:971–83; 3. Lee JM, et al. Neurology 2012;78:690–5;
4. Keum JW, et al. Am J Hum Genet 2016;98:287–98; 5. Wang G, et al. Proc Natl Acad Sci U S A 2016;113:3359–64; 6. Liu JP, Zeitlin SO. J Huntingtons Dis 2017;6:1–17; 7. Pla P, et al. PLoS One 2013;8:e73902;
8. Wexler NS, et al. Nature 1987;326:194–7; 9. Kremer B, et al. N Engl J Med 1994;330:1401–6; 10. Dürr A, et al. J Med Genet 1999;36:172–3; 11. Squitieri F, et al. Clin Genet 2003;64:524–5;
12. Mangiarini L, et al. Cell 1996;87:493–506; 13. Keiser MS, et al. Hum Mol Genet 2016;25:R53–64; 14. Ambrose CM, et al. Somat Cell Mol Genet 1994;20:27–38.

How can progression of Huntington's disease (HD) be measured?

HD is a multidimensional disease, with patients experiencing a wide range of symptoms that negatively impact their overall quality of life. Subtle symptoms can be present for many years before a diagnosis of HD is made[1–3]

Stages of HD[3]:



1. Pre-symptomatic

HD is a genetic (inherited) disease, but patients don't initially experience symptoms.
The mean age of onset for diagnosis of motor symptoms (affecting movement) is 45 years[1,2]

2. Prodromal

Gradual appearance of subtle signs and symptoms of HD[1–3]

3. Early

Increased symptoms begin to affect ability to carry out daily tasks, motor diagnosis received[1,2]

4. Moderate

Worsening of symptoms leading to a dramatic reduction in quality of life[1,2]

5. Advanced

Very severe impairment of movement and profound physical disability[1,2]
Dementia-like symptoms[1,2]

Symptoms usually affect three main areas or domains: movement, cognitive (difficulties with memory, thinking and planning) and psychiatric (changes in behaviour and personality)[4,5]

Cognition
- Ability to think clearly and quickly
- Attention
- Perception of time
- Difficulty learning new tasks

Motor function
- Jerky, involuntary movements
- Balance issues
- Fine motor issues
- Speech and swallowing issues

Behaviour
- Depression
- Apathy
- Irritability and angry outbursts
- Anxiety

Other/impacts
- Sleep problems
- Inability to work
- Isolation
- Pain

In patient registries (e.g. Enroll-HD) and clinical trials, doctors and scientists use assessment scales to diagnose and monitor the progression of these symptoms[6]

Rating scales for HD typically measure individual clinical domains or they summarise a number of assessments, which may have limited sensitivity for measuring changes associated with disease progression[6,7]

The Unified Huntington's Disease Rating Scale (UHDRS) is a collection of assessments of clinical HD features, including motor function, cognition, behaviour, and overall function[8]

Motor assessment

Cognitive assessment

Behavioural assessment

Independence scale

Functional assessment

Total Functional Capacity

There is a need for valid HD assessments that can reliably measure meaningful changes in disease progression, to enhance the potential to detect effects of investigational medicines[6]

One example of a holistic approach to measure patient experience is the composite Unified Huntington's Disease Ratings Scale (cUHDRS)[7,9]

The cUHDRS combines a subset of UHDRS scales (TFC, TMS, SDMT and SWR; sum of z-scores) that have been shown to reliably detect clinically meaningful changes associated with disease progression in patients with HD[9]

Overall function

Total Functional Capacity (TFC) scale

Motor function

Total Motor Score (TMS)

Cognitive function

Symbol Digit Modalities Test (SDMT)

Stroop Word Reading (SWR)

Studies using patient registry data (TRACK-HD, CARE-HD, COHORT, 2CARE) show that the cUHDRS provides an improved measure of clinical progression relative to individual motor, cognitive and functional outcome measures, in terms of both sensitivity and association with measures of brain atrophy[7]

The cUHDRS is valid, reliable, able to detect change, and associated with clinically meaningful differences (both cross-sectional and longitudinal) in function and independence across the spectrum of patients with early-manifest HD[9]

1. Reilmann R, et al. Mov Disord 2014;29:1335–41; 2. Bates GP, et al. Nat Rev Dis Primers 2015;1:15005; 3. Ross CA, et al. Nat Rev Neurol 2014;10:204–16;
4. Simpson JA, et al. J Huntingtons Dis 2016;5:395–403; 5. US Food and Drug Administration (FDA). The Voice of the Patient. Huntington's Disease Public Meeting Report. March 2016;
6. Arney K. Nature 2018;557:S46–7; 7. Schobel SA, et al. Neurology 2017;89:2495–502; 8. Huntington Study Group. Mov Disord 1996;11:136–42;
9. Trundell D, et al. European Huntington's Disease Network (EHDN) Plenary Meeting, Vienna, Austria. 14–16 September 2018.

The measure of you

Digital monitoring platforms are changing the way we understand health

Digital tools, such as smartphones or wearables, can now continually measure and collect health information from patients

Active tests

Patient-reported outcomes

Daily quality of life

EQ-5D-5L quality of life

Cognitive tests

Symbol digit modalities test

Word reading

Upper-body motor tests

Speeded tapping

Draw a shape

Chorea

Stability and gait

Balance

U-turn

Walk

Passive monitoring

Activities of daily living

Gait

Chorea

Activity levels

Digital monitoring tools can capture a range of information on symptoms, daily activities and quality of life

365 days living with a disease

Every dot on this graph represents a day in the life of a patient

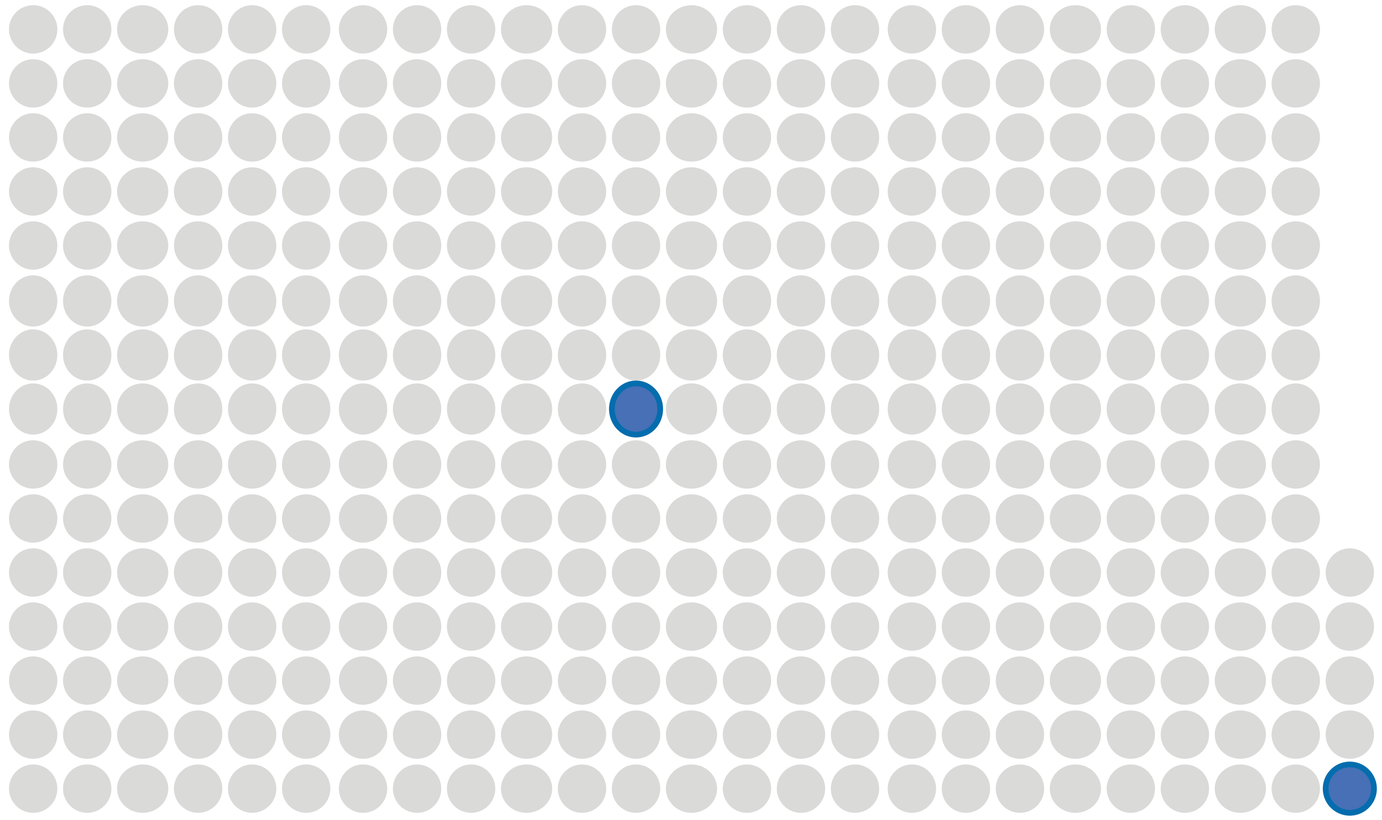
1

Day in the life with
weak symptoms

365 days living with a disease

Every dot on this graph represents a day in the life of a patient

2



Day in the life with weak symptoms

Day with a visit to the clinic/physician

365 days living with a disease

Every dot on this graph represents a day in the life of a patient

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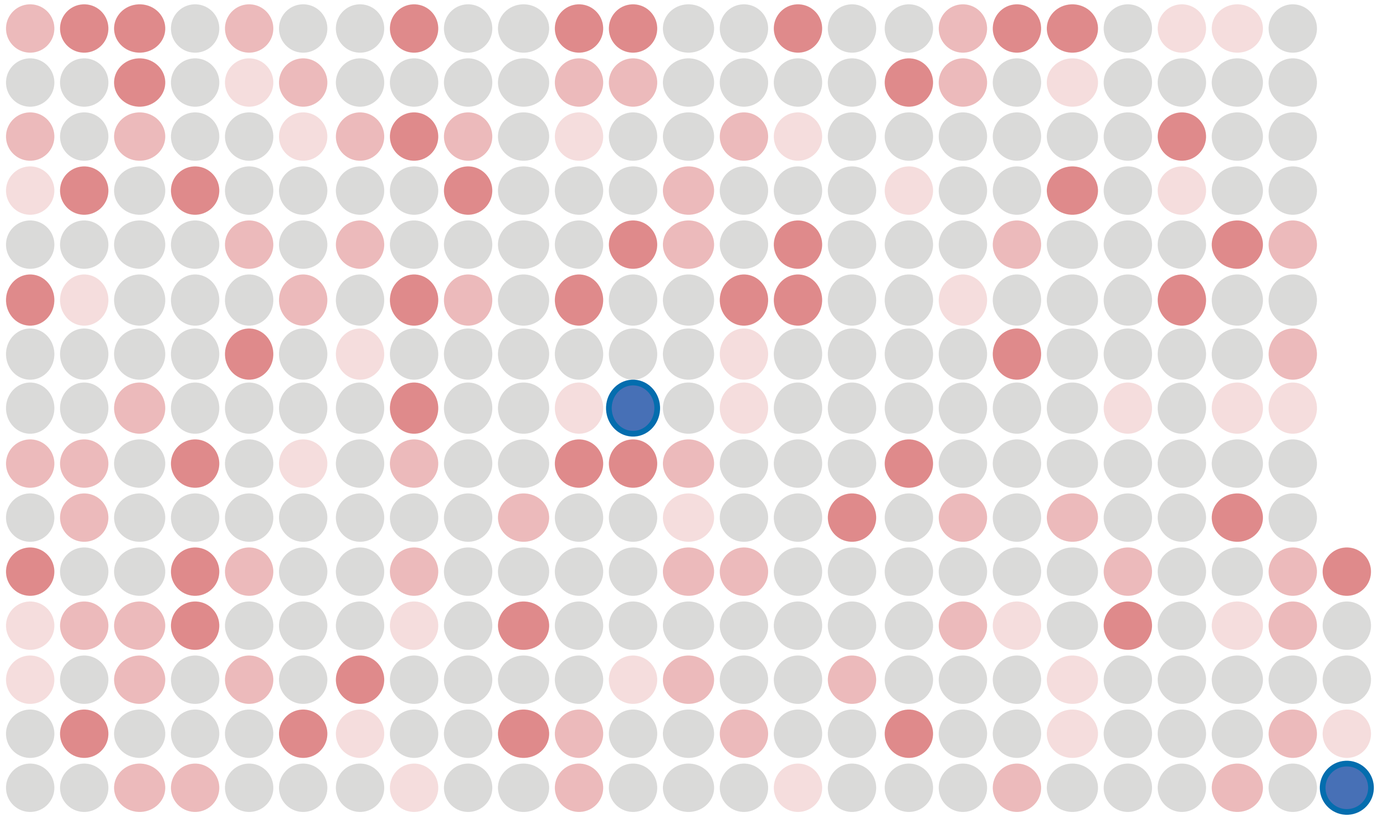

Day in the life with weak symptoms

Day with a visit to the clinic/physician

Day with stronger symptoms

365 days living with a disease

Every dot on this graph represents a day in the life of a patient

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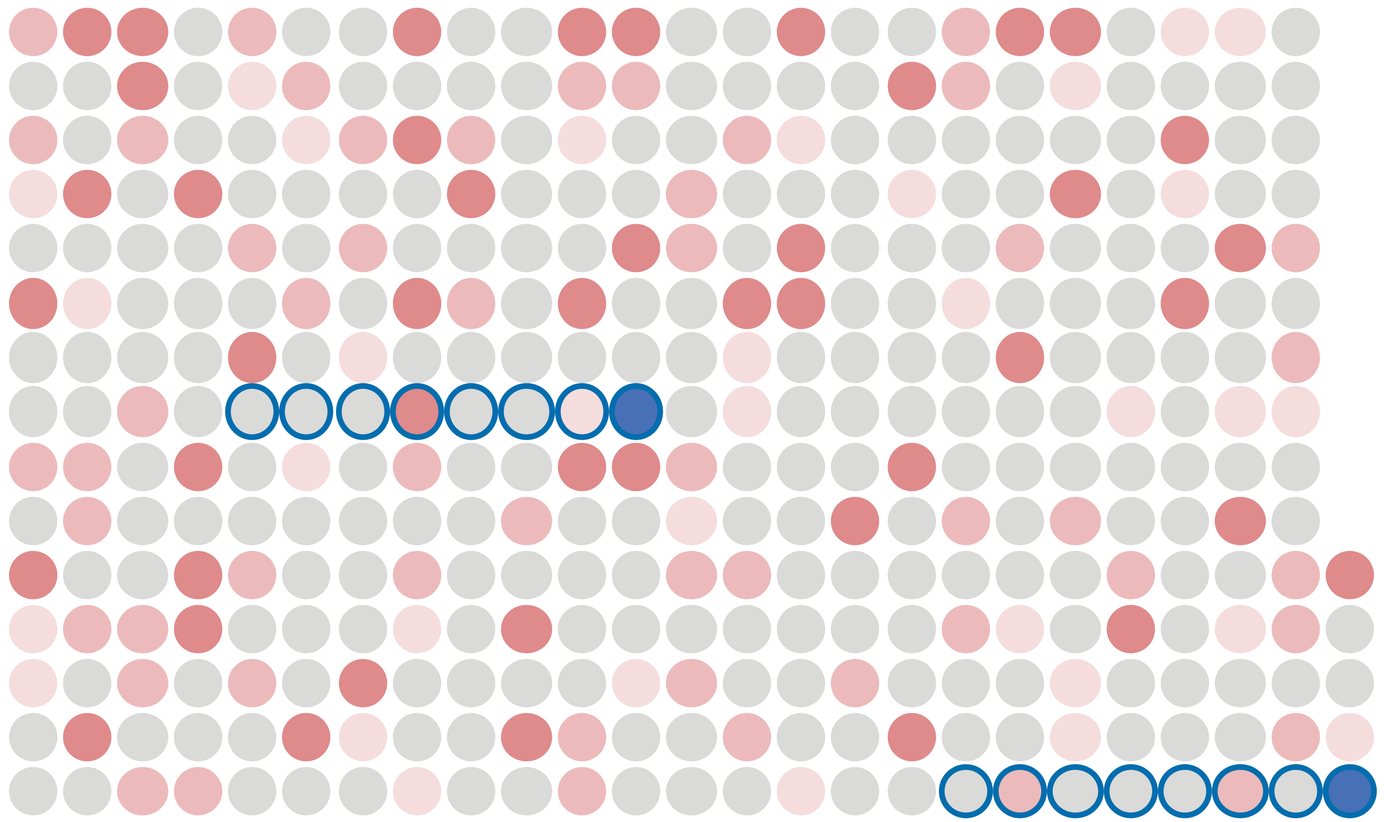


Day in the life with weak symptoms

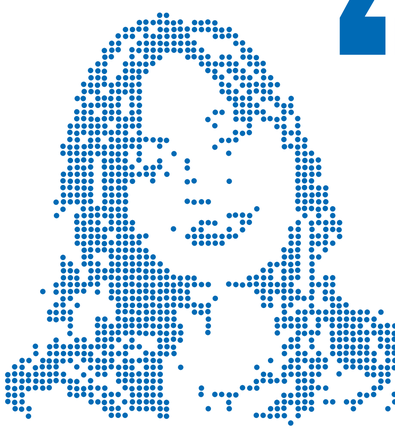
Day with a visit to the clinic/physician

Day with stronger symptoms

Symptom recall period

People living with a condition may only see a physician once or twice a year and may not entirely remember how they have felt on a specific day. Digital monitoring platforms help to provide a more comprehensive picture of how patients feel on a day-to-day basis

Patient perspective: Shining light on a hidden condition



> Every new symptom I notice I write down, and the day I go to my appointment I go with a little piece of paper so I don't forget anything.

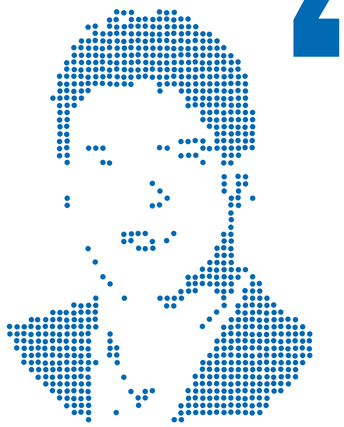
Martina Ribera, 49
Diagnosed with multiple sclerosis 20 years ago

Many of us find it hard to remember what we had for breakfast yesterday, what we were doing last Monday at 9 am or whether we slept well 2 weeks ago. But what if our health depended on it?

People living with a chronic condition may often not see a doctor for months or years at a time. This means they face the almost impossible task of trying to remember the sometimes subtle daily changes in their symptoms between doctor visits.

The challenge doctors face is trying to see exactly what is happening, hidden away inside the brain and central nervous system of patients. Being able to track and accurately measure any changes could lead to ways to slow, and even prevent, irreversible disease progression for patients.

Physician perspective: Fine-tuning treatment with constant monitoring

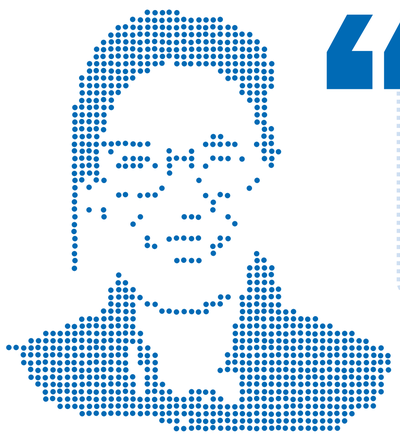


> As a doctor, it can sometimes be difficult to know if I am on the right track with treatment for patients. A phone in the pocket doing frequent assessments would allow me to start fine tuning.

Digital monitoring platforms can build on existing tests that patients and clinicians use, with other day-to-day passive monitoring. By combining this information with what they or their family are noticing, they can get a more complete picture.

Dr Ron Postuma, Parkinson's disease expert
Associate Professor
Department of Neurology and Neurosurgery,
McGill University in Montreal, Canada

Scientist perspective: Today's insights for tomorrow's treatments



> Sensor technologies give us a much fuller and more precise picture of patients' disease and response to treatment in our trials.

Kirsten Taylor, Cognitive neuroscientist
Biomarker and Experimental Medicine Leader, Roche, Basel

Advances in wearable devices, such as phones, watches, textiles or delivery devices, which track a patient's clinically relevant signals and monitor for symptoms, have the potential to vastly accelerate clinical development.

Because the data collected is objective and uses minimal patient involvement, clinical trials can potentially become more precise, faster and smaller.