Parkinson's disease: where we're at and challenges ahead

Dr Toni Pitcher
Senior Research Fellow
Dept. Medicine, University of Otago, Christchurch
New Zealand Brain Research Institute
25 May 2026

University of Otago
ŌTĀKOU WHAKAIHU WAKA

New Zealand Brain Research Institute

Parkinson's – motor symptoms

- Bradykinesia – slowed movements
- Rigidity – stiffness
- Tremor (resting)

- Postural instability
- Gait (walking)

Over 200 years since the symptoms of what is now known as Parkinson's disease were first described by Dr James Parkinson, a London-based surgeon.

He described the symptoms which he had observed across 6 people, some of which were patients of his and some were people he had observed in the street. He named this condition the 'shaking palsy'.

Use of the term Parkinson's disease was suggested by the renowned French Neurologist Jean-Martin Charcot in the late 1870s. He not only publicised Parkinson's observations, but also added his own observations, which included bradykinesia (slow movements) and rigidity (stiff muscles) were key components of the disease. James Parkinson had noted that patients were involuntarily weakened, but had not recognised that this was in fact due to bradykinesia and rigidity. Charcot noted that although tremor was typical of the disease it was not essential for diagnosis

A diagnosis of Parkinson's is made clinically, based on physical examination and medical history. Presence of the 3 core symtpoms of the disease, bradykinesia, rigidity and tremor are primarily considered, but postural instability and gail imapirments will also be assessed, as these are common symptoms.

Parkinson's – non-motor symptoms

- Sleep Disorders
  - Fragmented sleep and insomnia
  - REM behavioural disorder
  - Daytime sleepiness
- Sensory symptoms and pain
  - Loss of sense of smell
  - Abnormal sensations
  - Pain
- Autonomic Dysfunction
  - Orthostatic hypotension
  - Urogenital dysfunction
  - Constipation
- Neuropsychiatric
  - Depression
  - Anxiety
  - Apathy and anhedonia
  - Cognitive impairment and dementia
  - Hallucinations and psychosis
  - Impulse control

History of a range of non-motor symptoms will also assessed as these are now considered part of the disease complex.

Despite some non-motor symptoms being recognised by James Parkinson's – he described the need for the manual evacuation of the bowel in some individuals – our delay in realisation that others are related to or caused by the disease processes is that they are non-specific to Parkinson's and commonly occur as part of normal life and ageing process.

The non-motor symptoms affecct a number of different body systems and can have significant impacts on quality of life, sometimes more so than the motor impairments. Some of these symptoms may present very early in the disease and even pre-date the presentation of the motor symptoms by 10 years or more.

The most common non-motor symptoms presenting early are, RBD, constipation, loss of smell, and depression.

Challenge #1

Why does an individual get Parkinson's?

The majority of Parkinson's cases are of an unknown cause, however there are a number of factors that have been identified as contributing to an increased risk of developing the disease.

Firstly, the most robust risk factor is age, where increasing age, up to a point, increases the chances of a diagnosis.

We also know that males are twice as likely to receive a diagnosis than females, although the exact mechanism of this is unknown. Not all countries report this sex difference

Genetics also play a role, there are genetic forms of Parkinson's that arise from known mutations in specific genes, these however only account for around 10% of cases.

Outside of these genetic forms there are also a growing number of risk genes that have been identified as increasing a persons chance of getting Parkinson's. These genes are small changes in the genetic code that occur at greater rates in Parkinson's compared to the general population.

These risk genes alone are not able to cause Parkinson's, but having one or more of these in combination with exposure to other risk factors will increase the chance of getting Parkinson's.

Parkinson's – risk mediation

- Studies have indicated that Parkinson's risk can be mediated by medications
  - Salbutamol – asthma
  - Glitazone – diabetes
  - Calcium channel blockers – hypertension
  - Ambroxol – cough syrup

There are a few factors that have been identified that protect against Parkinson's. However they are not necessarily things that people are generally encouraged to do…..

Cigarette smoking remains the most robust finding for factors that associated with reduced risk of Parkinson's. The protective effect is greatest for current smokers, but ex-smokers do retain some benefit for a number of years after giving up. The mechanism for this protection is likely through increased dopamine levels due to chronic smoking.

The other factor that provides some protection against Parkinson's is daily caffeine consumption. The mechanism of action is likely via caffeine's action on the adenosine receptors within the brain and specifically on the dopamine neurons. These effects are through reduction of inflammation, excitotoxicity, mitochondrial function.

A number of medications, already in use, have been shown, through epidemiological studies, to be associated with a reduced risk of developing Parkinson's, these medications are used in the treatment of asthma and diabetes.

We have known for a number of years that the use of calcium channel blockers, which treat high blood pressure, also provide some protection against Parkinson's. One type of CCB has been tested in a clinical trial, unfortunately the result was negative, however, given the trial was enrolling people at time of diagnosis, it may have missed to window of opportunity for the benefits to be observed. It is possible that people identified in the prodromal phase of the disorder are the ones that are most likely benefit from these types of medications.

Ambroxol is currently in a phase III trial in the UK. Ambroxol is interesting in that it increases the activity of the enzyme that is coded by the GBA gene. It should benefit everyone, not just people with mutations/variations in this gene.

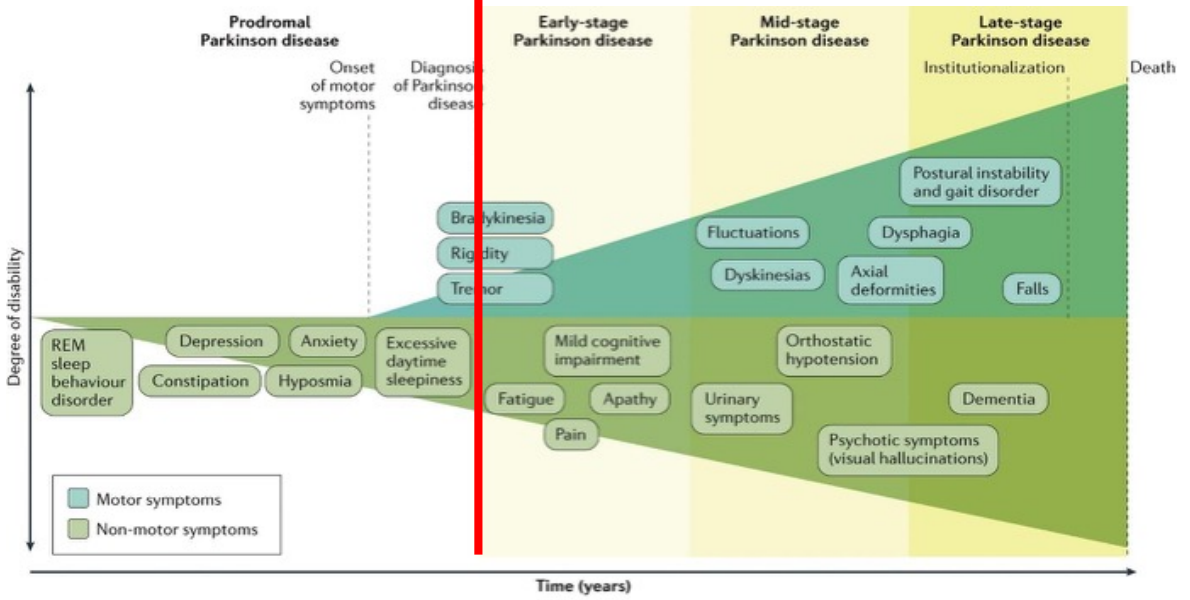
Risk factors - What challenges remain

- Very good at identifying the risk and ‘protective’ factors in isolation – not very good at combining them
  - Difficult to collect all relevant information from individuals
  - Difficult to get enough numbers to do meaningful analyses
  - Fancy statistics needed to ensure robust analyses
- Movement Disorders Society – Parkinson’s Exposome Taskforce

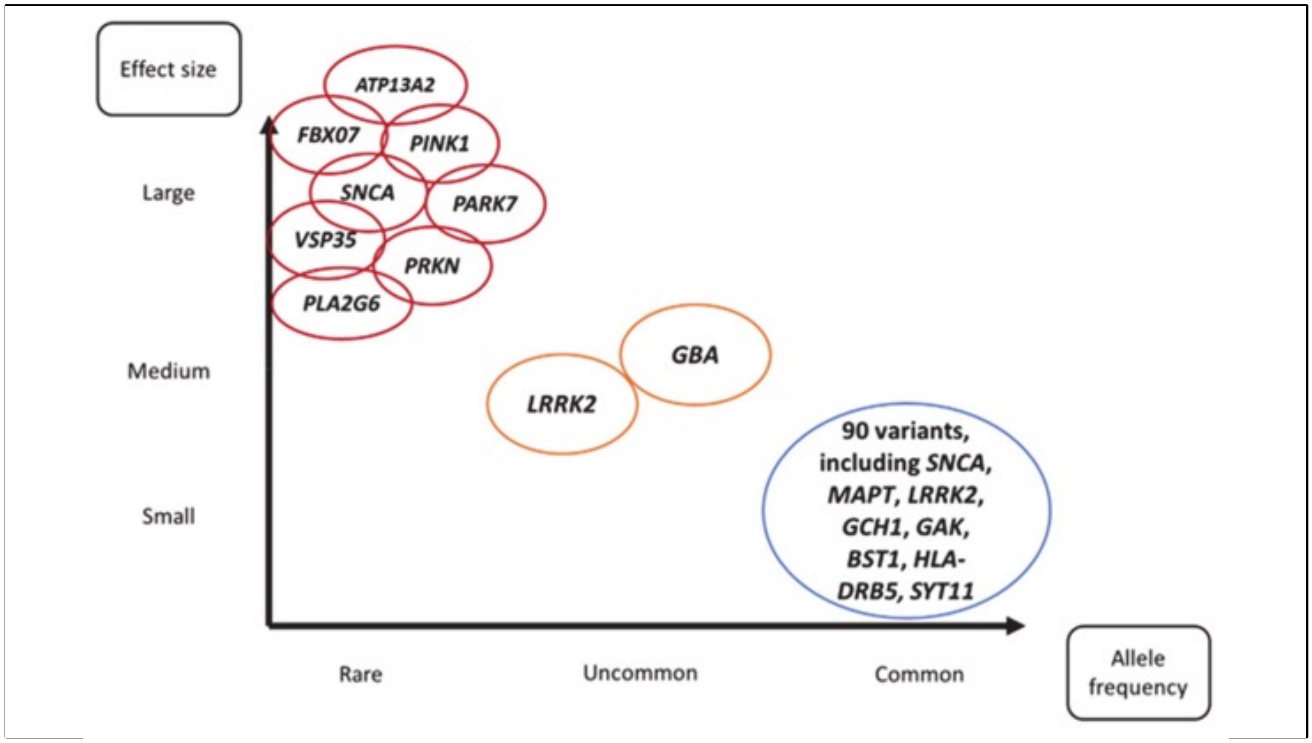
Challenge #2

Can we identify who is going to get Parkinson's?

Parkinson's - timeline



Poewe et al. 2017. Nature Rev Dis Primer



Day & Mullin 2021. Genes

Early detection - What challenges remain

- Some of the strongest predictors of future Parkinson's are not specific to Parkinson's
  - Loss of sense of smell – can also be related to Alzheimer's
  - REM sleep behaviour disorder – strongly related to α-synuclein pathology
    - Parkinson's
    - Dementia with Lewy Bodies
    - Multiple System Atrophy

This slide shows some famous faces who have been afflicted by Parkinson's.

Challenge #3

No diagnostic test available, there is a need for a ‘biomarker’

Parkinson's smell

- "Parkinson's smell"
- Joy Milne

- Dogs have been trained to identify the "Parkinson's smell"
- Scientists established the molecular signature of the scent - ~4 compounds have been identified

This line of research stems of observations made by Joy Milne from Scotland, her husband was diagnosed with Parkinson's at age 45, she had notice a change in his 'smell' some 12 years prior to his diagnosis. When they started attending Parkinson's UK events she realised that other people with Parkinson's had a similar 'woody musty smell' as her husband.

It was some years later and not until after the death of her husband, that she asked, at a public lecture, 'why do people with Parkinson's smell different?'

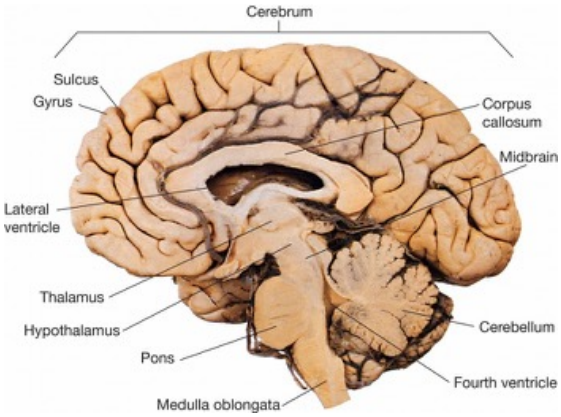
The presenter of the lecture had no answer, as he did not realise there was a distinct smell associated with the disease. A few months later the scientists, got together with Joy and tested her ability to smell the disease by presenting her with 12 t-shirts, 6 having been worn by people with Parkinson's and 6 worn by people without. She correctly identified all the Parkinson's t-shirts and even labelled one of the control shirts as having Parkinson's – remarkably this person was diagnosed with the disease 8 months later.

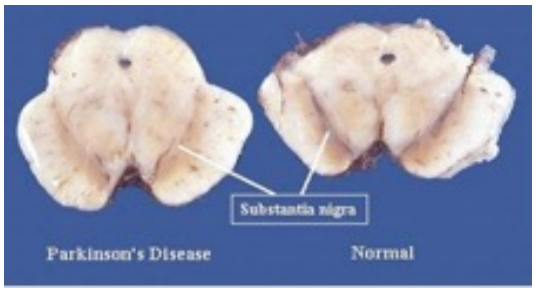
They have also trained sniffer dogs to identify the Parkinson's smell and scientists. This year they have published findings on the molecular signature of the scent. The hope is that they will be able to develop a test to identify this scent on people, not

only at the time of diagnosis but also prior to motor symptom onset.

Parkinson's – pathology

Death of dopamine producing neurons in substantia nigra

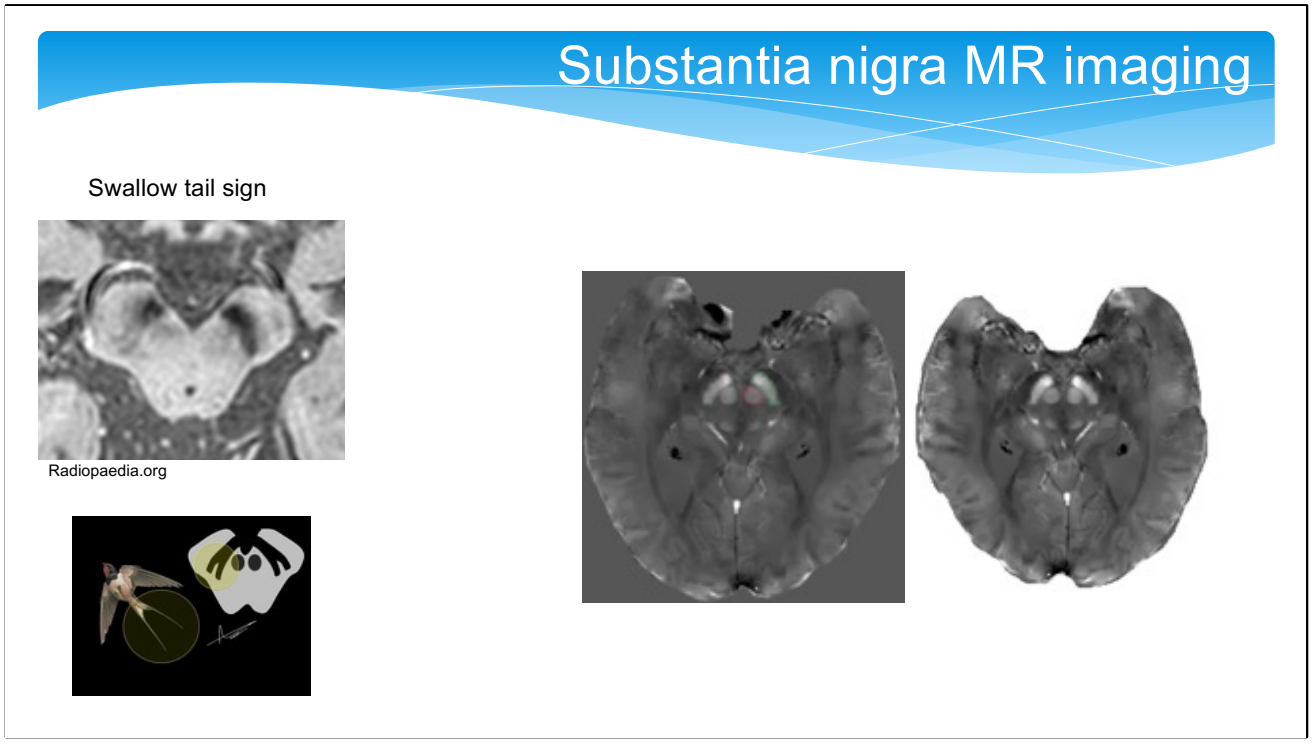




This figure shows the midline view of the brain after the two hemispheres have been separated. This section is the brainstem which connects the brain above to the spinal cord below. At the top of the brain stem is the midbrain and its here that the dopamine neurons are found.

If you cut through a healthy midbrain you would see two dark bands which show the location of the substantia nigra, which means 'black substance'. If you did the same to a midbrain from someone who had Parkinson's there would be a distinct absence of the dark bands, indicating the loss of the dopamine neurons. It is worth noting that by the time a diagnosis is made, over 50% of the dopamine neurons have already died.

Black due to the presence of neuromelanin



Visualising the substantia nigra in a living person is difficult because of its location deep in the brain.

There have been many attempts to use MR imaging to identify the substantia nigra and illustrate the loss of the dopamine neurons.
This image shows the so called swallow tail sign – whereby a normal SN looks a litttle like a swallow's tail – as shown on the left of the image, whereas the SN on the right is a much more uniform in width across its length.

It hasn't really taken off. But in the future if there is development of more refined sequences for capturing images that show the SN more clearly this could be used to help with diagnosis.

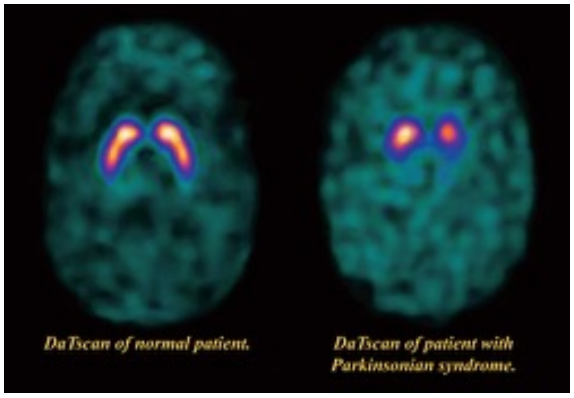
These images have been provided by my colleague Tracy Melzer. This is another type of MR imaging – QSM or quantitative susceptibility mapping. This type if imagin aims to identify the deposition of iron in the brain. On the left is a non-Parkinson's brain with the SN outlined in green and the round struture – the red nucleus outlined in red are showing as being much brighter than the other parts of the brain – that is because they have higher levels of iron than surrounding tissue. The image on the right is from someone with Parkinson's and you can see the both

the SN and red nucleus are showing as being brighter than those in the left image.

Dopaminergic nuclear imaging

DaTscan will help to differentiate between Parkinsonism and;

- Essential tremor
- Drug-induced Parkinsonism



There is one type of nuclear brain imaging, which is used – to varying degrees across countries to support a diagnosis.

It is called a DaTscan, whereby a radioactively labelled tracer is injected into the blood stream and binds to the dopamine reuptake transporter (or DAT) which is located at the ends of the axons of the dopamine neurons from the SN.

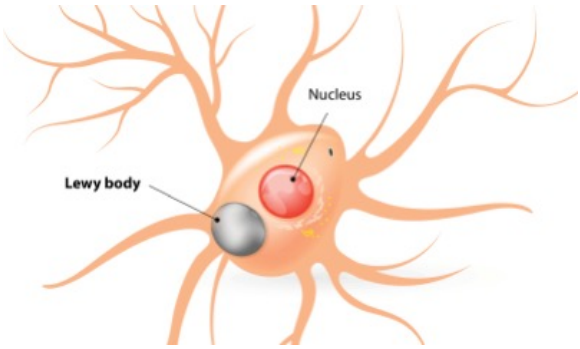
The 'normal' DaTscan shows the full shape of the putamen which receives a large amount of dopamine from the SN. The DaTscan from a parkinsonian disorder is missing the tail of the putamen, These scans are especially good at differentiating between Parkinsonism, which might be tremor dominant, and essential tremor, and drug-induced Parkinson's, particularly in those with a history of antipsychotic medication use.

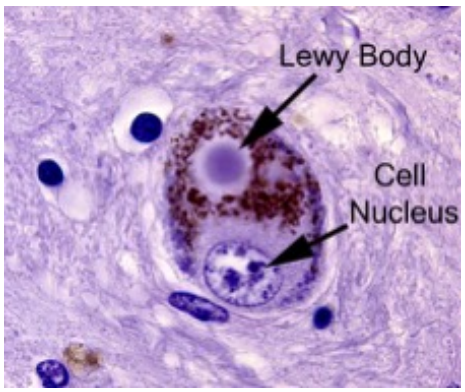
These scans are expensive, and not widely available in NZ.

https://www.cedars-sinai.edu/Patients/Programs-and-Services/Imaging-Center/For-Patients/Exams-by-Procedure/Nuclear-Medicine/DatScan/DaTscan-Procedure-Information.aspx

Parkinson's – pathology

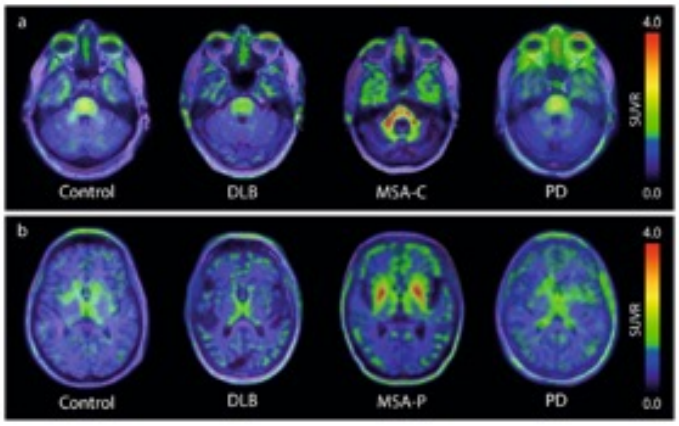
Lewy bodies within neurons – α-synuclein protein





α-synuclein protein – PET imaging

- Massive effort to develop a viable tracer – $10M from MJFF



One of the biggest challenges in the development of a PET tracer has been that alpha-synuclein is at much lower concentrations that other protiens associated with other disorders such as the b-amyloid and tau proteins that are associated with alzheimer's and both have PET tracers that are regularly used.

α-synuclein PET tracer [18F] ACI-12589. predominately Swedish group

α-synuclein protein – blood

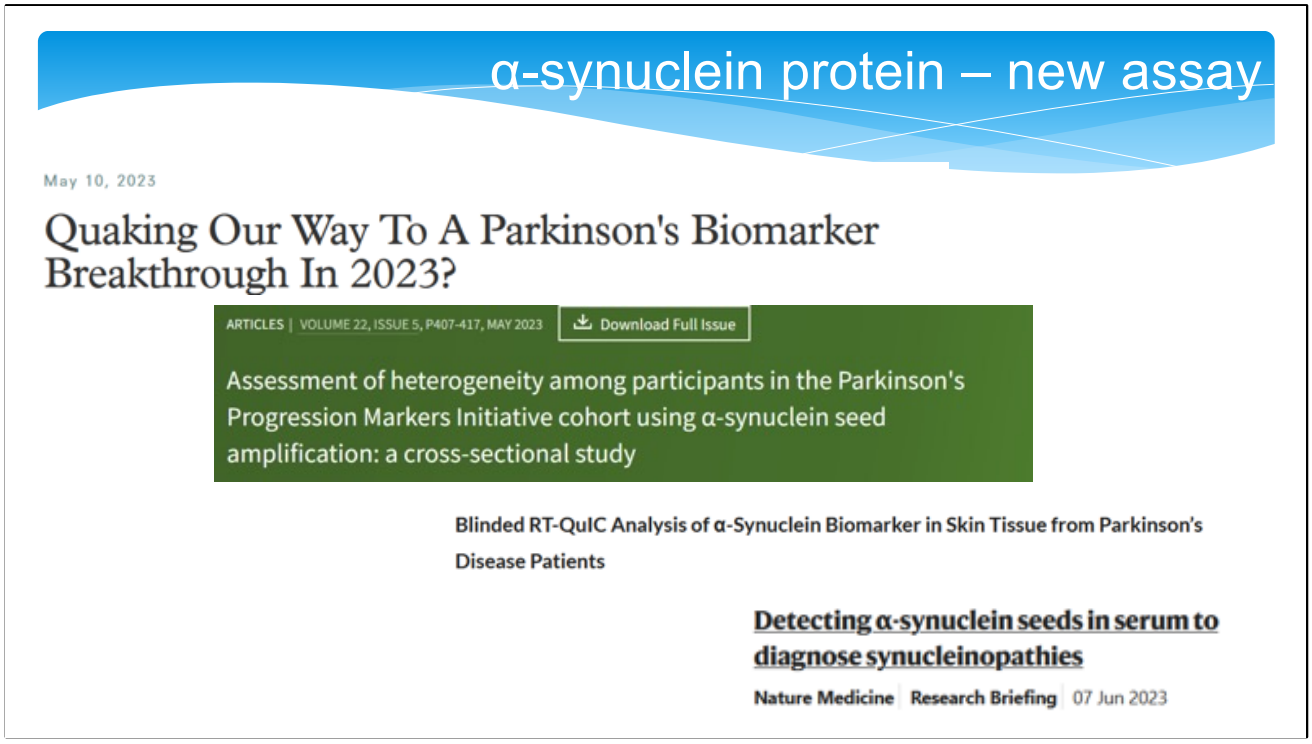
- Blood tests are simple

- α-synuclein concentration is low
- Red blood cells have α-synuclein

Why can't we just do a blood test – these are familair to most of us and well tolerated by the majority of the population.

It's been tried. The main problem is that 99% of the alpha-synuclein in blood is thought to come from red blood cells – this alone has led to an almost abandonment investigations into this as a diganostic test.

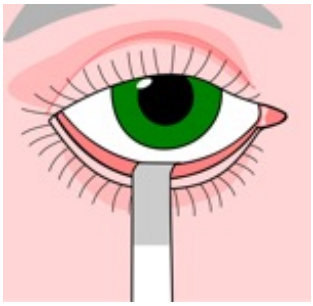
Us, along with others, have looked at an alternate way of using blood, and that is to utilise the EVs, which are in the blood.



Real time Quaking-induced conversion

Key difference to earlier assays – not measuring protein quantity but measuring samples ability to induce mis-folding

α-synuclein protein – tears



- Alternate to blood – eliminates the red blood cell problem
- Easier to collect, more suitable for regular collection

Biomarkers – challenges that remain

- Massive global effort to find a ‘biomarker’ of Parkinson’s
  - Diagnosis
  - Change with progression – testing of new therapies

- Somes challenges overcome
  - α-synuclein ‘behaviour’ rather than concentration

- Some challenges remain
  - Parkinsonian disorders – not just Parkinson’s


14 dementia risk factors
1 Physical inactivity
2 Smoking
3 Excessive alcohol consumption
4 Air pollution
5 Head injury
6 Infrequent social contact
7 Less education
12x5=60
8 Obesity
9 Hypertension
10 Diabetes
11 Depression
12 Hearing impairment
13 High LDL cholesterol
14 Vision loss