Biomarkers: What People with Ataxia Should Know

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What is a Biomarker?

- Symptoms:
  - The subjective experience of being ill
    - “I am clumsy”
    - “I am unsteady”
    - “I feel weak”
- Signs:
  - Objective measures that quantify illness
    - Illegible handwriting
    - Falls when pushed
    - Reduced grip strength when measured with a device

Biomarkers are the most objective, quantifiable, reproducible medical signs of illness that modern science allows us to measure.

How are biomarkers classified?

Molecular – have biophysical properties, which allow their measurements in biological samples (eg, plasma, serum, cerebrospinal fluid, bronchoalveolar lavage, biopsy)

Histologic – measurements in cells, tissues or fluids

Radiographic – Imaging

Physiologic – measures of body processes

What are some examples of biomarkers?

- Vital signs: Temperature, Heart rate, blood pressure
- Blood tests: like blood count, thyroid tests
- Spinal fluid test results
- Genetic test results from a biopsy
- Measures of motor function, like timed walking tests
- Standardized exam scores, like the SARA
- Standardized surveys, like the Beck Depression Inventory
- MRI results

What are biomarkers used for?

Clinical care of patients

- Screening, Diagnosis, Prognosis, and Monitoring
- Providing “individualized care” (cancer drugs)

Research

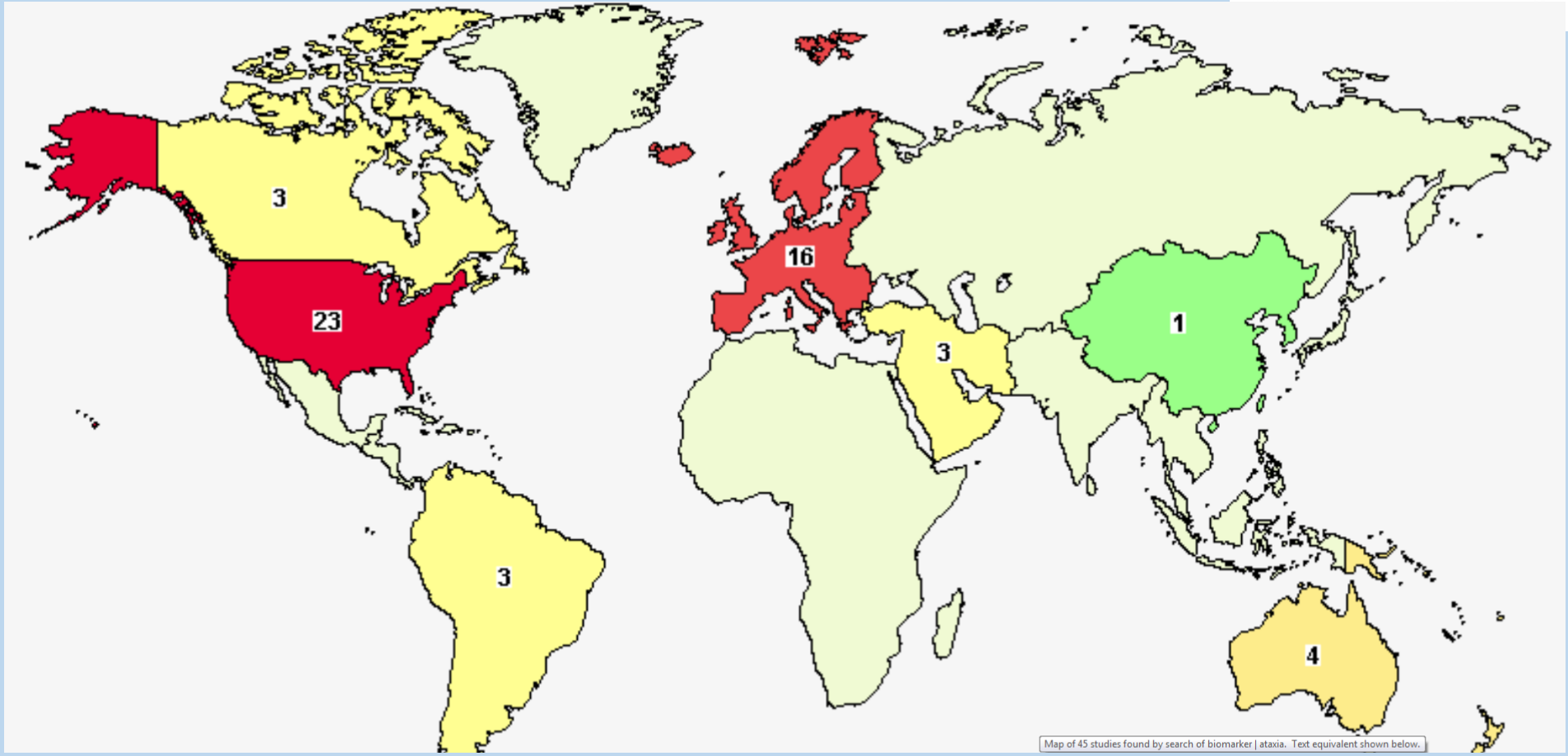
- Describing and classifying disease
- Improving disease diagnosis
- Improving early detection of disease, before symptoms start
- Drug Development

What are biomarkers used for?

Drug Development

- Improve the effectiveness and safety of existing medications
- Inform new drug development
- Help identify the right patients for trials of new drugs
  - Characterize patients before a drug trial starts
  - Monitor patients during the trial
  - Assess endpoints: Did the drug help or not?

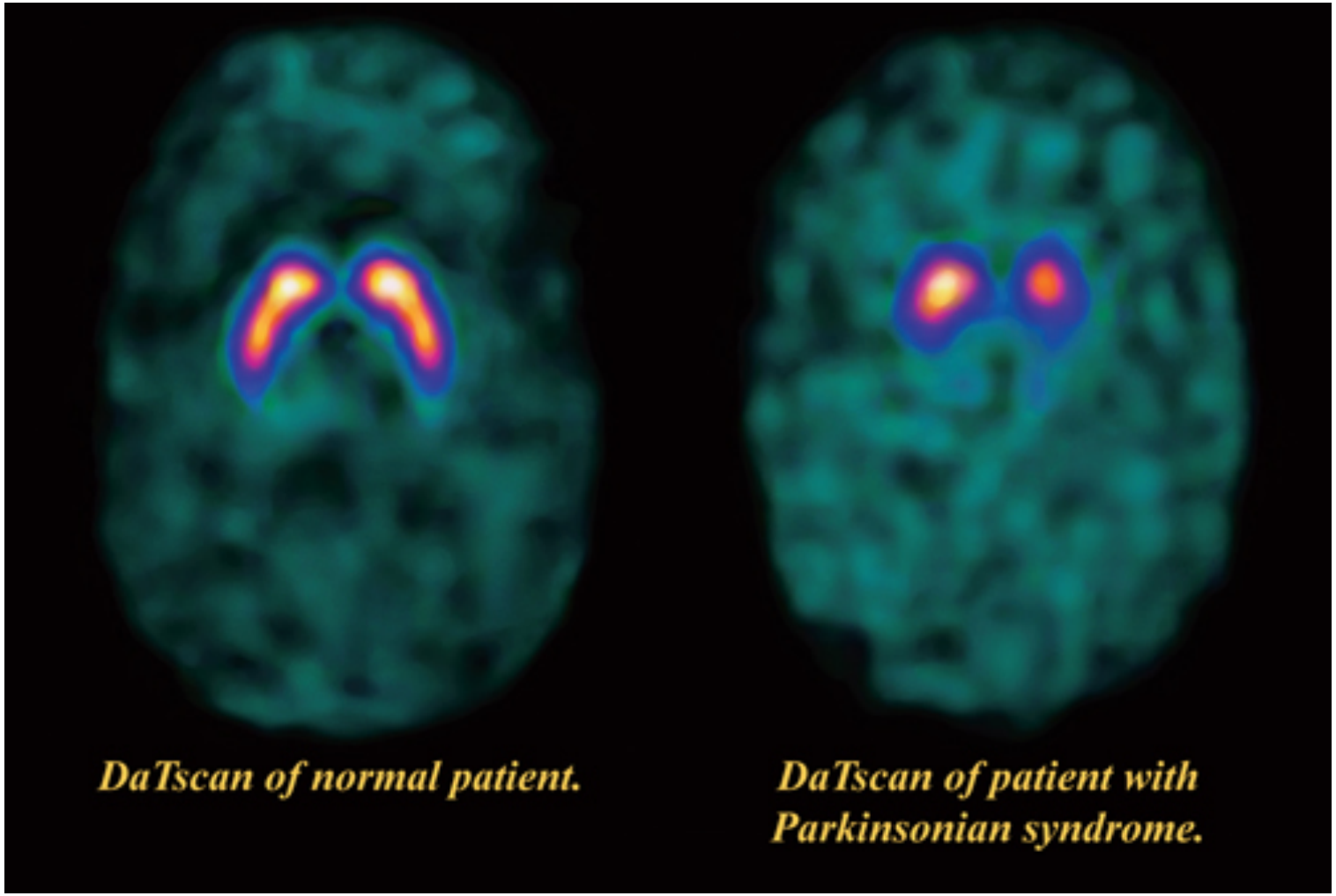
Biomarkers are HOT right now!



The biomarker challenge: the example of Parkinson's

- Parkinson's disease presents as slowness, stiffness, and tremors
- Over time, 80% of people with Parkinson's get dementia, and many become wheelchair-bound
- There is a desperate need for a cure, but you have to be sure of the diagnosis before you enroll a patient in a trial
- No blood tests or brain scans exist to diagnose Parkinson's
- 20% of people diagnosed with Parkinson's actually have something else!
- Diagnosing Parkinson's early, even before symptoms start, is desirable since we have no good medications to slow the progression of disease

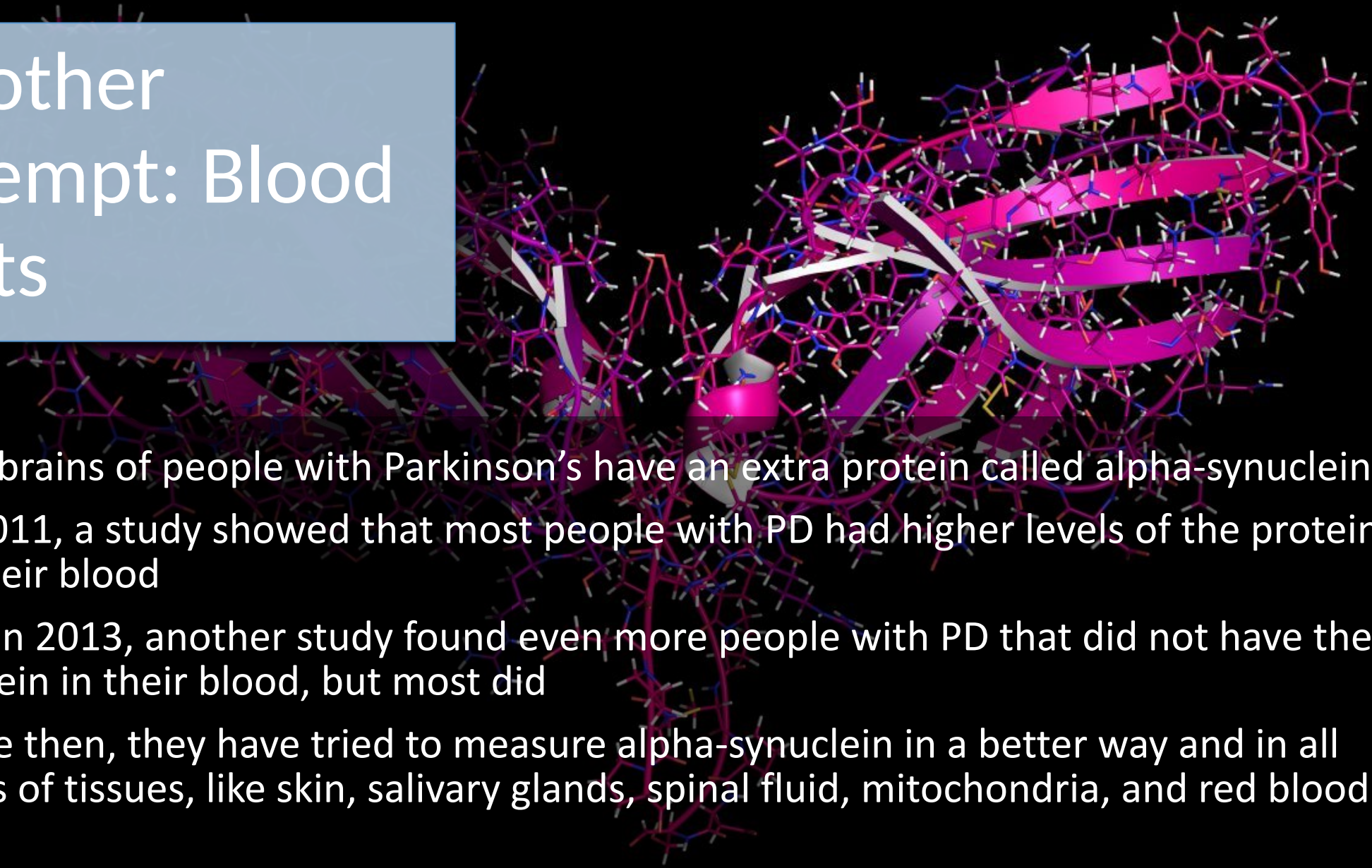
- It's not that we haven't tried to develop a test for PD!



One attempt: The DAT Scan

But diseases other than Parkinson's can cause a positive DAT scan!

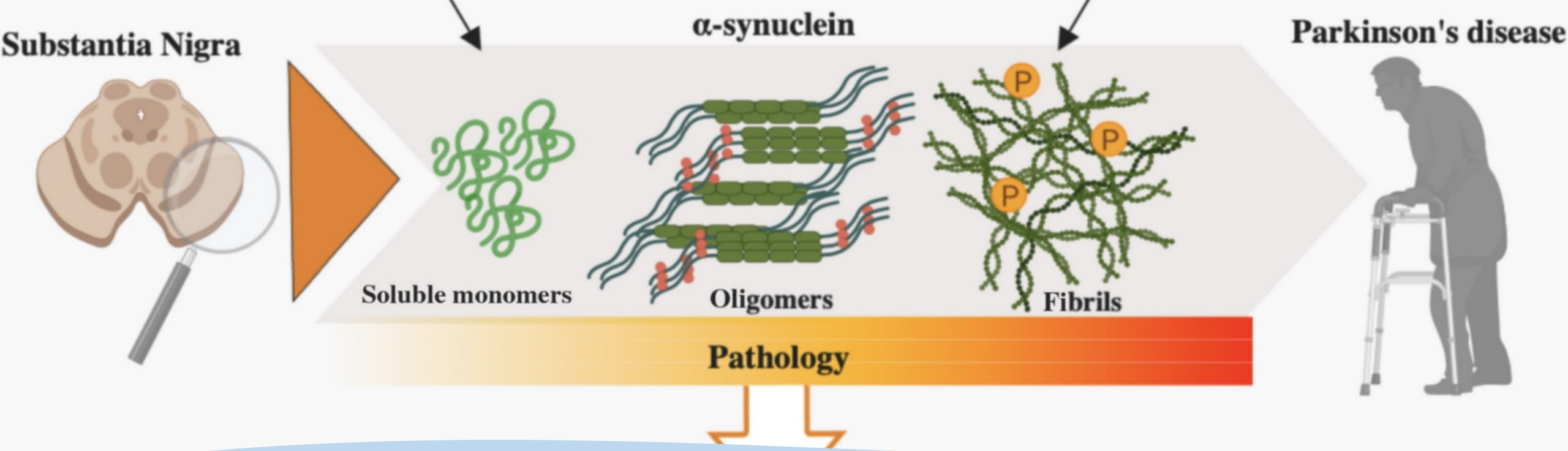
Another attempt: Blood tests



- The brains of people with Parkinson’s have an extra protein called alpha-synuclein
- In 2011, a study showed that most people with PD had higher levels of the protein in their blood
- But in 2013, another study found even more people with PD that did not have the protein in their blood, but most did
- Since then, they have tried to measure alpha-synuclein in a better way and in all sorts of tissues, like skin, salivary glands, spinal fluid, mitochondria, and red blood cells

Another attempt: Blood tests

- Challenges remain because:
  1) Alpha-synuclein can assume different forms
  2) Some forms are hard to measure
  3) We are not sure which forms are the most important to measure
  4) Not everyone with Parkinson's has the protein in all tissues, and
  5) Healthy people or people with diseases other than Parkinson's can have the protein in their tissues



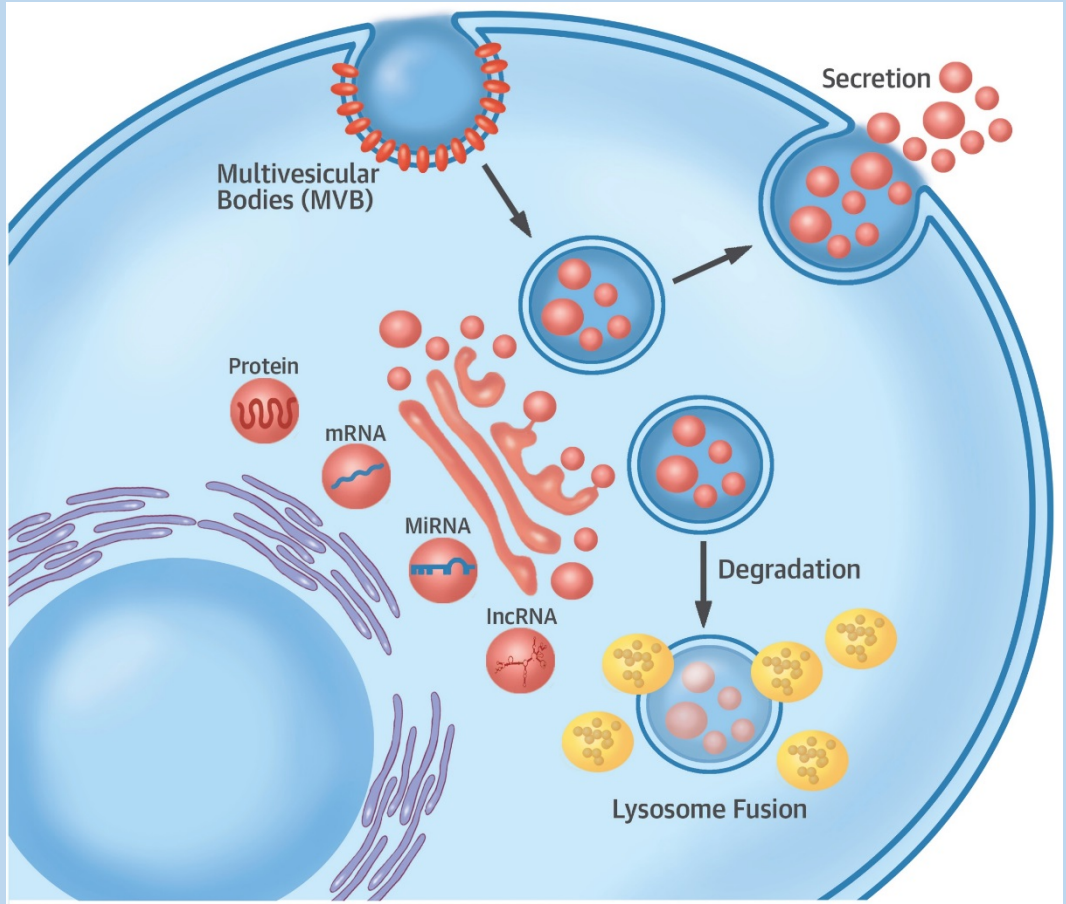
Alpha-synuclein is complicated!

The problem

Any single person with Parkinson's is unique! It is hard to reduce the complex disease into a single protein!

But there is hope!

- New methods for the detecting the protein have emerged, such as real-time quaking-induced conversion (RT-QuIC) and protein misfolding cyclic amplification (PMCA).
- The is a lot of money going towards biomarkers for PD right now
- Hot word: EXOSOMES
- There was a recent report of good results from a blood test looking at α-synuclein in plasma neuronal exosomes



Cardinal Features of Exosomes

- 30-150 nm particles
- Present in all body fluids
- Payload very cell-specific
- Released by nearly all cell types
- Loaded with miRs and other bioactive contents

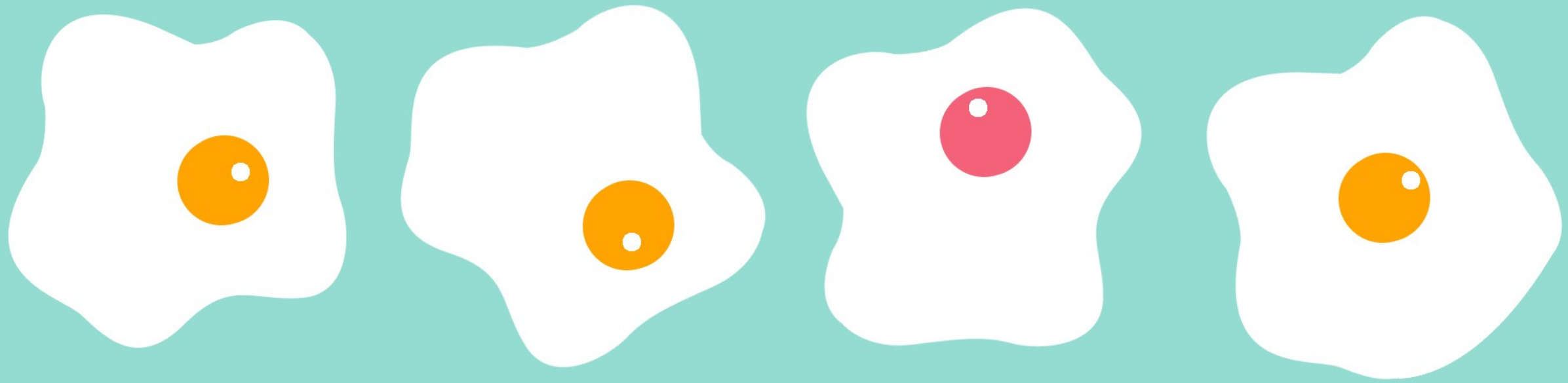
Moral of the Parkinson's story…

Biomarker development takes

TIME

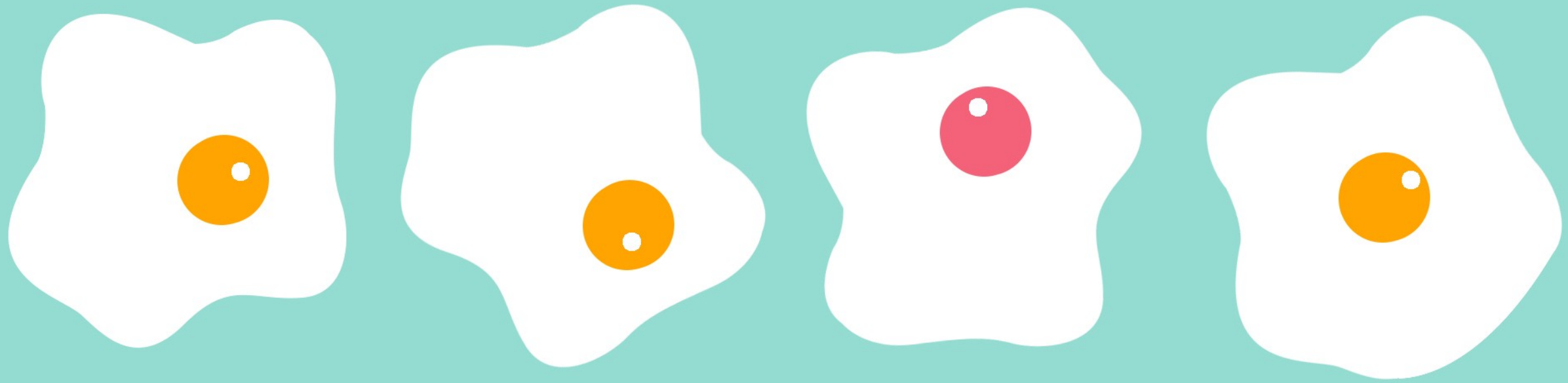
And

TWEAKING!



What makes a good biomarker?

- Cheap
- Easy and noninvasive to measure
- Reproducible (you get the same result every time)
- Accurate, with few false positives and false negatives
- Specific: Present in all of those with the disease or condition
- Sensitive: Not present in those without the disease or condition



What makes a good biomarker?

- Can be detected before the symptoms of the disease occur
- Changes its value to reflect the severity of disease
- Can be tracked in the same person multiple times without harm to the person (safe)

What biomarkers are there for ataxia?

Diagnosis:

- Many lab tests are run
  - Vitamin E, GAD-65 antibodies, vitamin 12
  - Genetic tests

Monitoring:

- SARA score (exam)
- MRI scans: cerebellar shrinkage

Prognosis:

- For some ataxias, disease severity correlates with the number of mutations in the gene

What is the SARA score?

1) Gait

Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.

- 0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)
- 1 Slight difficulties, only visible when walking 10 consecutive steps in tandem
- 2 Clearly abnormal, tandem walking >10 steps not possible
- 3 Considerable staggering, difficulties in half-turn, but without support
- 4 Marked staggering, intermittent support of the wall required
- 5 Severe staggering, permanent support of one stick or light support by one arm required
- 6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)
- 7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)
- 8 Unable to walk, even supported

2) Stance

Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.

- 0 Normal, able to stand in tandem for > 10 s
- 1 Able to stand with feet together without sway, but not in tandem for > 10s
- 2 Able to stand with feet together for > 10 s, but only with sway
- 3 Able to stand for > 10 s without support in natural position, but not with feet together
- 4 Able to stand for >10 s in natural position only with intermittent support
- 5 Able to stand >10 s in natural position only with constant support of one arm
- 6 Unable to stand for >10 s even with constant support of one arm

3) Sitting

Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.

- 0 Normal, no difficulties sitting >10 sec
- 1 Slight difficulties, intermittent sway
- 2 Constant sway, but able to sit > 10 s without support
- 3 Able to sit for > 10 s only with intermittent support
- 4 Unable to sit for >10 s without continuous support

4) Speech disturbance

Speech is assessed during normal conversation.

- 0 Normal
- 1 Suggestion of speech disturbance
- 2 Impaired speech, but easy to understand
- 3 Occasional words difficult to understand
- 4 Many words difficult to understand
- 5 Only single words understandable
- 6 Speech unintelligible / anarthria

What is the SARA score?

5) Finger chase

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband´s reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

- **0** No dysmetria
- **1** Dysmetria, under/ overshooting target <5 cm
- **2** Dysmetria, under/ overshooting target < 15 cm
- **3** Dysmetria, under/ overshooting target > 15 cm
- **4** Unable to perform 5 pointing movements

6) Nose-finger test

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedl with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

- **0** No tremor
- **1** Tremor with an amplitude < 2 cm
- **2** Tremor with an amplitude < 5 cm
- **3** Tremor with an amplitude > 5 cm
- **4** Unable to perform 5 pointing movements

7) Fast alternating hand movements

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

- **0** Normal, no irregularities (performs <10s)
- **1** Slightly irregular (performs <10s)
- **2** Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s
- **3** Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s
- **4** Unable to complete 10 cycles

8) Heel-shin slide

Rated separately for each side
Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

- **0** Normal
- **1** Slightly abnormal, contact to shin maintained
- **2** Clearly abnormal, goes off shin up to 3 times during 3 cycles
- **3** Severely abnormal, goes off shin 4 or more times during 3 cycles
- **4** Unable to perform the task

Why do we need better biomarkers for ataxia?

The clinical exam (SARA score) and brain shrinkage generally changes very slowly for most people with ataxia

If we found something that changed more quickly, we could more quickly find out if a treatment works

This could SPEED UP DRUG DEVELOPMENT!

Why do we need better biomarkers for ataxia?

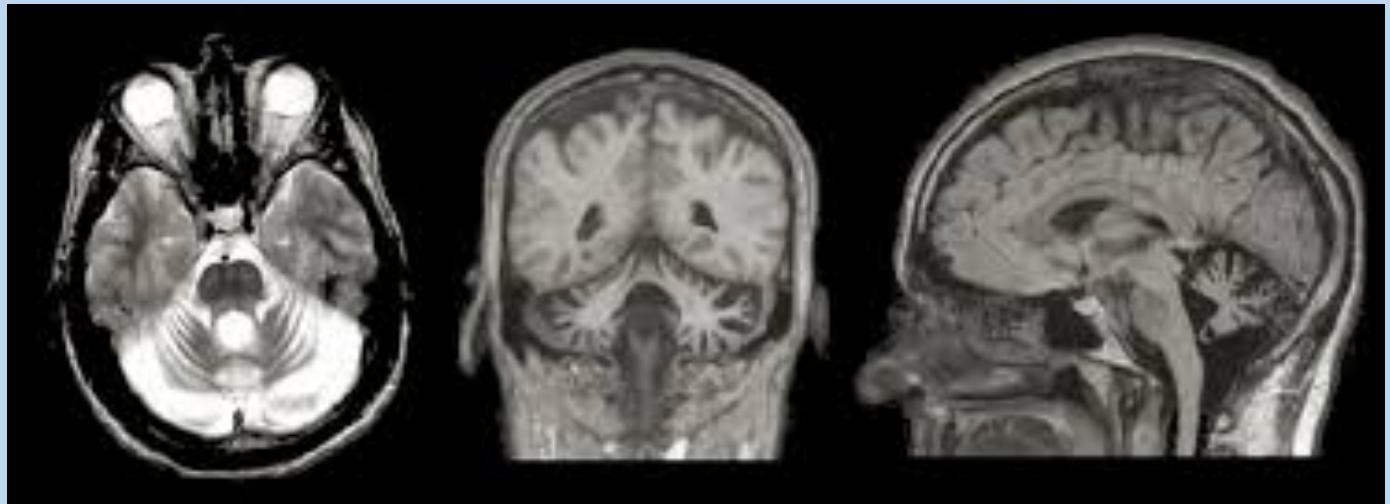
Current biomarkers are not able to measure anything in people who have not yet developed ataxia, but will

If we found something that could detect ataxia before it starts, we might be able to PREVENT ataxia developing in the first place!

This could help CURE ATAXIA!

Why is ataxia hard to develop biomarkers for?

- Ataxia is RARE
  - There is just 1 person with ataxia for every 100 people with Parkinson's
- No universal chemical or protein "target"
- Ataxia is usually a "wiring problem" rather than a chemical imbalance, which is harder to detect



Why is ataxia hard to develop biomarkers for?

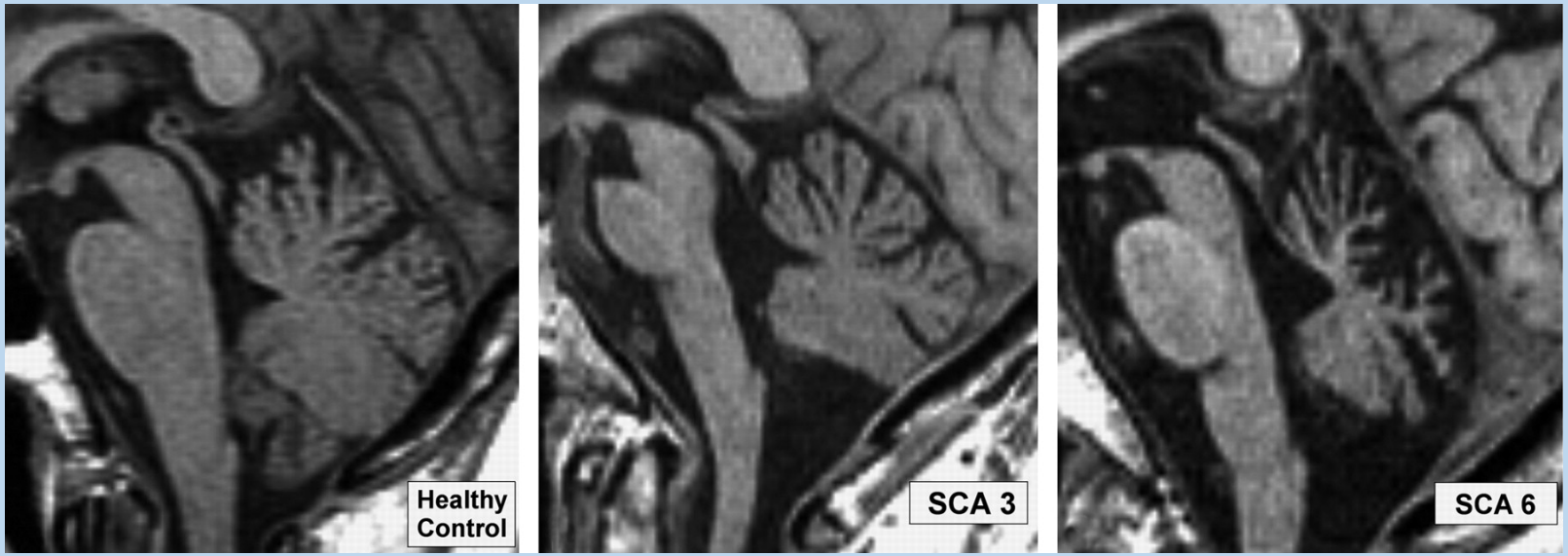
- There are MANY causes of ataxia, all with different mechanisms
- Highly variable in presentation = Even people with the same genes or underlying diagnosis can have different symptoms and severity of disease ➔ “The Parkinson’s Problem”

There are SO MANY Genetic Ataxias

Autosomal-dominant spinocerebellar ataxias (S.C.A.1,2,3,4,5,6,7 etc), Ataxia Telangiectasia, Fragile X premutation syndrome, Cerebellar Ataxia (with deafness, anosmia, absent corneals, nonreactive pupils, and hyporeflexia), RFC-1 CANVAS syndrome, Huntington's disease, Dentate cerebellar ataxia, Familial Ataxia with macular degeneration, Familial intention tremor, ataxia, lipofuscinosis, Friedreichs ataxia, Hereditary ataxia (with intellectual retardation, choreoathetosis, and eunuchoidism), Hereditary ataxia (with myotonia and cataracts), Acute Intermittent Cerebellar Ataxia, Ataxia (with Retinitis Pigmentosa, deafness, vestibullar abnormality, and intellectual dysfunction), Hypertrophic interstitial neuritis, Marinesco-Sjogren Syndrome, Pelizaeus-Merzbacher disease, Periodic ataxia (with attacks of vertigo, diplopia, and ataxia), Ataxia (with posterior, and lateral column difficulties, with nystagmus and muscle atrophy), Progressive cerebellar ataxia and epilepsy, Ramsey Hunt syndrome, Roussy-Levy syndrome…

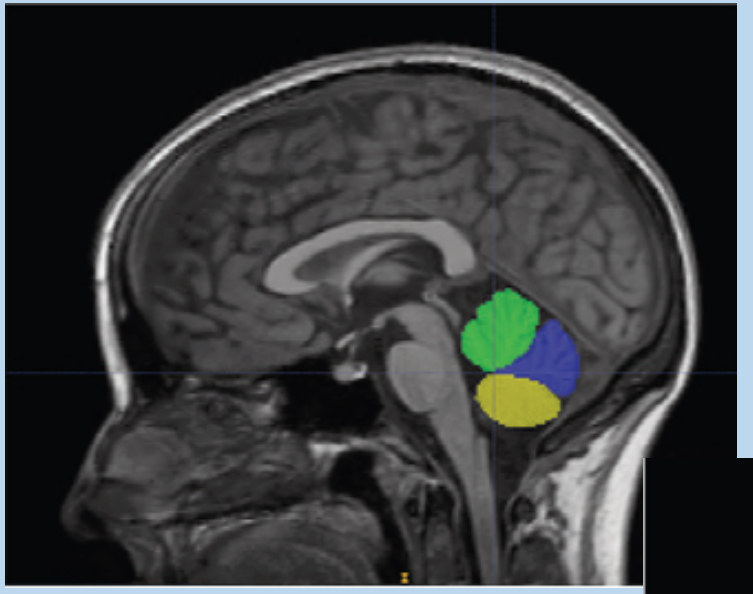
Example of biomarker research: MRI scans

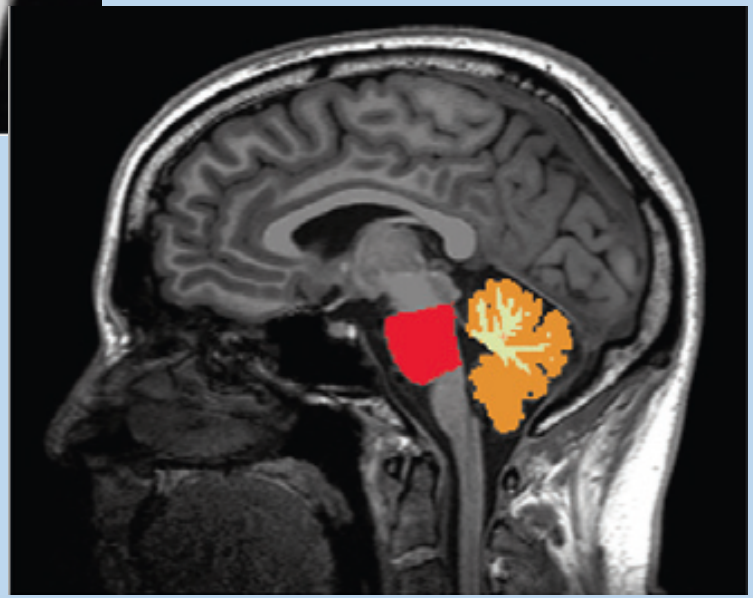
- In 2011, researchers measured the size of the cerebellum and brain stem on MRI and found that shrinkage of both parts went along with symptoms in people with SCA6, but only shrinkage of the brainstem seemed to connect with symptoms in people with SCA 3.



Things you can do with MRI scans

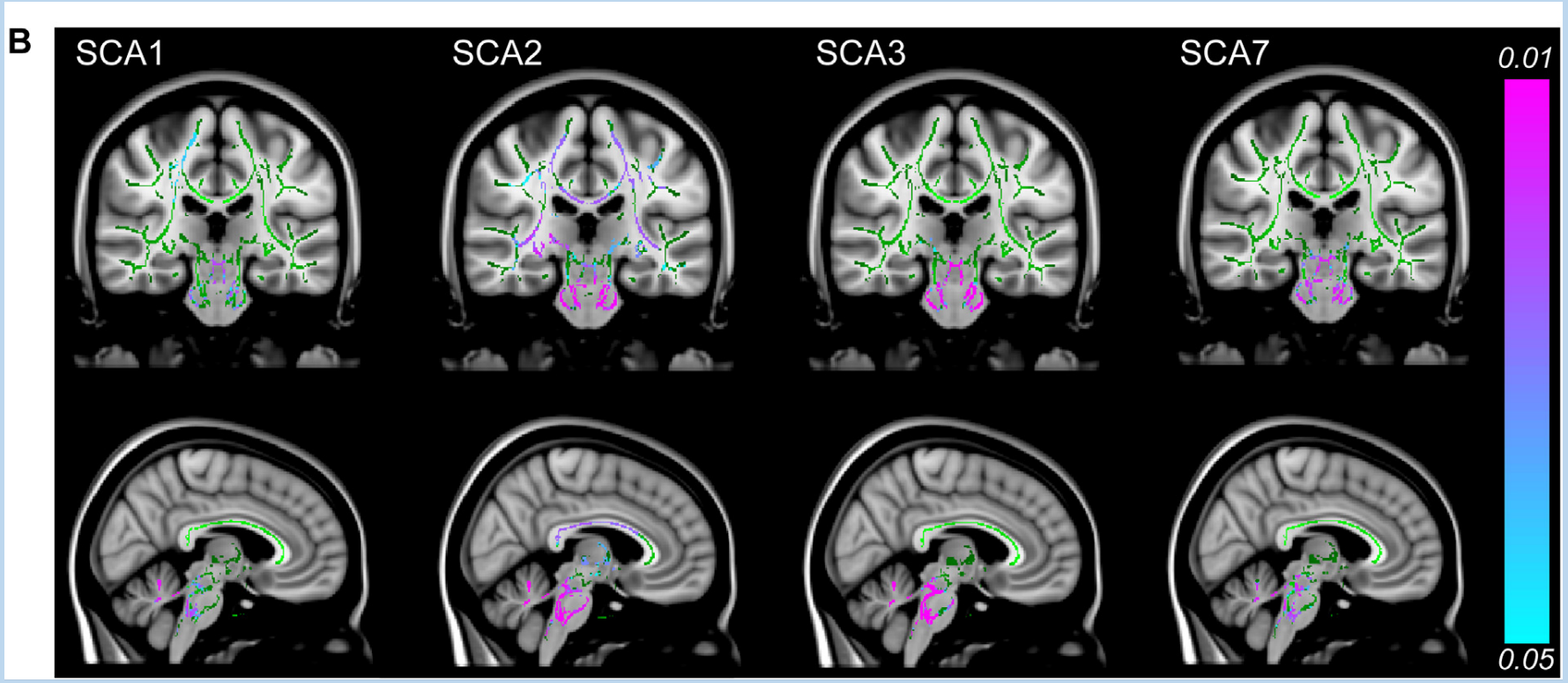
- Volumetrics: Measuring the size of parts of the brain
  - Lately: Complex computer programs and artificial intelligence has been making this better…and cooler looking!





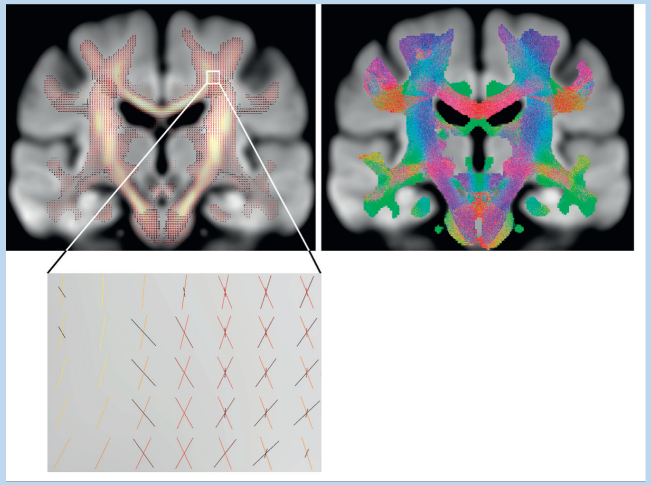
Things you can do with MRI scans

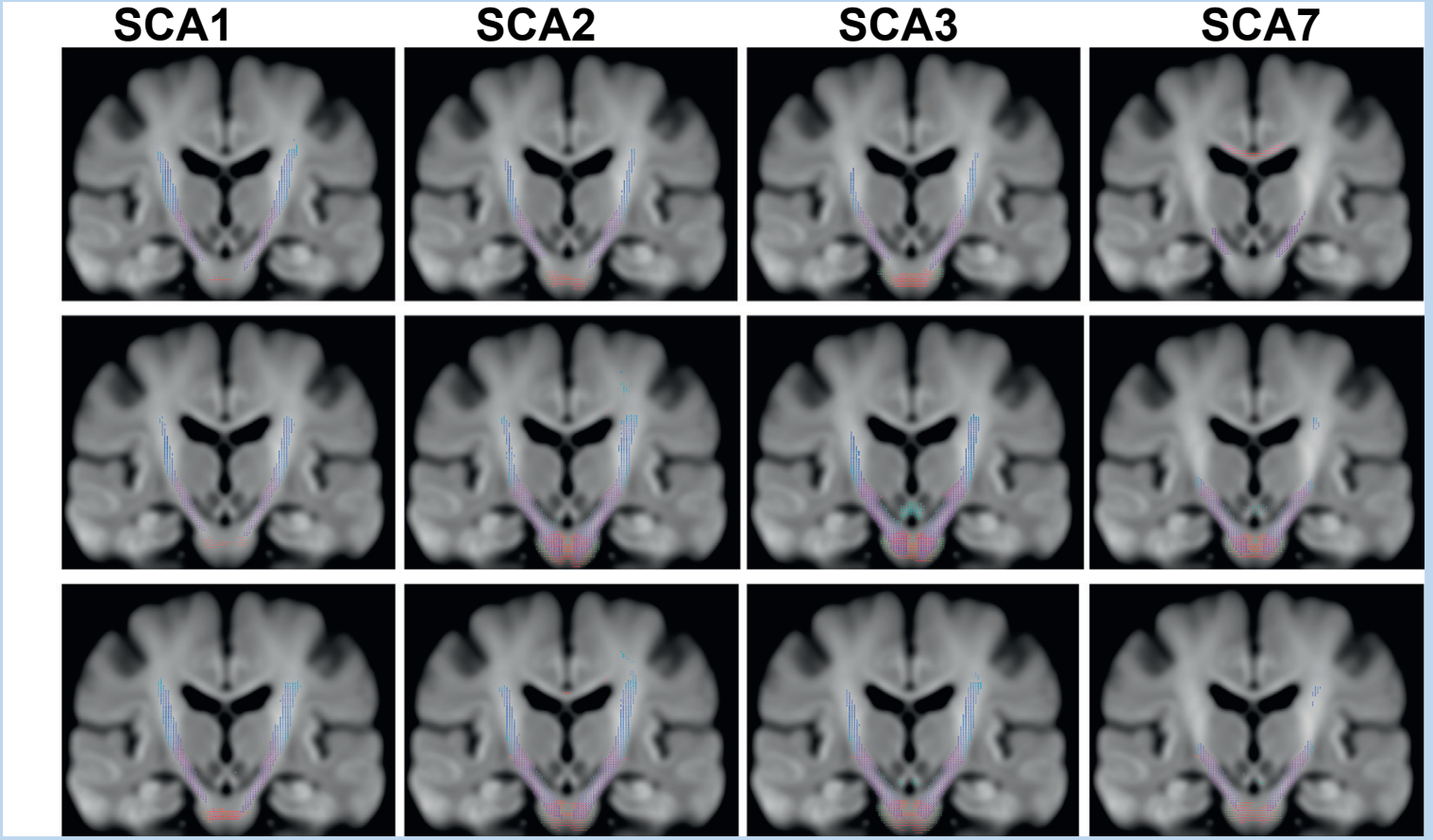
- Diffusion Tensor Imaging: A picture of the “disorganized” parts of the brain



Things you can do with MRI scans

- Connectivity-Based Fixel Enhancement
  - A fancy way to show the health of the networks in the brain: connections between parts that do the same thing.





What MRI scans have told us

- Using computers to extract from an MRI scan things like size, organization, and connectivity seems to better detect ataxia progression than the physical exam (SARA score) for many ataxia syndromes!

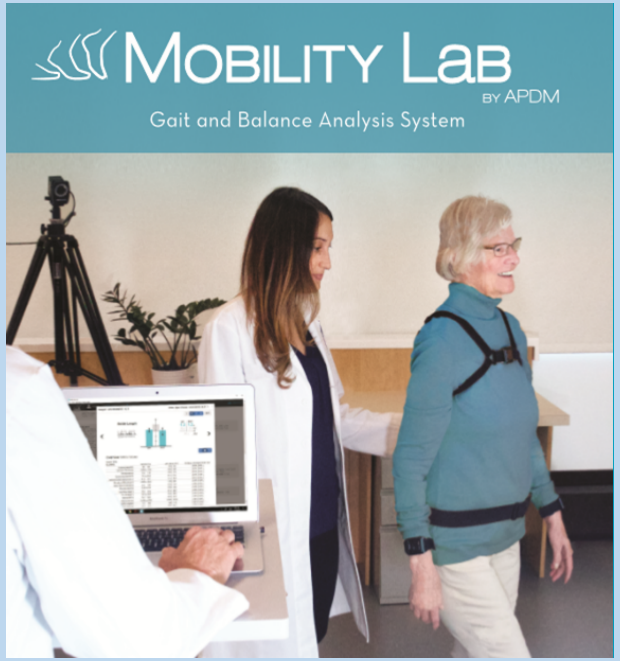
Why is this important?

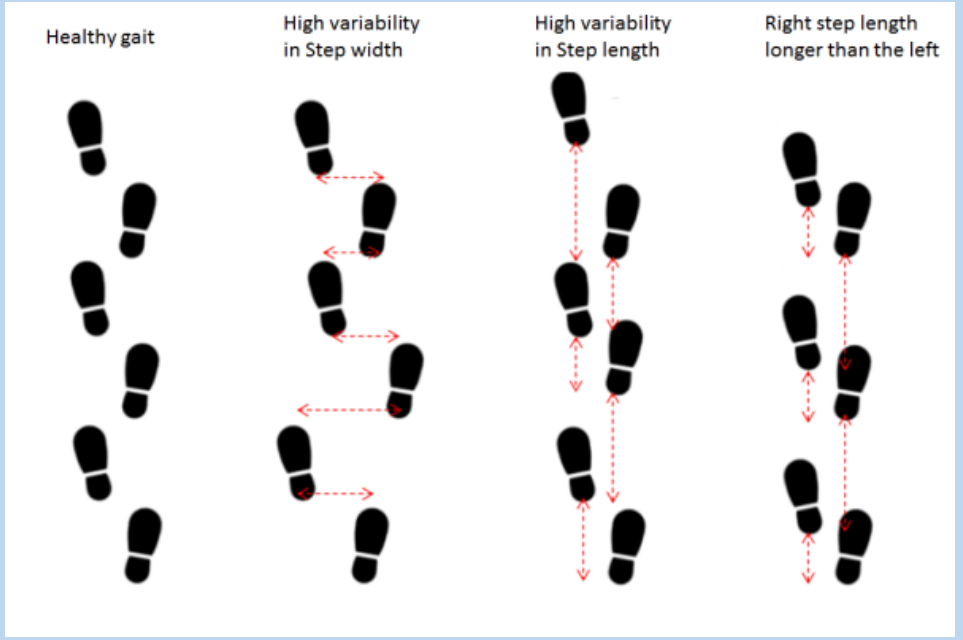
Finding a biomarker that can detect subtle changes can help SPEED UP DRUG DEVELOPMENT!

Example of biomarker research: TMS

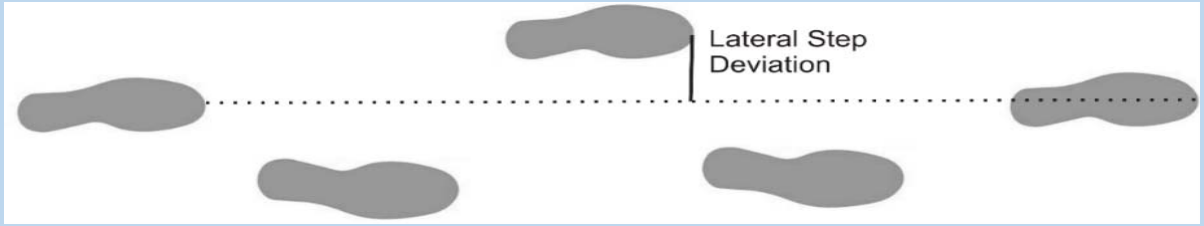
- Transcranial Magnetic Stimulation
  - Measures how well the motor system conducts electricity
  - Shows abnormalities before ataxia shows up in people with SCA 2

Example of biomarker research: Gait measurement



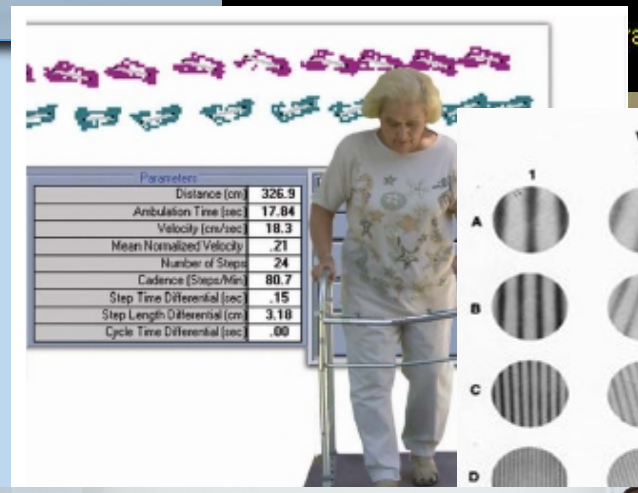


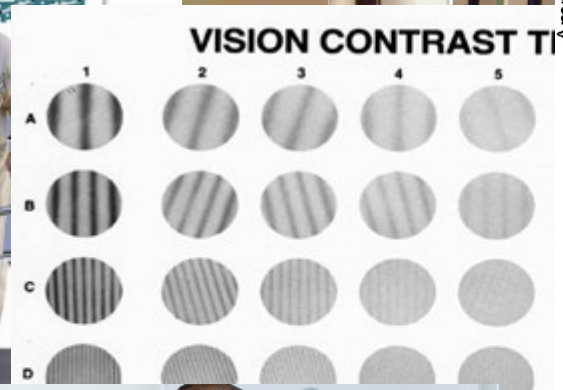
- Lateral step deviation and step-length variability seems to detect ataxia changes better than SARA scores, even telling the differences between people who differ by less than 1 point!

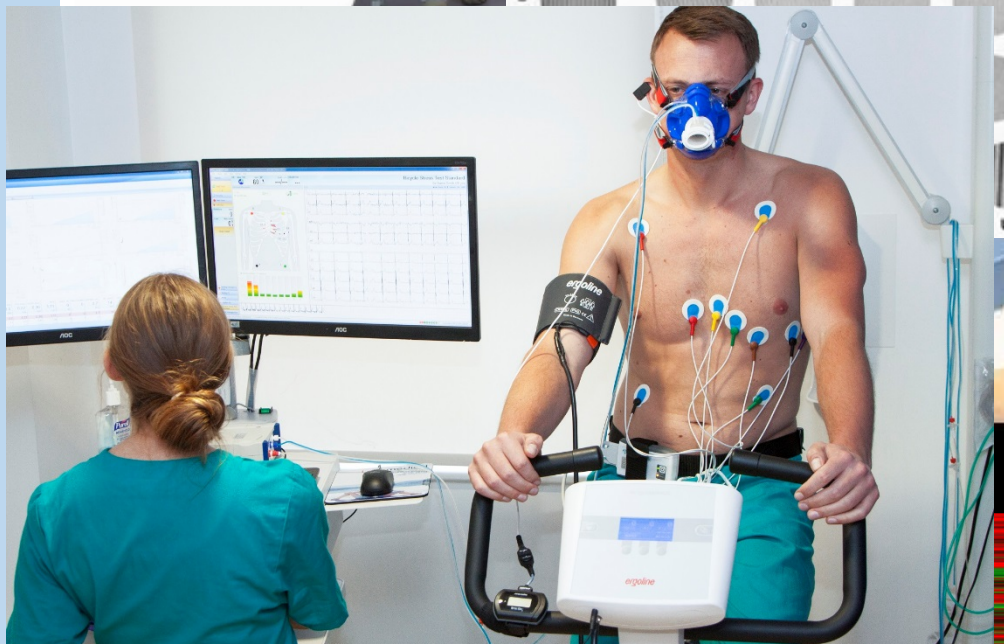


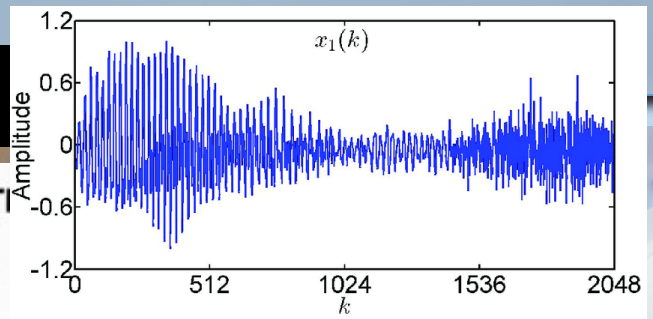
Example of biomarker research: FA

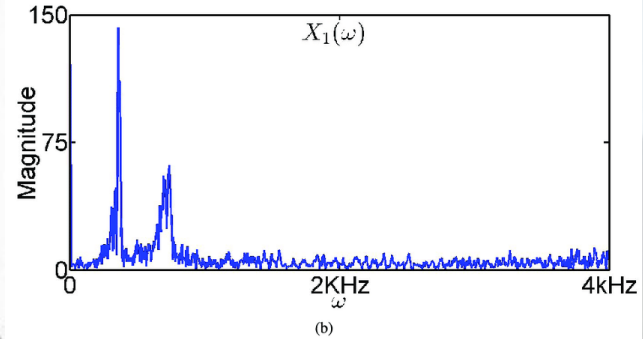
- Frataxin by Mass spectrometry
- Frataxin by ELISA
- Motor evoked potentials
- Meissner corpuscle imaging
- Nerve conductions
- Quantitative Sensory testing
- Cardiac MRI
- Metabolic isotopologues in platelets
- Magnetic Resonance Spectroscopy
- Gene expression panels
- 25-foot-walk
- 9-hole PEG test
- GaitRite quantitative gait assessment
- Contrast sensitivity
- Speech analysis
- Exercise testing

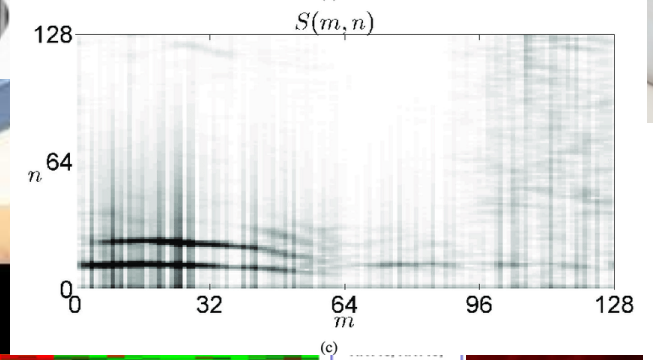


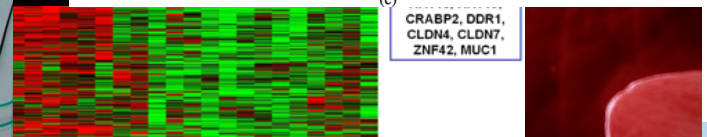












Whew!

- Anybody feel like a guinea pig???

Why are biomarkers important again?

- We still need ways to tell if our fancy new drugs are working!!!

RegenxBio and Pfizer Partner on Gene Therapy for Friedreich's Ataxia

Published: Jul 31, 2019 | By Mark Terry

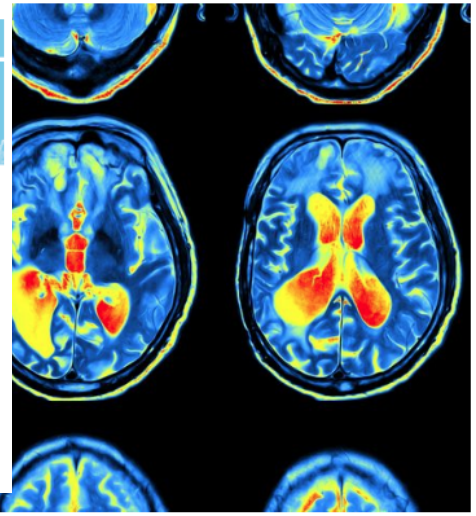
Neurocrine, Voyager Collaborating on VY-FXN01 Gene Therapy for Friedreich's Ataxia

doi:10.1093/brain/awv292 BRAIN 2015: 138; 3555–3566 | 3555

BRAIN
A JOURNAL OF NEUROLOGY

Broad distribution of ataxin 1 silencing in rhesus cerebella for spinocerebellar ataxia type 1 therapy

Megan S. Keiser,[1] Jeffrey H. Kordower,[2] Pedro Gonzalez-Alegre[3] and Beverly L. Davidson[4]



Why should I care about biomarkers?

- Biomarkers are measurable features of a disease.
- There is a big need for biomarkers for ataxia that can assess changes more quickly than what we have now.
- Biomarker development has the potential to speed up the development of treatments for ataxia.
- Participating in or supporting biomarker research may not be as sexy as enrolling in a drug trial, but it has the potential to not only help develop drugs to help one type of ataxia, but all types of ataxia!

Why should I care about biomarkers?

- Plus, You can make a bunch of nerds who like measuring things happy!

Thank you!

- Any questions?