Diagnostic flowchart for atypical parkinsonism and genetic PD
Introduction to the European Reference Network for Rare Neurological Diseases (ERN-RND):

ERN-RND is a European Reference Network established and approved by the European Union. ERN-RND is a healthcare infrastructure which focuses on rare neurological diseases (RND). The three main pillars of ERN-RND are (i) network of experts and expertise centres, (ii) generation, pooling and dissemination of RND knowledge, and (iii) implementation of e-health to allow the expertise to travel instead of patients and families.

ERN-RND unites 32 of Europe’s leading expert centres in 13 Member States and includes highly active patient organizations. Centres are located in Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Netherlands, Poland, Slovenia, Spain and the UK.

The following disease groups are covered by ERN-RND:

- Ataxias and Hereditary Spastic Paraplegias
- Atypical Parkinsonism and genetic Parkinson’s disease
- Dystonia, Paroxysmal Disorder and Neurodegeneration with Brain Ion Accumulation
- Frontotemporal Dementia
- Huntingtons’ Disease and other Chores
- Leukodystrophies

Specific information about the network, the expert centres and the diseases covered can be found at the networks web site www.ern-rnd.eu.

Recommendation for clinical use:

The European Reference Network for Rare Neurological Diseases developed the Diagnostic Flowchart for atypical parkinsonism and genetic Parkinson’s disease to help guide the diagnosis. The Reference Network recommends the use of this Diagnostic Flowchart.
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METHODOLOGY

The development of the Diagnostic Flowchart was done by the Disease group for Atypical Parkinsonism and genetic PD of ERN-RND.

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Flowchart development process:

- Development of flowchart – June – November 2017
- Discussion/Revision in ERN-RND disease – November 2017 – June 2018
- Consent on diagnostic flowchart during ERN-RND annual meeting 2018 – 08/06/2018
- Consent on document by whole disease group – 15/11/2018
Diagnostic flowchart for atypical PD

1. **Clinical diagnosis** "Parkinsonism"
   - "Red flags" for suspected atypical parkinsonism
     - Hypokinesia
     - Early instability
     - Cognitive dysfunction
     - Oculomotor abnormalities
     - Inspiratory sleep
     - Emotional incontinence
     - Abnormal postures
     - Severe autonomic failure

2. **PD by MDS criteria** positive Doparesponse (optional: positive DAT-scan)
   - PD by MDS criteria: suggestive for genetic form (positive family history or onset < 40 years)
     - Yes: targeted sequencing of most common genes
     - No: clinically probable specific PD

3. Targeted sequencing of most common genes
   - Genetic PD: Yes
     - Mutation detected
     - No: unclassified genetic PD

4. Panel or exome sequencing
   - Genetic PD: Yes
     - Mutation detected
     - No: unclassified genetic PD

5. Panel or exome sequencing
   - Other differential diagnoses (e.g., vascular parkinsonism of normal pressure hydrocephalus)
     - Yes: other differential diagnoses
     - No: MSA

6. MSA
   - Yes: diagnostic criteria and supporting evidence for MSA
   - No: PSP

7. PSP
   - Yes: diagnostic criteria and supporting evidence for PSP
   - No: CBS

8. CBS
   - Yes: diagnostic criteria and supporting evidence for CBS
   - No: unclassified genetic PD

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2 LRRK2, SNCA for dominant family history, Parkin, PINK1 DJ1 for early-onset disease.

