Committee on biomarkers in phoniatrics
Union of European phoniatricians
4th meeting
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CMC: Proposal for construction of the study model for the generation of a pre-clinical PD screening tool

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Biomarker: a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic interventions

Our research group problem:

How to select parameters that have accuracy?

In other words

What would be our model to detect the more subtle change from normal to PD?

Statements:

- Voice changes are a fiable marker in established PD
- Voice is a multidimensional phenomen

Desired framework:

- We want the easiest combination of parameters

- We want in the future to pass from laboratory/office
(i.e. praat analysis of controled ambient recording) to phone recording

- We want to use AI methods for classifiyng groups (prodromics PD/healthy control)

- We want to incorporate AI methods in the screening tool

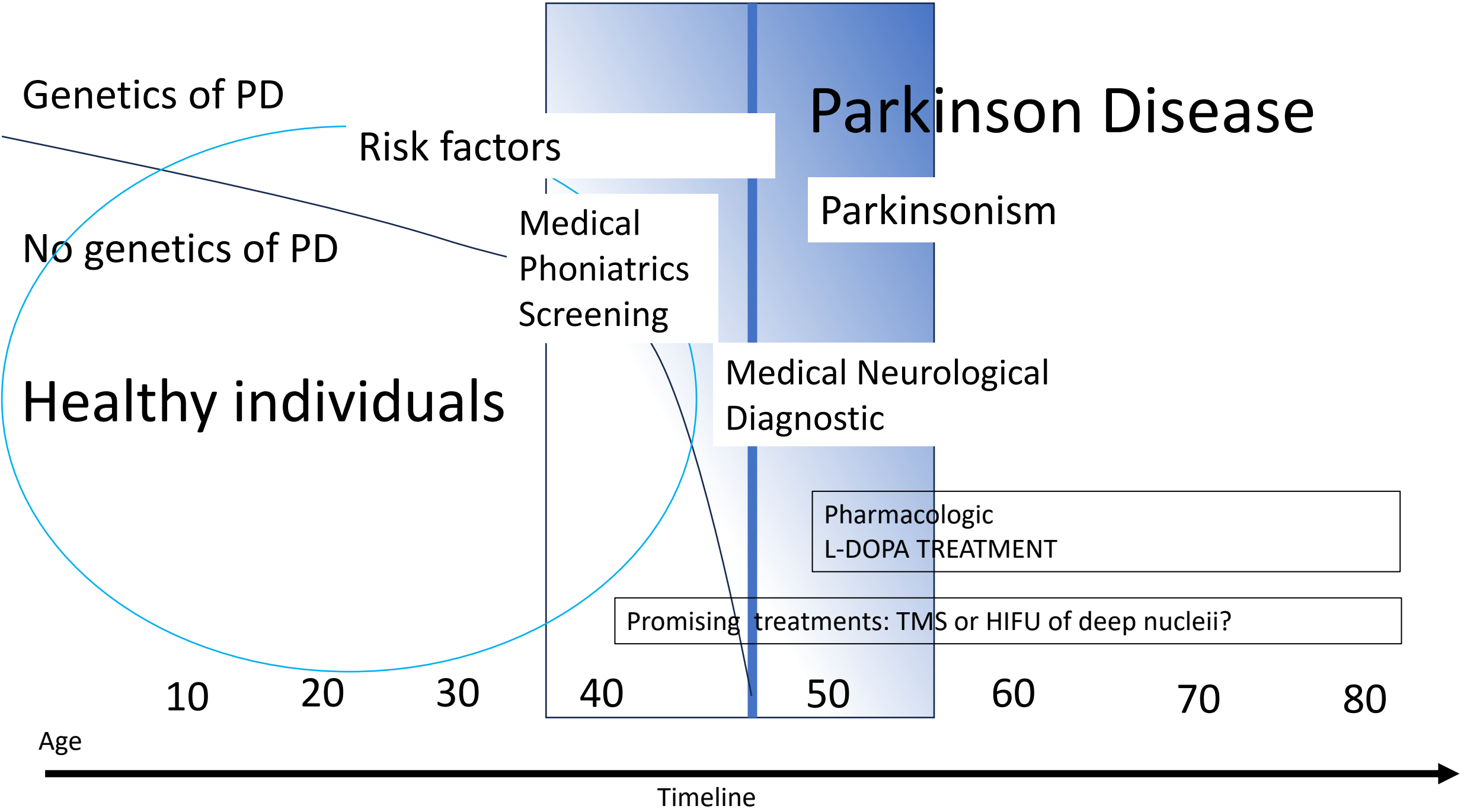
We need to consider that a screening tool technique must be:

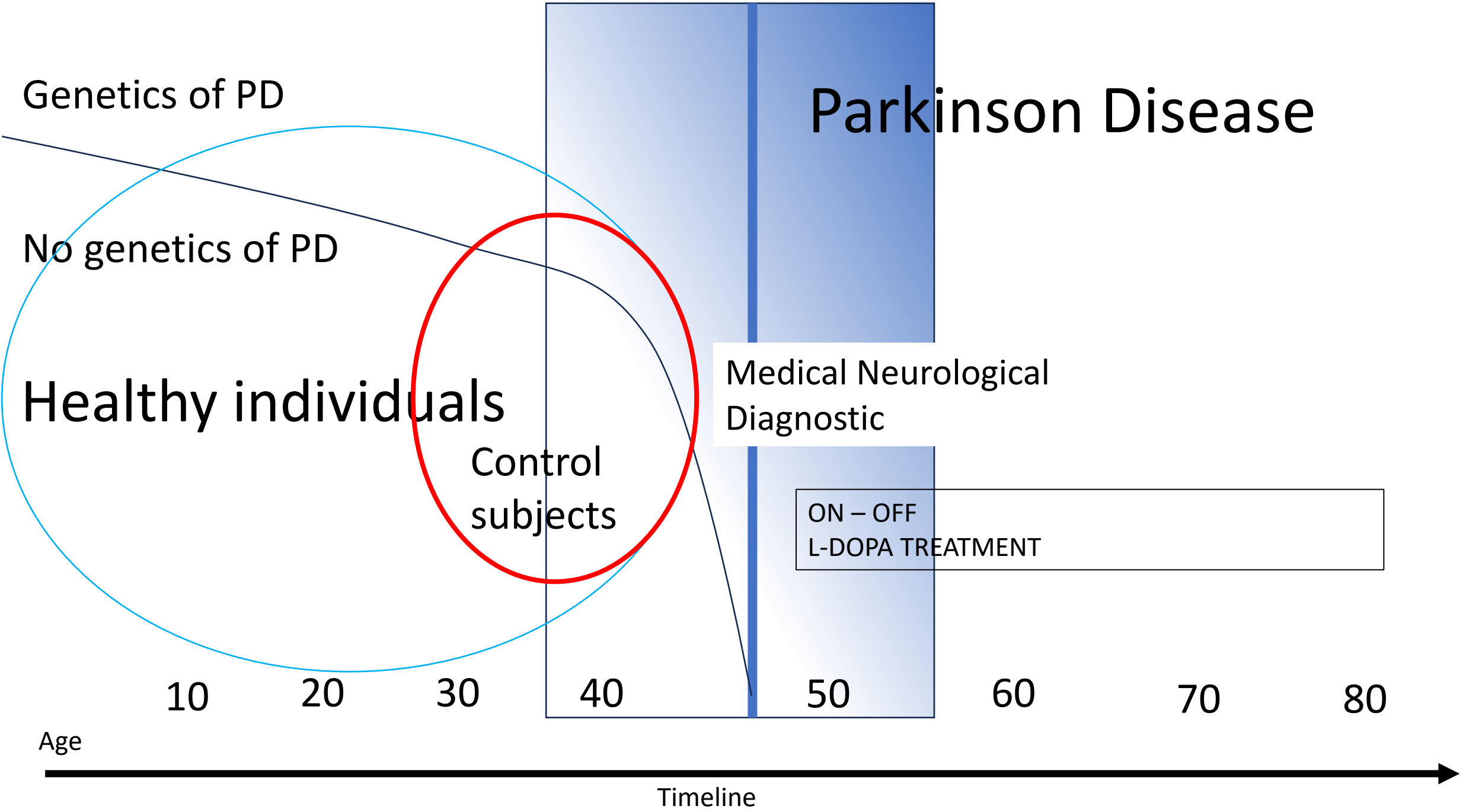
- Reliable
- Accurable
- High sensititivity and specificity (at least 90%/95%)
- Cheap
- Easy to use
- Accesible across worldwide (ideal)

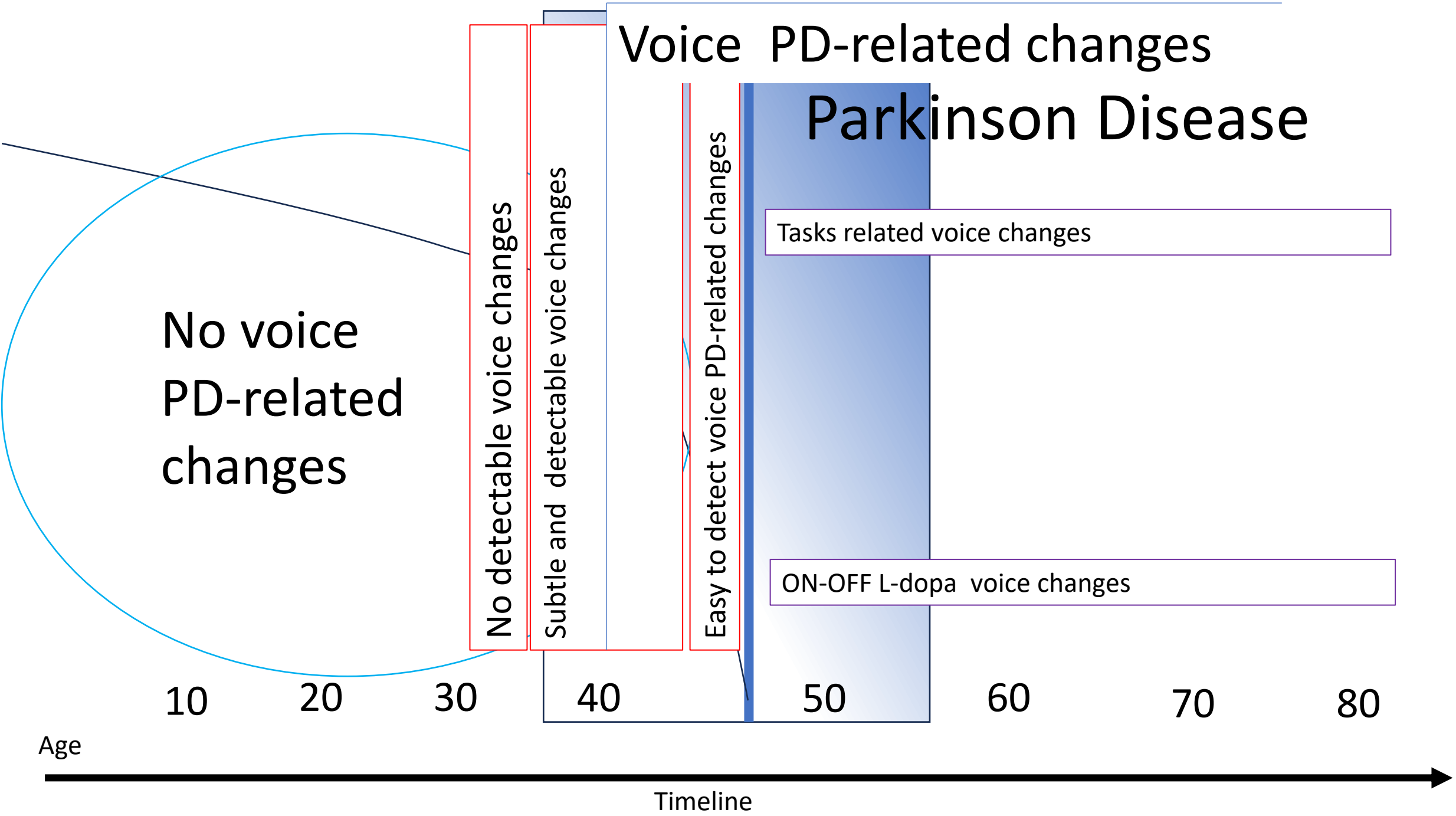
PD Prodromics

non-motor manifestations
(such as rapid eye movement sleep disorder, anosmia, constipation and depression)

First motor manifestations are very subtle:
in voice production, fingers skills, arm movement in gait


Genetics of PD
No genetics of PD
Healthy individuals
Risk factors
Medical
Phoniatrics
Screening
Parkinson Disease
Parkinsonism
Medical Neurological
Diagnostic
Pharmacologic
L-DOPA TREATMENT
Promising treatments: TMS or HIFU of deep nucleii?
10
20
30
40
50
60
70
80
Age
Timeline


Genetics of PD
No genetics of PD
Healthy individuals
Control subjects
Parkinson Disease
Medical Neurological Diagnostic
ON – OFF
L-DOPA TREATMENT
10
20
30
40
50
60
70
80
Age
Timeline


Voice PD-related changes
Parkinson Disease
No voice PD-related changes
No detectable voice changes
Subtle and detectable voice changes
Easy to detect voice PD-related changes
Tasks related voice changes
ON-OFF L-dopa voice changes
10
20
30
40
50
60
70
80
Age
Timeline

A consensus voice model exclude the posibility of only take in account acoustics measured changes?

ELS + UEP 2023 consensus guideline voice quality assesment

Seven-D model of voice assesment

VQ at baseline anamness :allergy, medical and surgical history, medication, addiction, singing practice, job, and posture

videolaryngostroboscopy (mucosal wave symmetry, amplitude, morphology, and movements),

patient-reported VQ assessment (30- or 10-voice handicap index)

perception (Grade, Roughness, Breathiness, Asthenia, and Strain)

Aerodynamics (maximun phonation time)

acoustics (Mean F0, Jitter, Shimmer, and noise-to-harmonic ratio),

clinical instruments associated with voice comorbidities (reflux symptom score, reflux sign assessment, eating-assessment tool-10, and dysphagia handicap index)

BMC – PD bm: Seven-D model of voice assesment

Apparent healthy and not PD diagnosed people

VQ at baseline anamness :allergy, medical and surgical history, medication, addiction, singing practice, job, and posture

+

Familial history of PD or parkinsonism & Another risks factors for PD

Inclusion criteria

yes

no

Risk Group

Not risk Group

exclusion criteria

History of voice impairment
Chronical or recurrent allergies
What another?

BMC – PD bm: Seven-D model of voice assesment

Apparent healthy and not PD diagnosed people

videolaryngostroboscopy (mucosal wave symmetry, amplitude, morphology, and movements)

some papers linking PD and VLS mention:

- glottic closure: incomplete / asymmetry – more the advance more notourius
- vocal fold hypoadduction/bowing – more the advance more notourius
- asymmetry in arytenoid cartilages movement –may be subtle
- Increased glottal opening time –may be subtle

Validated markers: **phase asymmetry increased**

these phenomena are likely related to rigidity or bradykinesia of the laryngeal muscles

PD-related voice changes 70-90%

Parkinson Disease

Not PD-related voice changes

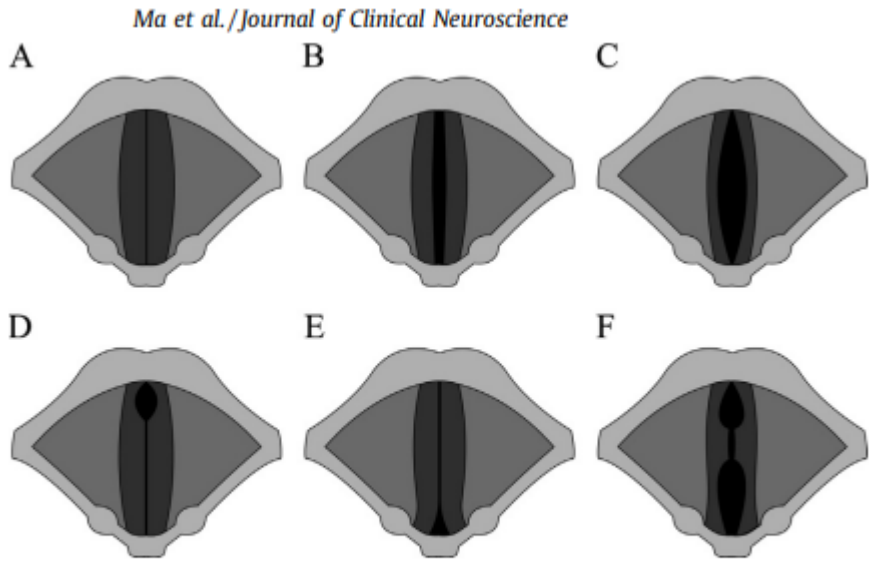


Fig. 2. Schematic diagrams of a laryngoscopic view of the larynx demonstrating the vocal fold abnormalities seen in PD. A, normal complete vocal fold closure. B, incomplete closure of the vocal folds. C, vocal fold bowing. D, anterior chink. E, posterior chink. F, hourglass deformity. Adapted from Bless et al. [47].

10 20 30 40 50 60 70 80

Age

Timeline

BMC – PD bm: Seven-D model of voice assesment

Apparent healthy and not PD diagnosed people

Other thecniques

Validated markers:

4D-CT automated measurement interarytenoyd distance reduced
threshold of detection' of early PD in a controlled study was a 0.87 mm

Laryngeal EMG: rest spontaneous activity of TA & CT muscles increased, CA reduced (intrinsic laryngeal muscles rigidness not dependent of diseases severity) asymmetry

PD-related voice changes

Parkinson Disease

Not PD-related voice changes

?

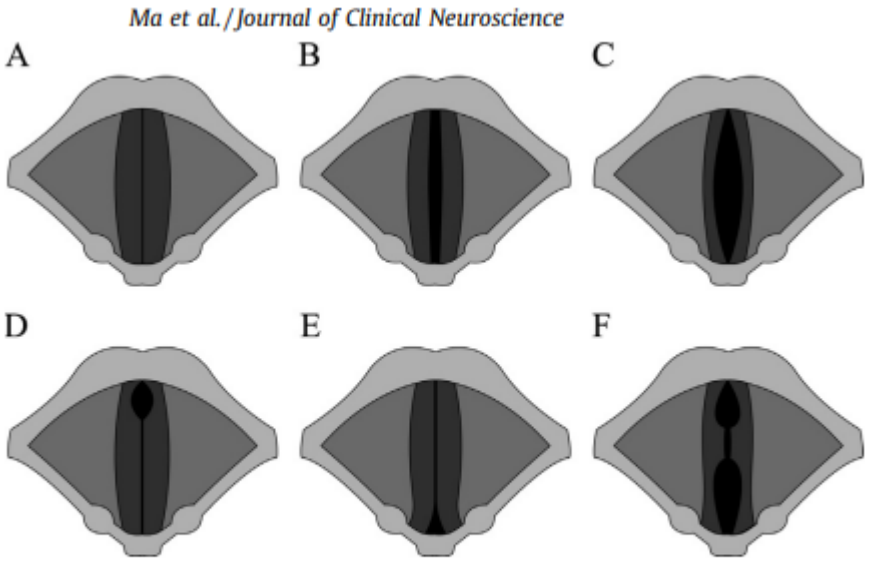


Fig. 2. Schematic diagrams of a laryngoscopic view of the larynx demonstrating the vocal fold abnormalities seen in PD. A, normal complete vocal fold closure. B, incomplete closure of the vocal folds. C, vocal fold bowing. D, anterior chink. E, posterior chink. F, hourglass deformity. Adapted from Bless et al. [47].

10 20 30 40 50 60 70 80

Age

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BMC – PD bm: Seven-D model of voice assesment

Apparent healthy and not PD diagnosed people

Have we got a VLS way to measure interarytenoid distance?

Have we got a VLS way to measure rigidity asymmetry?

BMC – PD bm: Seven-D model of voice assesment

Apparent healthy and not PD diagnosed people

patient-reported VQ assessment (30- or 10-voice handicap index)

Are there any doubt to use only VHI-30?

May the VAS patient-reported baseline help?

BMC – PD bm: Seven-D model of voice assesment

Apparent healthy and not PD diagnosed people

aerodynamics (MPT)

Are there any doubt to MPT?

Another parameters:

direct: mean sound pressure level (MSPL);

derived: mean phonatory resistance (MPR)

BMC – PD bm: Seven-D model of voice assesment

Apparent healthy and not PD diagnosed people

perception (Grade, Roughness, Breathiness, Asthenia, and Strain)

Are there any doubt to use only GRBAS?

Would be useful add I parameter to get a GIRBAS scale?

BMC – PD bm: Seven-D model of voice assesment

clinical instruments associated with voice comorbidities (reflux symptom score, reflux sign assessment, eating-assessment tool-10, and dysphagia handicap index)

This instruments would provide exclusión criteria

reflux symptom & sign lead to consider posible confounding causes of subtles changes in acoustics parametere no direct linked to PD

EAT-10 & DHI excluded more advanced compromise. Otherwise, subtle dysphagia symptoms could be so early as voice changes: **DISCUSSION POINT**

BMC – PD bm: Seven-D model of voice assesment

acoustics (Mean F0, Jitter, Shimmer, and noise-to-harmonic ratio)

Amount of papers validating AVA parameters studying PD

Parameters	Total
F0 (+stnd. dv.)	**40**
JITTER APS/%	**29**
Intensity	**24**
SHIMMER APS/%	**23**
HNR	**23**
Spekt LTAS	9
SNR	8
CEPSTRUM	5
VRP	4

Source: Pedersen and Girelli, 2nd BMC meeting CMC

Usual AVA parameters are short term

Long-term are les s studied

More complex parameters are barely studied

BMC – PD bm: Seven-D model of voice assesment

acoustics (Mean F0, Jitter, Shimmer, and noise-to-harmonic ratio)

Glottal to noise excitation ratio (GNE)
Normalised pitch period entropy (Norm. PPE)
Detrended fluctuation análisis (DFA)
Glottal closing quotient (ClQ)

BMC – PD bm: Seven-D model of voice assesment

acoustics (Mean F0, Jitter, Shimmer, and noise-to-harmonic ratio)

As in another dysphonic periodic voice short term parameters are more altered while more advanced is a disease, either inflammatory, degenerative, etc. until voice turns in aperiodic one

There is a continuum from normal voice to aperiodic voice through dysphonic periodic voice

Preclinical or prodromics PD we want to detect with screening is more near of normal than dysphonic, then, short term parameters could be not altered yet

*Short/long term refers to signal analysis window length

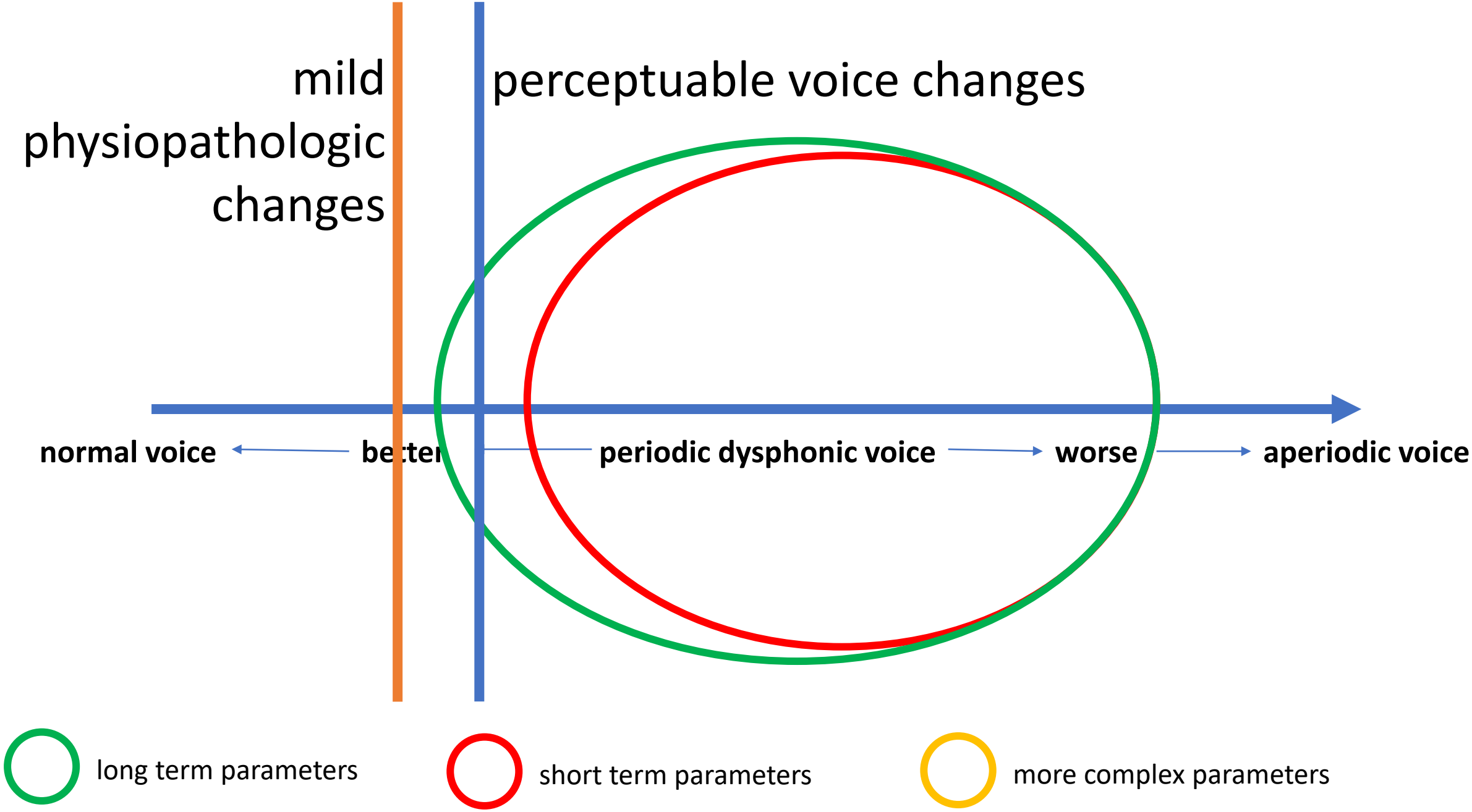
BMC – PD bm: Seven-D model of voice assesment

acoustics (Mean F0, Jitter, Shimmer, and noise-to-harmonic ratio)

Long term parameters would be more useful to detect subtle an incipient changes as occurs in any others voice screening situations like occupational voice screening

LTAS, CPP and all related variant parameters

*Short/long term refers to signal analysis window length

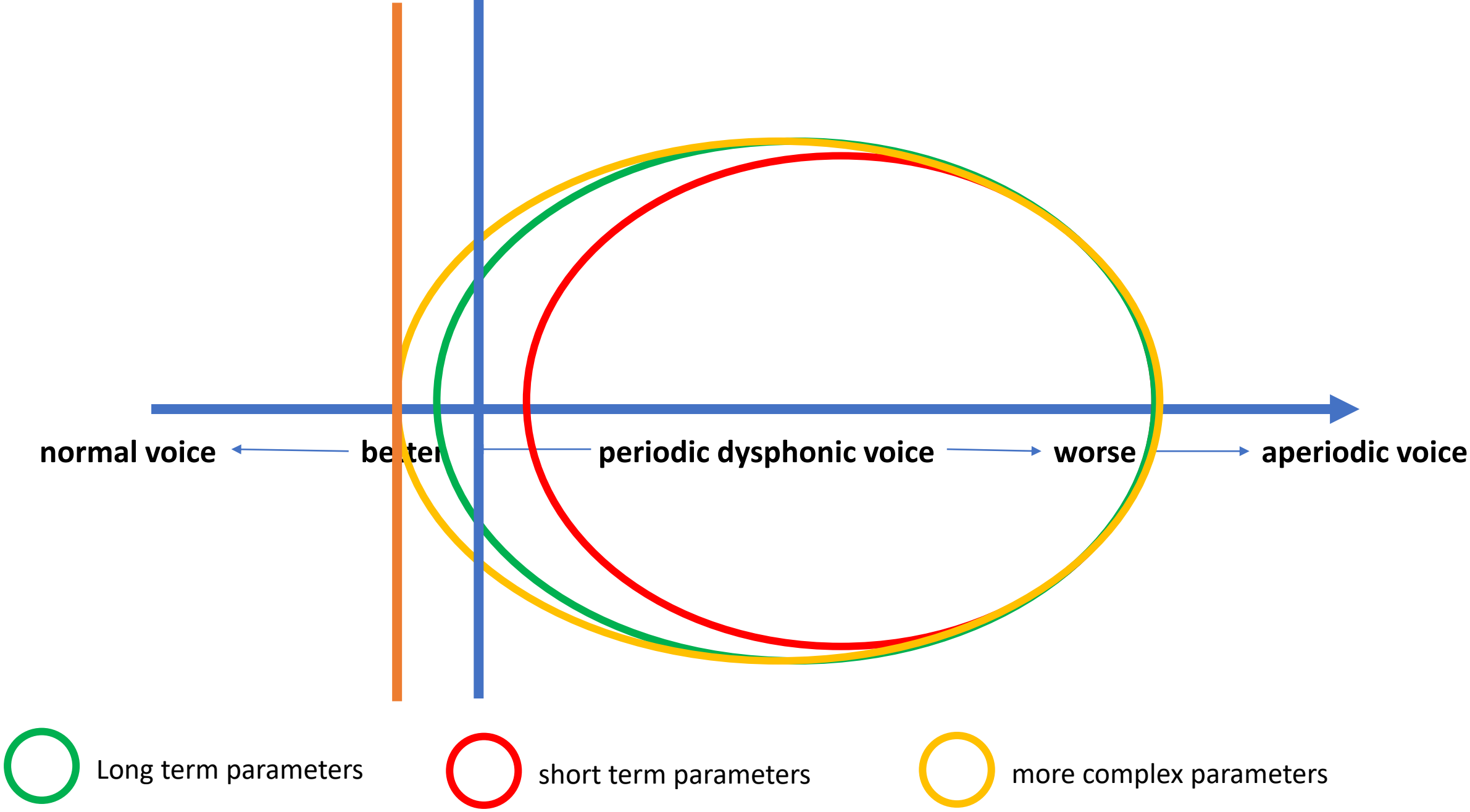

mild
physiopathologic
changes
perceptuable voice changes
normal voice
periodic dysphonic voice
worse
aperiodic voice
long term parameters
short term parameters
more complex parameters

BMC – PD bm: Seven-D model of voice assesment

acoustics (Mean F0, Jitter, Shimmer, and noise-to-harmonic ratio)

Other more complex as

Fractal dimension (FD)
Normalized mutual information (NMI)


normal voice
periodic dysphonic voice
worse
aperiodic voice
Long term parameters
short term parameters
more complex parameters

biosensors

MDPI

Article

Complexity Measures of Voice Recordings as a Discriminative Tool for Parkinson's Disease

Rekha Viswanathan [1], Sridhar P. Arjunan [2,*], Adrian Bingham [1], Beth Jelfs [1], Peter Kempster [3], Sanjay Raghav [1,3] and Dinesh K. Kumar [1]

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three different sustained phonemes have been investigated:
/a/, /u/ and /m/

the voice in PD has reduced complexity compared with CO

NMI and FD outperform other features (GNE, NPPE, DFA, CIQ) in differentiating between CO and PD

of the three phonemes tested, /m/ was the most suitable for screening and /a/ was the least suitable

Another tools, not ELS-UEP VQ assesment model

Hypomimics eye blinking shows significant statistics value in differentiating control /early PD

acoustic pharyngometry PD had smaller glottal area and oropharyngeal junction area than healthy people.

npj | parkinson's disease

Article | Open access | Published: 29 October 2022

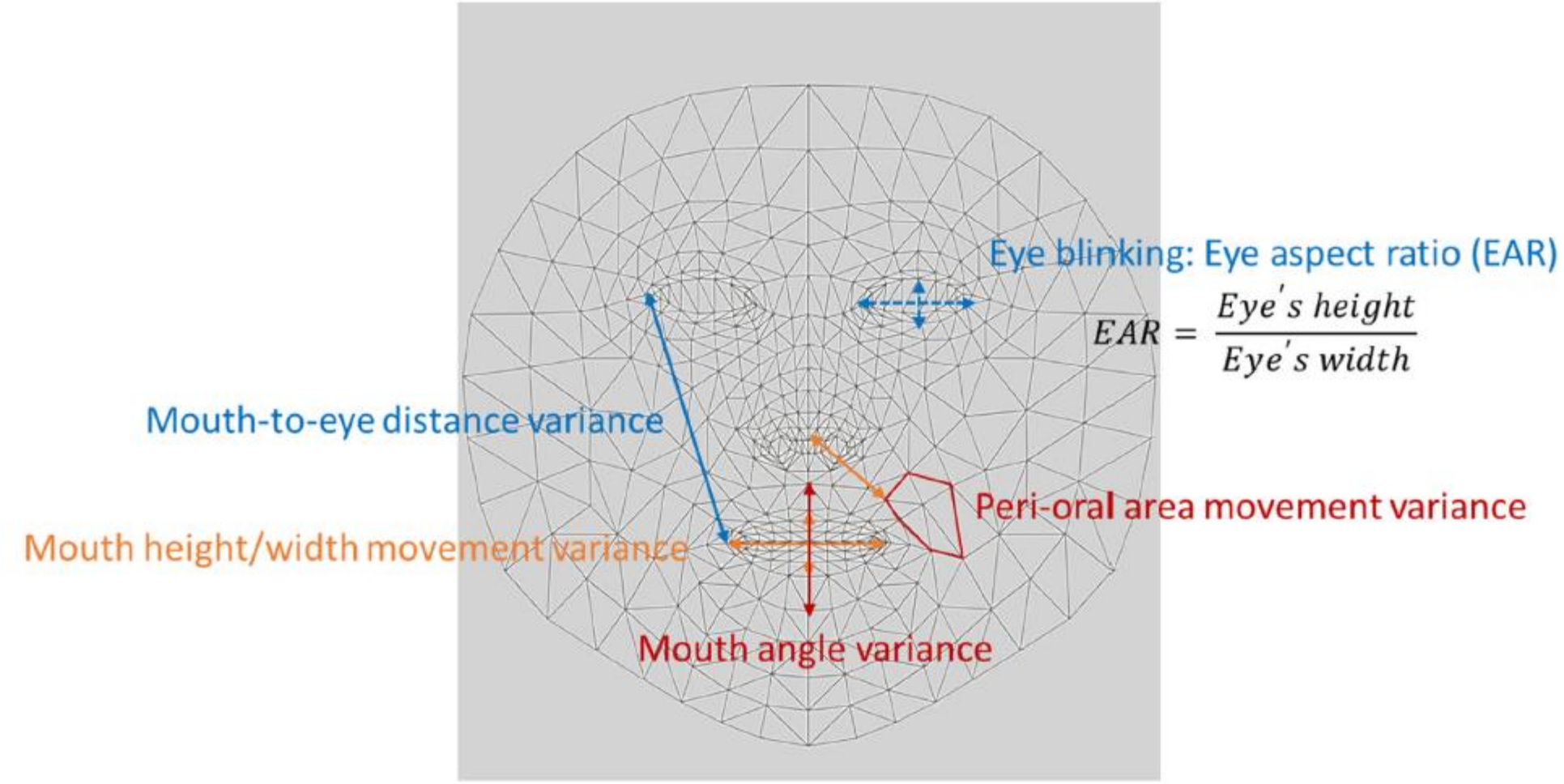
An integrated biometric voice and facial features for early detection of Parkinson's disease

Wee Shin Lim, Shu-I Chiu, Meng-Ciao Wu, Shu-Fen Tsai, Pu-He Wang, Kun-Pei Lin, Yung-Ming Chen, Pei-Ling Peng, Yung-Yaw Chen, Jyh-Shing Roger Jang & Chin-Hsien Lin ✉

npj Parkinson's Disease **8**, Article number: 145 (2022) | Cite this article

Abstract

Hypomimia and voice changes are soft signs preceding classical motor disability in patients with Parkinson's



Eye blinking (with different thresholds): the total time spent blinking the eyes during the 30-s recordings. We applied the eye aspect ratio (EAR) to determine whether the eye had blinked. The EAR was calculated as the eye height divided by the eye width. We calculated the rolling average of EAR values within every 30 frames (1 s/frame). An eye blink was defined as a valley with a lower value than the overall EAR mean (thresholds: 30, 50, 70, and 90% of the mean value). Once the total eye blinking time was acquired, the value was divided by the total frame number.

Conclusions

Our model must be based upon ELS + UEP 2023 consensus guideline voice quality assesment

Anamnesis: agree which indicators/background will be used for inclusion and exclusion criteria

Clinical instruments for voice comorbidities: reflux symptom score, reflux sign assessment, eating-assessment tool-10, and dysphagia handicap index will provide exclusión criteria

Conclusions

Validated markers in previous VA/PD (cont.) are:

- phase asymmetry (VLS)
- individual voice self-reported (VHI-30)
- perception (GRBAS)
- F0 mean, SDF0; jitter; shimmer; intensity; HNR; GNE, SNR, NPPE; LTAS; CPP (AVA-Praat software)
- Maximun phonation time; mean sound pressure level (MSPL);
- derived: mean phonatory resistance (MPR)

Conclusions

non voice markers cross-validated with voice parameters in previous VA/PD (cont.) are:

Eye-blink (as measured and described in: Shim Lim et al, 2022)

OPJunction area; glotal area (as m.&d. in: Souza et al 2022)

I brought these aspects up because I observed that published research strives to show that a cross *voice/other motor* function analysis could be more effective than voice analysis alone (this is a point to keep in mind)

Discussion