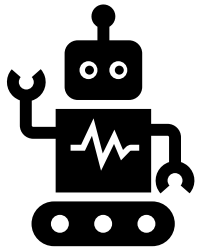
2nd UEP/EAP-BLA joint meeting

Zagreb, May 23-25th 2024

Voice related biomarkers

Mieke Moerman



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Voice related biomarkers

the UEP biomarkercommittee:

Ahmed	Abdelgoad
Neveen	Nashaat
Valentina	Camesasca
Daniele	Farneti
Ramon	hernandez Villoria
Ilona	Kaminska
Gavkhar	Khaydarova
Mieke	Moerman
Haldun	Oguz
alberto	Paderno
Mette	Pedersen
Virgilijus	Uloza
Necati	Enver
Das	Sneha

Definition

Biomarker

In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as
“a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”

Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers.

prognostic/predictive value & monitoring value

Definition

1. Specificity

Definition

1. Specificity

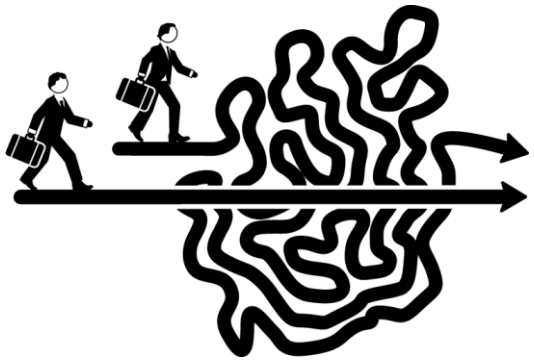
2. Effectiveness

Definition

1. Specificity

2. Effectiveness

3. Efficiency



Author(s)	Year	Title	Abstract
Idrisoglu et al.	2023	Applied Machine Learning Techniques to Diagnose Voice-Affecting Conditions and Disorders: Systematic Literature Review	This systematic literature review (SLR) investigated the state of the art of voice-based diagnostic and n
Worasawate et al.	2023	Classification of Parkinson's Disease from Smartphone Recording Data Using Time-frequency Analysis and Convolutional Neural Network	A total of 29,798 ten-second voice recordings on smartphone from 4,051 participants were used for th
Alghandi et al	2022	Neurogenerative Disease Diagnosis in Cepstral Domain Using MFCC with Deep Learning	From the German corpus Saarbruecken Voice Database (SVD), we used voice recordings of sustained v
Ngo et al	2022	Computerized analysis of speech and voice for Parkinson's disease: A systematic review	
Ma et al	2021	Deep dual-side learning ensemble model for Parkinson speech recognition	
Sahandi et al	2021	Exploring Test-Retest Reliability and Longitudinal Stability of Digital Biomarkers for Parkinson Disease in the m-Power Data Set: Cohort Study	Among the features differing between PD and HC, only a few tapping and voice features had good to e
Jeancolas et al	2021	X-Vectors: New Quantitative Biomarkers for Early Parkinson's Disease Detection From Speech	Several experimental and methodological aspects were tested in order to analyze their impacts on clas
Gupta et al	2021	Residual Neural Network precisely quantifies dysarthria severity-level based on short-duration speech segments	
Arora et Tsanas	2021	Assessing Parkinson's Disease at Scale Using Telephone-Recorded Speech: Insights from the Parkinson's Voice Initiative	Using robust feature selection methods we selected 27 dysphonia measures to present into a radial-ba
Yaman et al	2020	Automated Parkinson's disease recognition based on statistical pooling method using acoustic features	
Solana-Lavalle et al	2020	Automatic Parkinson disease detection at early stages as a pre-diagnosis tool by using classifiers and a small set of vocal features	
Sisto et al	2020	Lateralization of cochlear dysfunction as a	The observed asymmetry in the audiological response of patients with Parkinson's disease suggests tha
Tougui, Jilbab & El Mhamdi	2020	Analysis of Smartphone Recordings in Time, Frequency, and Cepstral Domains to Classify Parkinson's Disease	We present our methodology in which we distinguish PD patients from healthy controls (HC) using a lar
Tracy et al.	2020	Investigating voice as a biomarker: Deep phenotyping methods for early detection of Parkinson's disease	We analyzed a database of PD patient and non-PD subjects containing voice recordings that were used
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Upadhya	2019	Thomson Multitaper MFCC and PLP voice features for early detection of Parkinson disease	
Moro-Velazquez et al	2019	A forced gaussians based methodology for the differential evaluation of Parkinson's Disease by means of speech processing	
Ma, Lau & Thyagarajan	2019	Voice changes in Parkinson's disease: What are they telling us?	This review focuses on characterizing the voice changes in PD. These stand as a promising area of enqu
Postuma	2019	Voice changes in prodromal Parkinson's disease: Is a new biomarker within earshot?	This in an editorial. Set that there are probably three crucial next steps to establishing these
Wu et l	2018	Learning acoustic features to detect Parkinson's disease	
Montaña et l	2018	A Diadochokinesis-based expert system considering articulatory features of plosive consonants for early detection of Parkinson's disease	
Singh et Su	2018	RobustDetectionofParkinson'sDiseaseUsingHarvestedSmartphoneVoiceData: ATelemedicineApproach	
Califf, R.	2018	Biomarker definitions and their applications	A minireview farmacologic focused, explore the distinctions between biomarkers
Fuellen et al	2018	Health and Aging: Unifying Concepts, Scores, Biomarkers and Pathways	We define biomarkers of health by their attribute of predicting future health better than chronological
Rüttiger, Zimmermann and Knipper	2017	Biomarkers for Hearing Dysfunction:	We introduce functional and molecular biomarkers that are useful for categorizing
Galaz et al	2016	Prosodic analysis of neutral, stress-modified and rhymed speech in patients with Parkinson's disease	
Rektorova et al	2016	Speech prosody impairment predicts cognitive decline in Parkinson's disease	
Harris et al	2016	Speech dysprosody but no music 'dysprosody' in Parkinson's disease	
Mollaei et al	2016	Sensorimotor control of vocal pitch and formant frequencies in Parkinson's disease	
Bayestehtashk et al	2015	Fully automated assessment of the severity of Parkinson's disease from speech	
Péron et al	2015	Sensory contribution to vocal emotion deficit in Parkinson's disease after subthalamic stimulation	
Miller & O´Callaghan	2015	Biomarkers of Parkinson's disease: Present and future	In this short review we will examine 1) advances in our understanding of the molecular mechanisms un
Mekyska et al	2015	Robust and complex approach of pathological speech signal analysis	
Skodda et al	2011	Instability of syllable repetition as a marker of disease progression in Parkinson's disease: a longitudinal study	

Definition

Phoniatrics

The medical discipline regarding
communication (voice, speech, language & hearing) and **swallowing** problems

The START

Glottal Function

Voice & swallowing

The three most important and highly relevant functions of the glottis are to facilitate **ventilation**, facilitate **phonation**, and provide **airway protection**.

For Whom

Prevalence of swallowing & voice problems

Individuals

1. Dysphagia: 4% adult population
2. Dysphonia: 3-9% of adults

Patients

3. Parkinson: 80%
4. Alzheimer: 84-93%
5. H&N onco: +/- 40%

For Whom

Prevalence of swallowing & voice problems

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Patients

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5. H&N onco: +/- 40%

Country	Population	# Adults (25-65j)	Dysphagia (4% of adults)	Dysphonia (5%*37,5%)
Belgium	11,6M	52%	240K	217K
The Neth	17,5M	52%	364K	328K
Germany	83M	53%	1,80M	1,5M
US	332M	65%	8,6M	6,2M

Region	Population	Parkinson	Alzheimer	H&N onco
Europe	746M	1,2M	9,7M	450K
US	332M	1M	6,2M	66K

Region	Population	Parkinson (80%)	Alzheimer (90%)	H&N onco (40%)
Europe	746M	960K	8,7M	180K
US	332M	800K	5,6M	26K

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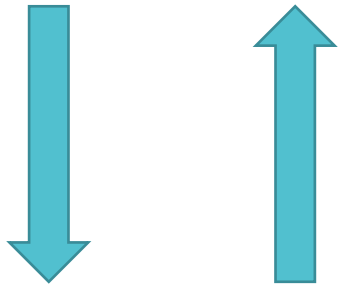
Voice related biomarkers

Disease

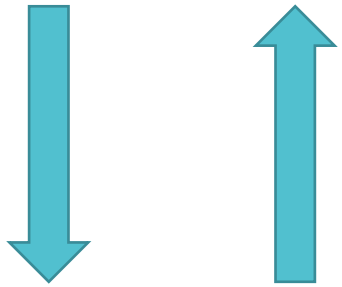


Voice Change

The Search

Voice related biomarkers

Disease



Voice Change

- Up to 78% of early stage **Parkinson-patients**
- **NDD:** early diagnostic

47 papers with Voice Parameters in Parkinson's Disease from 2013 to 2019, 3 including AI

Mette Pedersen MD PhD
and Vitus Girelli Meiner IT-
University of Copenhagen

Author	Number	Year	Patient nu	prospective	Randomize	Case/Control	Retrospective	HNR	SNR	F0(st)	Intensity	MPT	JITTER APS/%	SHIMMER APS/%	Spekt LTAS	CEPSTRUM	VRP	Telephone	Praat	VHI	GRBAS	Deep Brain.s	AI	Deep Learning	laryngoscopic	Software	Others
Louis, E. et al	98	2013	85			100	1													1							
Bauer,V. et al	97	2013	22			plus cc														1							
Péron, J. et al	96	2013				plus cc					1											1					
Bang, Y. et al	95	2013	7			7		1		1	1		1	1	1				1								
Teixeira, E. et al	94	2013	60			48				1	1																
Silbergleit, AK. et al	93	2014	27			22				1			1	1			1										
Jafari, A. et al	92		25			10		1		1							1										1
Smith, L. et al	91	2014	28			10									1												
Yang, S. et al	90	2014																					1	Kernal/SVM			
Silbergleit, AK. et al	89	2015	26			22			1			1	1				1										Cspeech Waveform Analysis Pr
Soares, DP. et al	88	2015	22				1	1		1	1		1	1													
Spazzapan, EA. et al	87	2015	19	1				1		1	1		1						1				1	peak-to peak amp var			
Tanaka, Y. et al	86	2015	108																	1	1	1				1	68 dps/40 Med
Manor, Y. et al	85	2015	21	1		11				1	1	1	1	1					1								
Tsuboi, T. et al	84	2015	47																	1	1		1	1		1	22 dps/25 Med
Crino, C. et al	83	2016										1								1							Acoust analysis
Watts, C. et al	82	2016	78				1				1																
Postuma, R.B	81	2016																									Editorial
Gillivan-Murphy, P.	80	2016	30	1		28														1						1	
Abrahao, L.J. et al	79	2016	15	1		5				1									1								Pharynx Pressure
Cannito, M.P. et al	78	2016	16				1	1							1												H1, H2, F3
Vernier, L.S. et al	77	2016																									Reaview
Neves, MRL. et al	76	2016	46					1		1	1								1		1						
Novotný, M. et al	75	2016	37	1		37																					1/3-octave band
Majdinasab, F. et al	74	2016	27	1		21		1		1			1	1					1								
Roubeau, B. et al	73	2016																		1						1	Acoustanal
Sidits, D. et al	72	2017							1	1			1	1								1					
Wu, Y. et al	71	2017								1	1												1		SVM		
Stegenmöller, E.L. et al	70	2017																									Voicequl
Parveen, S. et al	69	2017																		1							
Butala, A. et al	68	2017	30		1	32		1			1		1	1													singing, crossovers
Da Silva, V.G. et al	67	2017	10	1				1		1	1		1	1													Tube Treatment
kacha, A. et al	66	2017	205			74		1					1														No statistical difference
Lechien, J.R. et al	65	2018	20	1		10		1				1	1							1							Early diagnosis
Abur, D. et al	64	2018	16			19				1																	JND paradim, feedback
Vieira, M. et al	63	2018	23	1		20				1																	Vawel lenghtining
Motto, S. et al	62	2018	15	1		15					1	1								1							MESGP,MPR
Lechien, J.R. et al	61	2018																								1	Review, 1980-2017
Abur, D. et al	60	2018	20	1		23			1																		loudness slopes
Ko ,E.j. et al	59	2018	30									1															plus swallowing
Han, E.y. et al	58	2018										1							1	1							singing
Manor, Y. et al	57	2018	26	1		13														1	1						
Pinho, P. et al	56	2018								1	1																review 1960-2016, meta A
Gillivan-Murphy, P.	55	2019	38	1		28														1							
Shen, J. et al	54	2019	52	1		32		1		1			1	1	1					1							formant ratio
Saffarian, A. et al	53	2019	23	1	1															1							treatment
Romann, A.J. et al	52	2019	16							1												1					

51 papers with Voice Parameters in Parkinson's Disease from 2019 to 2023, 20 including AI

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Author	Number	Year	Patient nu	prospective	Randomize	Case/Control	Retrospective	HNR	SNR	F0(st)	Intensity	MPT	JITTER APS/%	SHIMMER APS/%	Spekt LTAS	CEPSTRUM	VRP	Telephone	Praat	VHI	GRBAS	Deep Brain.s	AI	Deep Learning	laryngoscopic	Software	Others
Arora, S. et al	51	2019	1483	1														1					1			Random forest	3+A51:AB10207 measures, crossover
Behroozmand, R. et al	50	2019	10		1					1			1									1					
Finger, M.E. et al	49	2019																		1							
Karlsson, F. et al	48	2019	22	1																							
Lechien, J.R. et alt	47	2019	20					1				1	1	1						1							Phonation quotient
manor, Y. et al	46	2019	104			82				1		1								1	1		1				
Sheiban, R. et al	45	2019								1													1			Class label prediction	Root Mean Score
Tamplin, J. et al	44	2020	75			44				1																	Singing, VQOL
Viswanathan, R. et al	43	2020	24			22			1	1													1			SVM	Glottal Closure qu
nakayama, K.	42	2020	24							1	1															Treatment	
Ma, A. et al	41	2020	3032																								Review
Morello; A.N.D.C	40	2020																			1	1	1			acoustanal	acoustanal
Chiaramonte, R. et al	39	2020																									Review, 14 pub, meta
Viswanathan, R. et al	38	2020	26			22																	1			LASSO ranking	
Altay, E.V. et al	37	2020																					1			nicgar, Voice data	
Park, J.E. et al	36	2020	47												1								1				Comparred to 39 tremor
Sarac, E.T. et al	35	2020	12					1		1			1	1					1								
Reyes, A. et al	34	2020	31		1							1														peak subg press	Treatment
Lechien, J.R. et al	33	2020	32			20		1		1	1																
Gaballah, A. et al	32	2021	51			51		1									1									SVR/RPDE	
Lechien, J.R. et al	31	2021		1																							Acoust meassurements
Jain, A. et al	30	2021	14																				1	1		p-CRNN	Ative phon plus pros features
Gaballah, A. et al	29	2021	51						1						1	1										svr	VAT, RPDE
Rajasekar, S.S	28	2021	23							1	1		1	1									1				AdaBoost classifier
Da Silva,j.M.S. et al	27	2021	20			20				1	1			1													treatment
Searl, J. et al	26	2021	15																	1							Vocal Monitor
Koyuncu, H. et al	25	2021	74																	1						diet	
Yasar, O.C. et al	24	2022	20					1		1			1	1	1				1				1	1			
Rajasekar, S.S	23	2022					1	1					1										1	1		lstm cnn	accuracy 85%
Suppa, A. et al	22	2022	115			108														1			1			Sup vector machine classifier	Audio recorder, LR- value
Yu, Q. et al	21	2022	80			40		1		1		1	1						1				1	1		SVM, accuracy 73%	27 voice features
Paulino, C.E.B. et al	20	2022	20			20									1	1											
Kopf, L.M. et al	19	2022	24																	1		1					Compares 12 STN/12 GPI
Vojtech, J.M. et al	18	2022	20			20																			1	utterance /ifi/	
Dos Santos, A.P. et al	17	2022	14	1	1	1				1	1					1										Voiss/V-RQOL	
Pah, N.D. et al	16	2022	50			50					1							1								SVM	Acuraccy 84%
Bao, G. et al	15	2022						1					1	1									1			PCA	SSCL, acuraccy 83%
Marchese, M.R. et al	14	2022	15							1	1	1					1			1	1						
Dao, S.V et al	13	2022																					1			GWO/LGBM	
Sapmaz, A.M. et al	12	2022	43			43		1		1		1	1	1					1	1			1			Audacity	WAS
Butala, A. et al	11	2022	26					1		1	1		1	1													singing
Lim, W.S. et al	10	2022	371															1					1			auroc	
Good, A. et al	9	2023	22							1	1		1	1					1								
Cabestany, J. et al	8	2023																									Editorial
Constantini, G. et al	7	2023	124	1		266		1	1	1	1		1	1	1				1				1	1		SVM/CFS	453 vocal features
Qiang, L. et al	6	2023	55	1		55															1						Not described accoustics
Olivares, A. et al	5	2023	20	1						1													1	1			
Silva, J. M. S. et al	4	2023	20	1		20			1	1	1		1	1													
Abraham, E. A. et al	3	2023	12	1		12				1			1	1							1						11 accoustic parameters MDVP
Lima, H. V. S. L. et al	2	2023	30			30	1		1				1	1			1										
Romero Arias, T. et al	1	2023	20	1						1		1	1	1						1	1						the Online Lab App tool?
Total			7561(23 without patienter)	25	5	1513	6	23	8	40	24	14	29	23	9	5	4	3	13	25	10	7	24	7	6	0	1

This validation is based on 7561 patients (23 papers without numbers) and 1513 controls (58 without numbers) in 98 papers from 2013 to 2023 (minus 5 reviews)

Most studies are on early and moderate cases of Parkinson's' disease. 7 papers present results of deep brain treatment

Mostly, validations in non-AI papers are:
HNR F0 intensity Jitter Shimmer and VHI
Also, in non-AI papers are:
SNR MPT Spectrography Cepstrum analysis VRP GRBAS

Praat is used in both non-AI and some AI cases. AI is used for validation in 24 papers and is often based on many more parameters

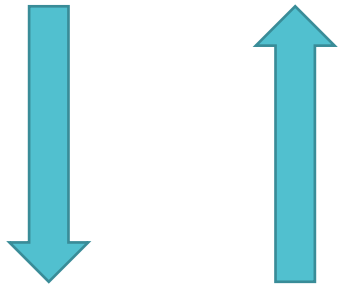
Parameters	Total
No Patient (cases)	7561 (23 without no.)
Prospective	25
Randomized	5
(Case) Controls	1513 (58 without no.)
Retrospective	6
HNR	**23**
SNR	8
F0 (+stnd. dv.)	**40**
Intensity	**24**
MPT	14
JITTER APS/%	**29**
SHIMMER APS/%	**23**
Spekt LTAS	9
CEPSTRUM	5
VRP	4
Telephone	3
Praat	13
VHI	**25**
GRBAS	10
Deep Brain.s	7
AI	**24**
Deep Learning	9
Laryngoscopy	6

Mette Pedersen MD PhD and Vitus Girelli Meiner IT-University of Copenhagen

The Search

Voice related biomarkers

Disease



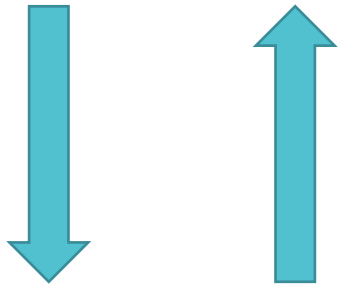
Voice Change

- Up to 78% of early stage **Parkinson-patients**
- **NDD:** early diagnostic

BUT…

Voice related biomarkers

Disease



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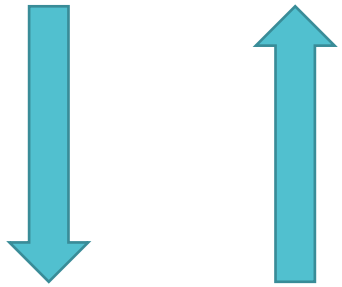
- Up to 78% of early stage **Parkinson-patients**
- **NDD:** early diagnostic
- **Alzheimer**, **cognitive** diseases: often combined with language, verbal fluency, word finding difficulties, semantic errors
- **MS** & **Reumatoid arthritis**: voice and phonatory behaviour (DBS!): >> articulation, respiration & prosody
- **Mental health & emotions**: acoustics & linguistics
- **Cardiovasc & diabetes**
- **Covid, resp condition**

Voice related biomarkers

Disease

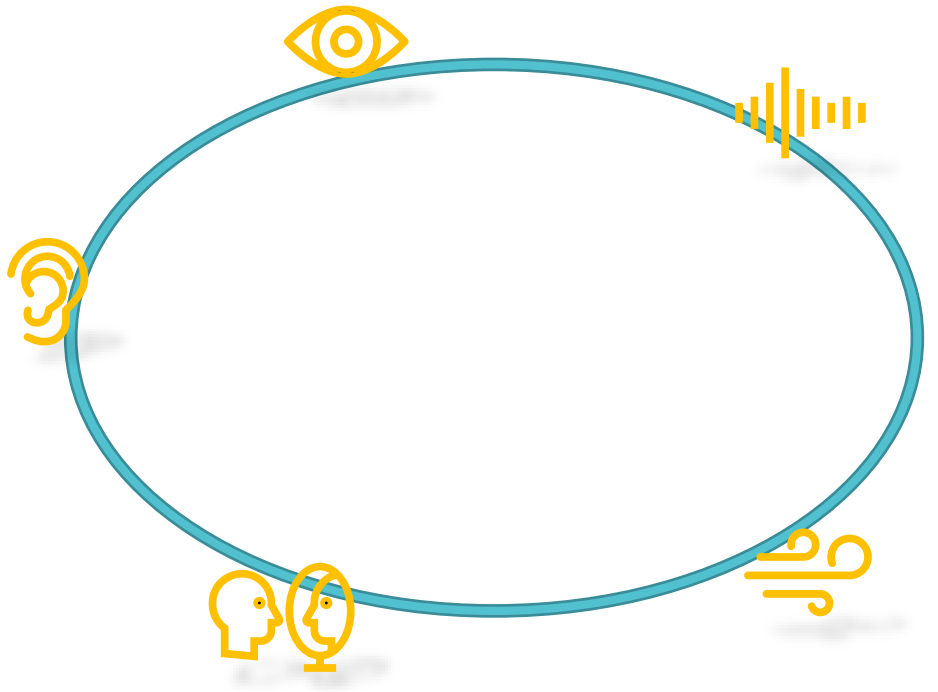


Voice Change

Voice Change (lit) ≠ Voice / glottal function

Innovation

Multidimensionality



Acoustics alone is not sufficient.
Linguistics, semantics & vocabulary, … do not reflect glottal function.

Innovation

Clinical BM_Glottal Function

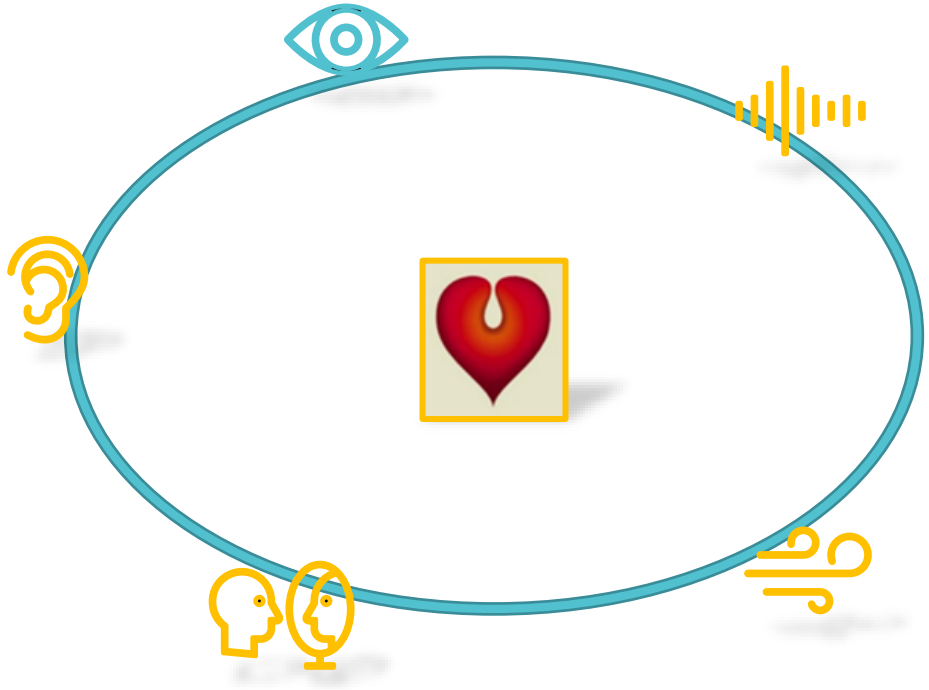
MEDTECH

Screening

Triage

Assisted diagnosis & therapy

Severity assessment



DIGITECH

IT driven medical guidance, analysis & automation

Tangible follow up

Self-management

Personalized guidance

Virtual testing
Available/Affordable/Accessible

The How

Towards a preliminary clinical protocol, suggested by the UEP BMC

1st target population

Parkinson's disease, other neuromuscular disorders

The sample

- sustained open **vowel** /a/ on a comfortable loudness and pitch
- sustained vowel /a/ as loud as possible (but no shouting)
- sustained vowel /a/ as silent as possible (but no whisper)
- sustained vowel /a/ on the highest possible pitch (chest register- no singing)
- sustained vowel /a/ on the lowest possible pitch (chest register- no singing)
- **sentence** without fricatives (for Dutch "aan die bemiddeling willen we meedoen")
- phonetically balanced **text** passage (for Dutch "Papa en Marloes"; for German "Nordwind und Sonne"; for English "The Rainbow Passage", …)

The How

Towards a preliminary clinical protocol, suggested by the UEP BMC

Important and easily accessible parameters with potential of leading to a biomarker for glottal closure

We suggest to keep **at least** the following parameters, considering their importance in the glottal closure:

- Perception: G & B from the GRBAS.
  In perspective of Voicing related parameters, the IINFVo perceptual rating scale might form an alternative (Eur Arch Otorhinolaryngol. 2006 May;263(5)
- Acoustics: NHR, Shimmer, dB, Voicing quantification parameters (Fractal Dimension, Normalized Mutual Information).
- Visualization: since this requires the intervention of a clinician, we ignore this for the moment. However, visualization of glottal closure can be used as a reference for the glottal insufficiency biomarker in a clinical trial.
- Aerodynamics: MPT, glottal closure quotient, the flow declination rate via inverse filtering (Sopran, Aalto Aparat, OnlineApp Lab tool)
- Self-assessment: specific items of the VHI linked to glottal closure/voicing.

Conclusions

Voice is different from speech and language

Voice is multidimensional

Glottal closure is vitally important

Determining a BM should be simple and straightforward, affordable, largely accessible and available

Presumably AI is needed to determine the weight of the different dimensions and to obtain an accurate BM

The committee decided to work on defining (and ultimately testing) biomarkers that reveal glottal function. And as the three most important and relevant functions of the glottis are to facilitate ventilation, to provide phonation and to protect the airways, the focus primarily lies on the glottal closure. Good glottal closure is not only necessary for a good voice, but also to prevent aspiration.

Invitation

Reflections on the suggested protocol?

Volunteers with access to NDD/parkinson's disease to participate in a clinical trial?

New members for the UEP BMC?

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