Global Innovator's Briefing: Rare Diseases

Multiple System Atrophy

*…For most rare diseases… it takes, on average, more than 5 years, 8 physicians and 2 to 3 misdiagnoses until a rare disease patient receives the correct diagnosis. **

Multiple System Atrophy (MSA)

- An atypical form of Parkinson's disease presenting initially with commonly seen symptoms (e.g., urinary incontinence, erectile dysfunction, genital hyposensitivity)
- Motor related symptoms can manifest immediately, or up to 4 years after these first more common symptoms
- Once motor symptoms manifest, average lifespan is approximately 6 years
- Typically, patients do not respond as well, to the same treatments as for Parkinson's disease
- There is no cure, and present treatments are entirely for symptom alleviation
- Typically manifests after 50 years of age in every geography with unknown cause or risk factors
- Accurate diagnosis of the disease has typically only been confirmable post-mortem

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Quote taken from: Schaefer, J., Lehne, M., Schepers, J. et al. The use of machine learning in rare diseases: a scoping review. Orphanet J Rare Dis 15, 145 (2020).

About Echino Innovator Briefings: Rare Diseases,

These briefings are designed as introductions for **early-stage innovators, covering a range of diverse rare diseases**. They are based upon freely available peer reviewed and referenced or professional information, that have been designed as a 'cog' between the two worlds of healthcare need and innovation implementation. Four are planned: some core sections will be identical throughout.

To stimulate or aid the innovator in any global geography, these introduce the state-of-the-art. the stakeholders and their interactions to anyone or any entity that is interested in innovating a solution (interventional, diagnostic, med tech, med device, digital health, healthcare process, occupational and physical therapy, patient support globalisation) for a Rare Disease, whether its social entrepreneurship, charitable or for-profit.

Why Innovator focused specific communication:
There is a knowledge gap with specific relevance to Rare Diseases between innovators and the stakeholder communities that play a pivotal and critical role in making sure innovations deliver real benefit, that has greater pertinence than more frequent diseases due to patient numbers and product development costs. It can be baffling to know where to start.

I have participated in sufficient investment committee review meetings with presentations focusing on rare diseases, often with a feeling of that only one or two stakeholders or issues have been truly considered: this makes the transition of the idea to a beneficial product or solution much more difficult.

Inversely, for an innovator to identify and understand the spectrum of knowledge needed is daunting: a significant amount of the information is very technical in content, with a broad spread across many sources and often focused on the authors immediate communities.

I have not tried to simplify the knowledge (except when it is very clinical terminology, specifically on symptoms), and always provided references. References are provided according to the schedule of people who work in innovation, where possible next to the pertinent information being discussed. For purposes of brevity, I have only indicated the first author et al, in most cases with the link (mainly to PubMed). I know this not the normal standard, but this is tailored for the audience.

References are not designed to favour any given stakeholder or KOL, nor are they are substitutes for digging much deeper if the innovator is serious. If, any KOL has felt they have been left out, this was not the intention (apologies): many more publications were read than referenced (the ones indicated by the book symbol are *suggested introductory starting points and are technical/specialised in most cases*).

The briefings were started over summer 2022, with the aim to be globally focused and comprehensive… and like all knowledge exploration exercises, the more you discover the more you realise you don't know... so they are not necessarily brief.

They do not include any specific references to standards or regulations applied in the different geographies for product development, manufacture and validation... for the innovator, this information is widely available and for you to find. They also do not include market valuations: there is sufficient information present in these briefs including the supplementary material of the references, plus easily available online price catalogues for you to do the calculation yourself. They are not competitive intelligence reports: company organisations, clinical trial databases and stock exchange company listings are good starting points to identify other commercial endeavours.

Sometimes only specific stakeholders and single geographies are prioritised with a focus on bottom-line returns, this is somewhat understandable but as a general principle Rare Disease focused work is a long-haul and avoiding care disparity is a major goal. This may require a global approach to innovation in solution pricing, and reflection on strategies related to the orphan drug legislation and designation, to make sure investment is not diluted too much on competing too-similar initiatives. A forward movement without balance between all stakeholders is a movement backwards.

Many patients with all types of rare diseases, and their caregivers have stepped up and got involved, knowing full well that their involvement will likely not generate a benefit for them in their lifetime or for the ones they care for, but may help the next generation. I don't think very many of them made that decision with another entities financial ROI as their main objective.

What these are not:
They are unfortunately not multilingual: I only had the time to write them in English. If anyone is interested in generating multilingual/multicultural sensitive versions, please reach out and I am happy to provide the original word doc. for translation.

These are **not adverts**: i.e., after reading, if stimulated, following further detailed reading that is needed first: the innovators next point of contact should be a KOL: Patient Association or a Medical Professional/Researcher.

Declaration:
I have no conflict of interest with any entity (public or private), I represent no faith or faith associated body, I represent no political view or political body, I represent nor am paid by any entity: non-profit, pharmaceutical or biotech, for these briefings.

And I am enormously grateful to the vast array of open-source publications, and authors, databases, charities, associations and NGOs that are making the knowledge and information for these long briefings freely available.

Preface: Multiple System Atrophy (MSA)

The number of patients: Estimated global prevalence

Peer reviewed reports for prevalence indicate the following

1) **3–4/100,000 people over 50:**
   Federoff M, et al 2015- **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5217460/ . Prevalence reported obtained from Bower JH, et al. Incidence of progressive supranuclear palsy and multiple system atrophy in Olmsted County, Minnesota, 1976 to 1990. Neurology. 1997;49(5):1284-8. **Link:** https://pubmed.ncbi.nlm.nih.gov/9371909/
2) **7.8/100,000 people over 40**
3) **4.4/100,000 people total**
   (Both 2 and 3 obtained from: Lee, HJet al. Models of multiple system atrophy. *Exp Mol Med* **51**, 1–10 (2019). **Link**: https://www.nature.com/articles/s12276-019-0346-8 that uses Schrag A, et al. as source. **Link**: https://pubmed.ncbi.nlm.nih.gov/10577638/.
4) **3.4/100,000 people in Iceland**.
   Bjornsdottir A, et al. Incidence and prevalence of multiple system atrophy: a nationwide study in Iceland. J Neurol Neurosurg Psychiatry. 2013;84(2):136-40. **Link:** https://pubmed.ncbi.nlm.nih.gov/23192520/
5) **4.0/100,000 people from one canton in Switzerland**
   Fleury V, et al . Descriptive epidemiology of parkinsonism in the Canton of Geneva, Switzerland. Parkinsonism Relat Disord. 2018;54:30–9. **Link**: https://pubmed.ncbi.nlm.nih.gov/29661694/
6) **5% (approx.) of patients originally diagnosed with Parkinson's Disease actually had MSA. ***
   Joutsa J, et al. Diagnostic accuracy of parkinsonism syndromes by general neurologists. Parkinsonism Relat Disord. 2014;20(8):840-4) **Link**: https://pubmed.ncbi.nlm.nih.gov/24816002/

*The latest prevalence figures for Parkinson's Disease have been reported***.**

Ou Z, et al. Global Trends in the Incidence, Prevalence, and Years Lived With Disability of Parkinson's Disease in 204 Countries/Territories From 1990 to 2019. Front Public Health. 2021;9:776847. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8688697/

*There is a sub-caveat with this assessment, as MSA exists in two '*main*' types: a parkinsonism type MSA-P, and a Cerebellar type, MSA-C. MSA-C types typically do not manifest Parkinsonism type symptoms, arguing that there may have MSA-C types missed in this study. However, MSA-P is recognised as the predominant type in the Western Hemisphere. MSA-C is understood to be more prevalent in Eastern Hemisphere (source: Orphanet). This study was done in Finland; therefore it is also fair to argue that the majority of patients with MSA would very likely have the Parkinsonism type and therefore MSA-C would not have hugely influenced this analysis.

- There has been no ethnic related prevalence reported (it appears to impact all the ethnicities with the same frequency)
- There has been no gender related prevalence reported (it impacts both genders at the same frequency)

Using the '*live population*' website **Link**: https://www.livepopulation.com we can obtain the following prevalence estimates

Age range	Africa	Asia	Europe	North America	Oceania	South America
Population >50	151,450,045	1,127,691,950	295,208,198	134,555,693	12,122,711	106,822,467
Population >40	267,142,318	1,738,958,059	397,925,763	179,948,326	173,14,298	164,791,304
Total population	1,340,103,338	4,598,426,260	739,725,262	371,268,609	42,131,266	438,126,101
3–4/100k >50	6,058	45,107	11,808	5,382	484	4,272
7.8/100k >40	20,837	135,638	31,038	14,035	1,350	12,853
4.4/100k total	58,964	202,330	32,547	16,335	1,853	19,277
4.0/100k total	53,604	183,937	29,589	14,851	1,685	17,525
3.4/100k total	45,563	156,346	25,150	12,623	1,432	14,896
Median value	45,563	156,346	29,589	14,035	1,432	14,896

From the publication of Ou Z et al, and Joutsa J et al, we could have the following prevalence possibilities:

	Africa	Asia	Europe	North America	Oceania	South America
Number of identified patients with Parkinson's Disease	554,000	4,453,000	1,753,000	956,000	76,400	281,000
Estimated Prevalence at 5%	27,700	222,650	87,650	47,800	3,820	14,050

Table 1: Possible prevalence range to be used for innovation design

	Africa	Asia	Europe	North America	Oceania	South America
Possible range of prevalence	27,700 – 45,563	156,346 – 222,650	29,589 – 87,650	14,035 – 47,800	1,432 – 3,820	14,050 – 14,896
As a % of population >45 – <70 years of age	0.016–0.026	0.013–0.018	0.012–0.035	0.012–0.041	0.013–0.035	0.013–0.014

Lo RY. Epidemiology of atypical parkinsonian syndromes. Tzu Chi Med J. 2021 Jan 19;34(2):169-181. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9020244/

Part 1:

The Patients' Journey

'Symptoms, Diagnoses and Treatment'

'*Diagnostic odyssey*' can be found in some articles and publications that refer to experience's patients with rare disease and their caregivers frequently go through from first symptom manifestation to a confirmed diagnosis.

In Part 1, in the context of MSA this is explained why this can happen: The innovator should be aware similar long processes have happened for many other patients with different rare diseases.

'

The full diagnosis of multiple system atrophy is usually reached within 5 years ***after*** *the onset of neurogenic orthostatic hypotension'*

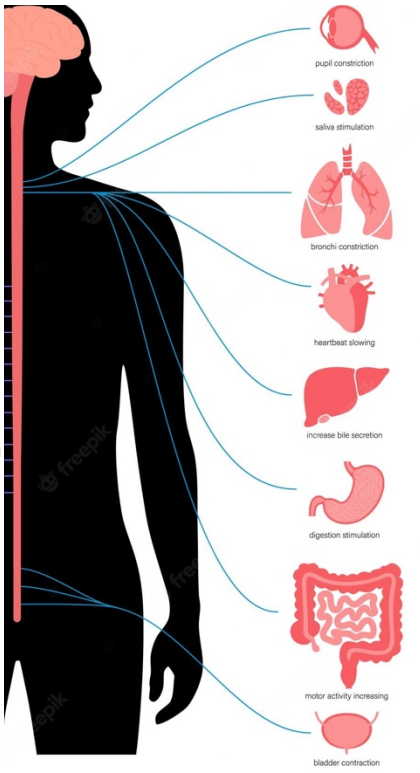
Palma JA, et al. Diagnosis of multiple system atrophy. Auton Neurosci. 2018;211:15-25.**link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5869112/

MSA Overview: pathophysiology, pathogenesis and symptoms

We all have an autonomic nervous system which is the neurological infrastructure inside of each of us responsible for subconscious actions. Examples of these actions include:

- Breathing
- Digestion
- Digestive control
- Heart beat
- Sexual arousal
- Bladder control

Schematic of central nervous system and examples of autonomic role



See **link** https://www.ncbi.nlm.nih.gov/books/NBK539845/)

In MSA, the neural cells responsible for running the autonomic nervous system accumulate a misfolded version of a protein, called alpha-synuclein that normally regulates neural signaling.

The misfolded protein creates aggregates that are insoluble and accumulate within the neural cell (Glial Cytoplasmic Inclusions), causing disruption and cell death.

Diseases in which this happens are called 'alpha-synucleinopathies'.

The process occurs over varying periods of time, giving rise to slow neurodegeneration that manifests as specific symptoms.

In MSA, the aggregates accumulate in specific neural cells, called Glia, located in the brain. Depending in which part of the brain the majority of this happens in, results in two main types of MSA: MSA-P, and MSA-C.

MSA-P type: (The P stands for Parkinsonian). Majority of cells damaged are in the striatonigral part of the brain: this part is responsible for enabling balance and movement. When this part is damaged symptoms include slow movement, slurred speech, instability and rigidity.

MSA-C type: (The C stands for Cerebellar). Majority of cells damaged are in the olivopontocerebellar part of the brain. This contains the Cerebellum, the Pons and the Inferior Olives. These parts of the brain are involved in the management of breathing, sleeping and waking, fine motor control, coordination and keeping balance.

Because it is a majority, not exclusive damage, patients with the different types of MSA have several overlapping symptoms and also unique ones.

MSA-P has been reported to have a greater prevalence in the western hemisphere, while MSA-C in the eastern hemisphere.

The mean age of onset is between 54 and 63 years for the majority of patients: it has never been seen before the age of 30, and rarely before 40 (termed Young-onset).

From the initiation of typically motor function related symptoms, the mean survival time is 6 years: death typically happens because of urinary tract infections transitioning to blood septicaemia, or respiratory failure, or cardiopulmonary arrest (sudden death).

The first manifested symptoms are rarely motor related (clearly identifiable slow movement, rigidity, or fine motor control) but rather symptoms that can occur for a significant amount of diseases health care practitioners (HCP) routinely see in clinic.

Patients can have MSA for up to 4 years or longer with non-motor symptoms before motor symptoms start to manifest.

MSA risk factors and aetiology

- Occurs completely idiopathically and sporadically (MSA can just develop for unknown reasons in anyone). The stimulus for the misfolding of the alpha-synuclein is not known.
- It does not appear to be hereditary, as no direct family links have been identified. There is no clear genetic indication.
- There have been observed changes in several genes (creation of new variants), that may be the clearest risk factor for developing the disease.
- It has been speculated that exposure to pollutants such as plastics and metal, and certain types of solvent may be linked to the aetiology of the disease, but nothing conclusive has yet been proven.

Symptoms of MSA-P vs MSA-C (non-exhaustive)

Source: Data in table below obtained from Orphanet 'rare diseases: clinical signs and symptoms'. For purpose of brevity, symptoms summarised and indicated by organ. The complete list can be found at the original source https://www.orpha.net/consor/cgi-bin/Disease_HPOTerms.php?lng=EN with a detailed explanation of the data.

Table 2: Symptoms observed in Multiple System Atrophy types

Frequency (%)	Symptoms observed in MSA-P and MSA-C
30–79	**Physical/Motor**: Frequent falls, Postural instability, Orthostatic syncope (fainting due to orthostatic hypotension), Orofacial dyskinesia (involuntary movements in mouth/face), Abnormal pyramidal sign, Axial dystonia (abnormal trunk posture), difficulty swallowing food (dysphagia) **Sexual:** Erectile dysfunction, Female genital hyposensitivity **Gastrointestinal**: Constipation, bladder dysfunction **Cognitive**: Abnormal rapid eye movement sleep **Vascular:** Orthostatic hypotension (low blood pressure when standing) Raynaud phenomenon (decreased blood flow to fingers) **Mental Health**: Depressivity, Anxiety, Apathy **Respiratory:** Stridor (irregular flow of air resulting in noisy breathing), Central sleep apnea (breathing repeatedly stops and starts while sleeping)
5–29	Camptocormia (spinal muscle atrophy)

Frequency (%)	MSA-P associated	MSA-C associated
30–79	Parkinsonism, Rigidity Bradykinesia (slowness of movement) Resting tremor	Gaze-evoked nystagmus (eye jumping movement) Dysarthria (slurred speech) Dysphonia (vocal disorders) Gait ataxia (wide paces with truncal instability) Limb ataxia (upper limb tremor)
5–29	Dysarthria (slurred speech) Gait ataxia (wide paces with truncal instability) Postural tremor	Parkinsonism Rigidity Bradykinesia (slowness of movement) Resting tremor

All the symptoms experienced by patients with MSA do not occur simultaneously: they can occur independently and then overlap, with variations between patients

Pathogenesis (disease progression)

The general pathogenesis of MSA, and its phases detailed below are generalised. Degenerative disorders and their progression are patient specific with fluctuating severity. Symptoms once started tend to continue throughout all the phases.

Table 3: Symptoms observed during phases of Multiple System Atrophy pathogenesis

Phase	Time from premotor manifestation (years)	Observed manifested symptoms that continue for duration of the diseases
Premotor	First symptom: t=0	Sexual dysfunction Urinary dysfunction REM sleep behaviour disorder Orthostatic hypotension
Possible MSA	0–3 years	Stridor, Parkinsonism, Cerebellar features, pyramidal signs, multidomain autonomic failure
Probable MSA	1.5–9 years (Overlaps with possible)	Pyramidal signs, multidomain autonomic failure, recurrent falls, indwelling catheter, frontal executive dysfunction, unintelligible speech, gastrostomy, tracheostomy, bronchopneumonia, uroseptic fever, sudden death
Established MSA to end-of-life	6 years–end of life (Overlaps with probable)	Indwelling catheter, frontal executive dysfunction, unintelligible speech, gastrostomy, tracheostomy, bronchopneumonia, uroseptic fever, sudden death

Table based upon data from: Fanciulli A, et al: link below

The rarity of the indication, and the consequential low number of patients, also means that knowledge is routinely generated and updated based upon published reports, as indicated in the references indicated below.

Fanciulli A, Wenning GK. Multiple-system atrophy. N Engl J Med. 2015;372(3):249-63. **Link**: https://pubmed.ncbi.nlm.nih.gov/25587949/

Monzio Compagnoni, G et al. Understanding the pathogenesis of multiple system atrophy: state of the art and future perspectives. *acta neuropathol commun* **7**, 113 (2019). **Link:** https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-019-0730-6

From an HCPs perspective and first patient contact at the family doctor, who may not be specialised in neurodegenerative disorder, these symptoms can also overlap with other rare and more frequent alpha-synucleinopathies.

'Given its varied clinical manifestation, MSA is frequently misdiagnosed, especially at disease onset. An autonomic presentation of MSA can be indistinguishable from pure autonomic failure (PAF). PAF is currently considered an idiopathic, sporadic, rare neurodegenerative disorder characterized by autonomic failure without other neurological symptoms or signs'

Chelban V, et al. An update on MSA: premotor and non-motor features open a window of opportunities for early diagnosis and intervention. J Neurol. 2020;267(9):2754-2770.Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7419367/

Pure Autonomic Failure (PAF: source Orphanet)

Also, sporadic and idiopathic, with unknown etiology: typically starts in adults >60 years of age, with higher frequency in males. Similar to MSA, first observed symptoms are urinary incontinence and erectile dysfunction.

Table 4: Symptoms observed in Pure Autonomic Failure

Frequency (%)	Some of the symptoms that could overlap or appear to with MSA types
80–99	Orthostatic hypotension (low blood pressure when standing), dysautonomia, constitutional symptom, abnormal levels of circulating catecholamine, Anhidrosis (absence of sweating)
30–79	Feinting, Bladder dysfunction (Urinary incontinence), Constipation, Dysuria (painful urination)
5–29	Erectile dysfunction

Hereditary late-onset Parkinson disease (HLOP: source Orphanet)

Occurs in 10% of confirmed Parkinson's disease cases, manifesting at 50-years of age and older. This overlaps with MSA and its prevalence is higher than MSA in the Parkinson's disease population, but very few Parkinson's diagnostic algorithms indicate genetic testing. In LMIC it is also unknown how many molecular diagnostic services are available.

Table 5: Symptoms observed in Hereditary late-onset Parkinson disease

Frequency (%)	Some of the symptoms that could overlap or appear to with MSA types
100	Parkinsonism
30–79	Resting tremor, Frequent falls, Bladder dysfunction, Constipation, Sexual dysfunction
5–29	Anxiety, Depressivity, Apathy Dystonia (repetitive or twisting movements), Rigidity, Bradykinesia (slowness of movement), Postural instability, Shuffling gait Orthostatic hypotension (low blood pressure when standing)

The more frequent alpha-synucleinopathy sporadic **Parkinson's disease** may potentially present with similar symptoms,

There are also other atypical Parkinson's diseases at disease onset, that are not alpha-synucleinopathies. (e.g., Peripheral Supranuclear Palsy, Dementia with Lewy Bodies, Corticobasal syndrome) in which there may be some symptom overlap.

Many of the initial symptoms have a multitude of reasons for manifestation in the age group in which MSA occurs, and patients with MSA, representing such a low percentage of the population that the primary care HCP will see, can mean significant delays to accurate diagnosis.

Monzio Compagnoni, G, et al. Understanding the pathogenesis of multiple system atrophy: state of the art and future perspectives. *acta neuropathol commun* **7**, 113 (2019).**Link:** https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-019-0730-6

Shin HW, et al. Clinical Aspects of the Differential Diagnosis of Parkinson's Disease and Parkinsonism. J Clin Neurol. 2022;18(3):259-270. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9163948/

Koga S, et al. Neuropathology and molecular diagnosis of Synucleinopathies. Mol Neurodegener. 2021;16(1):83. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8684287/

Wenning GK, et al. The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy. Mov Disord. 2022;37(6):1131-1148.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9321158/

Palma JA, et al. Diagnosis of multiple system atrophy. Auton Neurosci. 2018;211:15-25. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5869112/

Marmion DJ, et al. A historical review of multiple system atrophy with a critical appraisal of cellular and animal models. J Neural Transm (Vienna). 2021;128(10):1507-1527. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8528759/

Abos A, et al. Differentiation of multiple system atrophy from Parkinson's disease by structural connectivity derived from probabilistic tractography. Sci Rep. 2019;9(1):16488.**Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6848175/

Jellinger KA. Heterogeneity of Multiple System Atrophy: An Update. Biomedicines. 2022;10(3):599.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8945102/

MSD manuals: Multiple System Atrophy Professional version: https://www.msdmanuals.com/professional/neurologic-disorders/autonomic-nervous-system/multiple-system-atrophy-msa?query=Multiple%20System%20Atrophy%20(MSA)

Patient education version: https://www.msdmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/autonomic-nervous-system-disorders/multiple-system-atrophy-msa?query=Multiple%20System%20Atrophy%20(MSA)

The diagnostic journey of MSA

'Up to 75% of MSA cases have a prodromal phase with non-motor symptoms, such as cardiovascular autonomic failure, orthostatic hypotension, urogenital and sexual dysfunction, REM-sleep behavior disorder, and respiratory disorders. These may precede the motor presentation by months to years'

Chelban, V., et al. An update on MSA: premotor and non-motor features open a window of opportunities for early diagnosis and intervention. J Neurol 267, 2754–2770 (2020). **link**: https://link.springer.com/article/10.1007/s00415-020-09881-6

1. Primary Care: For almost all patients, independent of geography, the first visit is the nearest clinic to talk with a family doctor, community health worker or registered nurse.

They will likely not be specialists in rare neurodegenerative disorders, and will understandably err towards the more frequent indication, or which symptom seems predominant.

Following which interventions will be prescribed, or the patient referred onto a hospital based or specialty clinic-based doctor, who is expert in the indication linked to the symptom.

Table 6: Estimated HCP personnel per 10,000 population*

Region	Family doctors (GPs)	Nurses	Community Health Workers	Pharmacists*
Africa	2.19	11.29	3.66	1.10
Asia	3.26	26.24	6.05	5.06
Europe	9.10	90.83	Not available	7.75
Latin America	9.87	60.20	6.91	4.85
North America	7.86	149.44	Not available	9.62
Western Pacific	7.95	89.63	Not available	12.63

*data obtained from: https://www.who.int/data/gho/data/themes/topics/health-workforce

Family Doctors, community health workers, and registered nurses have very limited availability for consultations, across the full spectrum of healthcare conditions and patients of all ages, they routinely care for.

They would need to perceive the symptom or combination of symptoms severe, to recommend a visit to the specialist. This would require, the family doctor having sufficient time to talk to the patient to fully understand the impact and severity of the symptoms: assuming the patient feels ready to discuss them.

*'One hundred and seventy-nine studies were identified from 111 publications covering 28 570 712 consultations in 67 countries. Average consultation length differed across the world, ranging from **48 s in Bangladesh to 22.5 min in Sweden**. We found that 18 countries representing about 50% of the global population spend 5 min or less with their primary care physicians.'*

Irving G, et al. International variations in primary care physician consultation time: a systematic review of 67 countries. *BMJ Open* 2017;7**:** e017902. **Link**: https://bmjopen.bmj.com/content/7/10/e017902

Table 7: Examples of MSA symptoms that were present at the time of evaluation and their duration prior to diagnosis
(Shaded sections correspond to symptoms experienced by patients, reported in the pre-diagnostic phase, that would be addressed in primary care)

Category	Symptom	Duration (mean year ± SD) of symptom **prior** to diagnosis of MSA
Autonomic	Urinary frequency or urgency	4.1 ± 4.7
	Male Erectile Failure*	4.0 ± 2.6
	Postural lightheadedness	2.8 ± 3.2
	Orthostatic syncope	2.0 ± 1.6
	Urinary hesitancy	2.0 ± 1.6
	Urinary incontinence	1.7 ± 0.8
	Constipation	1.6 ± 1.4
Motor	Slowness of gait	3.2 ± 2.1
	Postural instablity	2.7 ± 2.5
	Tremor	2.6 ± 2.6
	Hand dyscoordination	2.0 ± 2.1
	Dysphonia (vocal disorder)	1.2 ± 1.2
	Dysphagia (swallowing disorder)	1.1 ± 1.0
	Dysarthria (slurred speech)	0.8 ± 0.6
	Dream enactment behaviour	3.2 ± 2.7
Sleep	Stridor	1.0 ± 0.1
	Sleep apnea	1.4 ± 1.1

**Female sexual dysfunction (genital hyposensitivity) not recorded at time of data collection.*
Table adapted from Table 1 McKay, J.H., Cheshire, W.P. First symptoms in multiple system atrophy. *Clin Auton Res* 28, 215–221 (2018). **Link:** https://link.springer.com/article/10.1007/s10286-017-0500-0 following the Creative Commons license **Link:** http://creativecommons.org/licenses/by/4.0/.

If the time above is all the HCP has, they need to know rapidly how severe the symptoms are, and what other symptoms are occurring?

2. Primary care to Specialist HCP referral: (disease not immediately identified as a neurological disorder)

For the majority of the initial symptoms in MSA, if severe or complicated enough to need a specialist, the most frequent one suggested by primacy care HCPs will be a Urologist, unless motor symptoms are visible.

If no motor symptoms are manifested the global high prevalence of diabetes and cardiovascular diseases, would mean that endocrinologists or cardiologists would also be specialty considered, *instead of a Neurologist*,

The limited HCP personnel availability creates time constraints, waiting lists and longer times to diagnosis: the innovator should not be misled by the numbers, healthcare in wealthier countries is also clearly understaffed.

Table 8: Estimated HCP specialist personnel per 10,000 population*

Region	Specialised Medical doctors (all disciplines	Urologist	Endocrinologist	Cardiologist
Africa	1.21	0.02	0.02	0.04
Asia	10.61	0.22	0.15	0.38
Europe	33.41	0.60	0.45	0.85
Latin America	24.97	0.50	0.35	0.89
North America	17.58	0.40	0.25	1.01
Western Pacific	21.81	0.44	0.30	0.78

3. Referral to a Neurologist: insufficient numbers & not all them movement disorders specialists

'The WHO Neurology Atlas (2017) provides estimates of 0.03 ***Neurologists*** *per 100 000 (0.003/10,000) population in low-income countries and 4.75 per 100 000 (0.475/10,000) population in high-income countries.'*

Parkinson disease: a public health approach. Technical Brief. Geneva: World Health Organisation; 2022. ***Link:*** *https://www.who.int/news/item/14-06-2022-launch-of-who-s-parkinson-disease-technical-brief*

When referral to a neurologist occurs, ideally, they need to be specialised in movement disorders, because not all neurologists are: consensus criteria have been established and published as freely available guidelines but *a Neurologist specialised in Movement disorders is still needed.*

Table 9: Movement Disorder Society Diagnostic criteria for clinically probable or established MSA†

	MSA-P or MSA-C	
Essential features	A sporadic, progressive adult (>30 years) onset disease	
Clinically **Probable** MSA Core clinical features	***At least 2 of***: unexplained voiding difficulties with post-void urinary residual volume; unexplained urinary urge incontinence; neurogenic OH (≥20/10mmHg blood pressure drop within 10 minutes if standing or head-up tilt test ***and at least one of:*** • Parkinsonism • Cerebellar syndrome (at least one of gait ataxia, limb ataxia, cerebellar dysarthria or oculomotor features) ***At least one*** supportive clinical feature (motor or non-motor)	
Clinically **Established** MSA Core clinical features	***Autonomic dysfunction defined as at least 1 of***: unexplained voiding difficulties with post-void urinary residual volume ≥ 100mL; unexplained urinary urge incontinence; neurogenic OH (≥20/10mmHg blood pressure drop within 3 minutes if standing or head-up tilt test ***and at least one of:*** • Poor L-dopa-responsive parkinsonism • Cerebellar syndrome (at least one of gait ataxia, limb ataxia, cerebellar dysarthria or oculomotor features) ***At least two*** supportive clinical features (motor or non-motor)	
Exclusion criteria	Absence of exclusion criteria	
	MSA-P exclusively	MSA-C exclusively
MRI markers (Magnetic Resonance Imaging)	*Atrophy of:* Putamen; Middle cerebellar peduncle; pons; cerebellum; 'hot cross bun' sign; *Increased diffusivity of*: Putamen, Middle cerebellar peduncle	*Atrophy of:* Putamen; Infratentorial structures (pons and Middle cerebellar peduncle diddle cerebellar peduncle); 'hot cross bun' sign; *Increased diffusivity of*: Putamen,

Table adapted from Table 1 on page 1134 of Wenning GK, et al The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy. Mov Disord. 2022;37(6):1131-1148. ***Link:*** *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9321158/ following the Creative Commons license* ***Link:*** *http://creativecommons.org/licenses/by/4.0/. The complete table includes full details of 'supportive non-motor and motor features' and full list of exclusion criteria.*

Clinically Definite MSA: The second consensus statement addresses Definite MSA that requires neuropathological demonstration: see *Gilman S, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 2008;71(9):670-6.* **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676993/

*Data obtained from: https://www.who.int/data/gho/data/themes/topics/health-workforce and online searches of medical specialty, number and continent. *Precise data on global numbers of specialists were obtained by searching for medical expertise number by continent, and continent population. In most cases precise numbers could be obtained for the USA and the EU: the mean ratios of specific specialty for the EU and the USA as a function of total number of specialised medical doctors were applied across all continents, as a best-case scenario of available expertise in the field.*

† *The MSA coalition with the Movement Disorder Society task force on MSA have created* ***a 'research criteria' for planning to resolve possible early diagnosis (primary care by combining urinary dysfunction, orthostatic hypotension and sexual dysfunction with subtle parkinsonian or cerebellar motor signs.*** *'Research criteria' to try to create a large enough patient data set to try to better early diagnostic algorithms.*

Diagnostic process at the neurologist

The infrastructure requirements at tertiary level care have been well documented.

The tests that need to be performed with the neurologist include (adapted from Palma JA reference):

- Detailed clinical evaluation and medical history review
- Physical exams addressing gait, coordination and muscle tone
- Complete review of non-motor symptoms (gastrointestinal, cardiovascular, urogenital, thermoregulatory)
- Imaging tests (MRI is gold standard and PET scan also used)*
- Potential cognitive decline
- Sleep evaluation
- Urological testing
- Olfactory testing

Palma JA, et al. Diagnosis of multiple system atrophy. Auton Neurosci. 2018;211:15-25. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5869112/

A core aspect of clinically established MSA is poor response to L-Dopa, the gold standard used for treating Parkinsonism. In patients that do respond to it, the beneficial effect is not observed within 3 years of clear diagnosis.

***Note: imaging tests require specific infrastructure, that has limited availability, see page 22**

During the diagnosis process, the patients will be prescribed symptomatic medicines (no Disease Modifying Therapies exist for MSA).

Table 10: Medicines prescribed during MSA progression

Symptom	Pharmacologic therapy	Nonpharmacologic therapy
Parkinsonism	Carbidopa/levodopa; Amantadine	Physical therapy (PT); Occupational therapy (OT) Regular activity, exercise
Dystonia	Trihexyphenidyl, botulinum toxin	PT and OT
Spasticity	Muscle relaxants (e.g., baclofen, tizanidine) Botulinum toxin	PT and OT
Dysarthria	–	Speech therapy
Dysphagia	–	SLP swallow evaluation, therapy
Autonomic failure		
Orthostatic hypotension	Fludrocortisone; Midodrine; Droxidopa; Pyridostigmine Atomoxetine ; Caffeine	Hydration, fluid intake; Increased dietary salt Abdominal binders; Waist-high compression stockings
Postprandial hypotension	Octreotide ; Acarbose	Eat smaller, more frequent meals; Avoid high-carbohydrate meals; Avoid alcohol; Remain seated (or lie down) after eating
Supine hypertension	Nightly clonidine; Hydralazine; minoxidil; Losartan; Nifedipine; Nitroglycerin; Sildenafil	Assess scheduled medications, Elevate head of bed Bedtime snack (postprandial effect)
Urge incontinence	Solifenacin; trospium; Mirabegron	Timed urination; Intermittent self-catheterization Suprapubic catheter placement
Incomplete bladder emptying	Tamsulosin ; Prazosin	
Sialorrhea	Botulinum toxin	Sugar-free lozenges, gum Papaya or grape seed extract
Nocturia	Desmopressin	No fluids 3-4 h before bed
Constipation	Stool softeners; Senna, laxatives, enemas; Polyethylene glycol 3350 ; Magnesium citrate; Linaclotide; Lubiprostone	Increased fluid, fiber intake Activity/exercise
Erectile dysfunction	Sildenafil; Tadalafil; Vardenafil ; Apomorphine subq injections; Prostaglandin E1 injections	Implants
Sleep disorders		
REM-behavior disorder	Melatonin extended release; Clonazepam	-
Restless leg syndrome (or RLS/PLMS)	Dopamine agonists: Pramipexole; ropinirole; rotigotine TD; Gabapentin *versus* gabapentin enacarbil; Benzodiazepines (i.e., clonazepam)—relative contraindication in sleep apnea	-
Nocturnal stridor	Botulinum toxin injection (dystonic stridor)* Minimally invasive procedures*†	First line—ventilation with CPAP Persistent/severe—consider tracheostomy
Sleep apnea	–	Change in sleep position, weight loss, Oral appliance therapy, CPAP *versus* AutoPAP (if central), Uvulopalatopharyngoplasty, Neurostimulation
Neuropsychiatric symptoms		
Depression	SSRIs/SNRIs	Psychotherapy Cognitive behavioral therapy
Anxiety	Anxiolytics, benzodiazepines Buspirone	
Pseudobulbar affect	Dextromethorphan/quinidine	

Table adapted (doses deleted) from: Burns MR, McFarland NR. Current Management and Emerging Therapies in Multiple System Atrophy. Neurotherapeutics. 2020;17(4):1582-1602. ***Link****: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7851250/*

Burns MR, McFarland NR. Current Management and Emerging Therapies in Multiple System Atrophy. Neurotherapeutics. 2020;17(4):1582-1602. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7851250/

Grossauer, A., et al. Symptomatic Care in Multiple System Atrophy: State of the Art. *Cerebellum* (2022). **Link:** https://link.springer.com/article/10.1007/s12311-022-01411-6

Part 2:

The Patients' support

Globally networked Patient Associations and HCPs

In part 2 we present how the patient associations and HCPs have networked and globalised, and go into detail on some of their actions. Detailing how this creates a forward momentum aimed to reduce the known burden of neurodegenerative disorders on quality of life, across multiple domains, that provides a framework to empower innovation design that provides benefit.

Approximately 50% of patients require walking aids within 3 years from the onset of motor symptoms; 60% require a wheelchair after 5 years with a median time to becoming bedridden of 6–8 years. However, a more benign MSA variant with longer survival of over 15 years has been reported in pathology-confirmed cases, as well as an aggressive MSA phenotype, with a very short disease duration of less than 3 years.'

Chelban, V., et al. An update on MSA: premotor and non-motor features open a window of opportunities for early diagnosis and intervention. J Neurol 267, 2754–2770 (2020).
link: https://link.springer.com/article/10.1007/s00415-020-09881-6

Measuring quality of Life in Neurodegenerative/Movement disorders and in MSA

- Connecting a change in a specific clinical outcome to a change in QoL adds definition to the benefit of the solution, with respect to every possible solution.
- QoL changes applies to the patient and the caregiver (see below and patient/caregivers voice on page 15)

Wiblin L, et al. The Importance of Connection to Others in QoL in MSA and PSP. Parkinsons Dis. 2017;2017:5283259. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5637852/

While not MSA focused, the Open Access Brain Science Special Issue on 'Caregiver burden in Movement disorders and neurodegenerative diseases' is also recommended. **Link:** https://www.mdpi.com/journal/brainsci/special_issues/Caregiver_Burden

Aza, A., et al. Listening to families with a person with neurodegenerative disease talk about their quality of life: integrating quantitative and qualitative approaches. Health Qual Life Outcomes 20, 76 (2022).**Link:** https://hqlo.biomedcentral.com/articles/10.1186/s12955-022-01977-z

- Depending on the clinical symptom being targeted and its severity, QoL changes may occur in the short term or over a longer period; or clinical symptom alleviation may not result in an identifiable change in QoL.
- Patient Reported Outcome Measures (PROMs) are designed to measure these. Their complexity can vary between use as *patient monitoring tools* such as in daily patient care, to larger scale multi-dimensional tools used in complex case management and clinical trials.

Introduction to PROMs:

Patient-reported outcome measures (PROMs) as proof of treatment efficacy

Kluzek S, et al. BMJ Evid Based Med. 2022 Jun;27(3):153-155.

Link: https://pubmed.ncbi.nlm.nih.gov/34088713/

For MSA, a large number of different PROMs have been used for patient monitoring and management and as secondary outcome measurements in clinical studies (primary outcomes are clinical benefits): see Schrag A et al 2006

Review of clinical trials on the clinicaltrials.gov website (see annex for tips on using this location) will reveal the wide array of different PROMs that are used as secondary outcomes: however, 2 stand out and should be understood by the innovator.

1) The Multiple System Atrophy QoL (MSA-QoL): developed in 2007 with input from patients, caregivers and clinicians: see Schrag A et al, 2007
2) The Unified Multiple System Atrophy Rating Scale (UMSARS): first developed in 2004. There are three publications, by the same overall group of KOLs, pertinent to UMSARS that the Innovator needs to be aware of, because it underscores a critical characteristic of innovation in rare diseases: see Wenning GK, Palma JA and Krismer F references below.

As the HCPs and KOLs acquire new knowledge, they autocritique their earlier work to update their outputs to make it more accurate, informative and beneficial for the patient: essentially also for the innovator because more accurate outcomes can be obtained during clinical testing of solutions.

This has ramifications for the innovation model that is chosen during development, as a function of long development times and also updating the innovation once it is put into use in the field, or as is used more frequently in the `real world'.

Schrag A, et al. Health-related quality of life in multiple system atrophy. Mov Disord. 2006;21(6):809-15. **Link**: https://pubmed.ncbi.nlm.nih.gov/16502399/

Schrag A, et al. Measuring health-related quality of life in MSA: the MSA-QoL. Mov Disord. 2007;22(16):2332-8.**Link:** https://pubmed.ncbi.nlm.nih.gov/17914730/

Wenning GK et al. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord. 2004;19(12):1391-402. **Link**: https://www.movementdisorders.org/MDS-Files1/Education/Rating-Scales/umsars.pdf

Palma JA, et al. Limitations of the Unified Multiple System Atrophy Rating Scale as outcome measure for clinical trials and a roadmap for improvement. Clin Auton Res. 2021;31(2):157-164**. Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7868077/

Krismer F, et al. The Unified Multiple System Atrophy Rating Scale: Status, Critique, and Recommendations. Mov Disord. 2022. Epub **Link**: https://movementdisorders.onlinelibrary.wiley.com/doi/full/10.1002/mds.29215

Urinary incontinence, social stigma and health-seeking behaviour

There is an added characteristic of quality of life and social stigma of urinary incontinence as one of the initial symptoms of MSA, that **may slow the decision to seek correct health support** (sexual dysfunction is discussed below on page 17 in detail),

Koch LH. Help-seeking behaviors of women with urinary incontinence: an integrative literature review. J Midwifery Womens Health. 2006; 51(6):e39-44. Link: https://pubmed.ncbi.nlm.nih.gov/17081925/

Southall K, et al. Assessing the stigma content of urinary incontinence intervention outcome measures. J Rehabil Assist Technol Eng. 2017;4:2055668317738943. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6453035/

Stickley, A., et al. Urinary incontinence, mental health and loneliness among community-dwelling older adults in Ireland. *BMC Urol* **17**, 29 (2017). Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5385037/

Patient support: MSA, atypical Parkinson's and Parkinson's disease

At the global and continent policy level, movement disorders can focus more on Parkinson's rather than atypical forms of Parkinson's: for the innovator focusing on MSA, approaching this as an overlapping concept could provide added value for three main reasons:

1. Patients with MSA and other forms of atypical Parkinson's disease are often misdiagnosed as having Parkinson's disease and vice versa.
2. Innovations could contribute to the long-term work of patient support groups working across the whole spectrum of mobility disorders.
3. The 'Basket trials' approach, while may be not immediately resolving the creation of disease modifying therapeutics, in the context of registries, clinical process, optimising care, better diagnostic procedures and possibly larger amounts of data on patient history and disease progression could have global impact when linked to innovation design.

Many forms of patient associations, information multipliers, overarching organisations and clinical networks exist. These types of organisations are the central cog in rare diseases and move mountains. Below we list them and in the following section, we detail some of the actions that have been performed: because these enable innovation.

In the context of global MSA patient population distribution, available healthcare infrastructure and the patient journey, it is useful to keep all in mind. They will impact the different forms of innovation strategy that could be necessary across continents and countries to enable solutions designed for patients with MSA.

Table 11: Non-exhaustive list of patient associations, organisations and bodies providing support and information

Name	Location	Geographic focus	Website	Languages
MSA focused Patient associations				
Defeat MSA Alliance	Global	Global	https://defeatmsa.org/about-us/ (network of MSA Patient association groups from US, Spain, France, Australia-new Zealand, Italy	>120 different languages and dialects
The MSA coalition	US	Global	https://www.multiplesystematrophy.org	English
MSA trust	UK	UK	https://www.msatrust.org.uk	English
MSA Landsforeningen	Denmark	Denmark	https://www.msa-danmark.dk	Danish
MSA South Africa	SA	SA		English
MSA India	India	India	https://www.facebook.com/groups/MSAIndia/?mibextid=6NoCDW	English
Parkinson's Disease, movement disorder & neurological focused organisations with sections on MSA				
International Parkinson and Movement Disorder Society	USA	Global	https://www.movementdisorders.org	>130 different languages and dialects
Michael J. Fox Foundation	USA	Global	https://www.michaeljfox.org	English/Spanish
American Parkinson Disease Association	USA	US/Global	https://www.apdaparkinson.org	English/Spanish
Brain Foundation	Australia	Australia/ Global	https://brainfoundation.org.au	English
Fight Parkinson's	Australia	Australia/ Global	https://www.fightparkinsons.org.au	English
Parkinson's Disease focused organisations with information on symptom management				
Parkinson's Disease and movement disorder society	India	India	https://www.parkinsonssocietyindia.com	Hindi/English
Parkinson's Africa	Africa	African Continent	https://www.parkinsonsafrica.org	Multiple African Continent languages
Clinical organisations/networks				
European reference networks for rare neurological diseases	Europe	Europe	https://www.ern-rnd.eu (spec: https://www.ern-rnd.eu/disease-knowledge-hub/msa/)	English
Pan-American Consortium of Multiple System Atrophy	Latin America/ US	Latin America	None -unknown if active: Link: https://pubmed.ncbi.nlm.nih.gov/25213997/	English
Japan Multiple System Atrophy Research Consortium	Japan	Japan	None -unknown if active: Link: https://www.neurology-jp.org/Journal/public_pdf/050110927.pdf	Japanese/English
Rare Disease organisations				
Orphanet	Europe	Europe/Global	https://www.orpha.net/consor/cgi-bin/index.php	English
NORD	US	US/Global	https://rarediseases.org	English
Indousrare	US	US/India/Global	https://www.indousrare.org	English
Information disseminators and patient advocacy				
Eurordis	Europe	Europe/Global	https://www.eurordis.org	31 languages
Orphanet journal	online	online	https://ojrd.biomedcentral.com	English
NIH GARD	US	US/Global	https://rarediseases.info.nih.gov	English

*'**Multiple system atrophy: Building a global community – 30 years of advocacy efforts**… Since the 1980s there has been a growing advocacy effort directed at this rare disease from advocacy groups, grassroots supporters, healthcare professionals and research networks. These stakeholders are beginning to unite their efforts and attack the disease from a global perspective in the hopes of improving outcomes for MSA patients in the future.'*

Bower PG. Multiple system atrophy: Building a global community – 30 years of advocacy efforts. Auton Neurosci. 2018;211:39-42. Link: https://pubmed.ncbi.nlm.nih.gov/29269241/

The MSA Patient Association – HCP ecosystem

One of the reasons for selecting MSA for an innovator briefing was significantly influenced by the global MSA community, their networking with the KOL HCPs, and the work of mobility disorder focused organisations, in which they also participate. This is not the only rare disease in which this has happened: there are several other examples.

For innovators considering solutions for MSA, such networks of stakeholders and experts are pivotal and essential for the design and validation process: they have their feet on the ground where healthcare happens and their finger on the pulse of patient need. They have generated a large number of key resources that can inform innovation design including the following examples:

The patient and caregiver's voice: daily quality of life in MSA

Understanding daily quality of life is essential for innovation design: (patient focused information, preparing for any travel, living with MSA, living with Parkinson symptoms, along with personal stories can be found in the links below)

MSA Trust UK: https://www.msatrust.org.uk/support-for-you/for-carers/
***Living with MSA**: https://www.msatrust.org.uk/support-for-you/living-with-msa/*
***Living with MSA: The emotional impact** https://www.msatrust.org.uk/support-for-you/for-people-affected-by-msa/living-with-msa-the-emotional-impact/*

International Parkinson and Movements Disorder Society (available in >30 languages): https://www.movementdisorders.org/MDS/Resources/Patient-Education.htm
(note: on left hand side is menu of choices that includes MSA and a wide range of information for symptom understanding and management across movement disorders).

The MSA coalition: https://www.multiplesystematrophy.org/msa-resources/for-patients/ and https://www.multiplesystematrophy.org/msa-resources/

American Parkinson Disease Association: planning for what ifs series: https://www.apdaparkinson.org/article/planning-for-the-what-ifs-multiple-system-atrophy/

The MSA coalition: https://www.multiplesystematrophy.org/msa-resources/for-care-partners/

DefeatMSA: https://defeatmsa.org/patient-programs/

Parkinson's focused:

Parkinson's disease and movement disorder society(India), resources in Hindi and English: https://www.parkinsonssocietyindia.com/resources/

Parkinson's Africa: Understanding Parkinson's disease, an introductory guide, found in print and digital educational material section in Amharic, Arabic, Luganda, Pidgin English, Somali, English, French, Swahili, Hausa, Twi, Igbo and Yoruba: https://www.parkinsonsafrica.org/resources

Professionally focused information such as HCPs and KOLs, and clinical locations:

MSA KOLs: DefeatMSA: https://defeatmsa.org/msa-research/#msa-experts

European MSA specialist centres:
ERN-RND MSA centres: https://www.ern-rnd.eu/disease-knowledge-hub/msa/ern-rnd-centres/

MSA Care specialists
MSA Trust UK: https://www.msatrust.org.uk/support-for-you/hcps/

Movement disorder KOLs and clinical locations:
International Parkinson and Movements Disorder Society: https://mds.movementdisorders.org/directory/index.php?mode=map

Regional (continental) chapters – links into regionally designed and focused initiatives:
International Parkinson and Movements Disorder Society: https://www.movementdisorders.org/MDS/Regional-Sections.htm

Guidelines and care standards:
ERN-RND MSA knowledge hub: https://www.ern-rnd.eu/disease-knowledge-hub/msa/

The MSA coalition: https://www.multiplesystematrophy.org/blog/new-diagnostic-criteria-for-multiple-system-atrophy/ (links into: Wenning GK, et al. The Movement Disorder Society Criteria for the

Diagnosis of Multiple System Atrophy. Mov Disord. 2022;37(6):1131-1148.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9321158/

Part 3:

Unmet need
and
adaptive multidisciplinary innovation

'More than 80% of rare diseases affect fewer than one patient in a million. This means that, for most rare diseases, even experienced physicians with a lot of patient contact never see a single patient in their lifetime. '

Schaefer, J., et al. The use of machine learning in rare diseases: a scoping review. Orphanet J Rare Dis 15, 145 (2020). ***Link:*** *https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01424-6*

Diagnostics: Awareness and Point-of-care

'Male patients with pre-motor MSA frequently undergo surgery for suspected benign prostate hyperplasia without realizing that MSA is the actual cause of their urinary problems. Urological surgery outcomes are rarely favorable in patients with MSA.'

Palma JA, et al. Diagnosis of multiple system atrophy. Auton Neurosci. 2018;211:15-25.**link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5869112/

Symptoms to Primary care: the problem of commonly manifested symptoms

For the typical prodromal non-motor symptoms indicated in table 7 above, that manifest in patients with MSA, the primary care HCP has a wide spectrum of possible types and reasons for their occurrence:

Urinary Incontinence:

4 different types associated with involuntary leakage of urine (stress, urge, mixed and overflow). Urge is the type more frequently associated with MSA. Patient needs to be able to effectively articulate the sensation.

Urge urinary incontinence also caused by diabetes, history of hysterectomy, obesity, smoking, constipation, urinary tract infection, prostate cancer or enlarged prostate (benign prostate hyperplasia) and certain medications (diuretic, antidepressants, blood pressure medicine).

If considered severe enough, the primary care HCP will normally recommend specialist care from a urologist.

Sexual dysfunction:

Erectile dysfunction: can be caused by prescription medicines, hypertension, high cholesterol, bodyweight, metabolic syndromes, various cardiovascular diseases, smoking, sleep disorders, low testosterone, diabetes, over use of alcohol, prostate treatments, depression, anxiety, stress, personal relationship related issues.

Genital hyposensitivity: can be caused by smoking, kidney related issues, blood pressure medicines, antihistamines, various cardiovascular diseases, antidepressants, lower estrogen levels, painful intercourse, anxiety, depression, long-term stress, body-image and self-perception, personal relationship related issues.

If considered severe enough, the primary care HCP will normally recommend specialist care from a urologist. However, if available, they may also recommend a psychotherapist

Postural lightheadedness/instability issues: can also be perceived as dizziness.

Can be caused by anxiety, depression, low blood sugar, potential cardiovascular diseases such as atrial fibrillation or neurocardiogenic syncope (fainting when body overreacts to specific triggers: heat, pain, sudden movement, dehydration). Also associated with diminished visual and hearing function, neck pain and certain prescription medications.

If considered severe enough, the primary care HCP will normally recommend specialists associated with cardiovascular, sensory, mental health or orthopedic focus.

Neurogenic orthostatic hypotension/syncope:

Can be caused by anaemia, dehydration, cardiovascular disorders, prolonged immobility, hypertension medicines, anti-depressants, diabetes, thyroid diseases, diuretics.

If considered severe enough, the primary care HCP will normally recommend specialist care from a neurologist.

For many people discussing urogenital symptoms are uncomfortable:
perform a web search using any of the following terms:

'Talk about erectile dysfunction' *'Talk about female sexual dysfunction'* *'How to talk about incontinence'*

There are significant self-esteem and mental health associated issues for both the patient and their partner or family members

McKay JH, Cheshire WP. First symptoms in multiple system atrophy. Clin Auton Res. 2018;28(2):215-221.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5859695/

Schrag A, et al. Pre-diagnostic presentations of Multiple System Atrophy case control study in a primary care dataset. Parkinsonism Relat Disord. 2022;99:101-104. **Link**: https://www.prd-journal.com/article/S1353-8020(22)00036-0/fulltext

Palma JA, et al. Diagnosis of multiple system atrophy. Auton Neurosci. 2018;211:15-25.**link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5869112/

Pellecchia MT, et al. Can Autonomic Testing and Imaging Contribute to the Early Diagnosis of Multiple System Atrophy? A Systematic Review and Recommendations by the Movement Disorder Society Multiple System Atrophy Study Group. Mov Disord Clin Pract. 2020;7(7):750-762. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7533961/

Chelban V., et al. An update on MSA: premotor and non-motor features open a window of opportunities for early diagnosis and intervention. J. Neurol 267, 2754–2770 (2020). **Link**: https://link.springer.com/article/10.1007/s00415-020-09881-6

Before the first HCP visit

The first pre-motor symptoms of Sexual dysfunction and urinary incontinence create a conundrum: stigma vs. indications of early-stage diseases (that include MSA).

Sexual Dysfunction

'Over 18 million adult men in the United States have erectile dysfunction. In fact, at least 50 percent of men over the age of 50 experience some loss of function. Despite being a common male condition, it is not normal, no matter how old you are. Only 10 percent of men seek treatment and many (50 percent) discontinue treatment once they start it because they are too embarrassed to discuss their sexual health issues with a doctor.'

Erectile dysfunction in men: University of Utah Health. Accessed November 2022: https://healthcare.utah.edu/menshealth/conditions/erectile-dysfunction/

*Several U.S. and international surveys of women recently found that **the majority of women surveyed did not discuss their sexual health-related symptoms with their HCPs**, and discomfort and/or embarrassment with having this discussion was often cited as a reason for avoiding the conversation. This finding was consistent for women across different demographics, including age, sexual orientation, race/ethnicity, educational level, and relationship status.*

Kingsberg SA. et al. Female Sexual health: Barriers to Optimal outcomes and a roadmap for improved patient-clinician communications. Womens Health (Larchmt): 2019;28(4): 432–443.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6482896/

*'A history of **male erectile dysfunction** was associated with 1.5-fold increased odds of an α-synucleinopathy diagnosis of any type in univariate analyses. When stratifying α-synucleinopathies by type, early erectile dysfunction was most frequent in MSA cases than matched controls (45% vs. 9%).'*

Hasan S, et al. Erectile Dysfunction Preceding Clinically Diagnosed α-Synucleinopathies: A Case-Control Study in Olmsted County. Parkinsons Dis. 2019;2019:6303945. **Link:** https://pubmed.ncbi.nlm.nih.gov/31093326/

***'Sexual dysfunction is highly prevalent in women with multiple system atrophy**. Screening for disturbances in specific sexual domains should be implemented in the clinical evaluation of women with suggestive motor symptoms.'*

Raccagni C, et al. Female sexual dysfunction in multiple system atrophy: a prospective cohort study. Clin Auton Res. 2021;31(6):713-717.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8629866/

Only 10% of men and 8% of women had been asked by a doctor about possible sexual problems during a routine visit in the last 3 years'

Buvat J, et al; Global Study of Sexual Attitudes and Behaviours (GSSAB) Investigators' Group. Sexual problems and associated help-seeking behavior patterns: results of a population-based survey in France. Int J Urol. 2009;16(7):632-8.**Link**: https://pubmed.ncbi.nlm.nih.gov/19456984/

(*The reference list at the end of this section illustrates the global relevance of sexual dysfunction and urinary incontinence stigma and healthcare seeking behaviour*)

Social stigma and urinary incontinence and health-seeking behaviour was referred to above on page 12.

There are a large number of digital solutions for resolving sexual dysfunction and urinary incontinence. The implication, though, is that self-help due to stigma is maybe being performed before discussions with an HCP.

If the reason for sexual dysfunction and urinary incontinence is neurogenic or cardiovascular, combined with being above or around the age of 40, but being negative for all other potential causes associated with the symptoms (with the potential exception of urinary tract infection) then could this be a first approach for filtering patients and shortening the diagnostic journey.

The study of McKay J.H. et al is revealing (see table 7, page 8 of this briefing, and original publication). The reported data was obtained by reviewing detailed clinical histories with the patient and their family and then queried on precise time of onset before MSA diagnosis. Some patients reported Urinary urgency nearly 9 years, and erectile dysfunction over 6.5 years before diagnosis.

'Self-help' first due to stigma could be counterproductive

Looking forward if discrete 'awareness and risk filtering' innovations are developed (such as mobile apps) and used before first HCP interaction (including direct communication of results), and combined with existing and emerging diagnostic solutions for movement disorders and alpha synucleinopathies, would this enable a more rapid movement of the patient towards a neurologist to perform the next series of tests?

In the context of a longer-term view of enabling AI and Machine Learning for resolving issues related to diagnosing MSA (and many rare and frequent diseases) this could represent a first step in permitting global comprehensive learning set generation: that when fed into a larger algorithm maybe able to alleviate bottlenecks and augment care in resource constrained settings.

'Disease management is dependent on a well-coordinated, multidisciplinary team. Nurse practitioners often see the earliest manifestations of disease and are ideally positioned to serve as care coordinators and to oversee end-of-life services.

However, awareness of MSA is limited among medical professionals.'

Bagchi, A. D. Multiple System Atrophy, The Journal for Nurse Practitioners. 2022: 18(9), 951–956. **Link:** https://www.sciencedirect.com/science/article/pii/S1555415522002562

Awareness:

This opening quote illustrates a frequent occurrence across rare diseases: awareness of the indication and its symptoms are often, understandably, not well understood.

Patients, patients' partners and caregivers and HCPs need support and education: internet searches that result in large volumes of information do not seem enabling, especially if solutions are not mobile friendly or are complex to navigate.

Patients:

Long-duration degenerative disorders predispose a structured educational strategy that aligns with:

- Level of understanding of the patient
- The indication pathogenesis
- The patients' exact symptoms, that will vary between patients
- The quality of life they are having
- The infrastructure (e.g. transport, ease of access to shops, theatre, social events) as a function of their socioeconomic environment
- Cultural sensitivities and different languages

Studies in other rare diseases (see: www.echino.eu/knowledge),) have also indicated, that communication needs to be tailored to educational level of the patient (this has relevance because to become too technical too soon, especially when educational level is integrated into the demographics of the patient population, while still keeping the information succinct, engaging and informative is a challenge).

The design of educational focused innovation in communication for MSA may be facilitated by studies on the educational preferences of patients with Parkinson's disease:

Gatsios D, et al. Education on palliative care for Parkinson patients: development of the "Best care for people with late-stage Parkinson's disease" curriculum toolkit. BMC Med Educ. 2021;21(1):538.**Link:** https://pubmed.ncbi.nlm.nih.gov/34696752/

Armstrong MJ, et al. Barriers and facilitators of communication about off periods in Parkinson's disease: Qualitative analysis of patient, carepartner, and physician Interviews. PLoS One. 2019;14(4):e0215384. **Link**: https://pubmed.ncbi.nlm.nih.gov/30998707/

Nijhuis FAP, t al (2019) The Patient's Perspective on Shared Decision-Making in Advanced Parkinson's Disease: A Cross-Sectional Survey Study. Front. Neurol. 10:896 Link: https://www.frontiersin.org/articles/10.3389/fneur.2019.00896/full

Gerritzen EV, et al. Online Peer Support for People With Parkinson Disease: Narrative Synthesis Systematic Review. JMIR Aging. 2022;5(3):e35425. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9377481/

Tuck KK, et al. Preferences of patients with Parkinson's disease for communication about advanced care planning. Am J Hosp Palliat Care. 2015;32(1):68-77. **Link:** https://pubmed.ncbi.nlm.nih.gov/24052430/

Pitts E, et al. Communication strategies used by Parkinson's nurse specialists during healthcare interactions: A qualitative descriptive study. J Adv Nurs. 2022;78(6):1773-1786. **Link:** https://pubmed.ncbi.nlm.nih.gov/35285973/

Points considered with weightings in these articles include:

- Use of graphics
- Information needs to be patient personalised
- That information leads to a shared decision making
- Is it consistent across sources?
- How visible is it, is it easy to find?
- Channels of communication (this applies across all groups in this section)
- Does it address cultural or sensory (hearing or vision) related factors?
- How most patients want to hear it initially communicated to them by an HCP

Caregivers:

The patient support associations indicated in part 2 above, provide very comprehensive insight, across all movement disorders, but also with a clear focus on MSA on what to expect, what the impact on them as caregivers will be, and how they can facilitate life for the person they care for.

For neurodegenerative disorders, across all indications, significant focus has made on educating and supporting the caregiver, which could serve as template across other rare diseases.

Across a wide range of rare diseases (as indicated in the voice of the patient reports from ICER, see: https://www.fda.gov/industry/prescription-drug-user-fee-amendments/condition-specific-meeting-reports-and-other-information-related-patients-experience), the patient and their caregiver can end up performing detailed searches on their own and becoming as informed as the HCP.

HCPs:

At the HCP level, the capacity to become aware is determined by 2 interacting factors:

i) Time availability:

As indicated on page 8, most primary care HCPs have limited time availability already to interact with their patients, so to become aware of a rare disease requires carefully tailored education.

Similarly, not all neurologists specialise in movement disorders, and not all radiologist are neuroradiologists: given their low numbers, their time for new knowledge acquisition is also limited.

It is therefore the responsibility of the innovator to make it easy for them: they have to role-play across the healthcare spectrum, and tailor the design of their educational solution accordingly, linked very specifically to a desired outcome, as a function of need in the healthcare location (primary to tertiary and high tech platforms).

ii) Teaching the teacher in understandable language:

Communication needs to be culturally sensitive, as well as multilingual and in a format in which the HCP can engage the patient and their caregiver in a mutual conversation (that they also understand), that extends beyond the healthcare appointment, into the continued journey that they will share.

Information also needs to be phased in: from symptoms into frequent diseases into movement disorders into alpha-synucleinopathies into rare alpha-synucleinopathies

Images and algorithms to explain, but also to facilitate on-the-ground decision making would be useful.

Where does this point to for the innovator?

Across the stakeholders, when combined with insights on digital infrastructure evolution, especially in LMIC countries, where a technology generation leap has occurred (fibre optic internet infrastructure is less frequent that mobile internet infrastructure: see belowin digital health), a significant proportion of education needs to occur in mobile based formats, for mobile phones and tablets.

This means, downloadable applications, that the patient, caregiver or HCP (across the whole patient journey) has access to, so that if the internet connection is poor, they still have the information.

It also means engaging with teachers of teenagers to determine educational strategy and structure of how to increase knowledge transfer, retention and application in diverse audiences, so as to bring understanding up to required levels in specific audience tailored formats: the global nature and rarity of MSA, suggest assumptions across cultures may not be ideal.

Point-of-care and laboratory-based diagnostics:

'There is no doubt that the neurodegenerative process in all synucleinopathies begins way before abnormal motor findings are recognized clinically.'

Watanabe H and Kaufmann H. Pitfalls in the diagnosis of MSA. International Parkinson and Movement Disorder Society. September 2018: Accessed November 2022. **Link:** https://www.movementdisorders.org/MDS/Scientific-Issues-Committee-Blog/Pitfalls-in-the-diagnosis-of-multiple-system-atrophy.htm

In addition to education, there is a large bottleneck in diagnostics: at the tertiary care level, educating neurologists and radiologists in movement disorder-based neurology and radioneurology is a clear need.

The guidelines for diagnosing and managing MSA that are updated by the KOLs with the support of the associations (patient and professional) correspond fundamentally to transition to tertiary care.

While not perfectly resourced, a neurologist talking to a movement disorder specialised neurologist can be facilitated by education, and as discussed below, telemedicine, but more focused on peer-to-peer, rather than medic-to-patient.

For the innovator, the bottleneck, is at primary care, while symptoms are premotor, and correspond to a wide array of more frequent disorders.

Which solution or solutions can be generated that enable HCPs in primary care, with no specific understanding of rare neurological diseases, to ensure their patient goes at a minimum to neurologist + another specialist HCP (where the other specialist HCP is a urologist, cardiologist, endocrinologist or psychiatrist).

Development of precisely a new diagnostic, especially if it is based on molecular signals for a rare disease needs to be carefully considered. The overriding point is that the final product used to measure the molecular signal must:

- Integrate into the existing care pathway and make diagnosis more accurate
- Be easy to use within the actual infrastructure, with little or no specialisation required
- It must also have sufficient patient specific statistical evidence to prove sensitivity and specificity.

Statistics/Biostatistics measurements:

You need to to identify the solutions diagnostic yield: basically, does the diagnostic provide the info needed.

1) Sensitivity and specificity: you must be able to differentiate patients. This is typically done comparing the existing gold standard with your innovation (high false signals stop development)

	Subjects with the disease	Subjects without the disease
Positive	True positive	False positive
Negative	False negative	True negative

2) Predictive values: measuring probability of having the disease in a defined population.

3) Accuracy measurements: this data is essential and ideally should be stratified for the relevant populations: -

- Likelihood ratio: best used for clearly identifying if a disease is actually present, so fundamentally diagnostic accuracy
- Receiver Operating Characteristic: every patient tested has a range of potential diagnostic scores, withcut off values, that indicates how the tests differentiates patients.
- Diagnostic odds ratio and Youden's index: two different methods that compare two or more diagnostic tests

Data management and security is also a critical consideration, especially in low resource settings:

> Numerous diagnostic products have been sent back to drawing board by regulatory authorities following due diligence of data management processes and methods that have not adhered to all the standards used for quality control and patient data privacy (these are different standards to those for medicines

The innovator needs to think of both positive and negative selection solutions: indicated below in clinical trials is a 'terminated clinical trials' section, some studies of which correspond to 'futility trials': setting out to prove something does not work.

The same concept can be applied to diagnostic algorithms: this requires the innovator having significant conversations with clinical KOLs to determine what would be 'exclusion' criteria.

If the patient has confidentiality informed the HCP, they have UI +/- sexual dysfunction, what else could be used to filter down the large patient number into those that should go to a neurologist?

- If the patient has UI, would a blood sugar measurement, suggest whether an endocrinologist should be the next referral?
- If there is no evidence of stridor, would a spirometry measurement indicate patients not to be considered for a neurologist, because it would be more likely they have COPD?
- Is there evidence of orthostatic hypotension?
- If the patient has a mobile phone, would an app that they can turn on to record themselves while they sleep, provide information on stridor manifestation: that the app automatically identifies and informs the HCP to contact the patient?

Some of these questions could be answered by point-of-care solutions that already exist on the marketplace, but would need to be bundled into packages for the primary care HCP to understand.

These then lead into biomarkers and processes for assessing either MSA specifically or movement disorders overall: the innovator would need to decide what they want their solution to do, at the pertinent location of healthcare.

For example, at a primary care level, in a rural setting, where healthcare resources are constrained and healthcare insurance or national coverage is limiting, what is the objective?

Precisely identify MSA, or identify a movement disorder at an early time point that informs and activates a different care algorithm, immediately with a neurologist and a more precise battery of tests? This informs the design of the innovative solution: especially with regard to biological measurements of alpha-synuclein, plasma-neurofilament light chain, or voice change patterns. (These are being identified as ways to identify alpha-synucleinopathies, or as ways to differentiate MSA from Parkinson's Disease and other alpha-synucleinopathies).

Do you design a highly precise kit that measures at markers as a function of pathogenesis?

or/

Do you design a screening solution, that indicates rapidly (in combination with additional metrics such as those above), that above a certain threshold vs. the non-indication specific population, that the patient needs to move to tertiary care for a detailed follow-up with a neurologist+?

Thomsen BLC, et al. Biomarkers in functional movement disorders: a systematic review. J Neurol Neurosurg Psychiatry. 2020;91(12):1261-1269. doi: 10.1136/jnnp-2020-323141. **Link**: https://pubmed.ncbi.nlm.nih.gov/33087421/

Morris HR. Blood based biomarkers for movement disorders. Acta Neurol Scand. 2022;146(4):353-361.**Link:** https://pubmed.ncbi.nlm.nih.gov/36156206/

Tönges L, et al. Blood-based biomarker in Parkinson's disease: potential for future applications in clinical research and practice. J Neural Transm (Vienna). 2022;129(9):1201-1217.**Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9463345/

Kim JY, et al. Alpha-Synuclein in Skin Nerve Fibers as a Biomarker for Alpha-Synucleinopathies. J Clin Neurol. 2019;15(2):135-142. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6444158/

Liu X, et al (2020) Optimization of the Detection Method for Phosphorylated α-Synuclein in Parkinson Disease by Skin Biopsy. Front. Neurol. 11:569446. **Link**: https://www.frontiersin.org/articles/10.3389/fneur.2020.569446/full

Han Y, et al. Skin alpha-synuclein deposit patterns: A predictor of Parkinson's disease subtypes. EBioMedicine. 2022;80:104076. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9148991/

Donadio V, et al. Phosphorylated α-synuclein in skin Schwann cells: a new biomarker for multiple system atrophy. Brain. 2022 :awac124**. Link**: https://pubmed.ncbi.nlm.nih.gov/35552610/

Dutta, S et al. α-Synuclein in blood exosomes immunoprecipitated using neuronal and oligodendroglial markers distinguishes Parkinson's disease from multiple system atrophy. *Acta Neuropathol* 142, 495–511 (2021). **Link:** https://link.springer.com/article/10.1007/s00401-021-02324-0

Pilotto A, et al. Plasma NfL, clinical subtypes and motor progression in Parkinson's disease. Parkinsonism Relat Disord. 2021;87:41-47.**Link**: https://pubmed.ncbi.nlm.nih.gov/33964785/

Zhang L, et al. Neurofilament Light Chain Predicts Disease Severity and Progression in Multiple System Atrophy. Mov Disord. 2022;37(2):421-426. **Link**: https://pubmed.ncbi.nlm.nih.gov/34719813/

Cuoco S, et al. The language profile in multiple system atrophy: an exploratory study. J Neural Transm (Vienna). 2021;128(8):1195-1203. **Link**: https://pubmed.ncbi.nlm.nih.gov/34216238/

Differential diagnosis between Parkinson's disease and Multiple System Atrophy using digital speech analysis – Voice4PD-MSA. Agence Nationale de la Receherche. Accessed November 2022: https://anr.fr/Project-ANR-16-CE19-0010

Sampath M, et al. Effect of Disease Severity on Respiratory Impedance in Parkinson's Disease. Ann Neurosci. 2020;27(2):63-66. **Link** https://pubmed.ncbi.nlm.nih.gov/33335358/

McDonald CM, et al. Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: long-term natural history with and without glucocorticoids. Neuromuscul Disord 2018;28:897–909. **Link** https://pubmed.ncbi.nlm.nih.gov/30336970/

LoMauro A, et al. Evolution of respiratory function in Duchenne muscular dystrophy from childhood to adulthood. Eur Respir J 2018;51:1701418. **Link** https://pubmed.ncbi.nlm.nih.gov/29437939/

Docu Axelerad A, et al. Respiratory Dysfunctions in Parkinson's Disease Patients. Brain Sci. 2021;11(5):595. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8147845/

D'Arrigo Aet al. Respiratory dysfunction in Parkinson's disease: a narrative review. ERJ Open Res. 2020;6(4):00165-2020. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7533305/

O'Callaghan, A. et al. A review of pulmonary function in Parkinson's disease**.** Journal of Parkinsonism and Restless Legs Syndrome 2018:8;13–23. **Link**: https://www.dovepress.com/a-review-of-pulmonary-function-in-parkinsons-disease-peer-reviewed-fulltext-article-JPRLS

The impact of the shortage of neurologists (also specialised in movement disorders) is compounded by imaging resource constraints

MRI imaging: Bottleneck - number of machines and radiologists

MRI: a non-invasive imaging technology that permits high resolution image generation of soft tissue: as such it is used for the diagnosis of any abnormality in any part of the body that is not bone. Explicitly:

- All diseases are letter coded (read: ICD codes) to enable differentiation of diagnosis.
- These are organised into 26 groups (A–Z), representing groups (condition, organ, characteristic) and within each group are a large series of subdivisions to specify precisely what the injury/disease being diagnosed is.
- MRI (and other imaging) is routinely used in the diagnosis of injuries and diseases in 19 of the 26 groups.

There are two key issues, that are global in nature:

- The number and quality of available imaging machines
- The number of available radiologists, of whom specialise in neuroradiology: Radiologists have to understand what they are looking at, which is why normal practice is the images generated have to be reviewed by at least two independent radiologists to reach an agreement on what they are seeing.

Table 12: MRI & PET imaging devices and expert staff availability by income status

	Median number of units per million people by location income status			
	High	Upper-middle	Low-middle	Low
MRI machines	12.6	3.4	0.4	0.07
All Radiologists	93.1	30.6	6.9	1.1
PET machines	1.2	0.2	0	0
All nuclear medicine physicians	6.5	1.5	0.1	0

Source: tables 2 and 3 from Hricak H, et al. Medical imaging and nuclear medicine: a Lancet Oncology Commission. Lancet Oncol. 2021 ;22(4):e136-e172.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8444235/

Imaging platforms require high capital investment with significant maintenance costs: mobile 3T MRI are available, but are structured around long articulated transports, meaning that good quality transport infrastructures are needed. And MSA will not be the only indication they are used for. Large incumbents maintain close collaborations with leading clinical centres and often codevelop innovations for their machines as a function of user feedback.

Specialised neurologists and neuroradiologists in movement disorders are required (the International Parkinson and Movements Disorder Society provides a significant amount of globally tailored education and support for this to happen, and the Patient Associations indicated in part 2 provide a large number of grants for training to occur).

Distance based digital solutions may provide some resolution, as discussed in the digital health section further down in the brief.

The number and ***quality*** of MRI machines has been reported in West Africa (low availability of 3T machines), for example see results section of: Ogbole GI, et al. Survey of magnetic resonance imaging availability in West Africa. Pan Afr Med J. 2018;30:240. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6295297/

Could this be an opportunity for AI and ML?

Potentially yes, but requiring a significant amount of effort and investment, performed globally. For this to provide benefit, it would require a vast undertaking, because of the frequency of patients with MSA within the 45 – 70 years age bracket highlighted in the preface on page 3.

The issue increases in scale of design as you move backwards through the pathogenesis of MSA and it starts to overlap not just in symptom diversity, but indication similarity of the symptom, requiring increasing numbers of complete patient data without any link to MSA being included in the learning set data, to be as accurate as possible.

This could potentially be addressed in a modular format as a function of resource used or location of data collection and follow-on healthcare action, but at some point, it would need to be integrated throughout. The healthcare community across all movement disorders and additional disciplines would need to be significantly involved.

The end objective would be for the AI/ML system to see very early on in data from a patient that they are likely developing MSA, as opposed to other movement disorders, and if extended into primary care, cardiovascular and other major diseases as well.

To illustrate the potential data need, in appendix 4 is a worked-up non exhaustive flow of how this could potentially look.

This could pose significant logistical challenges but it could also depend on the focus of the lens you were using for the benefit required: whether to look at the whole journey, or focus on linking imaging to novel alpha synuclein tests to enable informed decision making in locations where imaging infrastructure is less available.

Adapting Henderson-Clark's innovation model for rare diseases: Design to be radical, but start incrementally

The potential approach above to try to link better diagnosis for rare diseases in lower income countries requires adaptation of innovation models. The diagnostic journey, shortage of all types of resource (especially imaging), level of awareness across all stakeholders, number of unanswered questions (indicated above) and the ongoing work of HCPs and Patient Associations, meaning updates outside of the normal timeframes of healthcare solution development can cause many innovators to understandably pause.

Flexibility in innovation validation has been enabled through 'basket' clinical trials. The ramification is that developed solutions may be able to generate more benefit, over a long-time frame, if innovation flexibility is built into the design: one way to approach this is to revisit the Henderson-Clark model of innovation and adapt it to become a flowing-strategy for innovation, between quadrants.

The model itself hinges on innovation fitting into one of four quadrants:

- *Incremental innovation*: improved components, unchanged architecture
- *Modular innovation*: new/changed components, unchanged architecture
- *Architectural innovation*: improved components, changed architecture
- *Radical innovation*: new/changed components, changed architecture

In contrast, the dispersity of patient populations with rare diseases, and how their location defines available healthcare quality, if it can be easily implemented and if they can afford it: means that innovations for a rare disease need to be designed to be radical, but initially implemented incrementally.

Certain tools need to be designed to be used in all settings because it is affordable and feasible: other solutions defined by increasing costs of development need to be staggered across locations based on income status.

The implication being that incremental being low change requirement, low cost, higher benefit, that integrates into existing healthcare infrastructures and updates with it, and then moves through any of the other quadrants of the matrix as a function of resource change: but always generating benefit as it does.

The scalability of the innovation, should then mean, that a significant innovation 'bolt-on' that may have occurred in a wealthier location, can with further iterations be used more widely.

Inversely if incremental or modular innovations occur with high benefit, but low cost, and a low roll-out requirement, such as changes in clinical process, these will impact everywhere, independent of income status.

Revisiting and adapting Henderson-Clark within a ***multidisciplinary*** ecosystem may enable a dynamic innovation tailored across different geographies.

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Sheng, Z. (2021), Psychological consequences of erectile dysfunction. Trends Urology & Men Health, 12: 19-22. Link: https://wchh.onlinelibrary.wiley.com/doi/full/10.1002/tre.827

Abiola, Olajide O., et al. "Health seeking behaviour in management of erectile dysfunction among men in an urban African population." International Journal of Reproduction, Contraception, Obstetrics and Gynecology, vol. 7, no. 2, Feb. 2018, pp. 380+ Link: https://www.ijrcog.org/index.php/ijrcog/article/view/4108

European survey shows alarmingly low awareness of erectile dysfunction: Majority does not know what it is. European Association of Urology website. Updated 21 September 2020. Accessed November 2022. **Link:** https://uroweb.org/news/european-survey-shows-alarmingly-low-awareness-of-erectile-dysfunction-majority-does-not-know-what-it-is

Chu CM, et al. Impact of urinary incontinence on female sexual health in women during midlife. Womens Midlife Health. 2015;1:6. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6214215/

Women Don't Have To Tolerate Sexual Dysfunction. University Hospitals. Updated February 2021: Accessed November 2022.Link: https://www.uhhospitals.org/Healthy-at-UH/articles/2021/02/women-dont-have-to-tolerate-sexual-dysfunction

Siddiqui NY, et al. Urinary Incontinence and Health-Seeking Behavior Among White, Black, and Latina Women. Female Pelvic Med Reconstr Surg. 2016;22(5):340-5. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5002243/

Ibine B, et al. "I did not know it was a medical condition": Predictors, severity and help seeking behaviors of women with female sexual dysfunction in the Volta region of Ghana. PLoS One. 2020;15(1):e0226404.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6957185/

Boa, R. (2014). Female sexual dysfunction. *SAMJ: South African Medical Journal*, *104*(6), 445-446. Retrieved November 09, 2022, from http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S0256-95742014000600027

Clinically tested solutions for MSA: therapy, process, diagnostic, device, behaviour

The innovator needs to be aware of what has gone before, what is being done, at what stage other products are. There are three principal sources of information that need to be monitored and understood.

What the clinical KOLs think and do

For most rare diseases, the clinical KOL community is often smaller than for frequent disorders: they will write reviews and perspectives of specific types or classes of therapies that are in development, or may have been used off label.

For multi-tissue indications such as MSA, they also present an opportunity to review

- Treatment evolution
- Possible medical algorithms (diagnostic and treatment)
- Levels of integration into healthcare practice

2010: Flabeau O, et al. Multiple system atrophy: current and future approaches to management. Ther Adv Neurol Disord. 2010;3(4):249-63. **Link**: https://pubmed.ncbi.nlm.nih.gov/21179616/

2015: Perez-Lloret S, et al. Current Concepts in the Treatment of Multiple System Atrophy. Mov Disord Clin Pract. 2015;2(1):6-16. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6183186/

2020: Burns MR, et al. Current Management and Emerging Therapies in Multiple System Atrophy. Neurotherapeutics. 2020;17(4):1582-1602. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7851250/

How they are actually applied in clinical practice

Coon EA, Ahlskog JE. My Treatment Approach to Multiple System Atrophy. Mayo Clin Proc. 2021;96(3):708-719. Link: https://pubmed.ncbi.nlm.nih.gov/33673922/

What new concepts are in earlier stages of development

Heras-Garvin A, Stefanova N. MSA: From basic mechanisms to experimental therapeutics. Parkinsonism Relat Disord. 2020;73:94-104. Link: https://pubmed.ncbi.nlm.nih.gov/32005598/

Lemos M, et al. Current experimental disease-modifying therapeutics for multiple system atrophy. J Neural Transm (Vienna). 2021;128(10):1529-1543. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8528757/

Mészáros L, et al. Current Symptomatic and Disease-Modifying Treatments in Multiple System Atrophy. Int J Mol Sci. 2020;21(8):2775.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7215736/

What is ongoing preclinical to clinical?

While it is possible to screen the internet trying to find all the entities that are developing therapeutics: as projects stop and start, or are cancelled, while experimental and early preclinical work is not often presented, staying current can be problematic.

Sometimes, a review maybe written by a KOL (such as the *Heras-Garvin A and Stefanova N and Lemos M et al* references above), but not always.

Many patient associations actively report on all ongoing projects: those that they have financially contributed to and also those they have not.

The MSA coalition has a dedicated section on their website with this information: On the actual trial sections (ongoing and historical), of this website, there are links to Clinicaltrials.gov, that is presented next.

Link https://www.multiplesystematrophy.org/msa-research/msa-treatment-pipeline/treatment-pipeline-non-pharmaceutical/

What has been performed clinically, including staying current: using Clinicaltrials.gov

The NIH and the U.S. National Library of Medicine organise and maintain 'ClinicalTrials.gov' that is '*A database of privately and publicly funded clinical studies conducted around the world… Explore 432,129 research studies from 221 countries*.' This is an excellent source for innovators, and an extremely valuable source of information. Appendix 3 has suggested tips for searching this database.

'Basket trials'

For some clinical trials, why are there multiple neurological indications listed for the study?

This is a concept termed 'basket trials' and represents a methodology to optimise innovation: as indicated above, regulators understand that diagnosis is difficult, but need is great. It has been widely used for oncological diseases, and for rare neurodevelopmental diseases significantly aids innovative development.

Cummings J, et al. The role of basket trials in drug development for neurodegenerative disorders. Alzheimers Res Ther. 2022;14(1):73. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9131689/

What is presently being clinically tested:

Search location: clinicaltrials.gov **Condition or disease**: Multiple System Atrophy

Filters:

- **Recruiting** (not yet recruiting, recruiting, enrolling by invitation, active not recruiting)
- **Age and sex**: all
- **Study type**: all
- **Study phases**: early phase 1, phase 1, phase 2, phase 3, phase 4 (Therapeutic abbreviated to Tx)

NCT number	Phase/focus	Status	Intervention (phase), or Action	Enrollment (number of patients)
NCT05011773	Tx Early Phase 1	Enrolling by invitation	Device : Deep brain stimulation	20
NCT04620382	Tx Early Phase 1	Recruiting	Drug: Midodrine|Drug: Placebo pill|Device: Abdominal compression|Device: sham compression	31
NCT02726711	Tx Phase 1	Active, not recruiting	Drug: Trimethaphan|Drug: Placebo	2
NCT04685265	Tx Phase 1	Active, not recruiting	Drug: anle138b|Drug: Placebo	72
NCT04495582	Tx Phase 1	Active, not recruiting	Long-term Follow-up of Phase 1 Clinical Trial of CS10BR05(CS10BR05-MSA101)	8
NCT04680065	Tx Phase 1	Recruiting	Biological: AAV2-GDNF gene therapy|Procedure: Sham (Placebo) Surgery	9
NCT04165486	Tx Phase 1	Recruiting	Drug: ION464|Drug: Placebo	40
NCT05274568	Tx Phase 1	Recruiting	Drug: [18F]UCB-2897	14
NCT02429557	Tx Phase 1	Recruiting	Other: Abdominal compression|Other: Sham abdominal compression|Drug: Placebo pill|Drug: midodrine	29
NCT04246437	Tx Phase 1	Recruiting	Drug: [18F]FDOPA|Drug: Carbidopa 200mg oral dose|Drug: Entacapone 400mg oral dose	40
NCT02897063	Tx Phase 1	Recruiting	Drug: Droxidopa|Drug: Midodrine|Drug: Placebo	34
NCT05532358	Tx Phase 1	Recruiting	Drug: anle138b (TEV-56286)|Drug: Fluvoxamine 100 mg QD for 5 days	56
NCT02315027	Tx Phase 1|Phase 2	Active, not recruiting	Biological: Autologous Mesenchymal Stem Cells	30
NCT03482297	Tx Phase 1|Phase 2	Recruiting	Device: automated abdominal binder|Device: Sham binder|Drug: Placebo|Drug: Midodrine	31
NCT04876326	Tx Phase 1|Phase 2	Recruiting	Biological: Autologous Adipose Mesenchymal Stem Cell Implantation|Biological: Allogeneic Umbilical Cord Mesenchymal Stem Cell Implantation|Biological: Allogeneic Umbilical Cord Mesenchymal Stem Cell and Adipose Secretome Implantation	15
NCT05526391	Tx Phase 2	Not yet recruiting	Drug: TAK-341|Drug: Placebo	138
NCT05104476	Tx Phase 2	Recruiting	Drug: Lu AF82422|Drug: Placebo	60
NCT05109091	Tx Phase 2	Recruiting	Drug: ATH434 dose level 1|Drug: ATH434 dose level 2|Drug: Placebo	60
NCT05167721	Tx Phase 2	Recruiting	Biological: Autologous Mesenchymal Stem Cells|Other: Placebo	76
NCT04431713	Tx Phase 2	Recruiting	Drug: Exenatide Pen Injector [Bydureon]	50
NCT03901638	Tx Phase 3	Recruiting	Drug: Tllsh2910|Drug: Placebo	60
NCT03924414	Tx Phase 4	Recruiting	Drug: Zoledronic Acid 5Mg/Bag 100Ml Inj|Other: Placebo	3500

NCT05127057	Clinical procedure	Not yet recruiting	Proactive and Integrated Management and Empowerment in Parkinson's Disease (PRIME-UK): A New Model of Care (PRIME-RCT)	214
NCT04250493	Clinical procedure	Recruiting	Insulin Resistance in Multiple System Atrophy	124
NCT05121012	Clinical procedure	Recruiting	Synaptic Loss in Multiple System Atrophy	20
NCT03811808	Clinical procedure	Recruiting	Multiple System Atrophy Multidisciplinary Clinic	200
NCT03648905	Clinical procedure	Recruiting	Clinical Laboratory Evaluation of Chronic Autonomic Failure	140
NCT02795052	Clinical procedure	Recruiting	Neurologic Stem Cell Treatment Study: Procedure: Intravenous and Intranasal BMSC	500
NCT04706234	Clinical procedure	Recruiting	Systematic Assessment of Laryngopharyngeal Function in Patients With MSA, PD, and 4repeat Tauopathies	200
NCT04844060	Clinical procedure	Recruiting	Cerebro Spinal Fluid Collection (CSF): Other: Lumbar punction	10000
NCT05486806	Long studies/PROMs	Not yet recruiting	Longitudinal Tracking of Patients Diagnosed With Neurodegenerative Movement Disorders: Drug: 18F-PBR06|Radiation: 18F-PBR06	50
NCT02701036	Long studies/PROMs	Recruiting	Sporadic Degenerative Ataxia With Adult Onset: Natural History Study	300
NCT01799915	Long studies/PROMs	Recruiting	Natural History Study of Synucleinopathies	800
NCT02194816	Long studies/PROMs	Recruiting	Modifiable Variables in Parkinsonism (MVP)	2000
NCT04450992	Long studies/PROMs	Recruiting	TRACK-MSA: A Longitudinal Study to Define Outcome Measures in Multiple System Atrophy	50
NCT02778607	Long studies/PROMs	Recruiting	PROgressive Supranuclear Palsy CorTico-Basal Syndrome Multiple System Atrophy Longitudinal Study UK	900
NCT04965922	Long studies/PROMs	Recruiting	Quality of Life of Caregivers and Patients Suffering From Multiple System Atrophy	144
NCT04229173	Diagnostic	Active, not recruiting	Natural History and Disease Progression Biomarkers of Multiple System Atrophy	60
NCT03269201	Diagnostic	Enrolling by invitation	Brain Network Activation in Patients With Movement Disorders	300
NCT04700722	Diagnostic	Recruiting	Synuclein-One Study: Diagnostic Test: Skin Biopsy	500
NCT05453058	Diagnostic	Recruiting	Observational Study in Multiple System Atrophy: Diagnostic Test: plasma NfL and brain MRI (vMRI, DTI, and ASL [if feasible]) only for the EU cohort	140
NCT03872102	Diagnostic	Recruiting	Facilitating Diagnostics and Prognostics of Parkinsonian Syndromes Using Neuroimaging	90
NCT04518059	Diagnostic	Recruiting	Misfolded Proteins in the Skin of People With Parkinson's Disease and Other Parkinsonism	250
NCT03577483	Diagnostic	Recruiting	Differential Diagnosis Between Parkinson's Disease and Multiple System Atrophy Using Digital Speech Analysis	90
NCT03174938	Diagnostic	Recruiting	The Swedish BioFINDER 2 Study: Diagnostic Test: Flutemetamol F18 Injection|Diagnostic Test: [18F]-RO6958948|Diagnostic Test: Elecsys (Roche) Abeta42, Ttau and Ptau|Diagnostic Test: Lumipulse (Fujirebio) Abeta42, Ttau and Ptau	1505
NCT02114242	Biomarkers	Recruiting	Biomarkers in Parkinsonian Syndromes	100
NCT04020198	Biomarkers	Active, not recruiting	A Pilot Biomarker Study Assessing Alpha-synuclein Aggregates Across Biofluid Reservoirs in Patients With Synucleinopathies	8
NCT03623672	Communities	Enrolling by invitation	North American Prodromal Synucleinopathy Consortium	500
NCT05222386	Communities	Recruiting	Community Outreach for Palliative Engagement — Parkinson Disease	710

NCT04472130	Patient registry	Recruiting	Neurodegenerative Diseases Registry	1400
NCT01793168	Patient registry	Recruiting	Rare Disease Patient Registry & Natural History Study — Coordination of Rare Diseases at Sanford	20000
NCT02994719	Device	Active, not recruiting	Gait Analysis in Neurological Disease	120
NCT04313530	Device	Enrolling by invitation	TMS Treatment in Multiple System Atrophy With Fatigue	22
NCT03042988	Device	Recruiting	Overnight Trials With Heat Stress in Autonomic Failure Patients With Supine Hypertension: Other: Heating pad|Other: Sham control	20
NCT05197816	Device	Recruiting	MotIoN aDaptive Deep Brain Stimulation for MSA	5
NCT05557786	Device	Recruiting	Treatment of Transcranial Alternating Current Stimulation（tACS）on Cerebellar Ataxia	164
NCT05171205	Device	Recruiting	Spinal Cord Stimulation for Multiple System Atrophy	33
NCT03312556	Device	Recruiting	Treatment of Supine Hypertension in Autonomic Failure (CPAP)	12
NCT04782830	Device	Recruiting	Use of Accelerometer for Quantification of Neurogenic Orthostatic Hypotension Symptoms	29
NCT05489575	Device	Recruiting	CPAP for the Treatment of Supine Hypertension	59
NCT04920552	Device	Recruiting	Abdominal Binders to Treat Orthostatic Hypotension in Parkinsonian Syndromes: Device: Elastic abdominal binder|Device: Placebo binder	30
NCT05139342	Device	Recruiting	Evaluation of the Efficacy of a Two-week EMST on Dysphagia in Parkinsonian Patients: Device: expiratory muscle strength training (EMST)	75
NCT04617873	Device	Recruiting	DBS and SCS Therapy Improve Motor Function in Multiple System Atrophy With Predominant Parkinsonism	20
NCT03593512	Device	Recruiting	Deep Brain Stimulation for Autonomic and Gait Symptoms in Multiple System Atrophy	10
NCT04468919	Rehabilitation	Recruiting	Optimizing BCI-FIT: Brain Computer Interface — Functional Implementation Toolkit	60
NCT04782284	Rehabilitation	Recruiting	Comprehensive Swallowing Rehabilitation in Patients With MSA	24
NCT05238545	Lifestyle	Recruiting	The Effect of Gluten-free Diet on Parkinsonism	90
NCT04608604	Lifestyle	Recruiting	Mobility in Atypical Parkinsonism: a Trial of Physiotherapy	180

What was previously clinically tested:

When looking at completed studies a side-by-side comparison is needed with ongoing studies: so, if a therapeutic completed its phase 1, did it or has it transitioned into a phase 2 study or further. When analysing the clinicaltirals.gov database, the user can also select start and end dates, that permit this to be mapped. If it did not proceed further, or has not, the innovator should consider entering into discussion with KOLs to determine potential reasons.

Search location: clinicaltrials.gov **Condition or disease**: Multiple System Atrophy

Filters:

- **Recruiting** (completed)
- **Age and sex**: all
- **Study type**: all
- **Study phases**: early phase 1, phase 1, phase 2, phase 3, phase 4 (Therapeutic abbreviated to Tx)

NCT number	Phase/focus	Status	Intervention (phase), or Action	Enrollment (number of patients)
NCT04616456	Early Phase 1	Completed	Drug: [F-18]PBR06|Drug: Verdiperstat	19
NCT02214862	Early Phase 1	Completed	Drug: [F18]-FDDNP	40
NCT03265444	Phase 1	Completed	Biological: CS10BR05	9
NCT00103597	Phase 1	Completed	Drug: Fludrocortisone|Drug: Domperidone|Behavioral: Conservative Measures for Orthostatic Hypotension	50
NCT02270489	Phase 1	Completed	Biological: AFFITOPE® PD01A + Adjuvant|Biological: AFFITOPE® PD03A + Adjuvant|Biological: Adjuvant without active component	30
NCT00179023	Phase 1	Completed	Drug: Trimethaphan|Drug: Pseudoephedrine	128
NCT00223717	Phase 1	Completed	Drug: Clonidine|Drug: Nitroglycerin transdermal|Drug: Dipyridamole/ Aspirin (Aggrenox)|Drug: Desmopressin (DDAVP)|Drug: Sildenafil|Drug: Nifedipine|Drug: Hydralazine|Drug: Hydrochlorothiazide|Drug: Placebo|Drug: Bosentan|Drug: Diltiazem|Drug: Eplerenone|Drug: guanfacine|Dietary Supplement: L-arginine|Drug: captopril|Drug: carbidopa|Drug: losartan|Drug: metoprolol tartrate|Drug: nebivolol hydrochloride|Drug: prazosin hydrochloride|Drug: tamsulosin hydrochloride|Other: Head-up tilt.|Drug: aliskiren|Other: Local heat stress	152
NCT04208152	Phase 1	Completed	Drug: anle138b|Drug: Placebo	68
NCT03403309	Phase 2	Completed	Drug: 1) Inosine 5'-monophosphate|Drug: Placebo	43
NCT00750867	Phase 2	Completed	Drug: intravenous immunoglobulin (IVIg)	9
NCT01146548	Phase 2	Completed	Drug: FLUOXETINE	87
NCT00911365	Phase 2	Completed	Biological: autologous mesenchymal stem cells|Biological: normal saline	27
NCT00977665	Phase 2	Completed	Drug: rasagiline mesylate|Drug: placebo	174
NCT02064166	Phase 2	Completed	Drug: Intranasal Insulin	15
NCT03753763	Phase 2	Completed	Drug: Safinamide Methanesulfonate|Drug: Safinamide Methanesulfonate matching placebo	49
NCT02388295	Phase 2	Completed	Drug: AZD3241|Drug: Placebo	59
NCT04184063	Phase 2	Completed	Drug: NBMI|Other: Placebo	20
NCT02705755	Phase 2	Completed	Drug: TD-9855|Drug: Placebo	34
NCT00202397	Phase 2	Completed	Drug: Riluzole|Other: placebo	40
NCT02071459	Phase 2|Phase 3	Completed	Drug: L-Threo DOPS|Drug: placebo	107
NCT03952806	Phase 3	Completed	Drug: Verdiperstat|Drug: Placebo	336
NCT02008721	Phase 3	Completed	Drug: EGCG as putative neuroprotective agent|Drug: Placebo	92
NCT00146809	Phase 3	Completed	Drug: Minocyline	60
NCT04193527	Phase 3	Completed	Drug: DaTSCAN™ Ioflupane (123I) Injection	172
NCT00738062	Phase 3	Completed	Drug: Droxidopa|Drug: Placebo	103

NCT03750552	Phase 3	Completed	Drug: ampreloxetine|Drug: Placebo	195
NCT00782340	Phase 3	Completed	Drug: Placebo|Drug: Droxidopa	263
NCT00633880	Phase 3	Completed	Drug: Placebo|Drug: Droxidopa	181
NCT02586623	Phase 4	Completed	Drug: Droxidopa capsules|Drug: Placebo capsules	254
NCT03552484	Behavioral	Completed	Behavioral: Home Visit Program|Behavioral: Usual Care/Online Survey	71
NCT03076671	Behavioral	Completed	Behavioral: Palliative Care	783
NCT03452956	Behavioral	Completed	Other: None-Observation Only, Cognitive Impairement In Frontotemporal Dementia	997
NCT00742586	biomarker	Completed	Autonomic Failure Patients for RNA Blood Sampling	30
NCT02761707	biomarker	Completed	Biomarkers in Neural Disorders	54
NCT01888185	biomarker	Completed	Identifying Biomarkers of Parkinson's Disease Using Magnetic Resonance Imaging (MRI)	290
NCT01485549	biomarker	Completed	Oligomeric Alpha-synuclein in Multiple System Atrophy	48
NCT05067192	biomarker	Completed	Optimization of Morphomer-based Alpha-synuclein PET Tracers	12
NCT01353183	biomarker	Completed	Procedure: colonoscopy or rectosigmoidoscopy	34
NCT00465790	Biomarker	Completed	Research of Biomarkers in Parkinson Disease	219
NCT02640339	Biomarker	Completed	Retinal Abnormalities as Biomarker of Disease Progression and Early Diagnosis of Parkinson Disease	166
NCT01155492	Clinical procedure	Completed	Increased Gut Permeability to Lipopolysaccharides (LPS) in Parkinson's Disease	43
NCT01044992	Clinical procedure	Completed	Radiation: H215O PET|Drug: Levodopa	38
NCT04153110	Device	Completed	Device: Anodal cerebellar and cathodal spinal tDCS|Device: Sham cerebellar and sham spinal tDCS	61
NCT03120013	Device	Completed	Device: Anodal cerebellar and cathodal spinal tDCS|Device: Sham cerebellar and sham spinal tDCS	21
NCT04595578	Device	Completed	Device: Cerebellar repetitive transcranial magnetic stimulation	34
NCT00743561	Device	Completed	Device: Polysomnography|Device: ambulatory polygraphy	30
NCT04925622	diagnostic	Completed	Complex Eye Movements in Parkinson's Disease and Related Movement Disorders	90
NCT02132052	diagnostic	Completed	Defining Phenotypes of Movement Disorders :Parkinson's Plus Disorders (PD), Essential Tremor (ET), Cortical Basal Degeneration (CBD), Multiple Systems Atrophy (MSA), Magnetoencephalography.	81
NCT00001549	diagnostic	Completed	Diagnosis and Natural History Study of Patients With Neurological Conditions	600
NCT04858893	diagnostic	Completed	Diagnostic Test: CoMDA associated with Neural Net 91 classificator, Application of Machine Learning Method in Validation of Screening Cognitive Test for Parkinsonisms	562
NCT04287270	diagnostic	Completed	Other: Assesment	19
NCT02428816	diagnostic	Completed	Other: MRI acquisition|Behavioral: behavioral evaluations	94
NCT02035761	diagnostic	Completed	PET Imaging Study of Neurochemical and Autonomic Disorders in Multiple System Atrophy (MSA)	23
NCT01136213	diagnostic	Completed	Radiation: PET (Positron Emission Tomography) Study|Other: Brain MRI (magnetic resonance imaging)|Drug: Fluoxétine / PlaceboInvestigation of the Serotoninergic System in Multiple System Atrophy: a Positron Emission Tomography (PET) Study	53
NCT00368199	diagnostic	Completed	Transcranial Duplex Scanning and Single Photon Emission Computer Tomography (SPECT) in Parkinsonian Syndromes	196
NCT00004478	Drug no trial	Completed	Drug: droxidopa	NI
NCT01577992	Drug no trial	Completed	Drug: Levodopa test|Procedure: determination of objective and subjective pain threshold	42
NCT01044693	Drug no trial	Completed	Drug: Placebo|Drug: Nebivolol 5 mg|Drug: metoprolol tartrate 50 mg|Drug: Sildenafil25 mg	20
NCT01316666	Long studies	Completed	Norepinephrine Transporter Blockade as a Pathological Biomarker in Neurogenic Orthostatic Hypotension	50
NCT02185677	Long studies	Completed	Other: Clinical evaluation|Other: neuropsychological battery test|Other: MRI|Other: Actigraphy Cognitive and Behavioral Dysexecutive Syndrome in Multiple System Atrophy	40
NCT02417415	Long studies	Completed	Other: Passive heat stress|Other: Control (non-heating)	22

Which clinically studies were terminated:

It is also important to look at terminated clinical studies: some studies are designed to prove that an approach is not offering benefit (futility studies): this is an important concept and approach for reducing resource and time wastage.

Search location: clinicaltrials.gov **Condition or disease**: Multiple System Atrophy

Filters:

- **Recruiting** (terminated)
- **Age and sex**: all
- **Study type**: all
- **Study phases**: early phase 1, phase 1, phase 2, phase 3, phase 4 (Therapeutic abbreviated to Tx)

NCT number	Phase/focus	Status	Intervention (phase), or Action	Enrollment (number of patients)
NCT02149901	Early Phase 1	Terminated	Drug: Pseudoephedrine + 480 ml water|Drug: Pseudoephedrine + 50 ml water|Other: Placebo + 480 water (optional)|Other: Placebo + 50 ml water (optional)	35
NCT02591173	Early Phase 1	Terminated	Drug: Angiotensin-(1-7)|Drug: Saline	7
NCT01292694	Phase 1	Terminated	Drug: Losartan|Drug: Captopril|Drug: Placebo	12
NCT00547911	Phase 1|Phase 2	Terminated	Drug: Droxidopa|Drug: Carbidopa|Drug: Entacapone	14
NCT03589976	Phase 2	Terminated	Drug: Sirolimus 2 MG|Other: Placebo	47
NCT00997672	Phase 2	Terminated	Drug: Lithium Carbonate|Drug: Placebo	10
NCT01287221	Phase 3	Terminated	Drug: Rifampicin|Drug: placebo	100
NCT00211224	Phase 3	Terminated	Drug: Riluzole	800
NCT01927055	Phase 3	Terminated	Drug: Droxidopa|Drug: Placebo	61
NCT01607268	Imaging	Terminated	Procedure: Magnetic Resonance Spectroscopy Imaging	6
NCT00059033	Process	Terminated	Evaluation of Primary Chronic Autonomic Failure	325
NCT02445469	Imaging	Terminated	Other: MRI exam of the brain	130
NCT00745030	Not Applicable	Terminated	Drug: Rozerem|Drug: Placebo	3

Digital health: global IT infrastructure and software solutions

For rare neurodegenerative disorders, digital health solutions have to be carefully considered: creation of digital dependency probably frustrates the majority of the planet when a system has to update, or the connectivity is not strong enough, or a power cut turns off all the devices, including the router. For cognitive support, patient care and monitoring, reminders for prescription, aspects of neurodegenerative disorders creating dependency on a digitally facing solution that can be disrupted by the above normal events, will likely cause significant distress.

During the design phase, a '***what if***' role play is suggested to be performed, as a function of impact of the solution not working, and the resolution to the problem clearly identified. If that cannot be performed, then reflection, not only on design, but where and how the solution can be applied in the healthcare pathway has to be performed. This may mean the design of an initial incremental solution: but if rolled out over a greater geography, its impact may be significantly more.

This particular aspect has 2 forms of relevance, feasibility, as the experiences on digital health roll-out in LMIC indicate below, but also on direct benefit to patients with MSA and neurodegenerative disease. Digital health solutions in all their formats are dependent on two infrastructures: fixed connection or fibre optic, that for example would be used for good quality telemedicine, and mobile internet, potentially used for remote monitoring, self-management applications and potential point-of-care IT integrated solutions.

In LMIC, the speed of IT development has meant mobile coverage is being developed faster than fibre optics. For the digitally focused innovator 2 connection availability resources are recommended.

Global mobile internet coverage:

The GSMA mobile connectivity index represents an annual update and map country by country of critical parameters related to connectivity:

- Infrastructure
- Affordability
- Consumer readiness
- Content and services

Link: https://www.mobileconnectivityindex.com/#year=2021

Global internet (fixed and mobile) coverage:

For fixed line and fibre optic availability, the International Telecommunication Union, generates an annual Global Connectivity report, that can be downloaded. It is a thorough and comprehensive assessment in key regions of

- Fixed vs. mobile subscriptions and affordability
- Percent of population using the internet
- Differences between urban and rural areas
- Percent of population within reach of an operational fibre-optic network, by distance

Link: https://www.itu.int/hub/publication/d-ind-global-01-2022/

Evidence of digital healthcare provision in LMIC and a global guide: what works

Known barriers related cost of the subscription, digital literacy across all users and **cost of the device**. But there is space for social innovation and philanthropic entrepreneurship, if there is a motivation. The possibility to trade-in a device when buying a new one (phone, tablet or computer) could have *an additional option for the customer*: the entity could offer to refurbish, tailor with the needed apps/software and *give it for free to HCPs in LMIC* to distribute to their patients during their diagnosis and treatment period to enable a step towards better care.

The following articles have been selected as they are peer-reviewed and based on evidence obtained through actual usage in LMICs. While focused on low resource settings, these insights have equal pertinence in wealthier countries, where healthcare resources are also strained (albeit at a different level).

Dodoo JE, et al. The development of telemedicine programs in Sub-Saharan Africa: Progress and associated challenges. Health Technol (Berl). 2022;12(1):33-46. **Link**: https://pubmed.ncbi.nlm.nih.gov/34849325/

Owolabi, E.O., et al. Telemedicine in Surgical Care in Low- and Middle-Income Countries: A Scoping Review. World J Surg 46, 1855–1869 (2022). **Link:** https://link.springer.com/article/10.1007/s00268-022-06549-2

Acharibasam JW, Wynn R. Telemental Health in Low- and Middle-Income Countries: A Systematic Review. Int J Telemed Appl. 2018;2018:9602821. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6241375/

Labrique, A.B., et al. Best practices in scaling digital health in low and middle income countries. Global Health 14, 103 (2018). **Link:** https://globalizationandhealth.biomedcentral.com/articles/10.1186/s12992-018-0424-z

Telehealth around the world: A global guide, from DLA PIPER, written in 2020. *Visit the link, on the right-hand side is 'download pdf' that then permits downloading the full handbook* **Link:** https://www.dlapiperintelligence.com/telehealth/countries/index.html?t=01-availability-of-telehealth

Tele-education can be used extensively for medical education in most SSA countries… it can address the challenges associated with the lack of telemedicine expertise among clinicians, ethical and privacy concerns, which were identified as barriers to the successful implementation of telemedicine systems…it can address the challenges associated with the lack of telemedicine expertise among clinicians, ethical and privacy concerns, which were identified as barriers to the successful implementation of telemedicine systems.

Dodoo JE, et al (link above)

The comprehensive regulations of Telemedicine across borders are detailed in the DLA PIPER reference above. This should be read in detail, with regard to potential mobile based imaging, and transfer and storage of patient data outside of the country of origin with regard to privacy regulations. The shortage of radiologists is suggested international exchange but this needs careful consideration.

The International Parkinson and Movements Disorder Society has created a dedicated section on **telemedicine,** including:

- Telemedicine personal experiences and latest peer reviewed publications on telemedicine in movement disorder management

Link: https://www.movementdisorders.org/MDS/Telemedicine-Resources.htm

- Instructions and a step-by-step guide for the creation of Telemedicine systems and clinics

Link: https://www.movementdisorders.org/MDS/About/Committees—Other-Groups/Telemedicine-in-Your-Movement-Disorders-Practice-A-Step-by-Step-Guide.htm

With regard to specific '**mobile applications'** used for movement disorders, there are two comprehensive lists available from the International Parkinson and Movements Disorder Society and DefeatMSA: in both cases, it is explicitly stated that the list does not represent a recommendation, and that the digital solution should be discussed in detail between the HCP and the patient prior to use.

***Link:** https://www.movementdisorders.org/MDS/Application-Repository.htm

Link: https://defeatmsa.org/patient-programs/assistive-communication/

*For the IPMDS, they also have an added function, involving submitting your app for review by them prior to listing on their website.

Their offer is particularly relevant for the digital health developer when placed in context of the publications below that provide updated insight on digital health for movement related disorders:

Schmitz-Luhn B, et al. Ethical and Legal Aspects of Technology-Assisted Care in Neurodegenerative Disease. J Pers Med. 2022;12(6):1011. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9225587/

LoBuono DL, et al. Acceptance and perception of digital health for managing nutrition in people with Parkinson's disease and their caregivers and their digital competence in the United States: A mixed-methods study. Health Sci Rep. 2021;4(4):e412. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8581626/

De Marchi F, et al. Telehealth in Neurodegenerative Diseases: Opportunities and Challenges for Patients and Physicians. Brain Sci. 2021;11(2):237. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7917616/

Riggare S, et al. A Long Way to Go: Patient Perspectives on Digital Health for Parkinson's Disease. J Parkinsons Dis. 2021;11(s1):S5-S10.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8385497/

Spreadbury JH, et al A Comprehensive Literature Search of Digital Health Technology Use in Neurological Conditions: Review of Digital Tools to Promote Self-management and Support J Med Internet Res 2022;24(7):e31929 **Link**: https://www.jmir.org/2022/7/e31929

In addition to creating digital dependency and the impact of informatic failure on the provision of the solution and welfare of the patient, digital solutions for rare neurodegenerative disorders that can manifest with severe symptoms need to have '*and then what happens?*..' reflection, as a function of available infrastructure and ease of access to it.

The global shortage of neurologists means that for many people with rare neurodegenerative diseases they are often a long distance from informed and specialised care, even if the nearest clinical centre is down the road.

Considerations as a function of disease progression and pathogenesis should include:

Digital literacy of the patient
How easy is it to initiate using the approach
What is its source, & availability of energy
Are there evidence requirements needed before roll out
Can it be used with the existing connectivity
Motivation of the HCP to want to learn

Digital literacy of the HCP
Is technical support needed when it stops working
Impact of culture or religion on technology usage
Family pressure
Level of training needed

Digital Literacy: Digital literacy cannot be solved with a user guide. It represents a balanced equation, the components of which become more complex with continued use and expansion. A well-designed digital solution that addresses all needs and creates benefit will generate impact: it will also create a dependency. In healthcare implementation, such as a patient with MSA transitioning to a disease state that needs urgent care, if dependency has been created through utility, but then the system fails can be very harmful. Healthcare infrastructures rarely have the resources to dedicate to urgent informatic correction. The question then becomes in additional to ease of use, how easy is it for the users to resolve issues and maintain functionality, without support when a different part of the digital infrastructure fails.

Costs of treatment

The personalised experience of symptom manifestation means that obtaining a precise medication cost is difficult. The study of McCrone P et al, analysed the complete medical costs for patients with MSA, from France Germany and the UK with the following parameters:

- The inclusion criterium was a confirmed diagnosis of akinetic-rigid syndrome (bradykinesia: slowness of movement)
- Patient characteristics indicated a mean disease duration of 4.5 years
- Mean costs were collected over 3 years

McCrone P, et al. The economic costs of progressive supranuclear palsy and multiple system atrophy in France, Germany and the United Kingdom. PLoS One. 2011;6(9):e24369. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169589/

Based on the 2015 pathogenesis from Fanciulli A et al and the diagnostic criteria for MSA from 2022, this would place the patients in the possible/probable patient group.

Earlier healthcare costs related to premotor symptoms would not be included in these costs. Annual Urinary Incontinence care costs have been reported to be up to €900, Erectile dysfunction 595 and female sexual dysfunction around €540.

Subak LL, et al; Diagnostic Aspects of Incontinence Study Group. The "costs" of urinary incontinence for women. Obstet Gynecol. 2006 r;107(4):908-16.**Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1557394/

Goldmeier, D, et al. Cost implications of sexual dysfunction: the female picture. International Journal of Impotence Research, vol. 16, no. 2. 2004, p. 130.**Link**: https://pubmed.ncbi.nlm.nih.gov/14961049/

Their data was reported as mean 6-month costs (at euro equivalent at time of publication for Euro/GBP conversions), but in the table below, we have adapted this figure to annual costs.

Table 13: mean annual costs for patients with MSA over a three-year period (all prices in €)

	France		Germany		UK	
Description	Mean	SD	Mean	SD	Mean	SD
Neurologist	198	232	260	338	868	800
Other doctor	54	122	104	196	206	368
Day patient	684	1700	102	664	1518	8400
Residential care	1908	8698	448	5210	1678	8746
Neurology inpatient	790	3008	3964	6654	1094	3108
Other inpatient	3328	16962	2890	9850	1352	4482
GP	252	228	184	322	274	348
Physiotherapist	1546	1616	1728	1466	410	980
Social worker	1120	9200	6	42	172	414
Nurse	730	2052	642	3252	214	880
Speech therapist	480	1000	468	950	118	390
Home help	1254	3686	716	5200	694	2438
Blood test	42	86	100	172	44	76
CT scan	26	100	30	92	36	124
EEG	6	26	16	36	6	24
MRI	112	272	144	228	156	366
Prostheses	70	84	72	90	46	62
Adaptations	152	266	240	354	158	288
Unpaid care	42260	57162	38072	48098	28372	41278
Medication	724	668	634	1018	452	652
Total	57848	58634	51290	48568	38206	42744

Table adapted from McCrone P, et al. The economic costs of progressive supranuclear palsy and multiple system atrophy in France, Germany and the United Kingdom. PLoS One. 2011;6(9):e24369. ***Link:*** *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169589/ following the Creative Commons license http://creativecommons.org/licenses/by/4.0/. Adaptations made were doubling of cost figures to generate annual costs and number of patients reporting using health care unit.*

For definitions of the descriptions the reader is referred to the original publication.

When they stratified the patient population by severity, the total costs on averaged increased 4-fold from mildest reported symptom group to the most severe symptom groups (see figure 2 of publication).

It could be hypothesized that the most severe symptom groups would possibly correspond to later stage healthcare costs which would mean annual costs reaching over 70,000 euros per patient.

Absenteeism, reduced employment and disability income were not included in the calculations, but if data from the economic burden of Parkinson's Disease in the US is extrapolated to the calculation, this could possibly increase the total values indicated above by 20%.

Yang, W., et al. Current and projected future economic burden of Parkinson's disease in the U.S. npj Parkinsons Dis. 6, 15 (2020). **Link:** https://www.nature.com/articles/s41531-020-0117-1

Some final considerations for the innovator:

Join the dots: before designing, consider the whole ecosystem and the actors in it. Look at solutions that have been designed and rolled out, but maybe not expanded. If innovations are adapted, made multi-lingual combined, and those opportunities definitely exist for PE based on the work that has been done already by all the stakeholders; don't forget it still needs validation in a clinical setting.

PICO: Patient population, Intervention(product), Comparator, Outcome, should be applied to every type of product. The broader the impact the product, the more data and sensitivity you will need, especially if it's anything non-interventional that potentially results in a medical intervention. Rare disease patient populations are heterogeneous: their low number means precise pathogenesis is often incomplete, and as indicated above pathogenesis greatly impacts the type of innovation and its design.

Factor that in: you may consider your innovation to be applicable to a whole Rare Disease patient population, but often solutions are applicable to specific symptoms, age groups, phases or stages and underlying morbidities, or other SDOH related risks that the patient may be exposed to, some of which may be responsible for an idiopathic occurrence.

There is always a comparator, even in Rare Diseases, where interventions do not currently exist. In addition to direct clinical impacts, is your planned product reducing caregiver related burdens and costs, does it reduce burden on HCPs and/or processes, or will it increase the needs for more specialists and dedicated facilities, is your solution equitable, are you addressing the needs of one stakeholder, many or all of them?

Health Economic and Outcomes Research (HEOR): the aspect a lot of Innovators think about too late, it is not the same as clinical outcome, take a short online course on it or HTA to introduce it to yourself. While review and approval bodies are not always national or centralized, the economic evidence assessments they use tend to be based on the same concepts and then adjusted locally. Note that perspectives and calculations of value differ between locations (QALYs vs DALYs, differing PROMs, accepted outcomes).

The ISPOR US Healthcare System Overview-Decision makers and influencers gives a good illustration of what is needed from the pharmacoeconomic angle: https://www.ispor.org/heor-resources/more-heor-resources/us-healthcare-system-overview

While global country information, where available, can be found at their around the world section https://www.ispor.org/heor-resources/more-heor-resources/pharmacoeconomic-guidelines

Note that most of these only apply to therapeutic application, med tech, diagnostics, healthcare process, and now digital health, have differing requirements and are often not nationally homogenous.

Social determinants of health and wealthy countries vs. LMIC

Many available existing sources of information do not include every stakeholder or perspective, and some innovators may not know where to look, to complete the picture. Especially when evidence is generated in different geographies with different healthcare infrastructures e.g., Universal healthcare vs private or hybrid, timing and location of evidence generation and influence of Social Determinants of Health (SDOH) on the patient, their journey, quality of life, available care or infrastructure and epidemiological data.

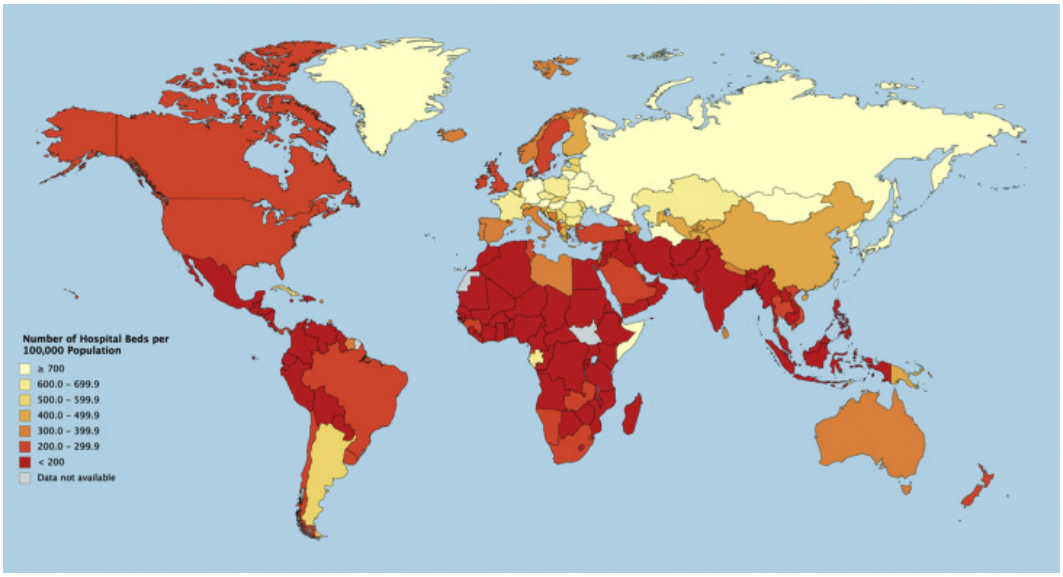
This is relevant for all countries irrespective of overall recognised income status. With this perspective, it may make the identification and development of innovative solutions for Rare Diseases global by design: solutions designed for wealthy countries (even if incidence and prevalence maybe influenced by socioeconomic status, ethnicity and gender within them), where available specialised Rare Disease healthcare is sparse, and SDOH and lifestyle risks can symptoms, may with partnering and redesign be applicable for patients with Rare Diseases in Low- and Middle-Income Countries, where resources are even more stretched, and *vice versa*.

Appendices:

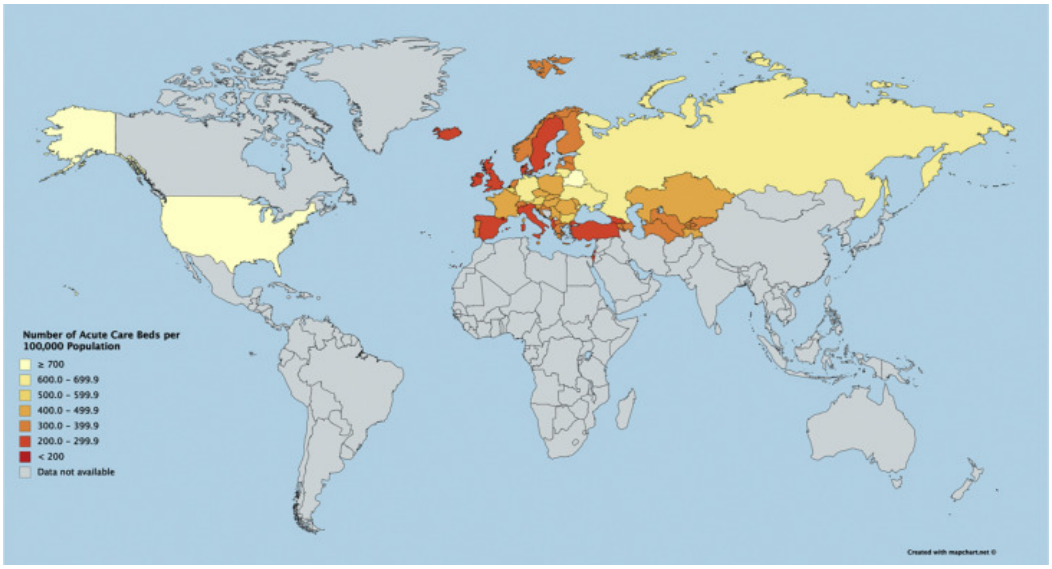
Appendix 1: Healthcare infrastructure as increased hospitalisation

Hospital bed capacity

1) Number of hospital beds per 100,000 population

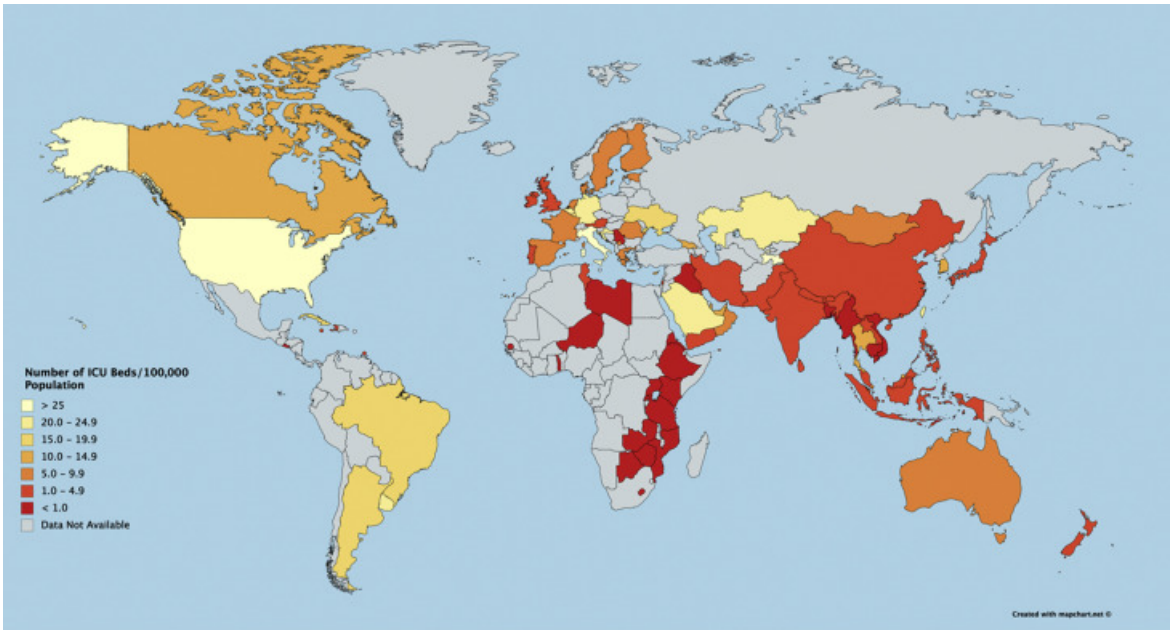


2) Number of acute care beds per 100,000 population



3) Number of ICU beds per 100,000 population

‘



Source of charts: Sen-Crowe B, et al. A Closer Look Into Global Hospital Beds Capacity and Resource Shortages During the COVID-19 Pandemic. J Surg Res. 2021;260:56-63. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7685049/ (Reproduced following the copyright and license information published on Elsevier connect)

Appendix 2: Innovation development costs (ball park figures: US Marketplace, unknown for LMIC) and pricing considerations for rare diseases

- Rapid POC diagnostic development: 1.4 million USD
- Standard in vitro diagnostic development: 2.5 to 2.8 million USD
- App or Wearable technology development: 425,000 to 500,000 USD
- Electronic Healthcare Record: 150,000 USD
- Health Tracker: 200,000 USD
- Imaging agent: 100 to 150 million USD
- New software solution for imaging platform: 50,000 to 400,000 USD
- Orphan drug (chemical entity/new molecular entity type) 250 million USD (*see Berdud et al, Jayasundara et al refs below*). This changes as a function of whether:
    - the drug is a biologic (antibody, peptide) or an advance therapy medical product (gene therapy, bioengineering)
    - If the rare disease is oncology focused or not (rare oncological diseases have similar patient number requirements as frequent oncological, whereas on average for orphan drugs 2 to 5 fold lower requirement in patient number based on phase of development)

Ball Park figures excludes costs of:

- Multiple clinical trial requirements within and across geographies
- Level of uniqueness of solution (costs can significantly increase to address statistical relevance, long-term impact and evidence requirements if significantly different to existing standard-of-care)
- Post approval studies can cost approximately a further 6 million USD.

Berdud, M., Drummond, M.F., and Towse, A. (2018) Establishing a Reasonable Price for an Orphan Drug. OHE Research Paper**. Available from** https://www.ohe.org/publications/establishing-reasonable-price-orphan-drug#.

Jayasundara K, Hollis A, Krahn M, Mamdani M, Hoch JS, Grootendorst P. Estimating the clinical cost of drug development for orphan versus non-orphan drugs. Orphanet J Rare Dis. 2019 Jan 10;14(1):12. **Link:** https://pubmed.ncbi.nlm.nih.gov/30630499/

Yates, N. and Hinkel, J. (2022), The economics of moonshots: Value in rare disease drug development. Clin Transl Sci, 15: 809-812. **Link:** https://ascpt.onlinelibrary.wiley.com/doi/10.1111/cts.13270

Villa F, Di Filippo A, Pierantozzi A, Genazzani A, Addis A, Trifirò G, Cangini A, Tafuri G, Settesoldi D and Trotta F (2022) Orphan Drug Prices and Epidemiology of Rare Diseases: A Cross-Sectional Study in Italy in the Years 2014–2019. Front. Med. 9:820757. **Link:** https://www.frontiersin.org/articles/10.3389/fmed.2022.820757/full

Pearson C, Schapiro L, Pearson SD. The next generation of rare disease drug policy: ensuring both innovation and affordability. J Comp Eff Res. 2022 Oct;11(14):999-1010. **Link:** https://pubmed.ncbi.nlm.nih.gov/35946484/

Appendix 3: Tips and suggestions for using clinicaltrials.gov

Some tips for searching 'clinicaltrials.gov'

Front page:

Status – select 'All studies'
Insert 'Multiple System Atrophy' in 'Condition or disease'

Result page:

Filtering the data: on the left-hand side in the 'List' tab is the option to apply 'Filters'.

Recruitment

- To know what is actually happening select 'not yet recruiting; Recruiting; enrolling by invitation; active – not recruiting'
- To know what happened before select 'completed'
- To know what happened before, but an anticipated negative result happened select 'terminated'

Study type

- Select 'All': this will provide data on therapies, diagnostics, registries, changes in protocols, biomarkers, digital health

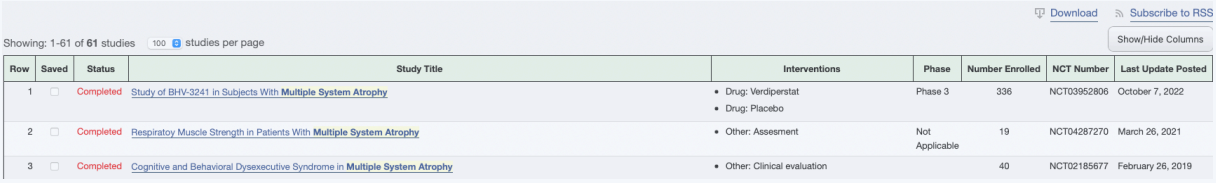
Study results: 'All' or 'With results' are both good options

'All' every trial is presented

'With results' when clicking on the actual trial that is displayed after applying the filter, on the three tabs at the top is 'study results'. If you click on this it will take you to the raw data.

This is not the complete Clinical Study Report, but does provide key outcome measurements that have not been charted or plotted. Not all study results are published as articles (where this has happened there are links to the publications at the bottom of the page), so more insight can be obtained here.

When the 'Apply' button is clicked after filter selection, you will be presented with the list of trials:



Row	Saved	Status	Study Title	Interventions	Phase	Number Enrolled	NCT Number	Last Update Posted
1		Completed	Study of BHV-3241 in Subjects With **Multiple System Atrophy**	• Drug: Verdiperstat • Drug: Placebo	Phase 3	336	NCT03952806	October 7, 2022
2		Completed	Respiratoy Muscle Strength in Patients With **Multiple System Atrophy**	• Other: Assesment	Not Applicable	19	NCT04287270	March 26, 2021
3		Completed	Cognitive and Behavioral Dysexecutive Syndrome in **Multiple System Atrophy**	• Other: Clinical evaluation		40	NCT02185677	February 26, 2019

Each trial can be individually clicked on and information on the study description, study design, interventions, number of patients, dates, sponsors, locations and outcome measures can be viewed.

The show/hide column on the top right, allows you to expand the number of fields you would like to view online.

The 'download' button takes you to a pop-up: In the number of studies you can select all the studies from your search, with further options of the downloaded file show 'all possible columns' or the fields you selected 'displayed'

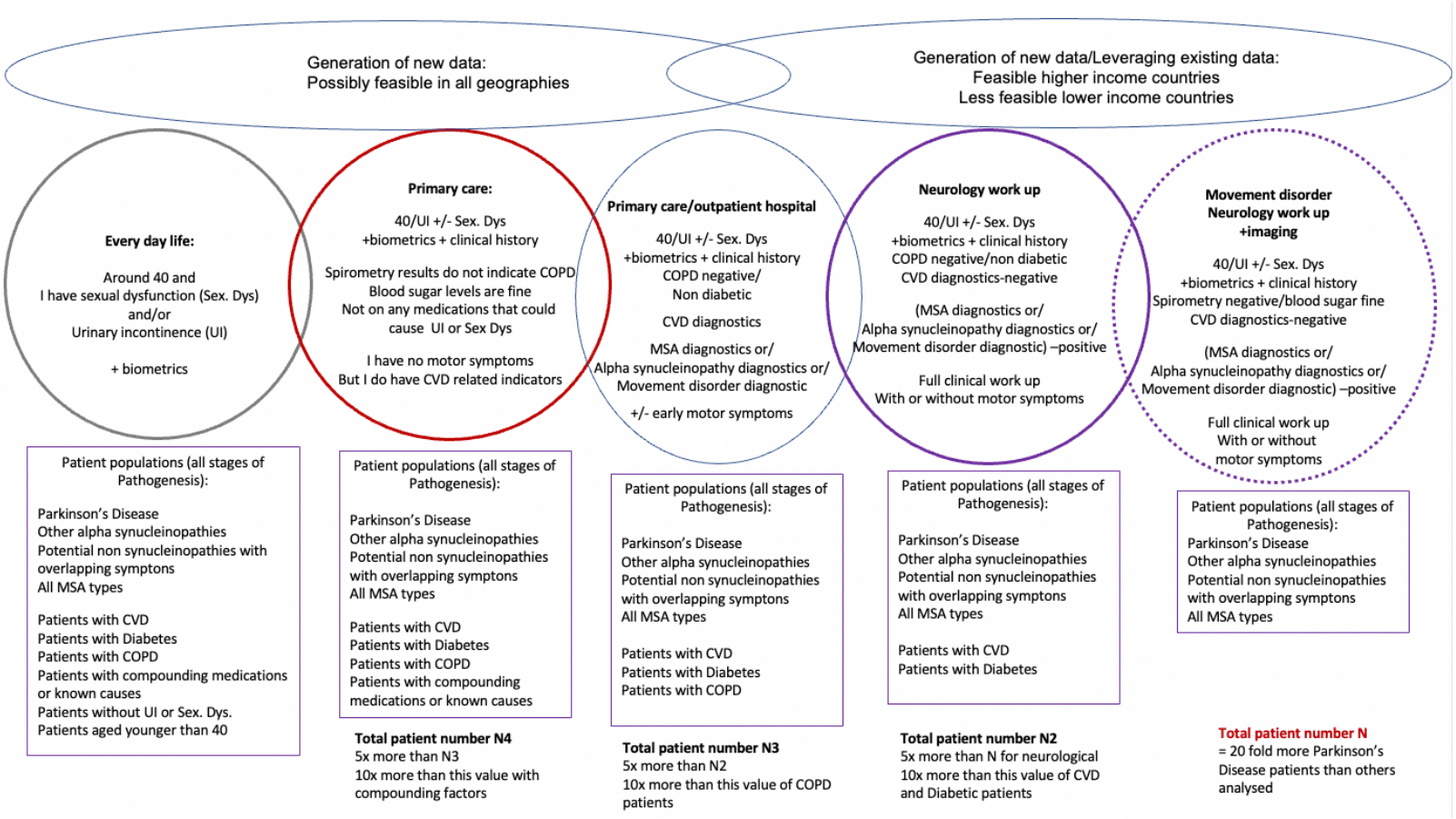
In the file format: select 'tab-separated values': When downloaded, for most software types, this will display each of the fields in separate columns, allowing you to filter and arrange the data as you see fit.

Note: the downloaded file only contains the information you see on the list of trials: the detail and structure you see online, can only be seen online.

Thinking outside the box, for the innovator, this means other indications can be searched in clinicaltrials.gov to assess if other innovations in clinical development (digital health, diagnostics, and potentially therapeutic) may be repositioned or after modifications edited for use in, for example MSA.

Appendix 4: Globally relevant AI/ML diagnosis for MSA: Possible data collection needs, location and feasibility through the journey of a patient with MSA to enable AI/ML to identify the patient or at-risk patient as early as possible with global applicability

(Note that if the AI/ML is to suggest a diagnosis it must also adhere to quality standards of false positive/true positive: false negative/true negative, to define specificity and sensitivity)



Nelson AE, Arbeeva L. Narrative Review of Machine Learning in Rheumatic and Musculoskeletal Diseases for Clinicians and Researchers: Biases, Goals, and Future Directions. J Rheumatol. 2022;49(11):1191-1200.**Link**: https://pubmed.ncbi.nlm.nih.gov/35840150/

Faviez C, et al. Diagnosis support systems for rare diseases: a scoping review. Orphanet J Rare Dis. 2020;15(1):94. **Link**: https://pubmed.ncbi.nlm.nih.gov/32299466/

Loftus TJ, et al. (2022) Uncertainty-aware deep learning in healthcare: A scoping review. PLOS Digit Health 1(8): e0000085. **Link:** https://journals.plos.org/digitalhealth/article?id=10.1371/journal.pdig.0000085

Schaefer, J., et al. The use of machine learning in rare diseases: a scoping review. Orphanet J Rare Dis 15, 145 (2020).**Link:** https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01424-6