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How to Improve Diagnosis and Therapy of Rare Neurologic Diseases in the World?

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Disclosures

- None

Learning Objectives

1 Review the use of rare neurological disease (RND) registries and how they might improve diagnosis and care

2 Examine the hub-and-spoke model of care, supported by well-trained primary centers, diagnostic tools, and telemedicine

3 Discuss improving knowledge, attitudes, and practice (KAP) locally and regionally to improve RND care

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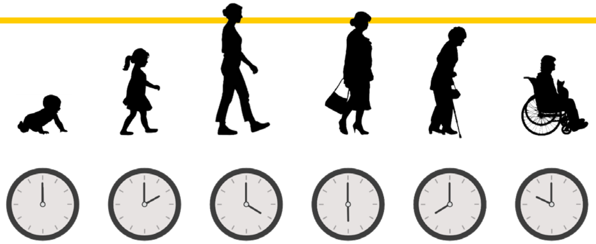
Registries and Making RNDs Reportable

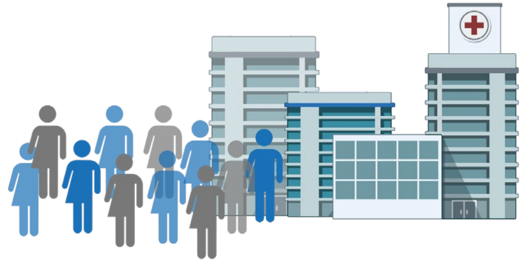
Registries are information hubs of:

- Demographic and general health data
- Risk factors
- Physical and neurological exams
- Lab tests of biospecimens/biomarkers
- Imaging and non-imaging diagnostics
- Functional status
- Medication use
- Quality-of-life and mental health

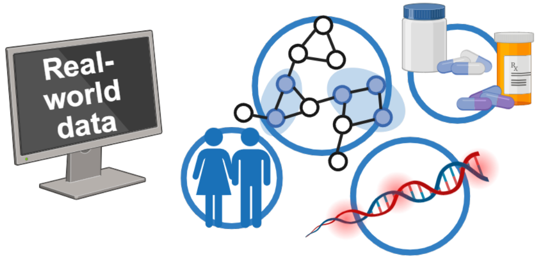
In **lower resource settings**, registries may reveal local patterns in RND incidence, providing diagnostic clues.



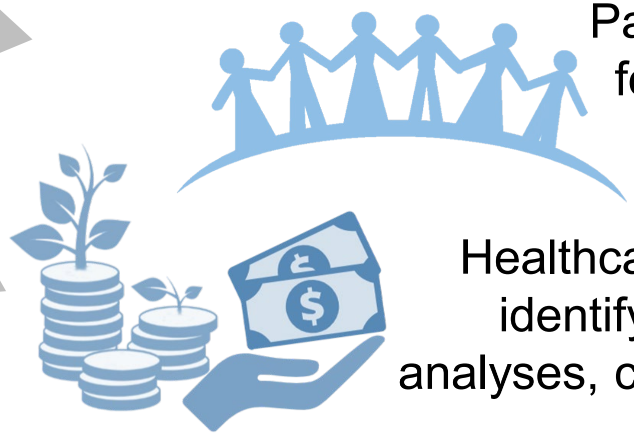
Natural history epidemiological studies, research of disease pathophysiology



Clinical trial readiness, recruit participants, baseline data to select endpoints



Real-world evidence of long-term treatment safety and efficacy, monitor off-label drug use



Patient empowerment and advocacy for research priorities, community-building, shape public policy

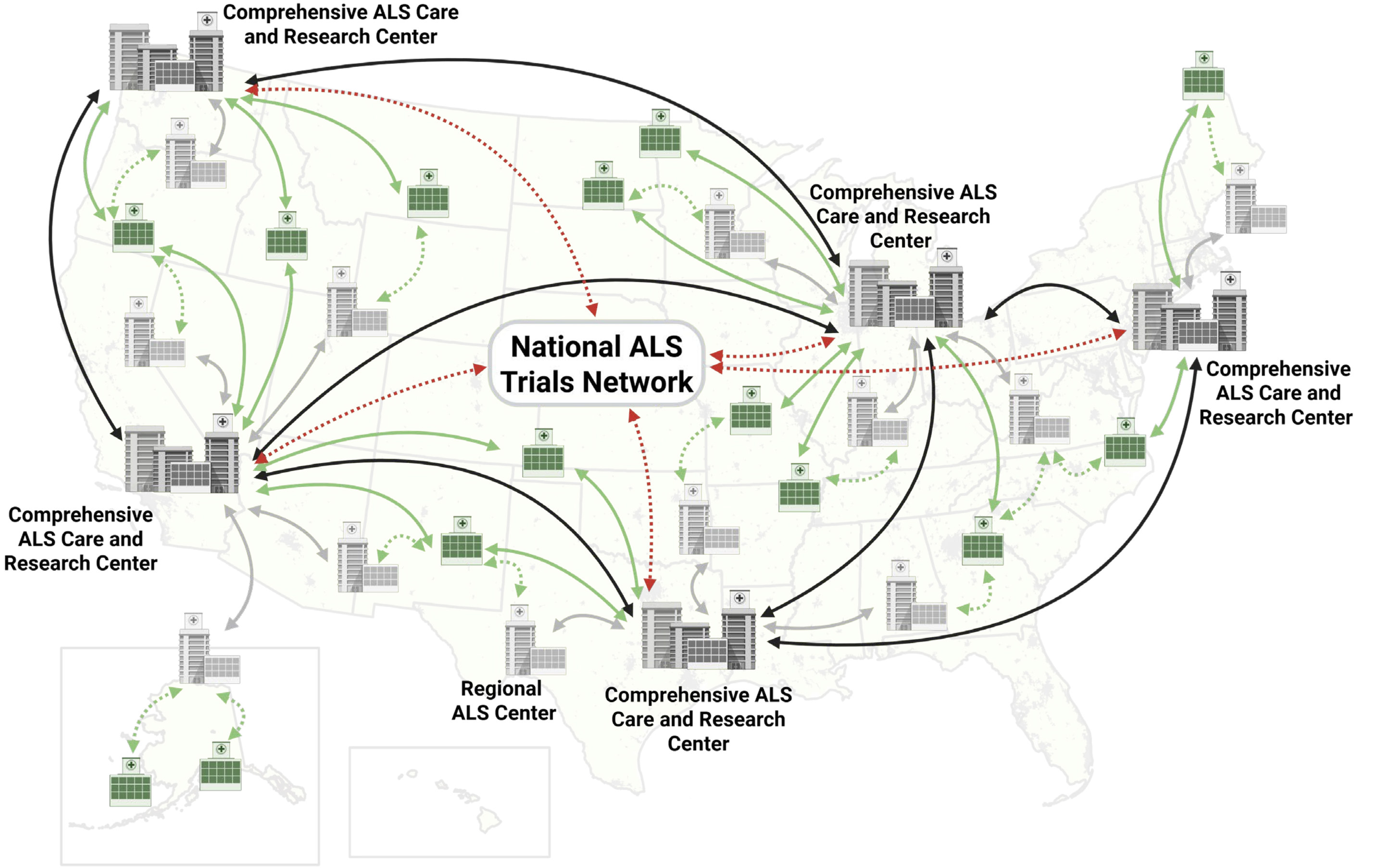
Healthcare planning, resource allocation, identify disparities, cost-effectiveness analyses, clinical guidelines and best practices

Barbalho et al., BMC Neurol, 2021

National Referral System: Hub-and-Spoke Model

- **Hub**: A central multidisciplinary care (**MDC**) facility that offers advanced, specialized care, e.g., complex diagnostics, genetic testing, advanced therapy, clinical trial participation, etc.

- **Spokes**: Smaller, regional hospitals or community clinics that provide routine or preliminary care and refer complex cases to the hub.



Even in **lower resource settings**, clear referral criteria in a hub-and-spoke model maximizes resources. Rotating specialists or visiting teams can disseminate expertise across hubs. Non-neurologists or primary care providers manage stable patients.

Howard et al., Ann Neurol, 2024

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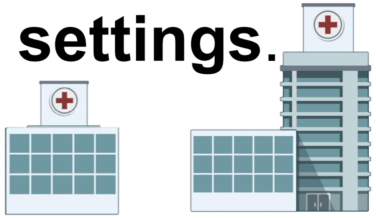
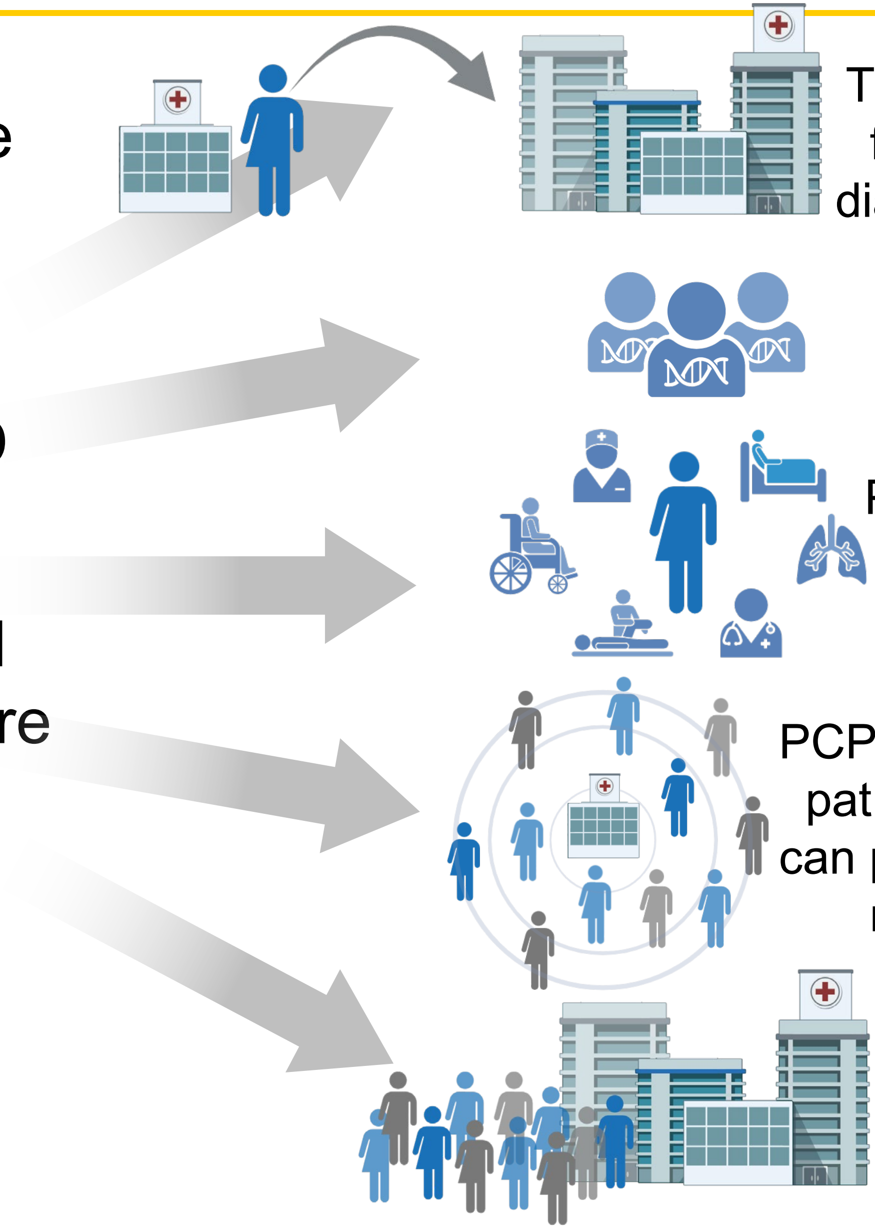
Well-Trained Primary Care

Well-trained primary care providers (**PCPs**) at smaller, local or regional hospitals or community clinics can facilitate RND care via multiple routes.

These approaches could especially bolster RND care in **lower resource settings**.





Trained PCPs can recognize RNDs early for referral to MDC centers, shortening diagnostic delays, initiating basic workups

Genetically literate PCPs can order genetic tests, counsel families

PCPs coordinate MDC with specialists, monitor comorbidities, ensure continuity of care across life stages

PCPs may be the sole point of contact for RND patients in rural or underserved areas; PCPs can provide psychosocial support via long-term relationships with patients and families

PCPs can help enroll RND patients into RND registries or clinical trials

Baynam et al., Lancet Glob Health, 2024

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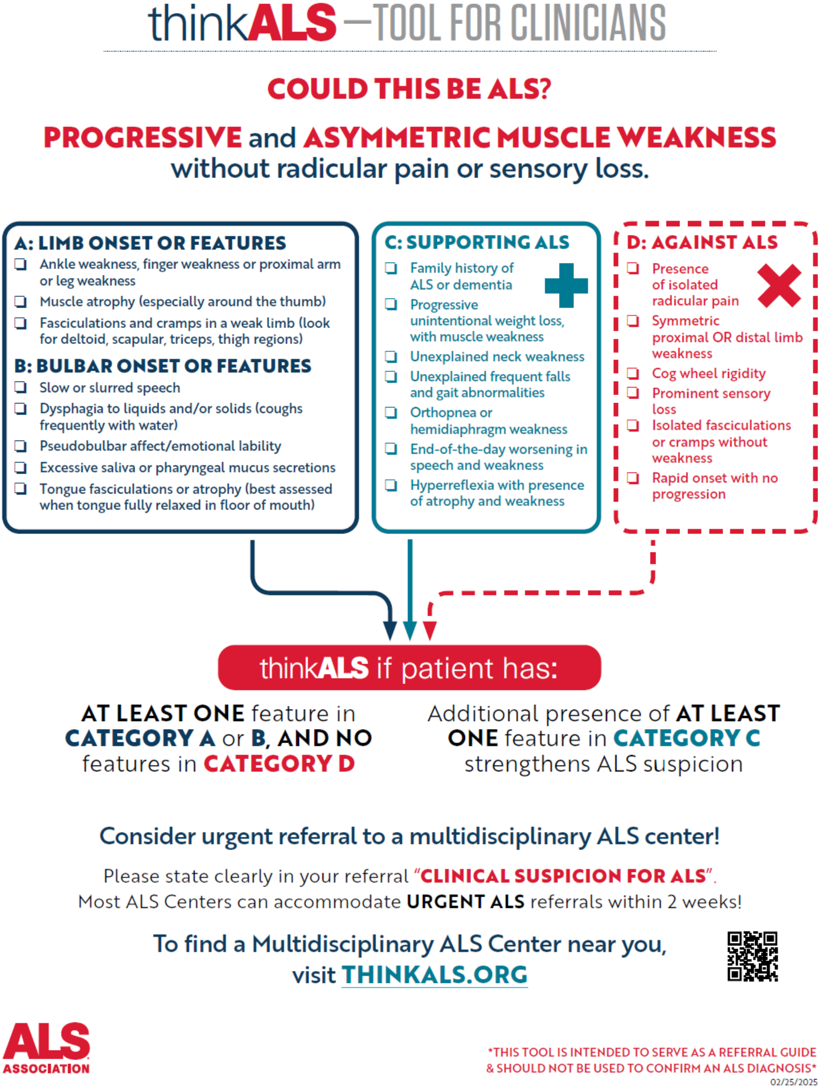
Widely Accessible Diagnostic, Database, Digital Tools



thinkALS —TOOL FOR CLINICIANS

COULD THIS BE ALS?

PROGRESSIVE and **ASYMMETRIC MUSCLE WEAKNESS**
without radicular pain or sensory loss.

A: LIMB ONSET OR FEATURES

- ☐ Ankle weakness, finger weakness or proximal arm or leg weakness
- ☐ Muscle atrophy (especially around the thumb)
- ☐ Fasciculations and cramps in a weak limb (look for deltoid, scapular, triceps, thigh regions)

B: BULBAR ONSET OR FEATURES

- ☐ Slow or slurred speech
- ☐ Dysphagia to liquids and/or solids (coughs frequently with water)
- ☐ Pseudobulbar affect/emotional lability
- ☐ Excessive saliva or pharyngeal mucus secretions
- ☐ Tongue fasciculations or atrophy (best assessed when tongue fully relaxed in floor of mouth)

C: SUPPORTING ALS

- ☐ Family history of ALS or dementia
- ☐ Progressive unintentional weight loss, with muscle weakness
- ☐ Unexplained neck weakness
- ☐ Unexplained frequent falls and gait abnormalities
- ☐ Orthopnea or hemidiaphragm weakness
- ☐ End-of-the-day worsening in speech and weakness
- ☐ Hyperreflexia with presence of atrophy and weakness

D: AGAINST ALS

- ☐ Presence of isolated radicular pain
- ☐ Symmetric proximal OR distal limb weakness
- ☐ Cog wheel rigidity
- ☐ Prominent sensory loss
- ☐ Isolated fasciculations or cramps without weakness
- ☐ Rapid onset with no progression

think**ALS** if patient has:

AT LEAST ONE feature in **CATEGORY A** or **B**, **AND NO** features in **CATEGORY D**

Additional presence of **AT LEAST ONE** feature in **CATEGORY C** strengthens ALS suspicion

Consider urgent referral to a multidisciplinary ALS center!

Please state clearly in your referral "**CLINICAL SUSPICION FOR ALS**".
Most ALS Centers can accommodate **URGENT ALS** referrals within 2 weeks!

To find a Multidisciplinary ALS Center near you,
visit **THINKALS.ORG**

ALS ASSOCIATION

THIS TOOL IS INTENDED TO SERVE AS A REFERRAL GUIDE & SHOULD NOT BE USED TO CONFIRM AN ALS DIAGNOSIS
02/25/2025

- Reduces diagnostic delays (often years in RNDs)
- Improves referral accuracy to specialists or MDC centers
- Supports registry and clinical trial enrollment
- Useful in **lower resource settings**

Method	**Description** (useful in **lower resource settings**)
RND matching	Connect clinicians / researchers with patients that have similar genotypes and phenotypes for diagnosis and discovery, e.g., GeneMatcher
RND databases	Integrate genomic and clinical data to support diagnosis and research, e.g., RD-Connect Genome-Phenome Analysis Platform, Orphadata, Orphanet Rare Disease Ontology, Online Mendelian Inheritance in Man
AI-based clinical decision support systems	Uses machine learning to analyze symptoms, imaging, and genetic data to suggest possible diagnoses
Digital phenotyping tools	Uses wearables and mobile apps to track motor and cognitive symptoms over time

Torri et al., Neurol Sci, 2024
Dias et al., Genome Med, 2019

Courtesy of the ALS Association ; Dave et al., ALS-FTD, 2025

Telemedicine

Telemedicine can liaise RND patients living in rural or underserved areas to specialists at MDC centers for follow-up care.

These approaches could especially bolster RND care in **lower resource settings** as telecommunications and digital technologies become increasingly accessible.

Telemed allows RND patients to consult specialists remotely, avoiding long, costly travel, especially valuable for immobile patients. Reduces caregiver burden.

Telemed can monitor disease progression, medication side-effects, and functional status, reducing missed appointments and improving adherence. Particularly helpful for chronic, progressive RNDs.

Telemed can facilitate coordination among the MDC team, supporting integrated care plans.

Telemed empowers RND patients to share in decision-making with the MDC team, and obtain, education, genetic counseling and psychosocial support

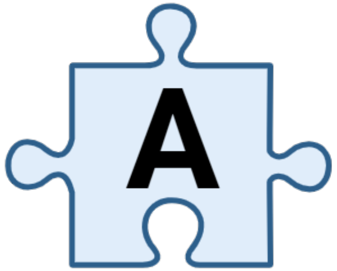
Telemed can help enroll RND patients into registries or remote clinical trials, expanding research and improving representation of diverse populations.

Eletti et al., Nutrients, 2025

Improving Knowledge, Attitudes, Practices

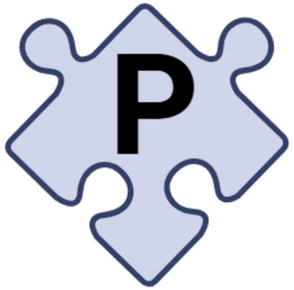
Build diagnostic confidence:

- Early recognition of RND presentations.
- Appropriate use of genetic testing, imaging, referrals.
- Reduce misdiagnoses and unnecessary interventions.
- Familiarity with RND-specific guidelines and registries.



Empathy and advocacy:

- Empathy for patient experiences, e.g., vague symptoms.
- Shared decision-making.
- Foster interdisciplinary collaboration and openness to second opinions.
- Reduce therapeutic nihilism—the belief that “nothing can be done” for RNDs.



Knowledge into action:

- Timely referrals to MDC centers.
- Support holistic care, including mental health, rehabilitation, social services.
- Encourages registry or trial participation.
- Promote continuity of care across life stages and specialties.

A 2025 survey on behalf of the World Federation of Neurology Subspecialist Group on Rare Neurologic Diseases examined KAP in neurologists (n=64) across the world (Africa, the Americas, Asia/Oceania, and Europe,).

Most respondents agreed RND patients should receive timely and effective care. There were differences across respondents’ country of practice to diagnose RNDs, highlights disparities in resources and preparedness for RNDs.

What can be done? Training centers for neurologists, training PCPs, disseminate diagnostic tools.

Jang et al., J Neurol Sci, 2025

Key Messages

1. RND registries improve RND care via epidemiological studies, clinical trials, real-world data, resource allocation, and empowering patients in prioritizing RND research.

2. Hub-and-spoke systems refer RND patients to MDC centers; PCPs help via early referrals, coordinating with MDC teams, registries, and clinical trials, psychosocial support, and liaising with patients in rural or underserved areas.

3. Diagnostic, database, and digital tool help PCPs identify that a patient may have an RND, prompting referral. Telemedicine can facilitate consults for patients in rural, underserved, or lower resource areas.

4. Improving KAP in providers builds diagnostic confidence, empathy and advocacy, and translates knowledge into action. In RND patients, KAP improves awareness and care of their condition.

References

- **Registries**: Barbalho et al., National registry for amyotrophic lateral sclerosis: a systematic review for structuring population registries of motor neuron diseases, BMC Neurol, **2021**, 21, 269.
- **Hub-and-spoke**: Howard et al., Priorities and recommendations to make ALS a livable disease emanating from the 2024 National Academies of Sciences, Engineering, and Medicine Report Living with ALS. Ann Neurol, **2024**, 96, 1035-1039; Pane et al., Gene therapy for Duchenne Muscular Dystrophy: assessing the readiness of Italian centres of expertise. Acta Myol, **2024**, 43, 95-101.
- **Primary care**: Baynam et al., Global health for rare diseases through primary care. Lancet Glob Health, **2024**, 12, e1192-e1199.
- **Diagnostic tools**: Dias et al., Artificial intelligence in clinical and genomic diagnostics. Genome Med, **2019**, 11, 70; Torri et al., The use of digital tools in rare neurological diseases towards a new care model: a narrative review. Neurol Sci, **2024**, 45, 4657-4668.
- **Telemedicine**: Eletti et al., Telemedicine for personalized nutritional intervention of rare diseases: A narrative review on approaches, impact, and future perspectives. Nutrients, **2025**, 17, 455.
- **Survey of KAP**: Jang et al., Awareness and care practices for rare neurologic diseases among senior neurologists: A global survey. J Neurol Sci, **2025**, 470, 123395.