Rational development of therapies for rare diseases

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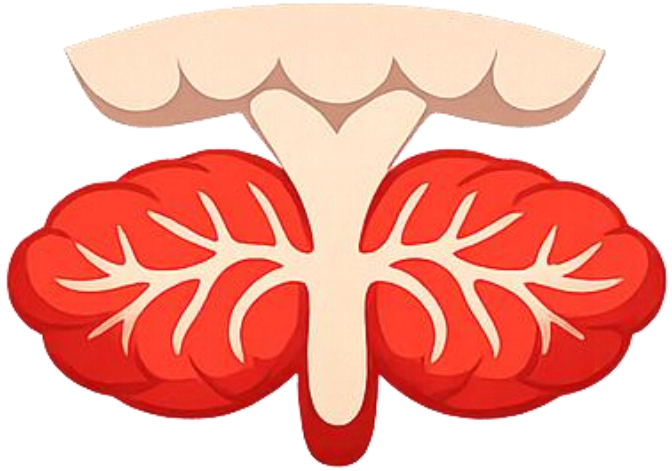

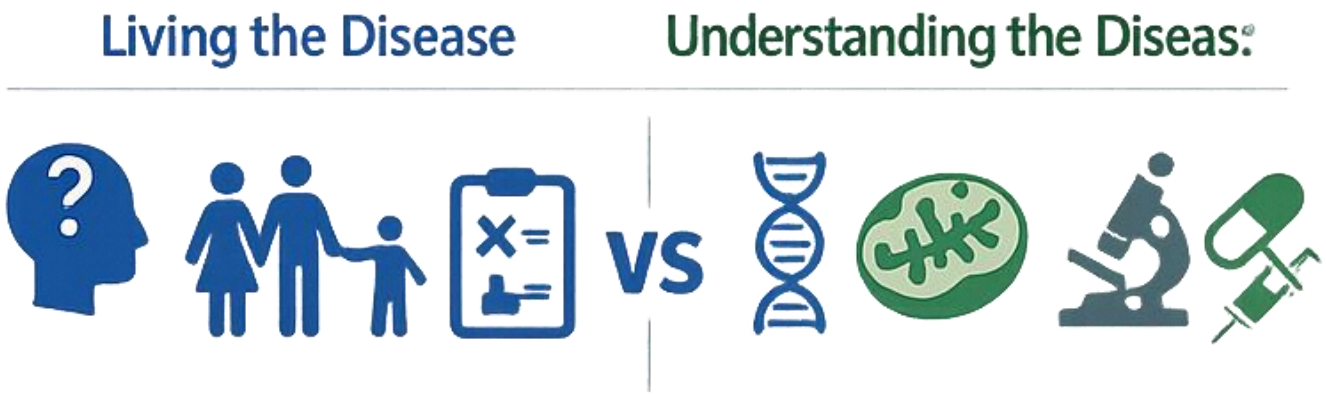

Example: **Ataxias**

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Why this framing: two levels must be integrated

Living the disease (patient level)

- Functioning + participation (ICF): mobility, speech, fatigue, work/school, autonomy
- Diagnostic odyssey and uncertainty are outcomes
- Care pathways exist even without disease-modifying therapy
- Personal utility: what matters to patients and families

Understanding the disease (clinician/science level)

- Diagnosis → mechanism → intervention (or cause → intervention)
- Natural history + biomarkers + stratification
- Mechanistic pluralism: many pathways and shared mechanisms
- Clinical utility: measurable change in course/complications

Therapy programs fail when they optimize one level while ignoring the other.

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Personal involvement in RD and ataxia research

EUROSCA

ataxia study group

ATAXIA GLOBAL INITIATIVE
worldwide platform for clinical research in ataxias

2003 — 2008 — 2012 — 2018 — 2021 — 2024

NeuroOmics

SolveRD
Solving the Unsolved Rare Diseases

ERDERA
European Rare Diseases Research Alliance

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Ataxias: one phenotype, many treatable mechanisms

Mechanistic pluralism is the rule in inherited ataxias

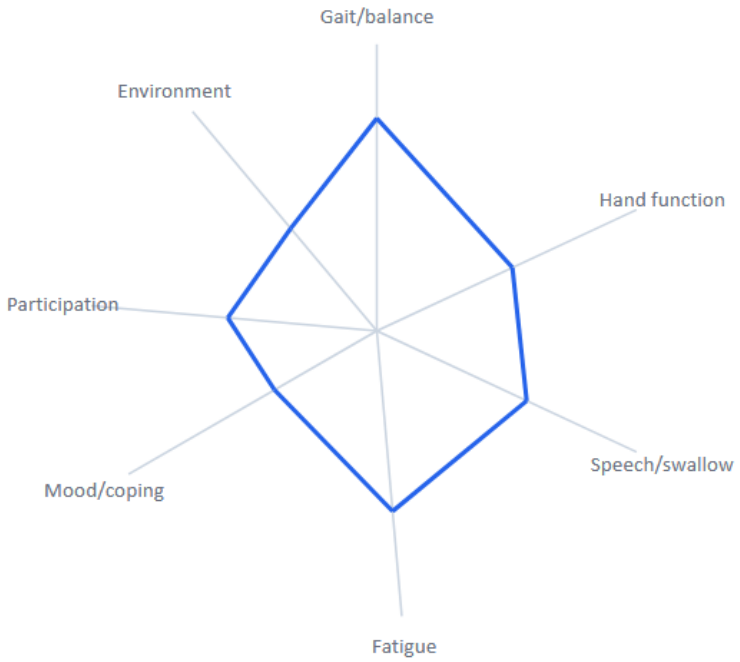
DNA repair/repeat instability • mitochondrial dysfunction • lipid metabolism • autophagy/proteostasis • ion channels • neuroinflammation

Small populations change what "rational" means

Natural history, sensitive endpoints, biomarkers, and external controls become central—not optional.

Living the disease: ICF-based functioning profiles are therapy-development assets

Example "ataxia functioning profile" (schematic)



How it informs rational development

- Define "meaningful change" with patients/caregivers
- Choose endpoints tracking participation (ADL, falls, speech, fatigue)
- Build rehab + assistive tech into baseline care
- Standardize multidisciplinary outcomes using ICF language

Design check:

Every endpoint should map to (1) functional life impact and (2) mechanism/cause hypotheses.

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Living the disease → measurable outcomes: digital biomarkers & home monitoring

Wearables can capture “real-life” gait and upper-limb function between visits, increasing power in small populations.

Friedreich ataxia

- At-home wearable monitoring predicts clinical measures and correlates with mFARS
- Instrumented walk tests show discriminative and reliable gait metrics

Spinocerebellar ataxias

- Digital gait biomarkers can capture 1-year longitudinal change in SCA3
- Oculomotor digital measures are converging toward consensus endpoints

Sensor (passive/active) → Feature engineering → Clinically validated endpoint → Regulatory fit-for-purpose

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Diagnosis links classification to action—often under uncertainty in rare diseases.

Understanding the disease: diagnosis as an "epistemic operator"

Classification	Explanation	Prediction	Action
What is it? (nosology, phenotype, genotype)	Why is it happening? (mechanism/cause)	What is likely next? (natural history, risks)	What should we do now? (therapy, surveillance, trials)

Program design checklist (science-level)

- Mechanism hypothesis → measurable biomarker(s) → dose/exposure rationale
- Natural history informs stage selection and trial duration
- Stratify by genotype, age-at-onset, repeat length (where relevant)
- Decide early: symptomatic vs pathway-targeted vs cause-based trajectory

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Advancement of Treatments

Functioning / participation

Example: ICF profile → rehab, speech therapy, assistive tech

Symptom-based

Example: Spasticity, dysphagia, pain, fatigue → evidence-based care

Program implication:
- Specify endpoints
- Specify evidence pathway
- Specify "handoff" to care

Mechanism-based

Example: Channelopathy / metabolic blockade → pathway drug / repurpose

Cause-based (molecular)

Example: Enzyme replacement, substrate reduction, ASO, gene therapy

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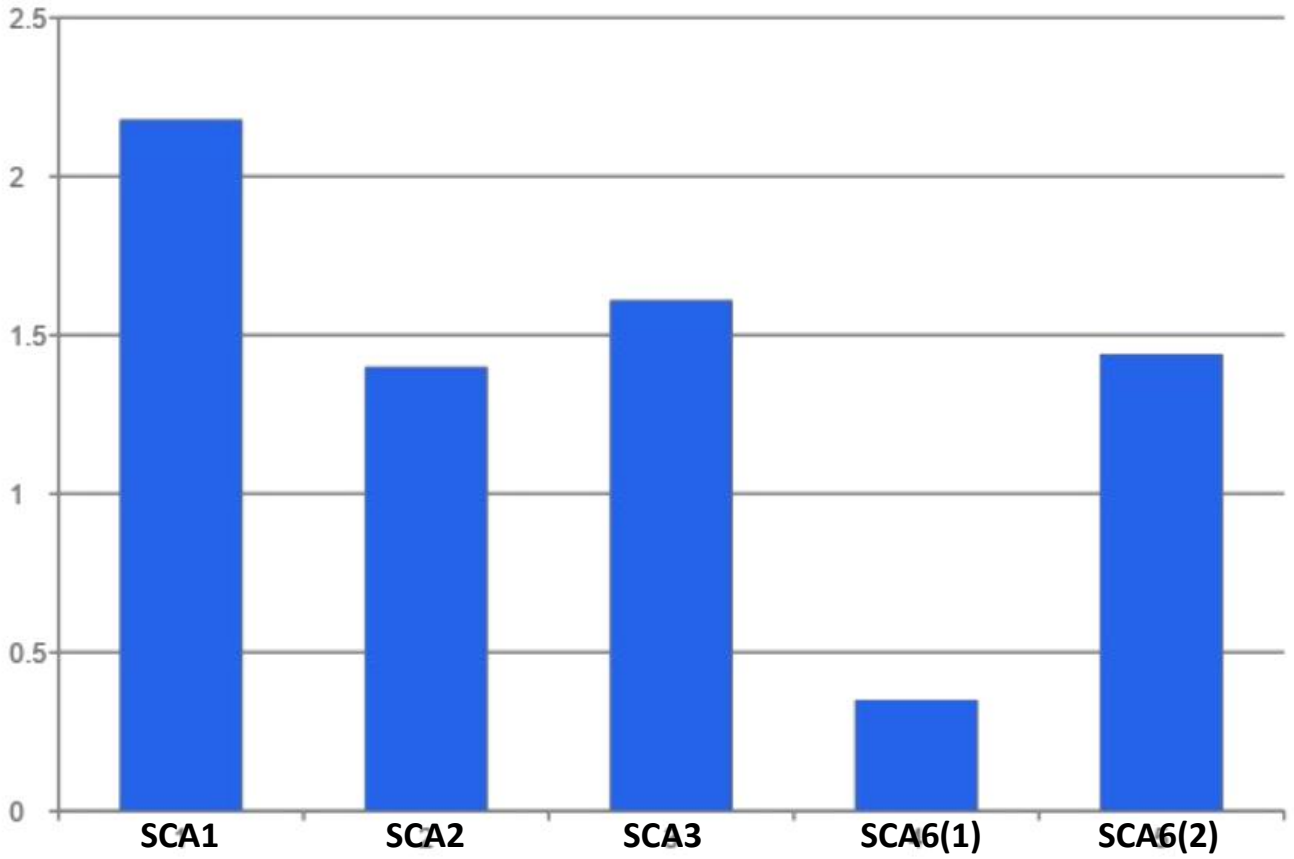
Under-standing the disease: natural history determines trial duration and power

EUROSCA provided quantitative annual progression rates on SARA across SCA subtypes



Design implications

- Subtype-specific rates → stratify and pre-specify analyses
- Slow/nonlinear progression (e.g., SCA6) may need longer follow-up or more sensitive endpoints
- Repeat length and age-at-onset can influence progression

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Clinical outcome assessments: choose what is sensitive *and* meaningful

SARA (across ataxias)

- Validated clinical scale; widely used in trials
- Sensitive to progression in multiple SCAs
- Beware ceiling/floor effects; ensure rater training

FARS / mFARS (FRDA)

- Psychometric validation supports use of FARS components
- mFARS used as primary endpoint in MOXIe; described as FDA-accepted for FRDA trials
- Remote/rater issues are active research areas

Endpoint strategy (recommended)

- Primary: impairment scale appropriate to subtype/stage (SARA or mFARS) OR a validated composite
- Key secondaries: ADL/QoL + participation + safety + biomarkers (fit-for-purpose)
- Pre-plan missing data + remote assessment contingencies

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Biomarkers: improve stage selection, power, and learning loops

Neurofilament light chain (NfL) is one of the most replicated fluid biomarkers across genetic ataxias.

SCA3 (example)

- Serum NfL elevated; correlates with severity; candidate for onset/progression and treatment response.

FRDA (example)

- Serum/plasma NfL evaluated as biomarker; interpret with age and disease stage.

"Biomarker ladder" for rational development

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Trial readiness: AGI and the move from “possible trials” to “meaningful trials”

AGI highlights recurring blockers: outcome sensitivity, biomarkers, infrastructure, and data access.

Ataxia Global Initiative (AGI) trial-readiness components

- Harmonized COAs and rater training (reduce noise-to-effect ratio)
- Natural history cohorts and registries (external controls; stage definitions)
- Biomarker qualification pathways (fluid, imaging, digital oculomotor)
- Global site infrastructure and feasibility
- Patient-group partnership: recruitment, meaningful endpoints, acceptability

Digital and neuroimaging endpoints

AGI consensus papers propose harmonized measurement parameters and candidate endpoints.

Bottom line

Trial readiness is the fastest path to more—and better—therapeutic learning per patient enrolled.

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Case study 1: channelopathy / episodic ataxias

In episodic ataxias, the diagnosis-mechanism-action link is often tight and clinically actionable.

EA2: 4-aminopyridine (4-AP)

- Randomized crossover trial showed reduced attack frequency and improved patient-reported QoL
- Established therapeutic option alongside acetazolamide

GAA-FGF14 (SCA27B): 4-AP as precision symptomatic therapy

- FGF14 GAA expansions are a frequent cause of downbeat nystagmus syndromes
- Real-world + preliminary placebo-controlled evidence supports 4-AP efficacy in this condition

Program-level lesson

Build an “actionability lane” into diagnostic workflows: if a treatable/channelopathy mechanism is plausible, act early while evidence is still maturing.

In trials: enrichment by mechanistic subtype can increase effect sizes and shorten timelines.

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Case study 2: treatable ataxias

Some “ataxias” are treatable because the causal defect has a direct intervention.

AVED (TTPA)

- Vitamin E supplementation can prevent/avert manifestations if started early.

CTX (CYP27A1)

- Chenodeoxycholic acid is established therapy; earlier diagnosis improves outcomes.

COQ8A

- CoQ10 supplementation can be beneficial in a subset; response heterogeneity matters.

Program-level lesson

- “Treatable ataxias” require explicit diagnostic algorithms and rapid referral
- In trials, these conditions exemplify how actionability can precede perfect certainty
- They also demonstrate the value of genotype-first diagnostics in an ataxia workup

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Emerging causative therapies:

ASO and gene therapy are entering the clinic

ASO (polyQ SCAs)

- VO659 targets expanded CAG repeats; Phase 1/2a includes SCA1 and SCA3
- Key risks: CNS delivery, safety, target engagement, and long timelines

RNA-targeted (SCA2)

- ARO-ATXN2 trial evaluates single intrathecal injection in adults with SCA2
- Shows how diagnosis → single target → early-phase program can be organized

Development guardrails (rare neurogenetic ATMPs)

- Demand early evidence of CNS target engagement + dose-exposure rationale
- Pair with natural history + sensitive endpoints (digital + biomarker) for learning loops
- Plan long-term follow-up and risk mitigation (immunogenicity, off-target effects)

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Integrated roadmap: "living" + "understanding" as a program architecture

	Living the disease	Understanding the disease
	Near-term care + outcomes • Rehab, assistive tech, falls prevention • Digital function measures • Care coordination burden	**Mechanism-informed program** • Biomarker ladder (PD → clinical) • Natural history & stratification • Dose/exposure rationale
	Evidence + impact loop • Personal utility + clinical utility • Registries and real-world evidence • Transparency about uncertainty	**Regulatory alignment** • Small-population methods • Surrogate biomarkers • External controls & adaptive designs

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Take-home messages

1. Start with **living the disease** to define meaningful success
2. Use **understanding the disease** to chose interventions, biomarkers, and trial designs that can deliver
3. Invest in trial readiness and fast diagnosis – because in rare ataxias, time lost is function lost

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Advancement of Treatments FOR RARE DISEASES

HLM RARE 2025

The European Reference Networks, MEP Vytenis Andriukaitis (S&D, Lithuania) and the Brains for Brain Foundation, hosted in Brussels from 9-11 December 2025 the first three-day High-Level Meeting on a European Innovation and Care Ecosystem for Rare and Complex Diseases (HLM Rare 2025). A key milestone of this meeting was the launch of a community-led Declaration.

WG 3: Accelerate equitable access to diagnostics and enable early treatment onset with innovative orphan drugs and digital innovation for unmet medical needs

ERN Coordinator Lead:
Luca Sangiorgi

WG 4: Foster EU leadership in clinical trials for rare diseases through inclusive collaboration between Academy, ERNs, patient groups and industry to accelerate innovation for PLWRD

ERN Coordinator Lead:
Holm Graessner

WG 7: Explore new early access models and mechanisms to prioritise equitable access to innovative orphan therapies and diagnostics, also supported by a European Guarantee Fund

ERN Coordinator Lead:
Maurizio Scarpa

WG 8: Ringfence European Reference Networks funding under the 2028-2034 Multiannual Financial Framework

Coordinator:
MEP Vytenis Andriukaitis (S&D, LT)

Health Leadership Mission Rare Disease

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