Building a Natural History and Patient Registry Platform for Coffin-Lowry Syndrome (CLS): A Roadmap for Therapeutic Readiness

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Objectives

Integrate existing CLS data sets, assessing for gaps and opportunities for drug development.

Define priority elements and establish a framework to enable comprehensive characterization of natural history.

Background

Coffin–Lowry syndrome (CLS) is a rare X-linked neurodevelopmental disorder caused by the *RPS6KA3 gene.* CLS is characterized by severe intellectual disability, distinctive craniofacial and skeletal findings, sensorineural hearing loss, and stimulus-induced drop attacks. No approved therapies exist, and natural history data remain limited. The absence of a comprehensive, CLS-specific registry restricts progress toward therapeutic readiness and hinders the development of measurable clinically meaningful endpoints. A structured natural history and registry development framework was derived from prior rare-disease registry models and expanded using multiple data sources.

Conclusions

No approved therapies, lack of longitudinal data, heterogeneity of phenotype, and lack of matched genotype:phenotype data create a need for a dedicated natural history and registry.

The proposed design, combined with strategic collaborations offers a feasible and impactful framework and provides early insights into burden of disease for CLS patients.

This framework will enable more rigorous natural history definition, support early-phase clinical-trial design, and accelerate therapeutic development for individuals with CLS.

Data Collected and Preliminary Analysis

Current Work: Foundational deidentified demographic information for 61 patients was provided by Coordination of Rare Diseases at Sanford (CoRDS), Sanford (Figure 1). Data elements from CORDS included demographics, genotype, developmental history, functional status, assessments, history of stimulus-induced drop episodes, quality-of-life measures, and caregiver burden. State level numbers were provided by the Coffin-Lowry Syndrome Foundation (CLSF) (Figure 2), Deidentified molecular data from nearly 300,000 WES/WGS samples identified 95 CLS patients was provide by GeneDx.

Early analysis of data include milestones by age (Figure 4), prevalence in WES/WGS samples and basic demographics of diagnosed patients (Figure 5), Preliminary insights reveal significant caregiver burden and need for specialists as 74% of CLS patients require specialty care and at least half receiving occupational therapy. More than half of the CLS patients are able to attend public school, with another 31% in a special needs schools.

Figure 1. Patient Reported Demographic Data from CoRDS

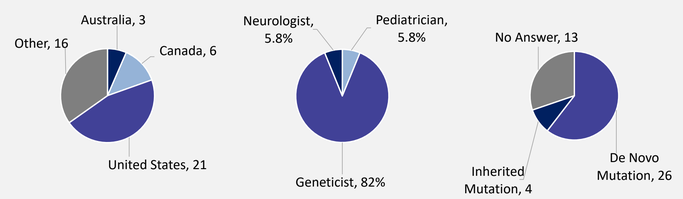


Figure 2. Deidentified WES/WGS data from GeneDx

- 3.2 in 10,000 with WES had p/lp variants in *RPS6KA3*
- 1.4 out of 10,000 had p/lp in Autism cohorts
- 73% of WES CLS patients were flagged with "GDD" in phenotype

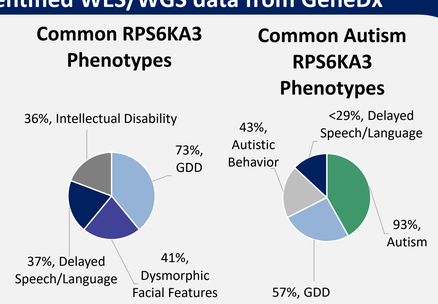
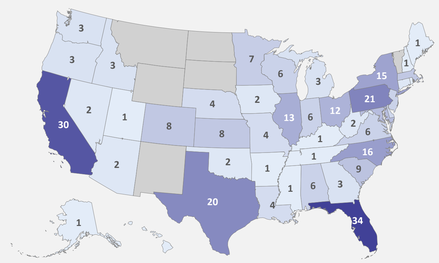
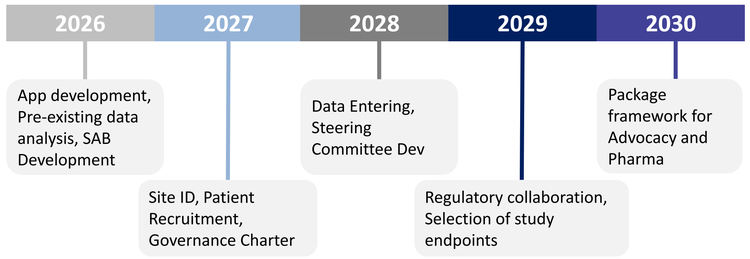


Figure 3. CLSF Patients by State



Natural History Timeline



CLS patients on average delayed in developmental milestones

Figure 4. Milestones Comparison by Age (Years)

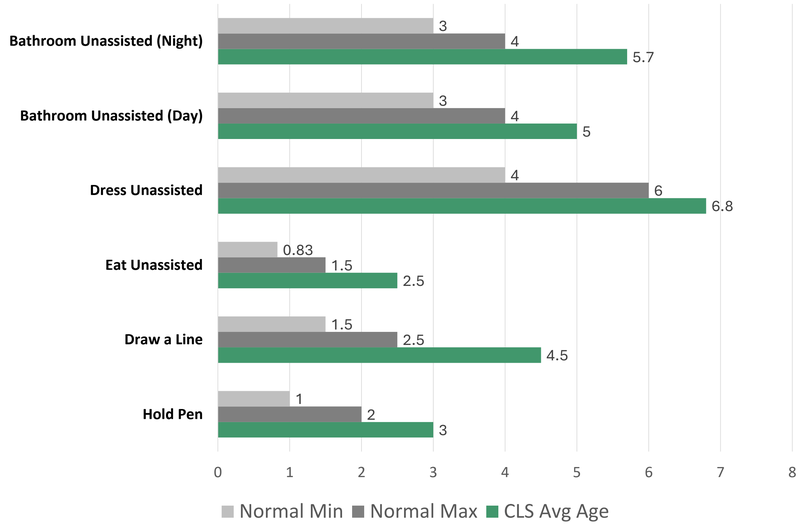
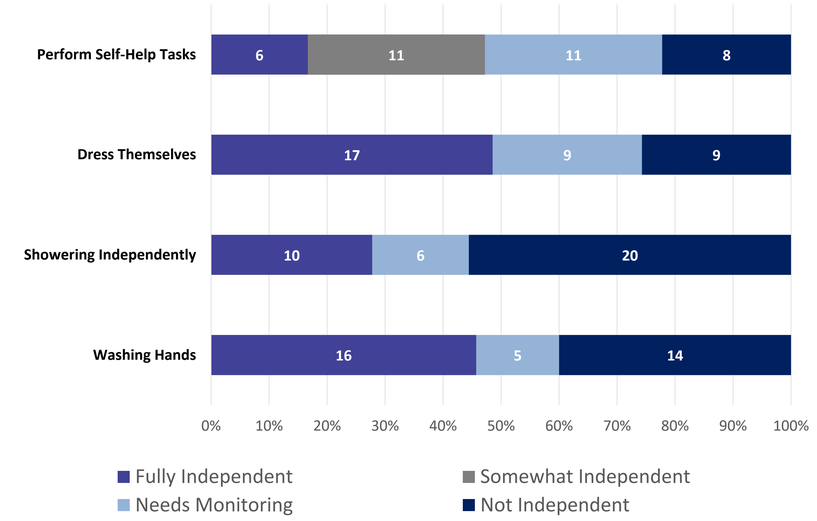


Figure 5. Ability to Perform Tasks Independently



Future Plans

Future Application Development Includes:
Planned work includes partnering with a third-party digital platform to consolidate medical records and leverage AI and speech capabilities to track symptoms and health outcomes changes for CLS patients.

Longitudinal follow-up options are structured as in-person or remote visits with interim digital diaries for high burden features.

Further analysis and scrutiny of existing data will aim to correlate any sex-specific differences as well as inform potential endpoints for future interventional studies.

Participants are being engaged to contribute to governance elements including a multi-stakeholder steering committee.

References

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