

Spinal and Bulbar Muscular Atrophy

(Kennedy Disease)

Molecular pathology • Motor neuron degeneration • Clinical diagnosis

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Learning objectives

- Localize the motor neuron and muscle abnormalities in Kennedy disease
- Explain why an AR CAG expansion produces a polyglutamine disorder
- Relate bulbar and limb findings to lower motor neuron degeneration
- Discriminate SBMA from ALS and 5q spinal muscular atrophy
- Interpret genetic testing and the inheritance pattern

Kennedy disease: Defining clinicopathologic combination

Neurodegeneration

- Spinal and brainstem lower motor neurons
- Limb amyotrophy and fasciculations
- Bulbar weakness, tongue atrophy, dysphagia

Androgen-receptor disease

- Expanded CAG repeat in AR exon 1
- Intranuclear inclusions of mutant protein
- Gynecomastia, testicular atrophy, oligospermia

Motor neurons are the principal anatomical target

Spinal cord

Anterior horn
Lower motor
neurons



Limb muscles

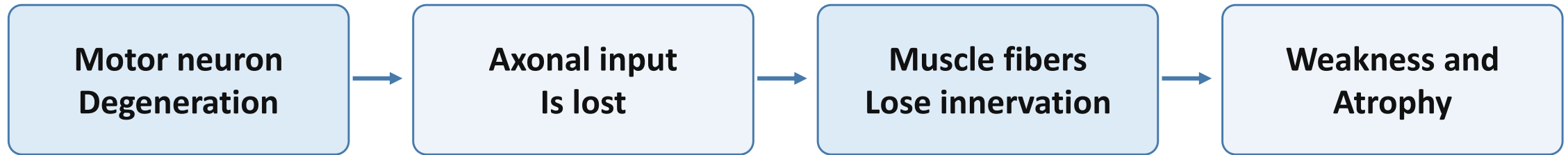
Brainstem

Cranial motor
Nuclei



Tongue / bulbar muscles

Lower motor neuron loss produces denervation



Fasciculations reflect spontaneous activity within surviving motor units.

Bulbar involvement is a localization clue

- Bulbar means motor systems controlling speech and swallowing
- Tongue atrophy and fasciculations indicate hypoglossal motor dysfunction
- Dysphagia links anatomical disease to aspiration risk
- Bulbar signs coexist with limb lower motor neuron deficits

A genetic motor neuronopathy, not a primary ALS subtype

Shared phenotype

- Progressive limb weakness
- Muscle wasting and fasciculations
- Bulbar dysfunction can occur

Distinct SBMA biology

- X-linked AR trinucleotide expansion
- Androgen-insensitivity manifestations
- Usually slow evolution rather than classic ALS course

The X-linked inheritance model

AR resides on the X chromosome

46,XY: One AR allele

46,XX: Two AR alleles

Males with a pathogenic expanded allele are hemizygous.

Why male phenotypes usually predominate

One X: Mutant AR has
No alternate X-linked copy



Typical symptomatic male

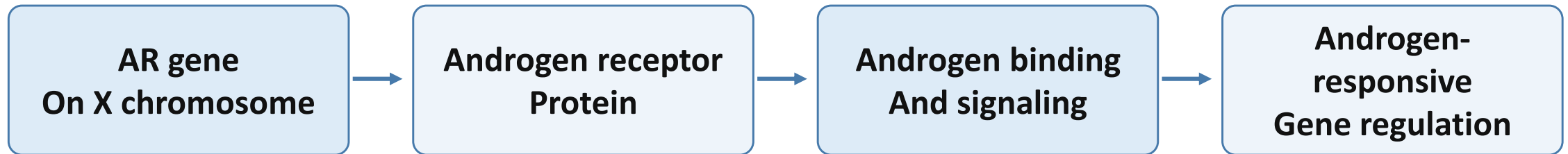
Two X chromosomes:
Heterozygotes often mildly affected



Variable carrier phenotype

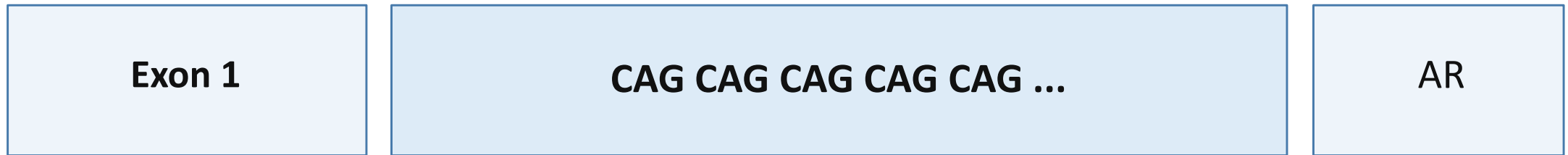
Sex-limited severity reflects both X-linkage and androgen-dependent biology.

AR encodes the androgen receptor



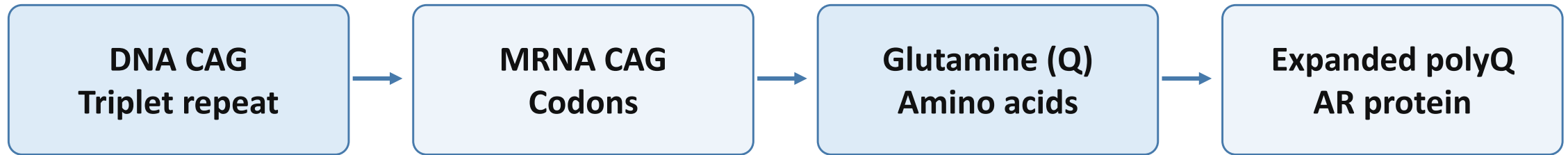
SBMA involves both abnormal protein toxicity and partial androgen insensitivity.

Exon 1 contains the disease-associated CAG tract



Repeat expansion increases the polyglutamine segment in AR.

CAG encodes glutamine: DNA to protein



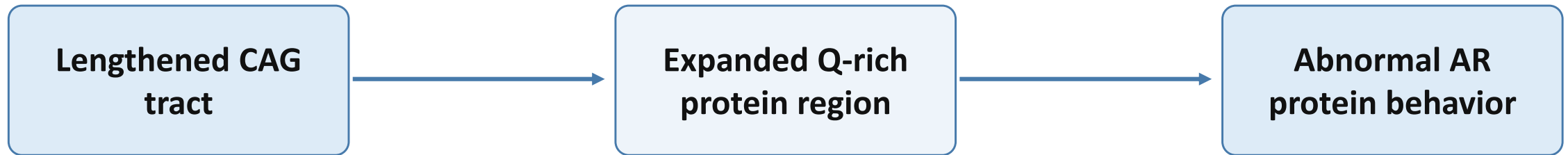
The mutation alters the protein sequence without being a conventional gene deletion.

Repeat length requires category-specific interpretation

AR CAG repeats	Interpretation
≤ 34	Normal range in GeneReviews
35	Uncertain clinical significance
36–37	Interpret with clinical and family context
≥ 38	Full-penetrance allele category

These categories come from GeneReviews (revised January 2026), not the Robbins paragraph.

Why a CAG expansion is a polyglutamine disease



PolyQ-expanded proteins may misfold and accumulate in vulnerable cells.

Polyglutamine disease does not mean complete AR absence

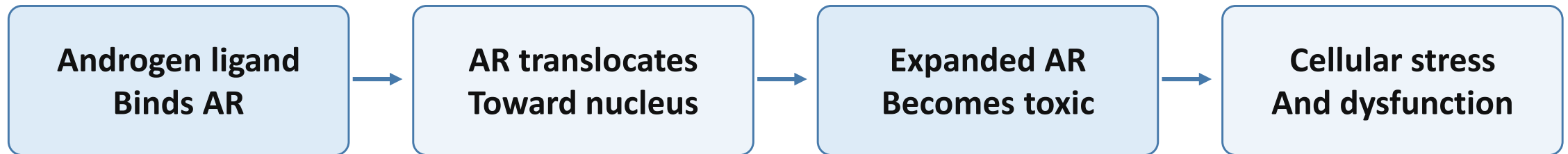
Toxic gain of function

- Mutant AR can disrupt cell homeostasis
- Nuclear accumulation / protein misfolding
- Neuronal and muscle pathology

Partial androgen insensitivity

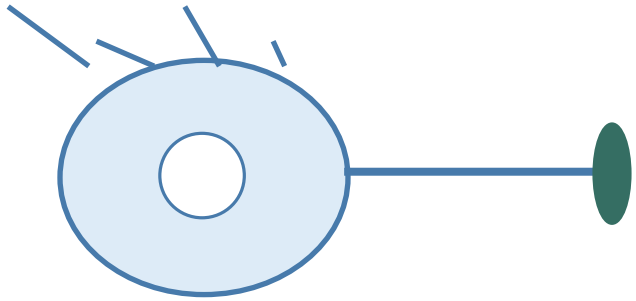
- Androgen-responsive function is altered
- Gynecomastia and reproductive features
- Clinical phenotype integrates both mechanisms

Androgen binding modulates mutant AR localization

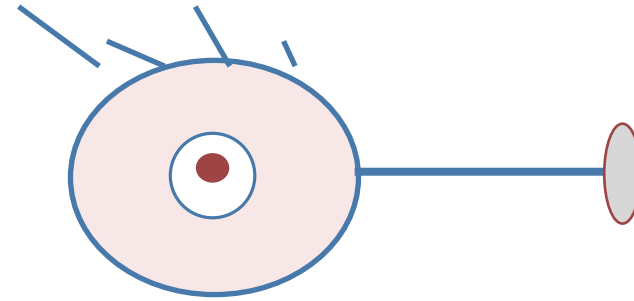


Ligand-dependent steps are supported by mechanistic studies; They do not imply proven therapy.

Mutant AR forms intranuclear inclusions



Conceptual normal motor neuron



Expanded AR: Nuclear inclusion

Red nuclear dot depicts a schematic inclusion—not microscopy.

Inclusion bodies are a pathologic signature

- Intranuclear inclusions containing the involved protein
- Inclusions support an abnormal protein-accumulation mechanism
- Their presence alone does not prove that visible aggregates are the toxic species
- Pathologic interpretation must distinguish association from causation

Selective motor neuron vulnerability remains unresolved

Established observations

- Spinal lower motor neurons degenerate
- Brainstem motor neurons degenerate
- Expanded AR accumulates in nuclei

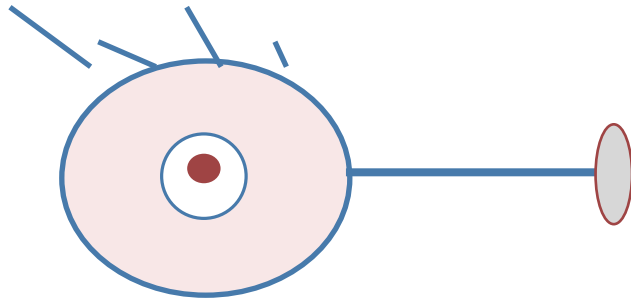
Mechanistic uncertainty

- Why particular neurons are vulnerable is not settled
- Inclusions may mark—not fully explain— toxicity
- Contributions from muscle are under investigation

Motor neurons and skeletal muscle can both be involved

Motor neuron compartment

Skeletal muscle compartment

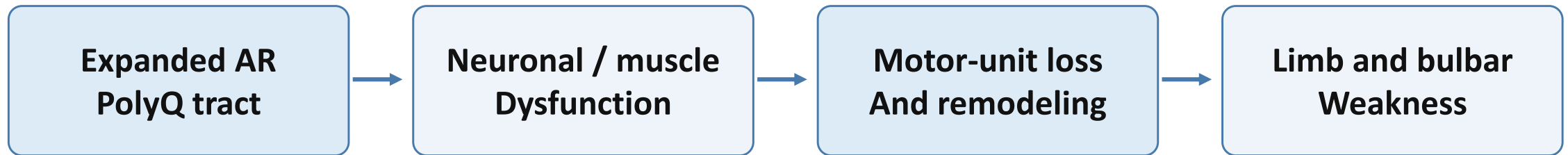


Muscle fiber: Myopathic
And denervation changes

Convergent muscle weakness

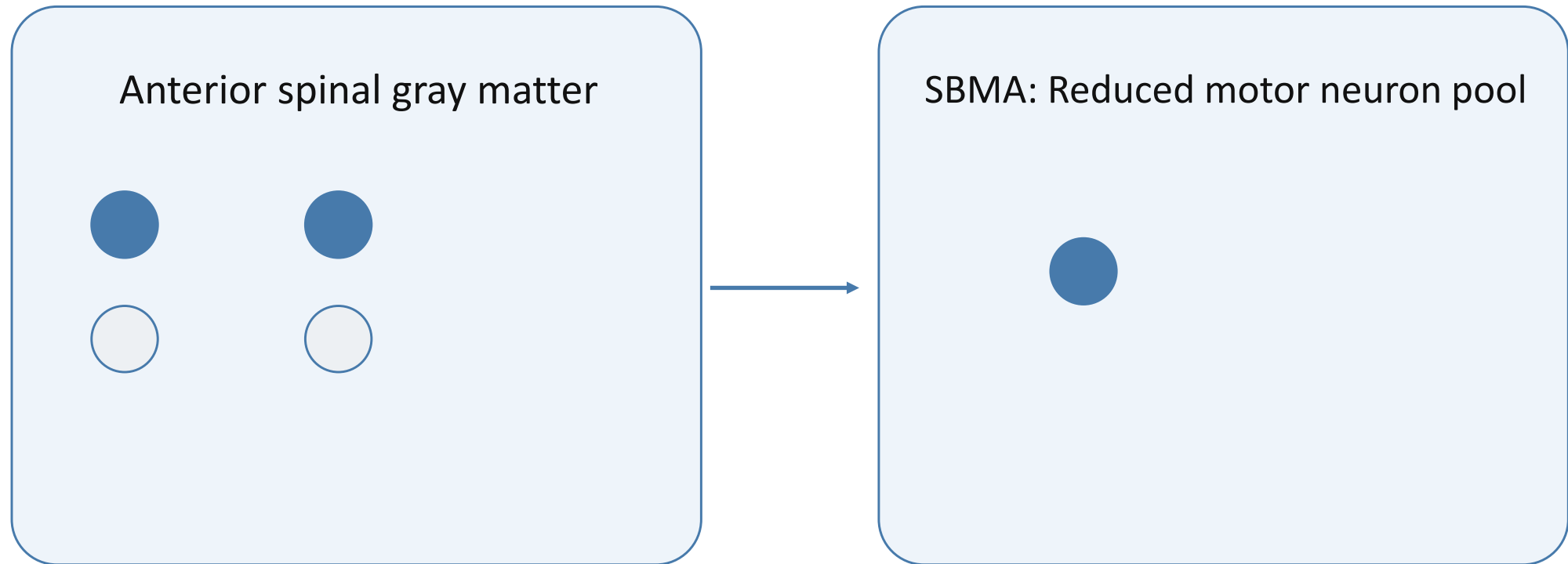
Both neurogenic and primary muscle contributions appear in contemporary literature.

From molecular change to functional disability



A mechanistic framework; Individual intermediate steps are still being studied.

Spinal cord pathology: Anterior horn neuron loss



Schematic cell counts are illustrative only—not measured tissue densities.

Brainstem pathology explains lingual weakness

Brainstem lower motor neurons

Hypoglossal motor nucleus



Tongue atrophy / fasciculations

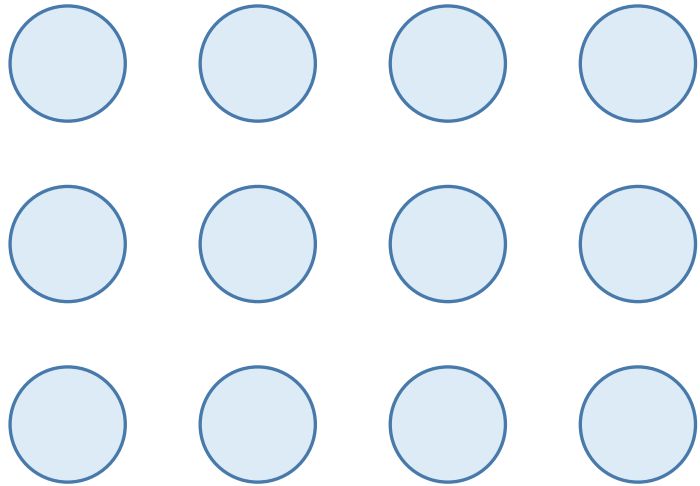
Other bulbar motor nuclei



Speech / swallowing abnormalities

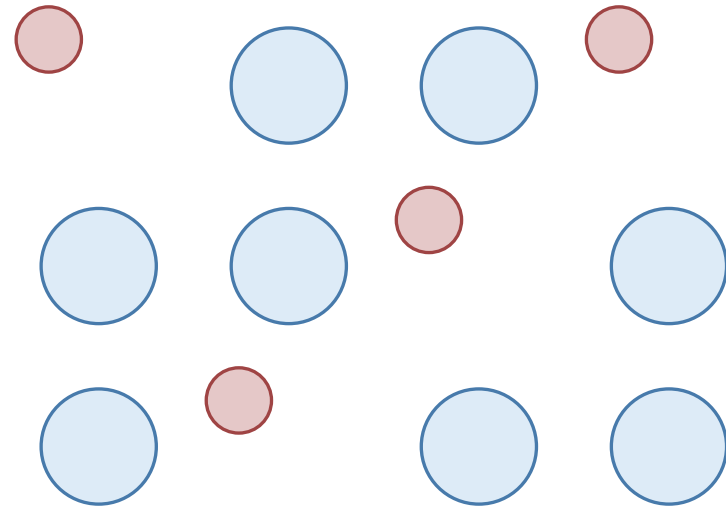
Denervation leads to neurogenic muscle atrophy

Intact innervation



Equal-sized fibers (schematic)

Motor-unit loss



Atrophic fiber subsets (schematic)

Neurogenic versus primary myopathic components

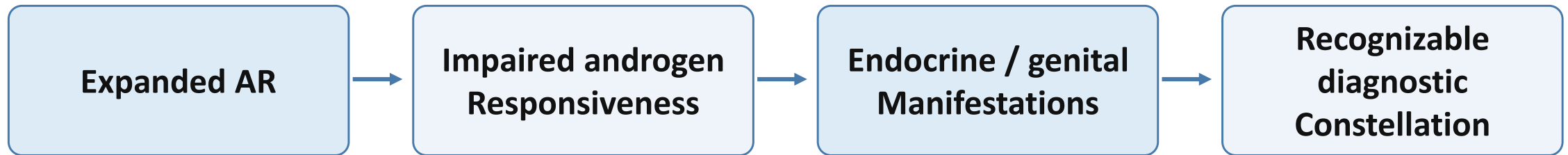
Neurogenic pathology

- Reduced motor-neuron input
- Denervation-driven muscle fiber atrophy
- Motor-unit remodeling

Myopathic contribution

- Muscle is also an AR-expressing tissue
- Myopathic changes can coexist
- Muscle pathology is not solely secondary in all models

Androgen insensitivity is part of the disease



Motor-neuron disease plus androgen-insensitivity signs is a major diagnostic clue.

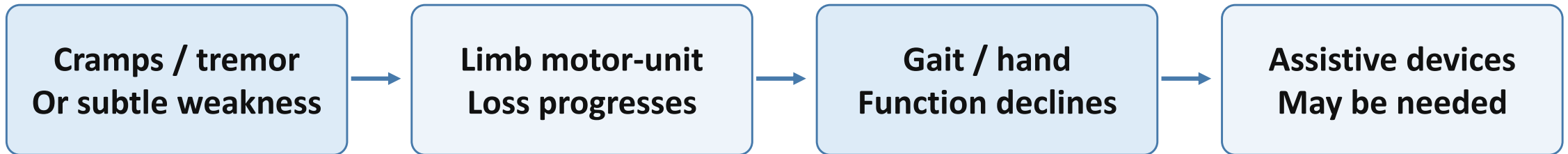
Gynecomastia has specific diagnostic value

- Breast enlargement can predate clinically obvious motor symptoms
- It reflects altered androgen signaling, not motor denervation
- The finding gains diagnostic value when paired with fasciculations or weakness
- Absence of gynecomastia does not exclude a pathogenic AR expansion

Testicular atrophy and reproductive features

- Testicular atrophy and oligospermia
- Reduced fertility may accompany partial androgen insensitivity
- Severity varies among affected individuals
- Reproductive history helps interpret the motor-neuron phenotype

Limb weakness usually evolves gradually



Early presenting symptoms may be nonspecific

- Muscle cramps and fine tremor may precede overt weakness
- Fasciculations are often noticed by patients
- Weakness may emerge in proximal limb groups and impair activities
- A long history of endocrine clues can shorten diagnostic delay

Limb amyotrophy reflects ongoing motor-unit loss



Weakness • visible wasting • reduced endurance

Bulbar disease produces dysarthria and dysphagia

Motor speech deficits

- Weakness changes articulation
- Tongue and facial muscles contribute
- Speech-language assessment is relevant

Swallowing deficits

- Bulbar weakness impairs bolus handling
- Aspiration and nutrition become concerns
- Clinical swallowing evaluation guides care

Tongue findings help localize lower motor neuron injury

Hypoglossal lower motor neuron degeneration



Loss of tongue muscle bulk

Tongue fasciculations

A combination of atrophy and spontaneous contractions points to LMN pathology.

Upper motor neuron signs are not typical

Expected SBMA pattern

- Atrophy and fasciculations
- Reduced or absent tendon reflexes
- No classic pyramidal pattern

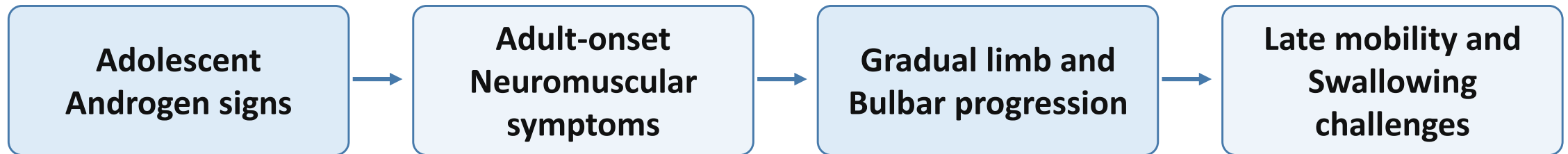
Consider ALS / alternative if

- Spasticity dominates
- Pathologic hyperreflexia
- Extensor plantar responses
- Rapid mixed UMN–LMN decline

Sensory abnormalities may accompany SBMA

- Some patients have sensory symptoms or abnormal sensory nerve studies
- This does not make SBMA a purely sensory neuropathy
- Sensory features can help distinguish it from classic ALS
- Interpret with motor findings and confirmatory AR repeat analysis

A clinical timeline has prognostic implications



Age at onset and course vary; This is not a fixed patient trajectory.

Laboratory and electrophysiology: Supportive, not defining

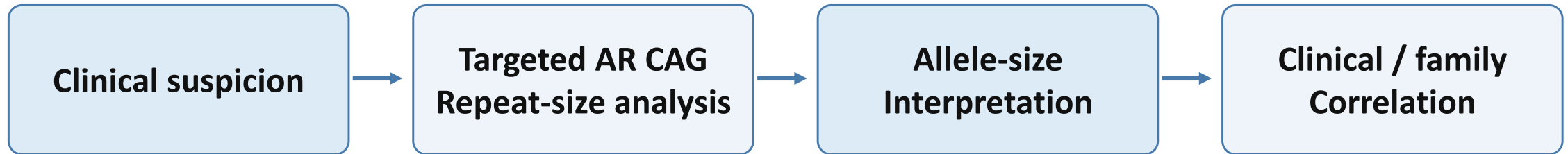
Useful supportive findings

- Elevated serum creatine kinase may occur
- EMG supports chronic denervation
- Nerve conduction can show sensory involvement

Diagnostic caution

- None of these is SBMA-specific
- Typical studies do not identify an AR expansion
- Genetic testing supplies molecular confirmation

The molecular test interrogates the CAG repeat



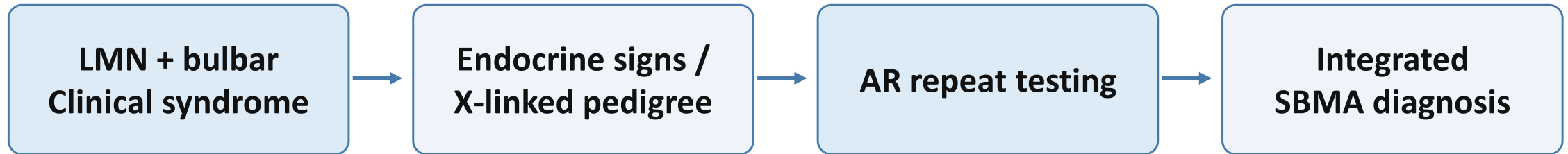
Routine sequencing panels may not characterize repeat expansions reliably without an appropriate assay.

Interpret borderline AR repeat sizes cautiously

Observed repeat	Clinical interpretation
≤ 34	Not in pathogenic repeat range
35	Questionable significance
36–37	Borderline: Clinical / family correlation
≥ 38	Full-penetrance category in GeneReviews

GeneReviews also notes that >35 repeats establishes molecular diagnosis in an appropriate male proband.

Diagnosis integrates genotype and phenotype



History and examination direct testing; The repeat expansion confirms the molecular diagnosis.

ALS is the most important mimic

Feature	SBMA	Typical ALS
Inheritance	X-linked AR expansion	Usually sporadic; Varied familial genes
Upper motor signs	Generally absent	Often present
Androgen signs	May be present	Not a defining feature
Progression	Usually gradual	Often more rapid

SBMA differs genetically from 5q-SMA

Question	SBMA (Kennedy)	5q-SMA
Main gene	AR	SMN1
Variant class	Expanded CAG repeat	Usually loss-of-function / deletion
Typical context	Adult male onset	Often childhood onset
Androgen signs	May occur	Not a defining feature

Other neuromuscular differentials

- Adult-onset inherited motor neuropathies and spinal muscular atrophy
- Charcot–Marie–Tooth phenotypes with prominent distal weakness
- Endocrine causes of gynecomastia without motor neuron disease
- Mixed presentations require localization, electrophysiology, and genetics

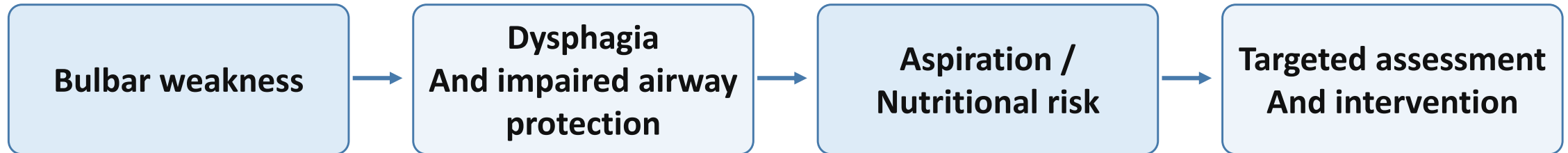
When is AR testing especially high yield?

- Adult male with slowly progressive lower motor neuron weakness
- Tongue fasciculations or dysphagia with absent UMN findings
- Gynecomastia, testicular atrophy, or reduced fertility
- Pedigree compatible with X-linkage—even if family history is negative

Course: Slow progression, variable disability

- Slow progression and prolonged preservation of ambulation
- Daily function may decline from combined limb and bulbar symptoms
- Clinical severity is heterogeneous even within families
- Life span is normal; Complications still require monitoring

Why swallowing surveillance matters



Dysphagia management is a functional safety priority even in slowly progressive disease.

Rehabilitation addresses functional consequences

Mobility / ADLs

- Strength and functional evaluations
- Physical and occupational therapy
- Braces, walkers, and fall prevention

Communication / swallowing

- Speech-language evaluation
- Diet and swallowing strategy assessment
- Follow-up as bulbar symptoms progress

Surveillance is system based

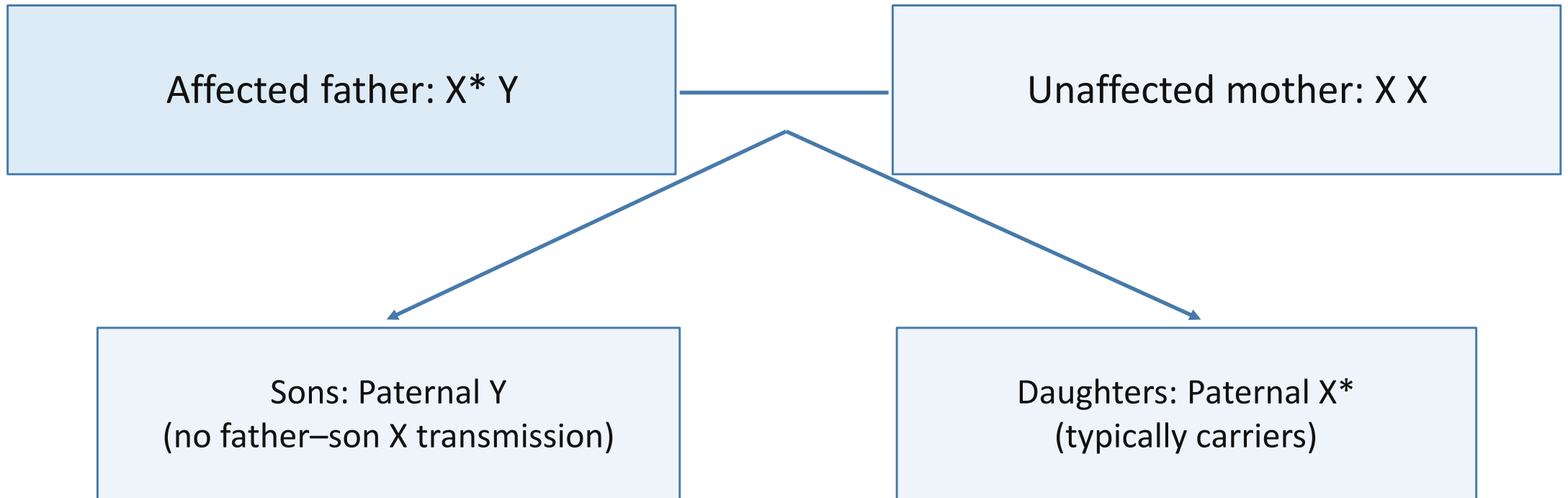
Domain	Recommended monitoring
Mobility / ADLs	Strength and rehabilitation evaluation
Speech / swallowing	Speech-language and feeding assessment
Advanced disease	Pulmonary function assessment
Cardiometabolic	Lipids, liver evaluation when indicated, cardiac review

GeneReviews (2026) suggests annual review or more frequently if clinically needed.

Endocrine and cardiometabolic care

- Assess bothersome gynecomastia and reproductive health concerns
- Individualize endocrine evaluation and supportive interventions
- Consider lipid profile and cardiovascular health monitoring
- Psychosocial and family support are longitudinal care needs

Affected fathers: X-linked transmission



Assumes an unaffected mother and conventional sex-chromosome transmission.

Carrier mothers: Probability per pregnancy

Carrier mother: $X^* X$

Unaffected father: $X Y$

Each child has a 50% chance of inheriting the expanded maternal X.

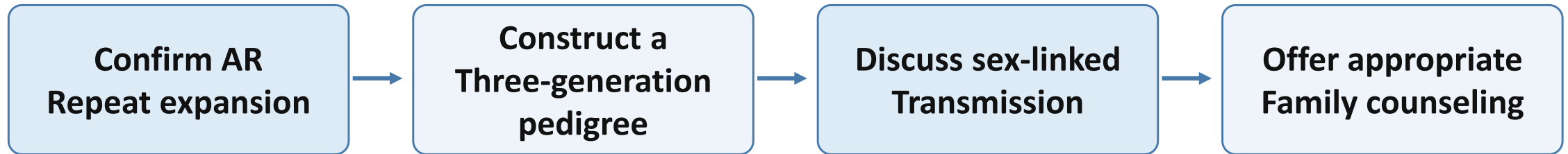
Affected sons if X^* inherited

Carrier daughters if X^* inherited

Female heterozygotes: Usually asymptomatic

- Most women carrying one expanded AR allele do not develop the male phenotype
- Mild cramps, tremor, or subtle symptoms can occur
- Carrier identification has reproductive and family implications
- Counseling should avoid asserting uniformly absent manifestations

Genetic counseling follows molecular confirmation

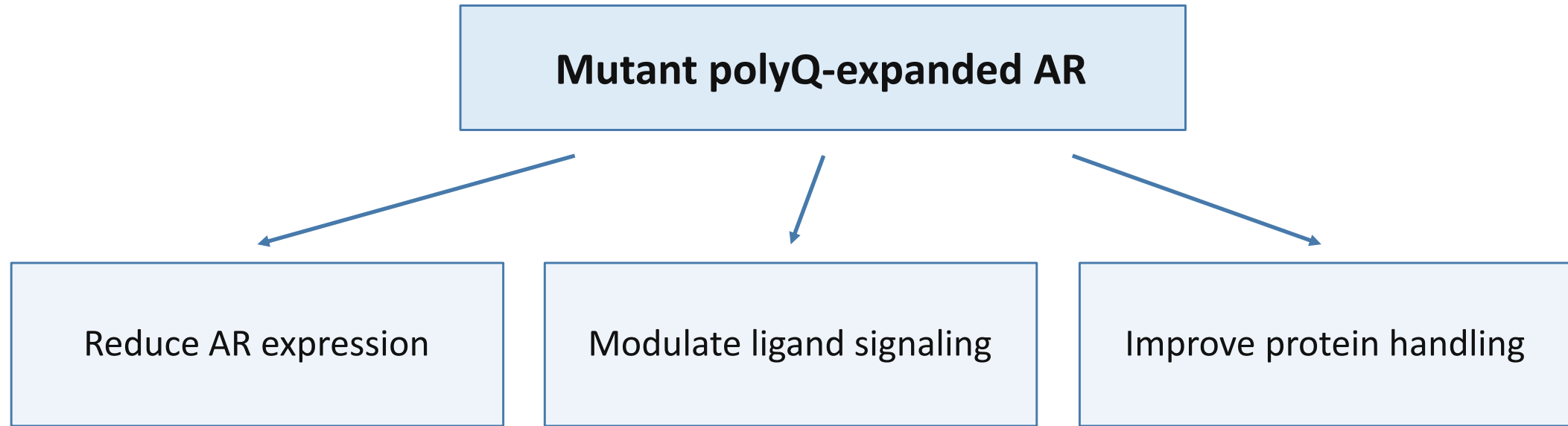


Counseling and testing decisions should account for autonomy and informed consent.

No established disease-modifying therapy

- Current care emphasizes symptoms, mobility, swallowing, and complications
- Androgen-pathway modulation has been investigated
- Reducing androgen signaling has not established a universally effective disease-modifying approach
- Experimental agents should not be presented as standard treatment

Research strategies target mutant AR toxicity



Investigational concepts; No efficacy or clinical availability is implied.

The neuroprotective mechanism remains an active question

Established target

- One pathogenic AR repeat-expansion class
- Lower motor neuron and muscle abnormalities
- Ligand-associated mutant AR toxicity

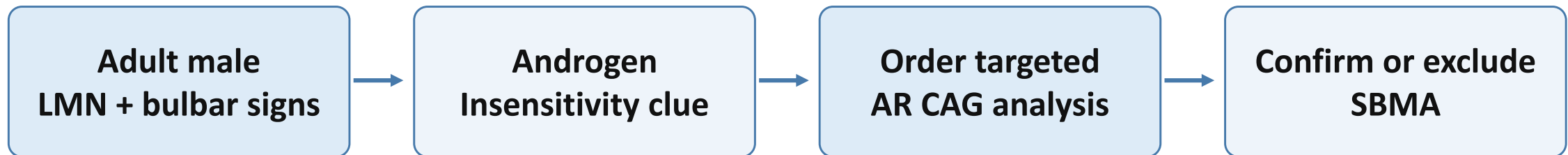
Open questions

- How cellular toxicity is initiated
- Relative importance of neuron vs muscle
- Which interventions preserve motor function

Case discussion: Adult-onset LMN syndrome

- A 49-year-old man reports years of cramps and progressive difficulty climbing stairs
- Examination: Tongue fasciculations, limb atrophy, reduced tendon reflexes
- No clear spasticity or other pyramidal signs
- History reveals longstanding gynecomastia

Case resolution: Combine localization and genetics



Electrophysiology helps characterize denervation but does not replace molecular testing.

Case discussion: Ambiguous repeat length

- An adult male has slowly progressive limb weakness and an AR result of 36 repeats
- His family history is uninformative; Endocrine findings are subtle
- Which result category applies?
- What clinical and familial evidence should accompany interpretation?

Borderline alleles should not be oversimplified

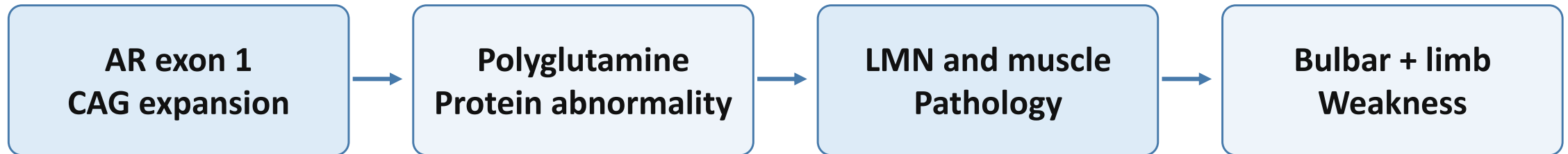
What is established

- GeneReviews places 36–37 in an intermediate interpretation range
- History and phenotype influence interpretation
- Within-family genotype data may assist

What not to conclude

- Do not equate every borderline allele with full penetrance
- Do not dismiss a phenotype without follow-up
- Do not use a single CK/EMG result as proof

Teaching synthesis: Molecular and anatomical axis



Partial androgen insensitivity supplies a parallel endocrine diagnostic clue.

Teaching synthesis: Discriminating features

Recognize

- Adult-onset, slowly progressive LMN syndrome
- Tongue atrophy / fasciculations and dysphagia
- Gynecomastia or reproductive features

Verify / monitor

- Confirm AR repeat expansion
- Distinguish from ALS and 5q-SMA
- Evaluate swallowing, mobility, respiratory status

Essential references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 28, p. 1173.
- La Spada A. Spinal and Bulbar Muscular Atrophy. GeneReviews; Revised 8 January 2026.
- Grunseich C, Fischbeck KH. Spinal and Bulbar Muscular Atrophy. Neurol Clin. 2015;33:847–854.
- MedlinePlus Genetics: Spinal and bulbar muscular atrophy. National Library of Medicine.

Further mechanistic reading

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- Grunseich C, Fischbeck KH. Neurol Clin. 2015;33:847–854. doi:10.1016/j.ncl.2015.07.002.
- Therapeutic targeting of the polyglutamine androgen receptor. Expert Opin Ther Targets. 2025. doi:10.1080/14728222.2025.2464173.
- Research models inform mechanism; only validated patient outcomes establish treatment benefit.