ISA INTERNATIONAL SOCIETY OF AMYLOIDOSIS

AMYLOIDOSIS FELLOWSHIP

Curriculum

ISA Fellowship Committee

Structured by: Core Competencies Required of All Amyloid Clinicians | Specialist Competencies for Sub-specialists

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Contributors:

Angela Dispenzieri (Hematology) | Helen Lachmann (Nephrology, Genetics) | Ute Hegenbart (Neurology) | Bruno Bueno (Cardiology)

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How to Use This Document

This curriculum reorganises the amyloid fellowship competency content from all contributing specialties into two tiers:

TIER 1 — CORE COMPETENCIES	TIER 2 — SPECIALIST COMPETENCIES
Required of ALL amyloid clinicians regardless of specialty background.	**Expected of sub-specialists within their discipline (Hematology, Nephrology, Cardiology, Neurology, Genetics).**

This curriculum also includes a matrix outlining suggested exposure (in weeks) to specific clinics and labs, organised by specialty track. This is found in Part Three of the framework.

PART ONE

Core Competencies Required of All Amyloid Clinicians

The following competencies must be demonstrated by every clinician undertaking an amyloidosis fellowship, irrespective of their specialty track.

C1. Foundational Knowledge and Disease Biology

Competency goal: Every amyloid clinician must command a working understanding of amyloid biology across all major types.

C1.1 Amyloid genesis

- Understand protein misfolding, fibrillogenesis, tissue deposition, and mechanisms of organ toxicity
- Recognise the distinction between direct fibril toxicity and mass effect
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C1.2 Amyloid Subtypes — Classification and Distinction

- Know the clinically important amyloid subtypes:
  - AL (light-chain): associated with plasma cell dyscrasia
  - ATTR (wild-type and hereditary): transthyretin-related
  - AA: associated with chronic inflammation
  - ALECT2: leucocyte chemotactic factor 2
  - Hereditary non-ATTR: AFib, ApoA1/A2, gelsolin, lysozyme
- Distinguish hereditary from acquired amyloidosis (ATTRwt, AL, AA)
- Distinguish localised from systemic amyloidosis
- Understand that amyloid type drives urgency, therapy, and prognosis — correct typing is foundational
- Understand amyloid nomenclature

C1.3 Genotype–Phenotype Principles

- Understand autosomal dominant inheritance patterns in hereditary amyloidosis
- Correlate major gene variants to dominant organ phenotypes (neuropathy, cardiomyopathy, renal disease)
- Define penetrance and variable expressivity and apply these concepts in clinical reasoning

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C2. Diagnostic Competency

Competency goal: Accurate and timely diagnosis with correct amyloid typing; avoidance of diagnostic misclassification.

C2.1 Clinical Suspicion — Red-Flag Recognition

- Recognise that amyloidosis is frequently missed because individual features are non-specific in isolation; suspicion should be triggered particularly by the combination of features across more than one organ system, rather than any single finding
- Apply a low threshold for investigation, as delayed diagnosis worsens both organ and patient outcomes
- Common examples of clinical features include (this is not an exhaustive list)
  - Nephrotic-range proteinuria with preserved kidney size
  - Restrictive cardiomyopathy / increased wall thickness on imaging, particularly with disproportionately low ECG voltages
  - Unexplained sensorimotor or autonomic peripheral neuropathy
  - Macroglossia, periorbital purpura, unexplained acquired bleeding disorder
  - Unexplained hepatomegaly or gastrointestinal dysmotility
  - Bilateral carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture
  - Family history of neuropathy, heart failure, or renal failure

C2.2 Laboratory Evaluation

- Serum free light chains with kappa:lambda ratio
  - Understand that different FLC assays are not interchangeable and that renally adjusted ratios should be used with the Freelite assay
- SPEP and UPEP with immunofixation
  - Understand and be able to explain the difference between electrophoresis and immunofixation
- Cardiac biomarkers: NT-proBNP and troponin
  - Understand their prognostic significance
- SAA (serum amyloid A protein) in suspected AA amyloidosis

C2.3 Tissue Diagnosis

- Understand the role and interpretation of Congo red staining with apple-green birefringence
- Know appropriate biopsy sites: abdominal fat pad, salivary glands, bone marrow, GI tract, or involved organ
- Understand why subtype confirmation is mandatory — Congo red alone is insufficient

C2.4 Amyloid Typing

- Understand the approaches to laboratory typing of amyloid
- Laser microdissection with mass spectrometry (LMD-MS)
  - High specificity; availability is limited to specialist centres
- Immunohistochemistry (IHC), using validated antibody panels
  - The primary method in many centres, given its wider availability, correctly typing the large majority of cases
  - Understand the limitations of IHC: antibody specificity and cross-reactivity
- Recognise that the presence of a monoclonal protein does not confirm AL amyloidosis and pathological typing is required

C2.5 Staging and Risk Stratification

- Apply Mayo cardiac staging systems (2004, 2012, revised) for AL amyloidosis

- Apply NAC, Mayo and Columbia staging systems for ATTR cardiomyopathy
- Understand renal staging systems and their prognostic relevance
- Recognise that organ dysfunction — not plasma cell burden — drives early prognosis in AL amyloidosis

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C3. Organ-Specific Assessment

Competency goal: Recognise and assess the extent of multisystem organ involvement.

C3.1 Cardiac Assessment

- Recognise cardiac features: increased wall thickness, diastolic dysfunction, low-voltage ECG, atrial fibrillation, atrial enlargement, aortic stenosis, GLS patterns, etc.
- Understand the role of echocardiography, cardiac MRI, and nuclear scintigraphy (DPD/PYP) in cardiac amyloidosis
- Interpret cardiac biomarkers (NT-proBNP, BNP, troponin) in the context of renal function, obesity and anaemia

C3.2 Renal Assessment

- Recognise major renal presentations: nephrotic syndrome, progressive CKD, CKD with minimal proteinuria
- Monitor proteinuria and eGFR as markers of disease and treatment response

C3.3 Neurological Assessment

- Recognise sensorimotor peripheral neuropathy and autonomic dysfunction as common amyloid presentations
- Know tools (and their limitations) to diagnose peripheral neuropathy (NCS) and autonomic neuropathy
- Understand nerve compression disorders (e.g., carpal tunnel syndrome, spinal stenosis) as an early ATTR feature

C3.4 Other Systems

Recognise hepatic involvement: hepatomegaly, raised alkaline phosphatase

- Recognise GI manifestations: dysmotility, malabsorption, bleeding
- Recognise musculoskeletal features: arthropathy, spinal stenosis
- Recognise pulmonary involvement: breathlessness due to alveolar septal infiltration, obstruction due to tracheobronchial deposits and nodular deposits.
- Recognise splenic involvement: splenomegaly, rarely hyposplenism or rupture

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C4. Multidisciplinary Integration

Competency goal: Function effectively within and coordinate a multidisciplinary amyloidosis team.

- Know which core specialties are involved in amyloid care and the contribution of each: cardiology, nephrology, neurology, haematology, pathology, genetics, transplant
  - Involve other specialities as appropriate
- Recognise when to refer urgently and to whom
- Engage collaboratively with nursing, physiotherapy, nutrition, and palliative care teams
- Understand the role of the amyloidosis centre model, with centralised multidisciplinary review supported by a network of regional centres and telemedicine to improve access and coordination of care

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C5. Therapeutic Principles

Competency goal: Understand the range of therapies used in amyloidosis and the principles governing their selection.

C5.1 AL Amyloidosis

- Know first-line treatment: proteasome inhibitor-based regimens
- Understand autologous stem cell transplantation: indications, contraindications, timing
- Understand dose modification requirements in advanced cardiac or renal disease
- Know that the goal is rapid and deep haematologic response to reduce direct organ toxicity and halt further fibril production

C5.2 ATTR Amyloidosis

- Know available disease-modifying therapies: TTR stabilisers and gene silencers (RNAi, ASO)
- Understand indications based on phenotype: cardiac vs. neurologic predominance

C5.3 AA Amyloidosis

- Understand that treatment targets the underlying inflammatory driver
- Know that SAA suppression can stabilise or improve renal outcomes

C5.4 Supportive and Preventive Care

- Avoid contraindicated medications: non-dihydropyridine calcium channel blockers, digoxin (selected cases), NSAIDs
- Manage volume overload and orthostatic hypotension
- Address anticoagulation in the context of cardiac arrhythmia and nephrotic syndrome
- Support nutritional status and manage peripheral neuropathic pain
- Integrate palliative care early — not only when disease-directed therapy has failed

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C6. Response Assessment and Longitudinal Care

Competency goal: Monitor disease trajectory and act on suboptimal response.

- Apply haematologic response criteria in AL amyloidosis (dFLC-based: CR, VGPR, PR)
- Assess organ response: cardiac biomarker trends, proteinuria, eGFR trajectory

- Understand that delayed or incomplete response worsens outcomes, especially in cardiac AL amyloidosis
- Plan long-term surveillance for disease relapse, treatment-related complications, and systemic progression
- Modify treatment based on depth and speed of response

C7. Genetic Principles and Family Risk

Competency goal: Appropriate recognition of hereditary disease and referral for genetic evaluation.

- Recognise indications for genetic testing: unexplained neuropathy, cardiomyopathy, early renal failure, family history
- Understand autosomal dominant inheritance and construct a three-generation pedigree
- Know the major hereditary amyloid genes: TTR, FGA, APOA1/2, GSN, LYZ
- Understand the concept of pathogenic variants, benign variants, and variants of uncertain significance (VUS) — avoid over-interpretation; prioritise phenotype
- Know when to refer for specialist genetic counselling
- Understand implications for family screening and cascade testing

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C8. Communication and Professionalism

Competency goal: Compassionate, clear, and expert communication with patients, families, and colleagues.

- Communicate complex information and prognostic uncertainty with clarity and empathy
- Engage in shared decision-making with patients and families
- Address implications of hereditary diagnosis for family members in accessible language
- Communicate uncertainty effectively (e.g., VUS, incomplete penetrance, evolving evidence)
- Support patients coping with chronic disease, uncertainty, and prognosis
- Coordinate longitudinal care across specialties and settings

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C9. Research Literacy and Clinical Trials

Competency goal: Engage critically with evidence and contribute to advancing the field.

- Interpret amyloidosis clinical trial endpoints (haematologic and organ response)
- Critically appraise published data and manage uncertainty when evidence is incomplete
- Know the landscape of ongoing clinical trials relevant to amyloidosis
- Understand ethical principles for enrolling patients in investigational studies
- Contribute to clinical trials, registries, outcomes research, and quality improvement

C10. End of Life and Palliative Care

Competency goal: Provide compassionate, skilled, and proactive end-of-life and palliative care across the full spectrum of amyloidosis — integrated with disease-directed therapy from the outset, not reserved for the final weeks of life.

Why This Competency Matters in Amyloidosis

- **Amyloidosis carries a high burden of multisystem morbidity, and, in advanced stages, a prognosis of months to a few years.**
- **The trajectory is frequently punctuated by acute organ decompensations.**
- **Disease-directed therapy and palliative care are not mutually exclusive**
- **Amyloid-specific symptom burdens: refractory oedema, autonomic dysfunction, neuropathic pain, profound fatigue, benefit from specialist palliative input.**
- **Patients often present late with advanced cardiac or renal failure, leaving a narrow window for prognostic conversations.**

C10.1 Prognosis and Disease Trajectory

- Apply the 'surprise question': 'Would I be surprised if this patient died within 12 months?'
  - if no, initiate proactive goals-of-care planning
- Recognise clinical signals for end-of-life discussion:
  - Failure to achieve haematologic response after two lines of therapy in AL
  - Progressive cardiac decompensation despite optimal medical therapy
  - Dialysis dependence with ongoing systemic disease activity
  - Recurrent hospitalisations for volume overload or arrhythmia
  - Risk of cardiac arrest
  - Significant functional decline, weight loss, or loss of independent ambulation
  - Patient or family expressing readiness to prioritise comfort

C10.2 Goals-of-Care Conversations

- Initiate advance care planning early, tailoring the approach to the differing national regulatory, legal, and cultural frameworks that govern end-of-life decision-making.
- Apply a structured communication framework to: prepare, elicit understanding, share information, explore values, align recommendations, document
- Lead sensitive discussions about specific interventions:
  - CPR: understand very low survival rates in advanced cardiac amyloidosis; lead DNACPR discussions with compassion
  - ICD deactivation: know how and when to facilitate this with device clinic and palliative care
  - Dialysis withdrawal: recognise this as an option; know expected symptom trajectory

C10.3 Symptom Management During Active Care and at End of Life

Advanced amyloidosis produces a distinct and complex symptom burden. Clinicians must anticipate and manage:

Symptom Domain	Amyloid-Specific Considerations	Management Principles
Refractory oedema	Diuretic resistance from low oncotic pressure, low cardiac output, and hypoalbuminaemia — aggressive diuresis risks haemodynamic compromise	Careful IV diuretic titration; use bioavailable loop diuretics and combination diuretic therapy; accept partial control; reframe goals with patient and family
Neuropathic pain	Severe, burning, distal pain in AL and ATTRv — often refractory; opioids less effective than for nociceptive pain	Pregabalin/gabapentin first-line; duloxetine; tricyclics; opioids for refractory cases; ketamine in specialist settings
Orthostatic hypotension	Cardiac amyloid and autonomic neuropathy synergise; severely limits mobility and quality of life	Compression garments; fludrocortisone; midodrine; droxidopa; simplify antihypertensives
Dyspnoea	Primarily cardiac; worsened by anaemia, pleural effusion, PE	Diuretics; low-dose opioids (effective for breathlessness); fan; repositioning; anxiolytics if distress prominent
Profound fatigue	Multifactorial: low cardiac output, anaemia, uraemia, malnutrition, depression	Address reversible contributors; occupational therapy; pacing strategies; energy conservation
GI symptoms	Dysmotility, nausea, diarrhoea, constipation from autonomic involvement and direct infiltration	Prokinetics; dietary modification; proactive constipation management; anti-diarrhoeal
Anorexia / cachexia	Malabsorption, early satiety, cardiac cachexia	Dietitian; small frequent meals; nutritional supplements; short-term corticosteroids for appetite
Anxiety and depression	Common, underdiagnosed; existential distress prominent in younger hereditary patients	Screen actively (PHQ-9, GAD-7); SSRI/SNRI; psychological support; chaplaincy; peer support

Consider:

- Opioid prescribing in renal failure: avoid morphine accumulation; co-prescribe laxatives
- Syringe driver indications and commonly used end-of-life combinations
- Prescribe anticipatory medications before community discharge
- Recognise the signs of dying and apply individualised care for the last days of life
- Stop non-essential medications; maintain only those contributing to comfort

C10.4 Transition to Palliative and Hospice Care

- Refer to specialist palliative care proactively
- Assess patient preference for place of care and death
- Coordinate discharge planning early
    - Provide clear handover of: prognosis, advanced care plans, symptom management plan with prescribing of anticipatory medications

C10.5 Support for Patients, Families, and Carers

- Recognise needs of family members and carers
    - Identify and address carer burden: fatigue, anxiety, financial strain, anticipatory grief
    - Screen for psychological distress in patients and carers and refer for support

- Recognise the unique burden on younger patients with hereditary disease: implications for children, siblings, and family identity
- Send a condolence to the family after a patient's death
- Facilitate a post-death family meeting where appropriate to answer questions and close the relationship

PART TWO

Specialist Competencies Expected of Sub-specialists

The following competencies are discipline-specific. Fellows achieve depth in their specialty track, with sufficient awareness of other disciplines to enable effective collaboration.

S1 — Hematology Specialist Competencies

Lead: Angela Dispenzieri

S1.1 Deep Understanding of Plasma Cell Biology

- Master the plasma cell dyscrasia spectrum: MGUS, smoldering myeloma, overt myeloma
- Understand the biology of monoclonal immunoglobulin production and light-chain toxicity
- Distinguish AL amyloidosis biologically and clinically from non-AL forms

S1.2 Advanced Diagnostic Expertise

- Expert use of serum free light chains, SPEP/UPEP, immunofixation, and bone marrow evaluation
- Understand the role and limitations of all amyloid typing methodologies
- Recognise rare AL presentations and avoid misclassification

S1.3 Therapeutic Expertise in AL Amyloidosis

- First-line regimens including daratumumab-CyBorD: dosing, schedule, monitoring
- Autologous stem cell transplantation: patient selection, mobilisation, risk mitigation
- Management of relapsed/refractory AL amyloidosis
  - Know possible treatments
- Emerging therapies: fibril-directed antibodies, monoclonal antibodies, gene-silencing strategies
- Understand when referral for organ transplant may be appropriate

S1.4 Dose Modification and Organ Tolerance

- Apply evidence-based dose modifications for advanced cardiac disease (Mayo Stage IIIb/IV)
- Modify regimens for advanced renal disease (eGFR <30, dialysis)
- Balance depth of haematologic response against organ tolerance and treatment toxicity

S1.5 Hematologic Response Assessment

- Apply dFLC-based criteria precisely (CR, VGPR, PR, no response)
- Role of MRD (BM and PB)
- Timing of evaluations
- Recognise that organ response lags haematologic response by 3–6 months (and longer)
- Differentiate drug toxicity from organ progression

S1.6 Long-Term Clonal Surveillance

- Monitor for disease relapse using serial free light chains and cardiac biomarkers
- Recognise and manage treatment-related complications: cytopenias, neuropathy, infection

- Understand risk of secondary malignancy and clonal evolution

S2 — Nephrology Specialist Competencies

Lead: Helen Lachmann

S2.1 Renal Amyloid Expertise by Subtype

AL Amyloidosis

- Confirm monoclonal protein; confirm subtype by biopsy with IHC and/or mass spectrometry
- Understand principles of plasma cell-directed therapy; know when and how to refer to haematology
- Monitor renal response to haematologic remission using proteinuria and eGFR

AA Amyloidosis

- Link inflammatory diseases to risk; treat inflammatory driver; manage nephrotic complications

ALECT2 Amyloidosis

- Suspect in CKD with minimal proteinuria, negative monoclonal studies, and relevant ethnicity
- Manage with conservative CKD measures, no targeted therapy currently exists

Hereditary Renal Amyloidoses

- Differentiate AFib, ApoA1/A2, gelsolin, lysozyme amyloidoses
- Understand disease course and indications for isolated renal or combined liver-kidney transplantation

Beta-2 Microglobulin Amyloidosis

- Recognise in long-term dialysis patients; understand prevention with high-flux HD/HDF and transplantation

S2.2 Advanced Cardiac Biomarker Interpretation in CKD

- Understand mechanisms of troponin and BNP/NT-proBNP elevation in CKD
- Apply dynamic change criteria to detect acute injury; interpret relative to trend, not absolute thresholds
- Integrate biomarkers with echocardiography, cardiac MRI, and bone scan in multimodal assessment

S2.3 Dialysis and Renal Replacement Therapy

- Assess HD vs. PD suitability based on cardiac status, albumin, nutrition, and amyloid subtype
- Recognise higher mortality in AL amyloidosis on HD; consider PD in cardiac amyloid

S2.4 Renal Transplantation in Amyloidosis

- General principles
  - Patient fitness: standard transplant work-up applies
  - Severe or progressive extra-renal involvement is a contraindication; assess cardiac, hepatic, and GI disease

    - Assess the status of the underlying amyloidogenic condition, including the risk of amyloid deposition in the graft and the availability of further disease-directed therapy if required post-transplant
- Subtype-specific:
    - AL: only after haematologic remission; cardiac involvement significantly affects outcomes
    - AA: viable once inflammation controlled; low recurrence risk
    - AFib: kidney-alone risks recurrence at ~10 years; liver ± kidney preferred in younger cases
    - ALys/AApoAI and ALECT2: excellent post-transplant outcomes; minimal recurrence
    - ATTRv: renal involvement uncommon; decisions based on cardiac/neurologic status

S2.5 Prognostic Assessment in Renal Amyloidosis

- Identify prognostic factors: amyloid type, proteinuria severity, baseline eGFR, response to therapy
- Counsel on recurrence risk post-transplant by amyloid subtype

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S3 — Cardiology Specialist Competencies

Lead: Bruno Bueno

S3.1 Advanced Cardiac Imaging in Amyloidosis

- Perform and interpret comprehensive echocardiography: wall thickness, ejection fraction, stroke volume, diastolic dysfunction, GLS, myocardial contraction fraction and assessment of aortic stenosis
- Interpret cardiac MRI: late gadolinium enhancement, T1 mapping, extracellular volume, and distinguish between HCM phenocopies and genotypes. Interpret bone scintigraphy (DPD/PYP/HMDP): grading of cardiac uptake for ATTR diagnosis on planar imaging AND most importantly on SPECT or SPECT/CT
- Recognise that planar imaging alone when interpreting bone scintigraphy is not sufficient and can lead to false-positive reads
- Differentiate cardiac amyloidosis from mimics: HCM, hypertensive heart disease, Fabry disease, sarcoidosis, athlete's heart, haemochromatosis

S3.2 Differential Diagnosis of Cardiac Amyloidosis

- Know red-flag ECG/imaging features
    - Low-voltage QRS with increased wall thickness:
    - Pseudo-infarct pattern (poor R-wave progression, Q waves without infarct)
    - Discordance between low QRS voltage and increased echocardiographic wall thickness
    - Conduction disease: first-degree AV block, bundle branch block, complete heart block
    - Atrial fibrillation, often with atrial mechanical dysfunction
    - Restrictive filling pattern with preserved ejection fraction
    - Reduced global longitudinal strain and apical sparing
    - Thickening of the right ventricle wall, heart valves, and interatrial septum
    - Biatrial enlargement
    - Diffuse circumferential subendocardial late gadolinium enhancement in MRI
    - Difficulty nulling the signal of the myocardium or blood pool in MRI
    - Non-response or worsening with standard heart failure therapy (ACE-I/ARB, beta-blockers)

Distinguish ATTRwt from ATTRv from AL cardiac amyloidosis using clinical, imaging, and biomarker approaches

- Understand the role of endomyocardial biopsy for diagnosis of cardiac amyloidosis and typing

S3.3 Heart Failure Management in Cardiac Amyloidosis

- Understand pharmacological restrictions: beta-blockers and reduced cardiac output, ACE inhibitors/ARBs and risk of hypotension, digoxin toxicity risk, understand high-dose diuretics and need for combination diuretic therapy with severe diuretic resistance, role of SGLT2i, MRAs
- Know indications and contraindications for device therapy (ICD, pacing, CRT)
- Understand the role of cardiac transplantation and combined heart-liver transplant or combined heart-kidney transplant in selected patients

S3.4 Arrhythmia Management

- Manage atrial fibrillation: rhythm vs. rate control; anticoagulation is indicated universally, regardless of the CHA_2DS_2-VA score
- Understand indications for ablation, short-term success, and high recurrence rates of atrial fibrillation catheter ablation
- Understand conduction system disease and indications for pacing
- Know risk of sudden cardiac death and limited ICD evidence in amyloid cardiomyopathy

S3.5 ATTR-Specific Cardiology Expertise

- Apply stabilisers: indications (ATTR-CM), dosing, monitoring and drug-drug interactions
- Understand gene-silencing agents (patisiran, eplontersen, vutrisiran) in ATTRv

S3.6 Perioperative Cardiac Risk Assessment

- Assess and manage perioperative risk in amyloid cardiomyopathy
- Understand that traditional calculators underestimate risk in restrictive cardiomyopathies
- Advise on anaesthetic risks, haemodynamic management, and postoperative monitoring

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S4 — Neurology Specialist Competencies

Lead: Ute Hegenbart

S4.1 Neuropathic Pattern Recognition

- Classify peripheral neuropathies: sensorimotor, pure sensory, small fibre, painful
- Recognise autonomic neuropathy: orthostatic hypotension, GI dysmotility, sudomotor changes, cardiac dysautonomia
- Distinguish amyloid neuropathy from diabetic, inflammatory (including CIDP), paraprotein-associated, toxic and hereditary neuropathies (such as Charcot-Marie-Tooth).
- Recognise nerve compression disorders as early ATTR features: carpal tunnel, spinal stenosis, biceps tendon rupture

S4.2 Neurophysiological Assessment

- Perform and interpret nerve conduction studies (NCS) in amyloid neuropathy

- Understand autonomic testing: tilt-table, heart rate variability, QSART, Valsalva manoeuvre, deep breath test
- Interpret skin biopsy for intraepidermal nerve fibre density (small fibre neuropathy)
- Apply validated neuropathy scoring tools: NIS+7, Norfolk QOL-DN, Neuropathy Symptom Score
- Assess the severity and range of dysautonomia using tools such as COMPASS 31

S4.3 CNS and Ocular Manifestations

- Recognise leptomeningeal amyloidosis: transient focal neurological episodes, dementia, seizures, cranial neuropathies
- Understand ocular manifestations: glaucoma, vitreous opacities (characteristic of some hereditary forms)

S4.4 Neurological Monitoring and Response Assessment

- Use validated scoring tools to track neurological disease progression
- Understand neurological response criteria in ATTRv clinical trials (NIS, mNIS+7)

S4.5 Neuropathic Symptom Management

- First- and second-line agents for neuropathic pain: pregabalin, gabapentin, duloxetine, tricyclics
- Manage orthostatic hypotension: compression garments, fludrocortisone, midodrine, pyridostigmine, droxidopa
- Manage GI autonomic dysfunction: promotility agents, dietary modification, somatostatin

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S5 — Genetics Specialist Competencies

Lead: Helen Lachmann

S5.1 Advanced Variant Interpretation

- Apply ACMG criteria for variant classification: pathogenic, likely pathogenic, VUS, likely benign, benign
- Use population frequency data (gnomAD) to contextualise variant risk
- Know the most common pathogenic variants in TTR and their relevant population distributions (e.g., V122I in Afro-Caribbean; V30M in Portuguese/Swedish/Japanese)

S5.2 VUS Management

- Formally counsel patients on VUS, explain uncertainty and its implications
- Apply a phenotype-first approach: do not over-interpret VUS without supporting clinical evidence
- Plan reclassification strategy: segregation analysis, functional studies, population-level data

S5.3 Penetrance, Expressivity, and Risk Counselling

- Describe age-dependent penetrance patterns for key variants (TTR V122I, V30M, T60A)
- Counsel on variable expressivity; apply penetrance and expressivity in prenatal and reproductive counselling

S5.4 Pedigree Construction and Inheritance Analysis

- Construct a three-generation pedigree: ages, diagnoses, age of onset, cause of death
- Identify autosomal dominant patterns and differentiate de novo from inherited disease

S5.5 Genetic Testing Strategy

- Select appropriate strategy: single-gene, gene panel, or whole exome sequencing
- Know genes associated with hereditary amyloid
- Coordinate cascade testing for at-risk relatives: timing, consent, result communication

S5.6 Integration with Clinical and Pathological Data

- Integrate genetic findings with clinical phenotype and mass spectrometry amyloid typing
- Differentiate hereditary ATTR from ATTRwt and from AL amyloidosis when monoclonal proteins coexist

S5.7 Asymptomatic Carrier Management

- Define recommended surveillance: neurological examination, cardiac imaging, renal evaluation, ophthalmology
- Understand surveillance intervals and trigger thresholds for treatment initiation
- Advise on preventive therapy in carriers: emerging evidence for early TTR stabiliser use

Summary Overview: Core vs. Specialist Competency Domains

The table below provides a comparative overview of the competency tiers across all domains, including End of Life and Palliative Care.

Competency Domain	Core (All Clinicians)	Specialist (Sub-specialists)
Foundational Biology	• Amyloidogenesis principles • All major amyloid subtypes • Basic genotype–phenotype links	• Plasma cell dyscrasia biology (Hem.) • Advanced ATTR molecular pathology (Card./Gen.) • Fibril-directed mechanistic understanding
Diagnosis	• Red-flag recognition across systems • Laboratory evaluation (FLC, IFE, biomarkers) • Congo red biopsy and typing principles	• Expert AL staging & haematologic workup (Hem.) • Advanced renal biopsy interpretation (Neph.) • Neurophysiological assessment (Neurol.) • Advanced cardiac imaging (Card.)
Organ Assessment	• Cardiac, renal, and neurological features • Biomarker interpretation (basic) • Systemic extent recognition	• Advanced echocardiography / MRI / scintigraphy (Card.) • CKD biomarker interpretation (Neph.) • EMG/ENG autonomic testing (Neurol.)
Treatment	• AL, ATTR, AA principles • Supportive care essentials • Contraindicated medications	• AL chemotherapy protocols & ASCT (Hem.) • Stabilizers and gene silencers (Card./Gen.) • Renal transplant criteria (Neph.) • Neuropathic symptom management (Neurol.)
Genetics	• Indications for genetic testing • Three-generation pedigree • VUS concept and referral	• ACMG variant classification (Gen.) • Penetrance counselling per variant (Gen.) • Cascade testing coordination (Gen.)
Multidisciplinary Care	• MDT roles and referral pathways • Communication across specialties • Early palliative care integration	• MDT leadership within specialty (all) • Clinical trial enrolment (all) • Registry and outcomes research (all)
End of Life & Palliative Care	• Prognostication by subtype and stage • Goals-of-care conversations and ACP • Symptom management at end of life • Transition to hospice/community care • Ethical and legal dimensions	• Advanced cardiac AL palliative management (Card./Hem.) • Dialysis withdrawal counselling (Neph.) • Neuropathic EOL symptom management (Neurol.) • Hereditary disease EOL implications (Gen.)

	• Family, carer, and bereavement support	

PART THREE

Recommended Exposure by Track over the Course of a Year (in Weeks)

	Cardiology Track	Hematology Track	Nephrology Track	Neurology Track	Genetics Track
Cardiology Clinic	16	8	6	4	6
Hematology Clinic	4	20	8	4	4
Nephrology Clinic	2	4	13	2	4
Neurology Clinic	2	2	2	17	6
Organ transplant	2	2	6	2	4
Cardiac scintigraphy	4	1	1	1	1
Cardiac ECHO	8	2	2	1	0
Cardiac MRI	4	1	1	1	1
Neurology labs	0	1	0	8	1
Genetics lab	1	1	2	2	15
Pathology lab	1	2	3	2	2
Research time	6	6	6	6	6

Framework compiled from pooled contributions: Hematology (Dispenzieri), Nephrology & Genetics (Lachmann), Neurology (Hegenbart), Cardiology (Bueno). C10 End of Life & Palliative Care integrated as universal core competency. Version 2.5 — International Society of Amyloidosis Fellowship Programme, 2026.