Management of Alström Syndrome

A Clinical Guideline

Alström Syndrome Guideline Development Group

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Introduction...

… to Alström Syndrome

Alström Syndrome (AS) is a rare disease with prevalence range from 1:10,000 in communities where first cousin marriages are customary to fewer than 1:1,000,000 in populations with low levels of consanguineous marriages. AS is characterized by cardinal clinical features (see below) that emerge throughout infancy, childhood, and young adulthood with wide clinical variability among affected individuals, even within the same family.

Cone-rod dystrophy (progressive visual impairment) presents with nystagmus and photophobia, usually within the first year of life. It progresses to severe visual impairment by the end of the second decade in 75% . Obesity develops in early childhood. Progressive bilateral sensorineural hearing loss is more variable, often presenting with high frequency loss in the first decade, but not detectable until much later in a minority. More than 60% of individuals with AS develop cardiomyopathy. This can present as potentially reversible dilated cardiomyopathy in infancy, or presenting de novo or recurrence in adolescence with progression to a restrictive pattern. Insulin resistance is present from infancy- and progression to glucose intolerance is partly related to degree of obesity. Other common endocrine abnormalities include hypothyroidism, growth hormone deficiency, hypogonadism in boys, and hyperandrogenism and polycystic ovaries in girls. Fibrosis of major organs is a common autopsy finding and can lead to renal failure, heart failure, hepatic cirrhosis and subtle pulmonary dysfunction. About 50% of individuals have delay in early developmental milestones; intelligence is usually preserved.

Molecular genetic testing of *ALMS1,* the only gene in which mutations are known to cause Alström syndrome, is estimated to detect mutations in 70%-80% of individuals of northern European descent, and approximately 40% world-wide.

… to the Alström syndrome guideline project

The guidelines have been developed by referring physicians and geneticists involved in the EURO-WABB project, according to the DYSCERNE guideline development process (www.dyscerne.org.dysc.home/). The experts who participated in the guideline development are listed on page 19.

… to the Alström syndrome clinical management guidelines

What are the aims of the guidelines ?

The guidelines aim to provide recommendations for the diagnosis, the management and the follow-up of patients with AS. These recommendations aim to support high quality care for children and adults with AS in a format that is accessible to anybody who is involved in the care of these patients. Note that transition is a process which includes the event of transfer from childrens' to adult services and needs to attend to the medical, psychosocial, and educational/vocational needs of the young person and his/her parents/carers. Care needs to be provided that includes attention to transition needs.

The guidelines are divided into:

- clinical features and diagnostic criteria
- baseline investigations
- any recommended tests, that are listed and organised into specific groups corresponding to the different symptoms and affected organs. Any recommendations that are specifically addressed either to children or to adult patients are specified.

A list of references starts on page 16, organised according to the different sections of the guidelines.

Additionally, there is a list of useful contacts for patients and families affected by AS, on page 20.

Note: N=normal; ABNL=abnormal

Diagnosis and clinical features of Alström Syndrome

Diagnostic criteria of AS

Age Range	Major	Minor	Minimum Required	Other Variable Supportive Evidence
Birth – 2 yrs	• Loss of function mutation in at least 1 allele of *ALMS1* AND/OR • Family history of Alström syndrome *(8/13)* • Vision (nystagmus/photophobia) *(5/13)*	• Obesity *(9/13)* • dilated cardiomyopathy (DCM)/congestive heart failure (CHF) *(8/13)*	2 major criteria OR 1 major + 2 minor criteria	• Recurrent pulmonary infections • Normal digits • (History of) delayed developmental milestones
3-14 yrs	• Loss of function *ALMS1* mutation in at least 1 allele AND/OR • Family history of Alström syndrome *(9/24)* • Vision (nystagmus, photophobia, diminished acuity, if old enough for testing: cone dystrophy by ERG) *(15/24)*	• Obesity *(20/24)* and/or insulin resistance and/or T2DM *(10/24)* • DCM/CHF *(9/24)* • Hearing loss *(11/24)* • Hepatic dysfunction • Renal failure *(1/24)* • Advanced bone age	2 major criteria OR 1 major + 3 minor criteria	• Recurrent pulmonary infections • Normal digits •(History of) delayed developmental milestones *(7/24)* • Hypertriglyceridaemia • Scoliosis • Flat wide feet • Hypothyroidism *(5/24)* • Hypertension *(6/24)* • Growth hormone deficiency • Recurrent UTI
15 yrs - adult	• Loss of function *ALMS1* mutation in at least 1 allele AND/OR • Family history of Alström syndrome *(7/13)* • Vision (history of nystagmus in infancy/childhood, legal blindness, cone and rod dystrophy by ERG) *(13/13)*	• Obesity *(10/13)*and/or insulin resistance and/or T2DM *(8/13)* • DCM/CHF *(4/13)* • Hearing loss *(12/13)* •Hepatic dysfunction • Renal failure *(4/13)* • Short stature • Males: hypogonadism • Females: irregular menses and/or hyperandrogenism	2 major + 2 minor criteria OR 1 major + 4 minor criteria	• Recurrent pulmonary infections • Normal digits • Delayed developmental milestones • Hypertriglyceridaemia • Kypho-scoliosis • Flat wide feet • Hypothyroidism • Hypertension *(9/13)* • Growth hormone deficiency • Recurrent UTI / urinary dysfunction • Alopecia

Table 1. Diagnostic Criteria by Age from Marshall et al. 2013. Figures in parentheses relate to prevalence in EURO-WABB Registry participants with confirmed molecular genetic diagnoses: n=13 aged birth-2yrs; n=24 aged 3-14yrs; n=13 aged 15 yrs plus
Note: The diagnosis is established in individuals of all ages in whom two pathological *ALMS1* mutations are identified. ERG = electroretinogram ; T2DM = type 2 diabetes mellitus ; DCM/CHF = dilated cardiomyopathy with congestive heart failure ; UTI = urinary tract infections

Recommended baseline investigations in Alström Syndrome

Clinical Features of AS	Baseline investigations
Cone-rod dystrophy	Ophthalmologic evaluation, electroretinogram, visual field testing, fundus examination
Obesity	Measurement of weight and height; calculation of body mass index (BMI) and waist circumference
Progressive bilateral sensorineural hearing loss	Audiometry with auditory brain stem response (ABR) and otoacoustic emissions (OAE); assessment of otitis media and conductive hearing loss
Cardiomyopathy	A detailed cardiac history and examination (auscultation), serial ECG's, echocardiogram (ventricular dilation and reduced ejection fractions)
Insulin resistance/type 2 diabetes mellitus	Fasting plasma glucose, even in infancy; glucose tolerance test (GTT) over age 6 years; HbA1c Fasting plasma insulin concentration, as hyperinsulinemia may be present from infancy
Hyperlipidemia	Fasting serum lipid profile
Endocrine abnormalities	Measurement of thyroid (plasma TSH and free T4), gonadal function (FSH and LH and testosterone or estrogen)
Bladder dysfunction	Screen urinary symptoms. If symptomatic or abnormal urinalysis : bladder and renal ultrasound (search pelvi-calyceal dilatation and post-voiding residual)
Renal disease	Baseline blood pressure; 24-hour blood pressure monitoring Measurement of plasma creatinine, urea and electrolytes.
Hepatic disease	Measurement of plasma ALT, AST, and GGT concentration ; Liver ultrasonography for fatty liver disease
Pulmonary disease	Chest radiography, pulmonary function tests (often difficult with dual sensory loss), oximetry during exercise helpful.
Gastrointestinal	If severe reflux esophagitis (acid blockers): barium swallow / upper GI endoscopy
Skin	Note acanthosis nigricans (indication of insulin resistance), alopecia, hirsutism
Orthopedic abnormalities	Note flat feet, scoliosis, barrel chest, kyphoscoliosis on physical examination
Neurologic manifestations	Neurologic evaluation. Note autistic-spectrum behavioral abnormalities.

Recommendations for the management of Alström Syndrome
Sensory involvement

Visual assessment : **Cone-rod dystrophy**

At diagnosis
Between birth and 15 months of age

Severe photophobia with nystagmus and initial preservation of night vision is characteristic. The photophobia is greatly helped by tinted glasses.

Follow up

Yearly eye examination: visual acuity (typically no perception of light by age 20 years); visual field testing where visual acuity permits; fundus examination (retinal photography where possible for later comparison); ERG (where recordable); screen for cataract, glaucoma and diabetic retinopathy where appropriate

ABNL

Cataracts are common and predate diabetes. If unsightly or impair residual vision then extraction should be offered. Regular visual acuity measurement with carefully planned visual aids, and input from experts in visual impairment are essential at all ages. Anticipate the need for Braille and mobility training. Early education interventions, computer digital and voice software for blind.

Hearing assessment : **Progressive bilateral sensorineural hearing loss**

At diagnosis
2-25 yrs

Audiogram (after one year, initial deficiency in the high frequency range)

ABNL

Auditory evoked potentials

Follow up

Yearly examination
Glue ear (long-standing sticky fluid in the middle ear) can lead to an additional conductive hearing loss

ABNL

Management in standard way by a specialist (myringotomy tubes and/or hearing aids)
Expert audiology assessment with attention to least irritant bilateral hearing aids with adaptations available for group involvement is crucial for family, school and work.

Recommendations for the management of Alström Syndrome

Endocrine System

Insulin resistance / Type 2 Diabetes Mellitus

At diagnosis

- Fasting plasma glucose (FPG), even in infancy
- An oral glucose tolerance test (OGTT) after six years of age. HbA1c level is less invasive as a screen for non-type 1 diabetes. A value equal to or greater than 6.5% is a sufficient criterion for diagnosis of diabetes.
- Fasting plasma insulin concentration, as hyperinsulinemia may be present from infancy

Follow up

- Anticipatory guidance promoting healthy eating, maintenance of a healthy weight and regular physical activity
- Yearly fasting plasma insulin concentration (hyperinsulinemia may be present from early infancy)
-Note that post meal C-peptide may supersede fasting insulin as a measure of insulin resistance.
- Measurement of fasting plasma glucose concentration and HbA1c annually
- Note acanthosis nigricans (indication of insulin resistance)

ABNL

Diagnostic criteria of diabetes

Fasting (at least 8 hours) Plasma Glucose (FPG) ≥ 7.0 mmol/L

Or

Casual postprandial plasma glucose ≥ 11.1 mmol/L + osmotic symptoms (polyuria, polydipsia and unexplained weight loss)

Or

2 hour PG ≥ 11.1 mmol/L in a 75-g oral glucose tolerance test

Or

HbA1c greater than 44mmol/mol

⇒ Insulin resistant diabetes mellitus occurs between 8-40y (mean 16y) in 70%

Recommendations for the management of Alström Syndrome
Endocrine System – Type 2 Diabetes Mellitus

Management of DM for children by an interdisciplinary pediatric diabetes healthcare team

Intensive education / Nutrition	Standard lifestyle interventions in the form of dietary and exercise recommendations and regular clinic visits, intensive counselling and family involvement; Management of psychological issues, such as depression, self-destructive behaviour patterns and avoidance of smoking.
Glycaemic targets	- Measurement of HbA1c concentration and serum glucose concentration regularly (every 3 months) - HbA1c target should be less than 7.5%.
Therapy	- Management in the standard way (adapted according to the presence of heart failure or liver dysfunction) - Lifestyle intervention (diet and exercise advice) to maintain glycemic control
ABNJ	if glycemic targets not achieved within 3 to 6 months using lifestyle modifications alone, then Metformin is the treatment of choice as it is weight neutral and improves insulin sensitivity. Incretin analogues such as Exenatide and Liraglutide have been successful in some cases. In the paediatric population the balance of risks of these therapies must be carefully assessed. Some AS patients may progress to relative insulin deficiency. Insulin regimens must be adapted to the individual and dosages required vary widely.
	Management of insulin therapy should include intensive education (injection, self-monitoring of blood glucose and ketone testing) with adapted devices for blind people (e.g. insulin pen with audible signal of insulin dose delivery). Hypoglycaemia is rare because of the insulin resistance but awareness of it and treatment must be taught.
	Organized transition services may decrease the rate of loss to follow-up.
	Re-appraisal of the need for insulin is important if incretin analogue therapy and or effective lifestyle changes are undertaken with good improvement in glycaemia. Keto-acidosis has only rarely been reported in the syndrome as insulin deficiency is unlikely to be so severe. If pregnancy were to occur in an insulin requiring AS patient then intense multidisciplinary ante natal care would be vital.

Recommendations for the management of Alström Syndrome
Endocrine System – Diabetes Mellitus

Management of diabetes complications and comorbidities in children with type 2 diabetes

Dyslipidemia	At diagnosis of diabetes and every 1–3 years thereafter depending on clinical presentation Fasting Total Cholesterol, HDL-C,Triglycerides, calculated LDL-C In children with familial dyslipidemia and a positive family history of early cardiovascular events, a statin should be started if the low-density lipoprotein cholesterol level remains >4.2 mmol/L after a 3- to 6-month trial of dietary intervention. The commonest problem is hypertriglyceridaemia which may be severe enough to cause pancreatitis. Levels more than10 mmol/l not responsive to diabetes control, diet and statin therapy may require nicotinic acid derivatives.
Hypertension	At diagnosis of diabetes and at every diabetes-related clinical encounter thereafter (at least twice annu ally) Blood Pressure measurement using appropriate size cuff
Nephropathy	Yearly screening starting at diagnosis of diabetes First morning (preferred) or random albumin to creatinine ratio (ACR) with confirmation at least 1 month later Follow-up with timed, overnight or 24-hour split urine collections for albumin excretion rate Repeated sampling every 3–4 months over a 6- to 12-months Referral to a pediatric nephrologist for management.
Neuropathy (rare)	Yearly screening starting at diagnosis of diabetes: symptoms of numbness, pain, cramps, and paresthesia and clinical examination for skin sensation, vibration sense, light touch and reflexes.
Polycystic Ovary Syndrome	Yearly screening starting at puberty in females with oligo/amenorrhea, acne and/or hirsutism Androgen levels, including DHEAS and free testosterone
Retinopathy	Diabetic retinopathy has rarely been reported in AS and is never the cause of visual loss. Diabetic photographic retinal screening therefore seems superfluous especially in view of the photophobia.

Alström Syndrome Clinical Management Guidelines

Recommendations for the management of Alström Syndrome
Metabolism and Endocrine System – Others

Obesity in early childhood		- Obesity primarily truncal with a body mass index (BMI) > 95thcentile. Gynaecomastia in boys. - Note : Hyperphagia may occur with excessive weight gain.
	ABNL	- In people affected by Alstrom syndrome, the dual sensory loss can make it difficult to follow long-term weight management programmes with increased activity levels. However the necessary provision of a helper for access to education, transport and recreation can be used to encourage lifestyle changes long term. Patients may require energy intakes which are well below Estimated Average Requirements (EAR) and there may be a role for reduced carbohydrate intake.
Hyperlipidemia primarily hypertriglyceridemia +/- hypercholesterolemia		A fasting lipid profile, including triglycerides
	ABNL	- If severe hypertriglyceridemia: nicotinic acid derivatives (if pancreatitis with well controlled DM) - Lipid lowering dietary advice if raised cholesterol. - Statins for long-term prevention of atherosclerosis in adults with low HDL, high LDL and DM.
Follow up **Risk of pancreatitis**		- Annual total lipid profile determination or more frequently if hyperlipidemia is present. - Care about risk for sudden increase in triglycerides precipitating life-threatening pancreatitis (especially if patient is ill and/or dehydrated).
Hypogonadism		**- Males :** symptoms of hypogonadotropic and/or hypergonadotrophic hypogonadism and testicular fibrosis to seek => delayed or arrested puberty, immature secondary sexual characteristics, gynecomastia - **Females :** to seek symptoms of hyperandrogenism (hirsutism), polycystic ovarian syndrome, precocious puberty (< age 8 years), endometriosis, a/oligomenorrhea. - Hormone levels : testosterone (or oestradiol), gonadotropin FSH and LH, inhibin B -Brain MRI**:** Abnormal brain MRI findings (empty sella turcica in some affected individuals)
	ABNL	-Management in standard way (*i.e* testosterone replacement in male patients, estrogen-progesterone replacement in female patients)
Hypothyroidism		Annually assessement of thyroid function : plasma free-T4 and TSH concentration, + free T3 If hyperthyroidism suspected.
	ABNL	Thyroid substitution therapy with L-Thyroxine - Note growth rates for young children, bone age, serum IGF1 - As children approach puberty, gonadotropin, sex hormones and thyroid function should be assessed to determine if hormonal adjustments are necessary.
Short stature	ABNL	-Although there are subtle changes in growth hormone dynamics replacement therapy is not usually necessary, and growth hormone axis not routinely tested. GH therapy in adult AS patients has been reported but remains under investigation

Recommendations for the management of Alström Syndrome
Cardiomyopathy

Dilated cardiomyopathy with infantile onset or restrictive cardiomyopathy in adolescents and adults

At diagnosis

Seek signs of cardiac failure (such as sweating, fatigue, lethargy, asthma, decreased physical activity, orthopnoea, dyspnoea) :
- **Between 2 weeks and 4 months : 42% Dilated CMP** (transient but severe; most children survive and make an apparently full recovery in infancy).
-**Between childhood and late 30s : 18% Restrictive CMP** (progressive)

A detailed cardiac history and examination including ECGs and echocardiography even if the individual is asymptomatic. Echocardiography (to demonstrate ventricular dilation, fibrosis, and decreased myocardial function). 24-hour ECG monitoring if indicated.

Follow up

Annual monitoring by a cardiologist or pediatric cardiologist, **even in the absence of symptoms related to left ventricular dysfunction**: detailed cardiac history and examination, including auscultation, echocardiography and ECGs. 24-hour ECG monitoring if indicated.

ABNL

- Treatment of cardiac failure : Angiotensinogen-converting enzyme (ACE) inhibitors, diuretics, digoxin, and possibly betablockers. The use of these agents must be monitored carefully, especially effects on blood pressure and renal function. The co-existence of hepatic and or renal fibrosis may result in pre-renal uraemia with these agents. Cardiac transplantation has been successful in a small number of AS persons with severe and progressive cardiac dysfunction.
- Prevention of acute decompensation : Care must be taken during sedation or operative procedures. The combination of dilated cardiomyopathy, congestive heart failure, pulmonary hypertension, and pulmonary fibrosis can cause sudden severe hypoxia in an affected individual following surgery or even during a minor infection. Close monitoring of cardiac status and oxygenation are necessary until the individual is fully recovered.

Recommendations for the management of Alström Syndrome

Pulmonary disease

At diagnosis

Ask about respiratory symptoms, and examine the pulmonary system

Detailed assessment of pulmonary function (chest radiography, pulmonary function tests (but note that many AS patients are unable to complete these) to determine if there is a chronic obstructive or restrictive lung disease (kyphoscoliosis and pulmonary fibrosis).
High-resolution chest CT scan to detect pulmonary fibrosis if restrictive pattern.
Pulmonary hypertension detected by cardiac assessment .

Follow up

Yearly pulmonary function tests to evaluate general lung function, even if symptoms of pulmonary fibrosis are not yet present. Assess spirometry to determine the presence of obstructive airways disease.

ABNL

- Care of recurrent pulmonary infections
- General activity, including breathing exercises, can reduce chronic hypoxia and improve wellbeing.
- Prevention of complications: susceptibility to sudden severe hypoxia postoperatively or during episodes of pneumonia (especially if combination of dilated cardiomyopathy, congestive heart failure, pulmonary hypertension, and pulmonary fibrosis). Care during sedation or operative procedures with close monitoring of cardiac status and oxygenation.

Liver and Gastrointestinal involvement

At diagnosis
Between 8y at 30y

Upper GI Gastro-oesophageal reflux disease (GORD) is common in the syndrome and usually responds to Proton pump inhibitors. Note that dysphagia is reported by the parents of a growing number of affected children aged less than 2 years
Large bowel One sibling pair has been described with caecal volvulus suggesting that there may be a generalised disorder of gastrointestinal autonomic nervous system.
Hepatic Abdominal examination is difficult to interpret because of the obesity. Serum transaminases are usually mildly elevated characteristic of non alcoholic fatty liver.

Follow up

ABNL

Staging liver involvement relies on hepatic ultrasound, measuring spleen size and portal hypertension, enhanced liver fibrosis test and fibroscan.
In early childhood :
- Measurement of plasma ALT, AST, and GGT concentration and ultrasound.

In the second to third decades: Unexplained anaemia or GI Haemorrhage are indications for referral for investigation of possible varices.

Recommendations for the management of Alström Syndrome
Renal and Urological involvement

Urologic disease : detrusor-urethral dyssynergia ; Adolescence – adult ; present in ~50%

At diagnosis	- Ask about urinary symptoms and complete voiding diary (urgency, hesitancy, poor urinary flow, urinary frequency, incontinence, lower abdominal and perineal pain), clinical examination ABNL - Bladder and renal ultrasound (post-voiding residual volume (PVR)); urodynamic testing
Follow up in adolescence (++ females)	Yearly assessment : - Ask about urinary symptoms and complete voiding diary - Consider bladder and renal ultrasound - Clinical examination - Consider urodynamic testing ABNL Severe urethral detrusor dys-synergia not responsive to alpha blockers or anticholinergic therapies indicates referral for specialist urology to consider intermittent self catheterisation or surgery.
Screening urinary infections	Mid stream or clean catch specimen of urine for culture and sensitivity

Renal disease: chronic renal failure (high variable severity and progressive)

At diagnosis	- Renal dysfunction in AS usually attributed to syndrome related global renal fibrosis is symptomless and accompanied often by only mild proteinuria. Diagnosis and treatment of hypertension and urinary tract infection is important.
Follow up in mid-childhood even without diabetes	-Measure yearly urinalysis and plasma electrolyte concentrations, urea and creatinine. - Every one to two years, renal and bladder ultrasound if symptomatic or abnormal urinalysis.
	ABNL -Early renal transplantation before dialysis, if possible, is the treatment of choice in otherwise fit AS patients developing end stage chronic kidney disease. With shortage of cadaveric organs this may only be achievable with a live related donor.

Recommendations for the management of Alström Syndrome
Other involvement

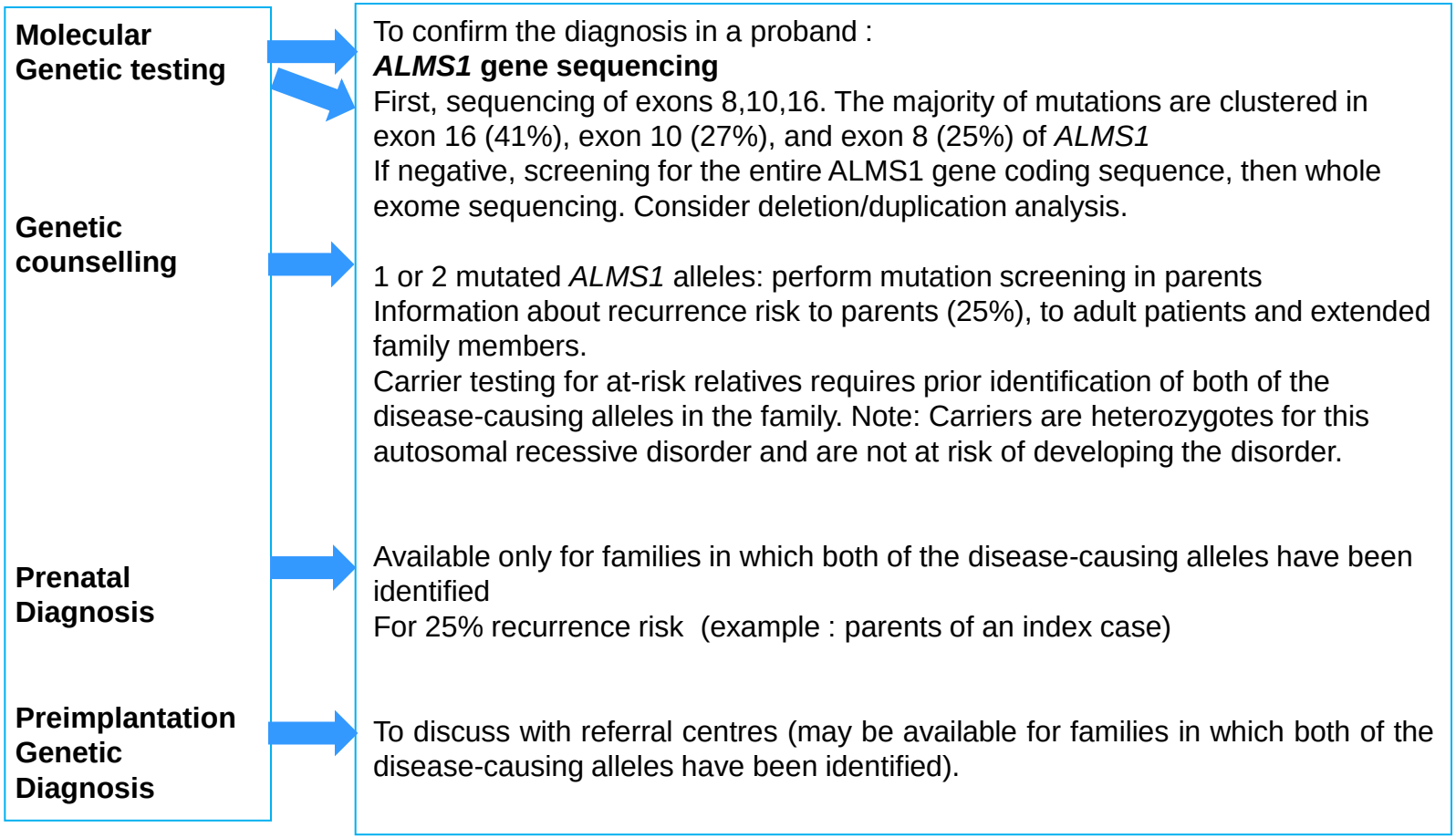
Dysmorphic features

Orthopedic abnormalities	ABNL	- Look for flat feet, scoliosis, barrel chest, scoliosis and kyphosis (varying severity; 30%-70%): yearly.
At diagnosis And Follow up		- X-ray and referral to an orthopedist.
	ABNL	- Note dental abnormalities - Refer to a dentist.

Neurological involvement

Developmental delay Birth-adolescence 25%-30%		- Delay in early developmental milestones, including fine and gross motor delays as well as expressive and receptive language delays - Learning disability
Others		- Tonic-clonic seizures; absence seizures, tics, tactile sensitivity, excessive startle response - Cognitive impairment (IQ <70) is very rare - Severe and unexplained peripheral pain
Neurobehavioral manifestations		- autistic spectrum behaviors in some children -Disrupted sleep patterns
Follow up		- Neurologic evaluation: regularly in infancy and childhood then 1-3 yearly (autistic-spectrum behavioral abnormalities, excessive startle, tactile defensiveness, unexplained joint or muscle pain, muscle dystonia, or hyporeflexia)
	ABNL	- EEG if seizures suspected. - Abnormal brain MRI findings if neurological signs - Education intervention, as indicated by evaluation and IEP (individual education plan) with the expectation of blindness and hearing loss

Recommendations for the management of Alström Syndrome
Genetics



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Information for patients, carers and families

Sources of information and support

The groups/websites listed below are useful sources of support and information

•**Alstrom Syndrome International** **www.alstrom.org**

•**Alström Syndrome UK** **www.alstrom.org.uk**
Contact : Mrs Kay Parkinson Tél. 44 (0)1803 524 238 Email. info@alstrom.uk

•**EURO-WABB project – www.euro-wabb.org**
The general objective of this project is to support efficient diagnosis, treatment, and research for Wolfram, Alström, Bardet-Biedl (WABB) and other rare syndromes. The project is managed by a collaboration of scientists, clinicians, and patient groups. The website contains useful information about these rare diseases, some of it in several European languages.

• **Orphanet (www.orpha.net)**
Orphanet is an online database of rare diseases and related services provided through Europe. It contains information on over 5 000 conditions and lists specialised clinics, diagnostic tests, patient and organizations, research projects and clinical trials

• **OMIM (http://www.omim.org/)**
OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 12,000 genes. OMIM focuses on the relationship between phenotype and the entries contain copious links to other genetics resources.

• **RareConnect** (https://www.rareconnect.org/en)
RareConnect was created by EURORDIS (European Rare Disease Organisation) and NORD (National Organization for Rare Disorders) to provide a safe space where individuals and families affected by rare diseases can connect with each other, share vital experiences, and find helpful information and resources