WOLFRAM SYNDROME UK

IMPORTANT MEDICAL INFORMATION ENCLOSED
For the attention of:

RESPIRATORY

In alliance with

WellChild

Birmingham Children's Hospital NHS Foundation Trust
I would like to thank you for receiving and reading this information pack about Wolfram Syndrome. Wolfram Syndrome is a rare progressive neuro degenerative condition with limited life expectancy and no cure. It affects 1 in 770,000 in the UK. There are currently 100 people (adults and children) diagnosed with WS and it is thought that there are at least another 50 people either undiagnosed or misdiagnosed. The aim of this pack is to inform medical professionals in each of the 16 hospital departments that may see a child with WS, what to be aware of to aid a quicker diagnosis and so prevent years of uncomfortable and intrusive testing. Please share the information amongst the staff in your department.

Inside this pack you will find the following:

Information sheets regarding:

Urology
Neurology
Ophthalmology
Paediatricians and Healthcare Professionals
Endocrinologists
Diabetologists
Wolfram Syndrome MDT Clinical Guidelines
WSUK Charity leaflet
Letter from Dr Fumi Urano
WellChild flyer

Some of the packs have a copy of the Euro-WABB Booklet. This can also be accessed by going to www.wolframsyndrome.co.uk/resorce.html

If you would like any further information about Wolfram Syndrome then please contact the office either by phone or email.

Yours sincerely

Tracy Lynch
Chief Executive
Wolfram syndrome guide for urologists

Management of urological involvement by urologists, rehabilitation physicians and neurologists

Urge incontinence due to bladder sysynnergia or neuropathic bladder has been reported in up to about 60% of affected people. These features can present during childhood. The pathology is not well understood, but it is thought that there is a loss of upper motor neurone control over the detrusor muscle; in addition, autonomic nervous system dysfunction may lead to altered bladder sensation. Reports from case series show pelviureteric dilatation on ultrasound scans. The part played by cranial diabetes insipidus is unclear.

Baseline investigations
- Ask about urinary symptoms, complete a voiding diary, undertake a clinical examination for evidence of neurological involvement.
- Check renal function (blood electrolytes, urea, creatinine, glomerular filtration rate (GFR))
- Bladder and renal ultrasound (residual urine)
- Urodynamosic testing to include flow rates on emptying the bladder, and residual bladder volume.

Management may involve:
Treatment options include advice about double voiding technique; electrical stimulation; anticholinergic drugs to stabilise the detrusor muscle; botulinum toxin; clean intermittent self-catheterization; permanent indwelling catheter; ileal conduit surgery.

Screening urinary infections
Urine culture if fever or other symptoms

Intermittent self-catheterization
Preliminary assessment of the ability to self-catheterization, taking into account ataxia, low vision or cognitive deficiency (PP-Test)

Indwelling urinary catheter
Risk factors for bladder tumors

Sexual dysfunction
Management in standard way
Wolfram Syndrome guide for neurologists

Management of neurological involvement by neurologists or neuro-paediatricians

In Wolfram Syndrome almost every organ/body system may be affected. Wolfram Syndrome is typically associated with sensorineural hearing loss, and other progressive neurological abnormalities. The natural history of Wolfram Syndrome was described in 45 individuals studied (mean age 16 years, range 5-32 years) from 29 families in the UK (Barrett et al 1995). Hearing impairment was present in 64%. Sixty percent of all individuals had one or more of the following signs and/or symptoms: ataxia, peripheral neuropathy, mental retardation, early onset dementia (disinhibition and/or short term memory loss), psychiatric illness (most commonly depression), and central sleep apnoea. MRI scans in individuals with this syndrome may show generalised brain atrophy with loss of the posterior pituitary bright spot, thinning of the optic nerves, and loss of volume of the cerebellum and brainstem.

Suggested management

Annual neurological examination for asymptomatic patients and bi-annually for symptomatic patients

Brain MRI scan at diagnosis and to be repeated if acute deterioration of neurological signs and/or symptoms or at adult age

Cerebellar ataxia assessment:
- Use of validated ataxia-specific rating scales for measuring progression : SARA (see supplementary data)
- Washington unified rating scale (WURS)

Management – Multidisciplinary team input and rehabilitation including:
- Ophthalmology services and visual impairment team input to optimise visual functioning
- Physiotherapy and occupational therapy team input with regards physical (gross motor and fine motor / coordination) difficulties
- Speech and language therapy input with regards dysarthria (speech difficulties) and swallowing difficulties (which may lead to recurrent chest infections due to aspiration)
- Drug treatments for spasticity (oral anti-spasticity medications such as baclofen, and/or botulinum toxin injections)

Brainstem (respiratory drive) involvement assessment:
- Screening by polysomnography or nocturnal oximetry (every 2 years)
- If symptoms: bronchoscopy (vocal cord mobility, obstructive cause), spirometry and morning blood gases

Management – as per respiratory / ventilation experts (tracheostomy and ventilatory support if needed)

Peripheral neuropathy assessment:
- Presence of symptoms such as numbness, tingling, burning, jabbing or electric-like pain or absence of deep tendon reflexes
- Presence of signs and / or symptoms of cardiovascular and / or gastrointestinal autonomic neuropathy
- Nerve conduction studies, Tilt-test in presence of autonomic cardiovascular symptoms, other investigations as per advice of cardiology and / or gastroenterology specialists

If neuropathic pain is present consider starting treatment for this – eg. Gabapentin, Pregablin, Carbamazepine, Amitriptyline, Lidocaine patch and / or transcutaneous electrical nerve stimulation (TENS)

Epilepsy assessment:
Electroencephalography if seizures occur
Treatment - Anti-epileptic drugs and counselling

**Cognitive assessment:**
Neuropsychological testing adapted to age (Children: WISC-IV; Adult: MMSE, FAB) and to vision difficulties

Management - Rehabilitation, special education

**Mental health assessment:**
Assessment includes taking a complete history and performing a detailed examination. Consider patient’s appearance, behaviour, speech, mood, thinking and any abnormal perceptions

Screening for anxiety, depression, abnormal behaviour (obsessive-compulsive behaviours, aggression, eating disorders etc.) or psychosis

Management – consider referral for expert psychiatric input
Wolfram syndrome guide for ophthalmologists

The combination of insulin dependent diabetes mellitus presenting under 15 years and progressive optic atrophy is pathognomonic for Wolfram syndrome. The PPV and NPV is estimated at 85% (Barrett et al 1995).

Diagnostic criteria for optic atrophy: optic atrophy is defined as generalised pallor of the optic discs on direct fundoscopy. The presenting symptoms are decreasing visual acuity and loss of colour vision, and affected patients commonly complain of ‘everything going grey’. The optic atrophy classically occurs before 15 years of age, and is progressive, leading to reduced visual acuity less than 6/60 within a median of 8 years (ref Barrett Eye). Visual evoked responses show normal latency but very low amplitudes (Mtanda). Other ophthalmologic findings reported in WFS but not confirmed as part of the phenotype include cataracts, described in eight patients [Hansen et al 2005], and nystagmus. Optic atrophy presented in 38 patients with reduced visual acuity and colour vision defect (median age 11 years), progressing to visual acuity of 6/60 or less in 35 patients (median time 8 years, range 1-25 years). Visual field examinations recorded before acuity deteriorated showed central scotomas with peripheral constriction. Blind patients had absent pupillary reflexes. Horizontal nystagmus was seen in patients with other signs of cerebellar degeneration. There was no pigmentary retinal dystrophy; only 3 patients had background diabetic retinopathy, despite a median duration of diabetes of 24 years. Electoretinography was normal in 3 patients and showed reduced amplitude in 3 patients; visual evoked responses were abnormal (10/10 patients: reduced amplitude to both flash and pattern stimulation). Magnetic resonance imaging showed generalised brain atrophy with reduced signal from the optic nerves and chiasm. A post-mortem brain specimen from one patient revealed atrophy of the optic nerves, chiasm, cerebellum and brainstem. This primary neurodegenerative disorder presents with diabetes mellitus and progressive optic atrophy, probably due to pathology in the optic nerve.

Management:
At diagnosis: eye examination, including refraction and visual acuity, slit-lamp examination, colour vision testing, visual field (Goldman perimetry), fundoscopy, OCT scan of the retinal nerve fiber layer, visual evoked potentials. Fundus auto fluorescence testing, fluorescein angiography and electoretinogram may be required in case of retinal involvement.

Correction of refractive error (myopia, hyperopia), filtrating glasses (if photoaversion)

Yearly eye examination: visual acuity, funduscopy, visual field and OCT scan are mandatory. Other tests as described at diagnosis, depending on the course of the disease

Cataract surgery if needed. Magnifying glasses, digital systems, voice systems depending of the level of visual acuity. Loss of visual field requires assistance and rehabilitation procedure for moving outside.
Consider Wolfram Syndrome

Does a child under the age of 16 years complain of:
- Decreasing visual acuity/ ‘greying of vision’
- Loss of colour vision

Does the child have any of these diagnostic features?
- Progressive Optic Atrophy
- Diabetes Mellitus

Does the child have any supportive features?
- Diabetes insipidus
- Sensorineural deafness
- Neurological signs (ataxia, epilepsy, neuropathy, cognitive impairment)
- Renal tract abnormalities
- Family history of Wolfram syndrome

Look for additional features
- Cataracts
- Nystagmus
- Poor papillary reflexes
- Hypogonadism (males)
- Psychiatric disorder
- Gastrointestinal disorders

Investigations
- Visual fields-Central with peripheral scotomas
- OCT – RNFL analysis
- VEP- normal latency but low amplitude
- ERG
- MRI generalised brain atrophy with reduced signal from optic nerve and chiasm
- Genetic tests WFS1/CISD2
- Absence of type 1 diabetes autoantibodies

Management
- Correct refractive error
- Filtration glasses if photosensitive
- Vision support: Magnifying glasses, digital systems, voice systems,
- Educational support: Touch screen laptops, mobile devices, networking
- Rehabilitation

Further information Wolfram Multidisciplinary Services
Birmingham Children’s Hospital NHS Foundation Trust
University Hospitals Birmingham NHS Foundation Trust

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Version 2 August 2014 Miss Archana Kulkarni, Mr John Ainsworth
Wolfram syndrome guide for paediatricians and other health care professionals

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Wolfram syndrome (WS) (OMIM 222300) is the inherited association of childhood onset diabetes mellitus (usually before 15 years) with progressive optic atrophy (Wolfram and Wagener 1938), also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness). It is a progressive neurodegenerative disorder, and many patients also develop urinary tract atony, ataxia, peripheral neuropathy, dementia and other psychiatric illnesses. Although associated with a shorter life span, some patients have been known to survive into their 6th decade. This is an autosomal recessive monogenic disease, and most affected patients have mutations in the WFS1 gene.

Wolfram syndrome-like disorder has been proposed as a name for two families who were characterised by older onset diabetes mellitus, sensorineural hearing loss, psychiatric illness and variable optic atrophy. Both families had a missense mutation in the WFS1 gene, apparently dominantly inherited.

Finally, WFS1-related Low Frequency Sensorineural Hearing Loss (LFSNHL) is also caused by mutations in the WFFS1 gene. It is characterised by the autosomal dominant inheritance of congenital, non-syndromic, slowly progressive, low-frequency (<2,000Hz) sensorineural hearing loss.

WS occurs:

- In children presenting most often during the first decade of life, with a mean age of diagnosis of ~11 years. This coincides with the development of optic atrophy in addition to diabetes mellitus.
- In all races, but at a greater prevalence in those where first cousin marriages are common, reflecting the autosomal recessive inheritance of the syndrome
- Usually without a family history of diabetes; but there may be a greater risk for psychiatric illness such as depression in first or second degree relatives.
- In the presence of ketosis or ketoacidosis in a minority of patients. This presentation is responsible for the misclassification of WS patients as Type 1 diabetes mellitus (T1DM).
- Without T1DM associated HLA-haplotypes, and without associated islet cell autoimmunity. The underlying pathology is progressive beta cell loss probably through apoptosis.

Other conditions that may be confused with WS include:

- **WFS1-related Low Frequency Sensorineural Hearing Loss (WFS1-related LFSNHL)** Approximately 20% of genetic hearing impairment is inherited in an autosomal dominant manner, a small fraction of which is LFSNHL. Mutations in WFS1 were identified in ten out of 13 families with autosomal dominant LFSNHL in whom linkage studies either showed linkage or were compatible with linkage to chromosome 4p. In five of 30 Danish families and three of nine Japanese families with characteristic findings on audiogram and/or a positive family history that were unsuitable for linkage analysis, molecular genetic testing showed heterozygous WFS1 mutations.

- **Wolfram syndrome-like disorder**. There are a small number of patients who have been described with onset of diabetes mellitus and / or progressive optic atrophy in adulthood. In the family
reported by Eiberg et al [2006], autosomal dominant optic atrophy, hearing impairment, and impaired glucose regulation were observed. The occurrence of (milder) optic atrophy in patients/families with dominantly inherited WFS-like disorder suggests that diabetes mellitus and congenital moderate hearing impairment in the absence of optic atrophy may be an under-recognized presentation of heterozygosity for WFS1 mutations, behaving in a dominant fashion.

- **Wolfram syndrome type 2** (WFS2) (OMIM 604928), diagnosed in four Jordanian families and caused by mutations in CISD2 on chromosome 4q22, is characterized by juvenile-onset diabetes mellitus, optic atrophy, high-frequency sensorineural hearing impairment, urinary tract dilatation, impaired renal function, hypogonadism, and severe gastrointestinal ulcer and bleeding, but not diabetes insipidus. The disorder is apparently very rare and may be confined to a certain ethnic background. Of note, molecular genetic testing of 377 hearing impaired people did not reveal additional individuals with CISD2 mutations, indicating mutations in this gene not explain a substantial fraction of nonsyndromic hearing impairment.

- **Mitochondrial diabetes.** Maternal transmission of mutated or deleted mitochondrial DNA can result in diabetes. The commonest (albeit rare) form is a point substitution at nucleotide position 3243 (A to G) in the mitochondrial tRNA (leu UUR) gene. This form of mitochondrial diabetes is associated with high tone sensorineural deafness and occasionally short stature. The diabetes is characterised by progressive non-autoimmune beta cell loss and insulin dependence.

- **Thiamine responsive megaloblastic anaemia syndrome** (Roger’s syndrome). This is the triad of early onset (under 5 years of age) diabetes mellitus, sensorineural deafness and megaloblastic anaemia (Rogers 1969). This is due to mutations in the SLC19A2 gene. The diabetes is insulin dependent, but may respond to pharmacologic doses of vitamin B1 (Thiamin). Most patients develop an insulin requirement by puberty.

- **Alström syndrome** is characterized by infancy onset cone-rod dystrophy and obesity. Other features include progressive sensorineural hearing impairment, dilated cardiomyopathy, severe insulin resistance, and developmental delay. Cone-rod dystrophy presents as progressive visual impairment, photophobia, and nystagmus starting between birth and age 15 months. Affected individuals have no light perception by age 20 years. Children usually have normal birth weight but become obese during their first year. Progressive sensorineural hearing loss begins in the first decade in as many as 70% of individuals. Severe insulin resistant diabetes often presents by puberty. Other endocrine abnormalities can include hypothyroidism and male hypogonadotrophic hypogonadism. Over 60% of individuals with Alström syndrome develop cardiac failure as a result of dilated cardiomyopathy at some stage of their lives. Approximately 50% of individuals have delay in early developmental milestones. Urologic disorders of varying severity, characterized by detrusor-urethral dyssynergia, appear in females in their late teens. Severe renal disease is usually a late finding. This is a monogenic, recessively inherited form of diabetes, due to mutations in the ALMS1 gene.

- **Bardet-Biedl syndrome** (BBS) is characterized by rod-cone dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotrophic hypogonadism, complex female genitalourinary malformations, and renal dysfunction. Birth weight is usually normal, but significant weight gain begins within the first year. Insulin resistant diabetes manifests in adolescence or adulthood. A majority of individuals have significant learning difficulties. Renal disease is a major cause of morbidity and mortality. Mutations have been found in at least nineteen genes, and inheritance is autosomal recessive.

- **Friedreich ataxia** (FRDA) is characterized by slowly progressive ataxia with mean age of onset between ten and 15 years and usually before age 25 years. FRDA is typically associated with depressed tendon reflexes, dysarthria, muscle weakness, spasticity in the lower limbs, optic nerve atrophy, scoliosis, bladder dysfunction, and loss of position and vibration senses. About two thirds
of individuals with FRDA have cardiomyopathy, 30% have diabetes mellitus, and approximately 25% have an "atypical" presentation with later onset, retained tendon reflexes, or unusually slow progression of disease. **Mutations** in **FXN** are causative. Inheritance is **autosomal recessive**.

- **Kearns-Sayre syndrome** (see **Mitochondrial DNA Deletion Syndromes**). Mitochondrial DNA (mtDNA) deletion syndromes comprise three overlapping phenotypes that may be observed in different members of the same family or may evolve in a given individual over time: Kearns-Sayre syndrome (KSS), Pearson syndrome, and progressive external ophthalmoplegia (PEO). Individuals with KSS have the onset of pigmentary retinopathy and PEO before age 20 years and at least one of the following: cardiac conduction block, cerebrospinal fluid protein concentration greater than 100 mg/dL, or cerebellar ataxia. Other frequent but not invariable clinical manifestations include short stature, hearing loss, dementia, limb weakness, diabetes mellitus, hypoparathyroidism, and growth hormone deficiency. Approximately 90% of individuals with KSS have a large-scale (i.e., 1.3-10 kb) mtDNA deletion that is usually present in all tissues; however, mutant mtDNA is often undetectable in blood cells, necessitating examination of muscle. When inherited, mtDNA deletion syndromes are transmitted by maternal inheritance.

- **Optic Atrophy type 1** (OPA1, or Kjer type optic atrophy) (OMIM 605290, OMIM 165500) is characterized by bilateral and symmetric optic nerve pallor associated with insidious decrease in visual acuity usually between ages four and six years, visual field defects, and color vision defects. Visual impairment is usually moderate (6/10 to 2/10), but ranges from mild or even insignificant to severe (legal blindness with acuity <1/20). Other findings can include auditory neuropathy resulting in sensorineural hearing loss that ranges from severe and congenital to subclinical (i.e., identified by specific audiologic testing only). Mutations in **OPA1** are causative. Inheritance is autosomal dominant.

- **Deafness-dystonia-optic neuronopathy syndrome** (DDON, or Mohr-Tranebjærg syndrome) (OMIM 304700). Males with DDON have a progressive auditory neuropathy with prelingual or postlingual sensorineural hearing impairment, slowly progressive dystonia or ataxia in the teens, slowly progressive decreased visual acuity from optic atrophy beginning at about age 20 years, and dementia beginning at about age 40 years. Psychiatric symptoms such as personality change and paranoia may appear in childhood and progress. The neurologic, visual, and neuropsychiatric signs vary in degree of severity and rate of progression. Females may have mild hearing impairment and focal dystonia. Mutations in **TIMM8A** are causative. Inheritance is X-linked.

**Genetic testing**

- **Index case**: **WFS1 +/- CISD2** screening
- 1 or 2 mutated alleles: perform mutation screening in parents of index case

**Genetic counselling**

- Information about recurrence risk to parents (25%), to adult patients and extended family members.

**Prenatal Diagnosis (PN)**

Available only for families in which the disease-causing mutation has been identified

- For 25% recurrence risk (example: parents of an index case)

**Preimplantation Genetic Diagnosis (PGD)**

To discuss with referral centres (may be available for families in which the disease-causing mutation has been identified).
Wolfram syndrome guide for endocrinologists

Apart from diabetes mellitus, other common endocrine findings in Wolfram syndrome include:

Diabetes insipidus.
Diabetes insipidus of central origin occurred in 72% with a median age of onset of 15.5 years (Barrett et al 1995). The range in age of onset is broad, possibly because of delays in establishing the correct diagnosis. Common symptoms include polyuria and polydipsia; the differential diagnosis includes polyuria secondary to poor glycemic control, and neuropathic bladder.

Useful investigations include 24 hour urine collection to assess volume, particularly if the patient denies symptoms. To make the diagnosis of cranial diabetes insipidus, an assessment of the concentrating ability of the urine is required. It is easiest to collect morning paired fasting urine and fasting plasma for osmolality and sodium concentration. Water deprivation tests are best avoided as they can be dangerous. A urine osmolality > 500mOsmol/L with normal serum sodium (up to 145mmol/L) and serum osmolarity (up to 295mOsmol/L) in the presence of normal serum glucose effectively excludes diabetes insipidus. A confirmation of diabetes insipidus would by a urine osmolality <150mOsmol/L, with serum Na > 145, and serum osmo > 295mOsmol/L.

Management is with desmopressin replacement according to local practices. The options are usually intranasal, buccal or oral. The intranasal preparations are about 20 times more potent than the oral, and about 15 times more potent than the buccal preparations. A safe starting dose in a child over 5 years would be 2.5 micrograms intranasal at night; and for an adult, 5-10 micrograms intranasal. The dose needs to be titrated according to symptoms, and by blood and urine biochemistry.

Hypogonadism.
Hypogonadism is more prevalent in males than in females. It can be either hypogonadatrophic (i.e., central) or hypergonadotrophic (i.e., secondary to gonadal failure). The underlying pathology of either type is not understood. Females usually retain their ability to become pregnant; about six successful pregnancies are described in the literature. One female had absence of the uterus [Tranebjærg, unpublished].

Symptoms to enquire about include for children, delayed puberty (the absence of secondary sexual characteristics by 14 years in a girl or 16 years in a boy), pubertal arrest. In adult men, ask about erectile impotence, reduced libido, and any history of impaired fertility or oligo/azoospermia. On examination, small, soft testes have been reported. For women, ask about amenorrhoea or oligomenorrhea, infertility loss of libido, and dyspareunia. Helpful investigations include assessment of sex hormone levels (testosterone or oestradiol), FSH and LH, and inhibin B in males.

Management involves hormone replacement in the standard way (i.e testosterone substitution in male patients, estrogen-gestagen substitution in female patients).

Hypothyroidism
The frequency of thyroid dysfunction in Wolfram syndrome is not known. It is prudent to include an assessment of TSH in annual review investigations; and in the presence of symptoms, to measure free-T3, free-T4 and TSH. Thyroid substitution therapy can be given if required with L-Thyroxine (starting dose 25micrograms/day in children, 50 micrograms/day in adults)

Growth retardation. Most adults have normal height, but growth retardation is not infrequent. This may relate to pubertal disturbance in those with hypogonadism. Linear growth should be monitored in children using standard growth charts.
Wolfram syndrome guide for diabetologists

The combination of insulin dependent diabetes mellitus presenting under 15 years and progressive optic atrophy is pathognomonic for Wolfram syndrome. The positive predictive value and negative predictive values are estimated at 85% (Barrett et al 1995).

Diagnostic criteria for diabetes mellitus are based on plasma blood glucose measurements and the presence or absence of symptoms. Diabetes is diagnosed when:

- A fasting plasma glucose (FPG) is ≥ 7.0mmol/L (126mg/dl) (on two occasions if there are no symptoms of diabetes).
- OR the post challenge plasma glucose is >11.1mmol/L (200mg/dl) 2 hours after a glucose load containing the equivalent of 1.75mg/kg (max 75g) of anhydrous glucose dissolved in water
- OR there are symptoms of diabetes and a random plasma glucose ≥11.1mmol/L (300mg/dl). The symptoms may include polyuria, polydipsia, and unexplained weight loss.

The diagnosis of diabetes mellitus is usually confirmed quickly in symptomatic children by measurement of an elevated blood glucose level. In this situation, if ketones are present in the blood or urine, treatment is urgent.

Type 1 diabetes associated auto-antibodies are most often absent (glutamate decarboxylase (GAD), tyrosine phosphatase (IA-2) and insulin antibodies, if available islet cell Ab (ICA) or ZnT8 Ab). Absolute insulin deficiency does occur, with ketosis, but insulopaenia is common, and may be assessed by basal and/or post stimulated C-Peptide measurements.

Management of diabetes mellitus

Intensive education
The principles are similar to management of type 1 diabetes. Intensive education is needed regarding insulin injection techniques, dosage adjustment, blood glucose and ketone testing, exercise, nutrition, formal smoking prevention and cessation, prevention and management of DKA and hypoglycaemia.

Glycemic targets
The aim is to improve metabolic control to reduce diabetes-related complications with strategies tailored to each individual, according to individual risk factors and vulnerability to severe hypoglycemia. HbA1c goals should be adapted to age: in non pregnant adult, <7%, for a child between 6 and 12yr, 7.5% and for an adolescent (12-19yr) <7.5%. Less stringent A1C goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and/or extensive comorbid conditions.

Insulin therapy
Insulin regimen chosen according to age, duration of diabetes, lifestyle, socioeconomic factors, and family, patient and physician preferences. Intensive management is frequently required: continuous subcutaneous insulin infusion or multiple daily injection regimens using basal insulin analogues. Use insulin pen with audible signal of insulin dose delivery if available.

Glucose monitoring
Self-monitoring of blood glucose (adapted devices for blind people) and quarterly HbA1c measurement. If necessary and available, Continuous Glucose Monitoring System (CGMS) can be used.

Nutrition
Regular evaluation (at least annually) with dietetic advice (based on the nutritional needs, eating habits, lifestyle, ability and interest) ensuring normal growth and development without disturbing glycemia.

Hypoglycemia
Significant risk of hypoglycemia often necessitates less stringent glycemic goals or the use of a continuous glucose monitoring system. Severe hypoglycemia should be treated with intravenous dextrose (hospital) or subcutaneous glucagon (at home) according to local protocols for type 1 diabetes.

Management of diabetes complications
Nephropathy
- Yearly screening, starting at 12 years of age, or in patients with duration of diabetes >5 years
  - First morning urine albumin to creatinine ratio, and persistence of elevation demonstrated.

Retinopathy
- Yearly screening in patients with duration of diabetes more than 5 years
  - Fundoscopy, OCT scan and fluorescein angiography if signs of diabetic retinopathy are present

Neuropathy
Yearly neurological exam to look for numbness, pain, cramps and paresthesia
  - Nerve conduction studies and dysautonomia assessment in presence of clinical signs or symptoms

Dyslipidemia
Screen at 12 and 17y (when stabilized), or <12y if risk factors exist (obesity, familial hyperlipidemia...)
  - Fasting total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides

Hypertension
Screen at least twice a year, use appropriate cuff size, +/– 24 hour ambulatory blood pressure monitoring
  - Lifestyle modification and anti-hypertensive drug therapy
Management of Wolfram Syndrome
A Clinical Guideline
Wolfram Syndrome Guideline Development Group
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Introduction...

... to Wolfram Syndrome

Wolfram syndrome (WS), also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus (DM), Optic Atrophy (OA), and Deafness) is a rare autosomal recessive disorder. The estimated prevalence of WS is 1 in 770,000. The minimal criteria for diagnosis are juvenile-onset DM and OA but patients may also develop diabetes insipidus, sensorineural deafness, renal tract abnormalities, and neuropsychiatric disorders; and variants exist with only partial features. The prognosis is mainly linked to the severity of the neurological symptoms.

WS is a genetically heterogeneous disease. Most patients carry mutations in the \textit{WFS1} gene, encoding an endoplasmic reticulum membrane embedded protein called Wolframin. \textit{CISD2} is a second causative gene associated with WS. It encodes a mitochondrial protein.

In addition, mutations in the \textit{WFS1} gene are also associated with the poorly defined ‘Wolfram-Like Syndrome (WS-like) disorders’ including DM, OA, or deafness in dominant or recessive families, and in dominantly-inherited low-frequency sensorineural hearing loss (LFSNHL).

... to the Wolfram syndrome guideline project

These guidelines have been developed by referring physicians 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 17.

... to the Wolfram syndrome clinical management guidelines

\textit{What are the aims of the guidelines?}

The guidelines aim to provide recommendations for the diagnosis, management and the follow-up of patients with WS. As it is a multisystemic disorder, WS patients may require various tests, screening and multidisciplinary interventions at different stages of their lives. These recommendations aim to support high quality care for people with WS 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 children’s 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.

\textit{How are they organised?}

The guidelines are divided into
- clinical features and diagnostic criteria
- baseline investigations
- 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 14, organised according to the different sections of the guidelines.

Additionally, there is a list of useful contacts for patients and families affected by WS, on page 18.

Note: N=normal; ABNL=abnormal
Wolfram Syndrome Clinical Management Guidelines

Diagnosis and clinical features of Wolfram Syndrome

**Diagnostic criteria of WS**

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<th>Minor criteria</th>
<th>Minimum required</th>
<th>Other variable suggestive evidence:</th>
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<td>- Diabetes mellitus &lt; 16 yrs</td>
<td>- Diabetes insipidus</td>
<td>-2 major OR</td>
<td>- Hypogonadism (males)</td>
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<tr>
<td>- Optic atrophy &lt; 16 yrs</td>
<td>- Diabetes mellitus &gt; 16 yrs</td>
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<td>- Absence of type 1 diabetes auto-antibodies</td>
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<td></td>
<td>- Optic atrophy &gt; 16 yrs</td>
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<td>- Renal tract abnormalities</td>
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<td>- 1 loss of function mutation in WFS1/CISD2 AND/OR family history of Wolfram syndrome</td>
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Table 1: Diagnostic criteria.
Note: The diagnosis is established in individuals of all ages in whom two pathological WFS1 or CISD2 mutations are identified.

**Wolfram Syndrome-like disorders: variable mode of inheritance**

At least 1 criterion among diabetes mellitus (or glucose intolerance), optic atrophy or deafness
AND
At least one loss of function WFS1 or CISD2 mutation

**Differential diagnosis includes:**

- Mitochondrial disorders: Maternally Inherited Diabetes mellitus and Deafness, Leber Hereditary Optic Neuropathy
- Thiamine-responsive megaloblastic anemia, diabetes and deafness
- Autosomal Dominant Optic Atrophy
- X-linked Charcot-Marie-Tooth disease type 5
- Deafness, Dystonia, Optic Neuronopathy syndrome
- Friedreich ataxia
- Bardet-Biedl syndrome
- Alstrom syndrome
### Recommended baseline investigations in Wolfram Syndrome

<table>
<thead>
<tr>
<th>Clinical Features of WS</th>
<th>Baseline investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine system</strong></td>
<td><strong>Fasting plasma glucose and HbA1c. Type 1 diabetes associated auto-antibodies most often absent: mainly glutamate decarboxylase (GAD), tyrosin phosphatase (IA-2) and insulin antibodies, if available islet cell Ab (ICA) or ZnT8 Ab. Low insulin reserve assessed by basal and/or post standard meal stimulated C-Peptide measurements</strong>&lt;br&gt;<em>Note that Wolfram patients present rarely with diabetic ketoacidosis.</em>&lt;br&gt;<strong>Morning paired urine and fasting plasma for osmolarity and sodium concentration after nocturnal and morning euglycaemia.</strong></td>
</tr>
<tr>
<td></td>
<td>Testosterone, FSH and LH, inhibin B</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td><strong>Visual acuity, fundus examination, visual field, OCT scan, visual evoked potentials, colour vision testing</strong></td>
</tr>
<tr>
<td><strong>Diabetes Insipidus</strong></td>
<td><strong>Audiogram, auditory evoked potentials</strong></td>
</tr>
<tr>
<td><strong>Hypogonadism (male)</strong></td>
<td><strong>Neurological examination with brain MRI and cognitive assessment</strong>&lt;br&gt;<strong>Other specific investigations according to the results of clinical examination. Mental health assessment. Consider test of olfaction</strong></td>
</tr>
<tr>
<td><strong>Sensory involvement</strong></td>
<td><strong>Questionnaire regarding urinary symptoms with voiding diary,</strong>&lt;br&gt;<strong>Assessment of renal function (blood electrolytes, urea, creatinine, GFR), ultrasound renal tract and urodynamic testing.</strong></td>
</tr>
<tr>
<td><strong>Optic Atrophy</strong></td>
<td><strong>WFS1. Analysis of CISD2 only if negative WFS1 screening,</strong>&lt;br&gt;<strong>characteristic phenotype, or middle eastern origin</strong></td>
</tr>
<tr>
<td><strong>Hearing Loss</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Neurological signs</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Urological signs</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Confirmation of WS diagnosis**
Recommendations for the management of Wolfram Syndrome

Endocrine System – Diabetes Mellitus (I)

Diagnostic criteria of diabetes

- Fasting (at least 8 hours) Plasma Glucose (FPG) ≥ 7.0 mmol/L
- Casual PG ≥ 11.1 mmol/L + symptoms of diabetes (polyuria, polydipsia and unexplained weight loss)
- 2 hour PG ≥ 11.1 mmol/L in a 75-g oral glucose tolerance test

If there are no osmotic symptoms or ketone production, then a confirmatory glucose test must be done on another day. In a child, raised glucose measurement should lead to same day referral to a hospital specialist experienced in management of childhood diabetes and should not delay initiation of treatment to avoid rapid deterioration (diabetic ketoacidosis: DKA).

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

- **Intensive education**: Insulin injection, dosage adjustment, blood glucose and ketone testing, exercise, nutrition, formal smoking avoidance, prevention and management of DKA and hypoglycemia.

- **Glycemic targets**: Improve metabolic control to reduce diabetes-related complications with strategies tailored to each child, according to individual risk factors and vulnerability to severe hypoglycemia. HbA1c goals should be <7.5%. Less stringent A1C goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions.

- **Insulin therapy**: Insulin regimen chosen according on age, duration of diabetes, lifestyle, socioeconomic factors, and family, patient and physician preferences. Intensive management is usually required: continuous subcutaneous insulin infusion or multiple daily injection regimens using basal insulin analogues.

- **Glucose monitoring**: Self-monitoring of blood glucose (adapted devices for vision impaired people), glucose diary, and quarterly HbA1c measurement. If necessary and available, Continuous Glucose Monitoring System (CGMS) can be used.

- **Nutrition**: Regular evaluation (at least annually) with nutrition counseling (based on the nutritional needs, eating habits, lifestyle, ability and interest) ensuring normal growth and development with optimal glycaemic control.

- **Hypoglycemia**: Significant risk of hypoglycemia often necessitates less stringent glycemic goals or the use of a continuous glucose monitoring system. Severe hypoglycemia should be treated with intravenous dextrose (hospital) or subcutaneous glucagon (at home) followed by buccal glucose syrup.
Recommendations for the management of Wolfram Syndrome

**Endocrine System – Diabetes Mellitus (II)**

<table>
<thead>
<tr>
<th>Management of DM for children by an interdisciplinary pediatric diabetes healthcare team</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic poor metabolic control</td>
</tr>
<tr>
<td>DKA</td>
</tr>
<tr>
<td>Psychological issues</td>
</tr>
</tbody>
</table>
Recommendations for the management of Wolfram Syndrome

Endocrine System – Diabetes Mellitus (III)

<table>
<thead>
<tr>
<th>Management of diabetes complications</th>
<th>Nephropathy</th>
<th>Retinopathy</th>
<th>Neuropathy</th>
<th>Dyslipidemia</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Yearly screening, starting at 12 years of age, in patients with duration of diabetes &gt;5 years</td>
<td>- Yearly screening in patients with duration of diabetes more than 5 years</td>
<td>- Yearly neurological exam to look for numbness, pain, cramps and paresthesia (cf. neurological section)</td>
<td>- Screen at 12 and 17y (when stabilized), or &lt;12y if risk factors exist (obesity, familial hypercholesterolaemia)</td>
<td>- Screen at least annually, use appropriate cuff size, +/- 24 hour ambulatory blood pressure monitoring</td>
</tr>
<tr>
<td></td>
<td>- First morning or random urine albumin to creatinine ratio, and microalbuminuria demonstrated.</td>
<td>- Fundoscopy, OCT scan and fluorescein angiography if signs of diabetic retinopathy are present</td>
<td>- Nerve conduction studies and dysautonomia assessment in presence of clinical signs or symptoms</td>
<td>- Fasting total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides</td>
<td>- Lifestyle modification and anti-hypertensive drug therapy</td>
</tr>
<tr>
<td></td>
<td>- Introduce renoprotection with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as soon as microalbuminuria is confirmed.</td>
<td></td>
<td>- Treat symptoms</td>
<td>- Lipid lowering drug therapy</td>
<td></td>
</tr>
</tbody>
</table>

Fasting total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides

Lipid lowering drug therapy

Lifestyle modification and anti-hypertensive drug therapy
### Recommendations for the management of Wolfram Syndrome

#### Endocrine System – Others

**Diabetes insipidus**

- Symptoms to seek: polyuria and polydipsia (could be masked by the polyuria induced by poor glycemic control)
- Assessment of concentrating ability of the urine: morning paired urine and fasting plasma for osmolarity and sodium concentration – even if the patient denies symptoms. Prerequisite for the evaluation of morning urine osmolarity: nocturnal and morning euglycaemia (blood glucose levels beneath the renal threshold)
- Follow up and management in standard way (according to criteria for desmopressin administration)

**Hypo or hyper gonadotrophic hypogonadism**

- Symptoms to seek:
  - Boys and girls: delayed puberty or pubertal arrest
  - Male adolescents and men: impaired fertility, oligo/azoospermia, erectile dysfunction, reduced libido, testicular hypotrophy
  - Women: a/oligomenorrhea, infertility, loss of libido, dyspareunia,
- Hormone levels: testosterone (or oestradiol), FSH and LH, inhibin B
- Management in standard way (i.e. testosterone replacement in male patients with testosterone enanthate gradually increasing 50-250mg i.m. every 3-4 weeks at age less than 18 years; alternatively testosterone undecanoate i.m.every 3 months or testosterone gel 50mg/day at age over 18 years. Oestrogen-gestagen replacement in female patients)

**Hypothyroidism**

- Free-T3, free-T4 and TSH if presence of symptoms
- Thyroid substitution therapy with L-Thyroxine (starting dose 25µg/day)

**Growth retardation**

- Monitoring of linear growth in children using standard growth charts
**Recommendations for the management of Wolfram Syndrome**

**Sensory involvement**

**Visual assessment**

- **At diagnosis**
  - Eye examination, including refraction and visual acuity, slit-lamp examination, color vision testing, visual field (Goldman perimetry), funduscopy, OCT scan of the retinal nerve fiber layer, visual evoked potentials, systematic retinography. Fundoscopy and OCT scan if signs of diabetes retinopathy are present. Fluorescein angiography could be discussed according to the severity of retinal involvement.
  - Correction of refractive error (myopia, hyperopia, astigmatism).

- **Follow up**
  - Yearly eye examination: visual acuity, funduscopy, visual field and OCT scan are mandatory. Other tests as described at diagnosis, depending on the course of the disease.
  - Cataract surgery if needed. Magnifying glasses, digital systems, voice systems depending on the level of visual acuity. Loss of visual acuity requires support from vision impairment specialists.

**Hearing assessment**

- **At diagnosis**
  - Audiogram
  - Auditory evoked potentials

- **Follow up**
  - Test every 2 years
  - Hearing Loss Management with hearing aids
**Recommendations for the management of Wolfram Syndrome**

**Neuro-psychiatric involvement**

Management of neurological involvement by adult or paediatric neurologists

<table>
<thead>
<tr>
<th>Neurologic examination yearly for asymptomatic patients and twice a year for symptomatic patients</th>
<th>Brain MRI to repeat if acute aggravation of central disorders or at adult age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebellar ataxia assessment</strong></td>
<td><strong>Brainstem involvement assessment : Central respiratory failure</strong></td>
</tr>
<tr>
<td>- Use of validated ataxia-specific rating scales for measuring progression (E.g. SARA: <a href="http://www.neurology.org/content/suppl/2006/06/07/66.11.1717.DC1/E1.doc">http://www.neurology.org/content/suppl/2006/06/07/66.11.1717.DC1/E1.doc</a>)</td>
<td>- Screening by polysomnography or nocturnal oximetry (every 2 years)</td>
</tr>
<tr>
<td>- Therapy or rehabilitation for:</td>
<td>- If symptoms: bronchoscopy (vocal cord mobility, obstructive cause), spirometry, morning blood gases</td>
</tr>
<tr>
<td>- Nystagmus (if disability),</td>
<td>- Management in standard way by respiratory physician (tracheostomy, optimal ventilation)</td>
</tr>
<tr>
<td>- Cerebellar intention tremor (drug, physiotherapist, intervention),</td>
<td></td>
</tr>
<tr>
<td>- Dysarthria and swallowing disorder (swallowing therapy by speech therapist), prevention of pneumonia aspiration disease (pulmonary infection)</td>
<td></td>
</tr>
<tr>
<td><strong>Peripheral neuropathy assessment</strong></td>
<td><strong>Electromyography, tilt-test in presence of symptoms, then if acute aggravation:</strong></td>
</tr>
<tr>
<td>- Symptoms to seek (numbness, tingling, burning, jabbing or electric-like pain) or arreflexia</td>
<td>- Treatment for relieve the pain (Anti-epileptic, antidepressants, lidocaine patch, TENS) or hypotension</td>
</tr>
<tr>
<td>- Consider cardiovascular and gastrointestinal autonomic neuropathy</td>
<td></td>
</tr>
<tr>
<td><strong>Epilepsia assessment</strong></td>
<td><strong>Cognitive assessment</strong></td>
</tr>
<tr>
<td>- Electroencephalography (EEG) if seizures occur</td>
<td>- Neuropsychological testing adapted to age (Children: WISC-IV) and to low vision</td>
</tr>
<tr>
<td>- Anti-epileptic drugs</td>
<td>- Review yearly if cognitively impaired. Rehabilitation, special education</td>
</tr>
<tr>
<td><strong>Mental health assessment</strong></td>
<td></td>
</tr>
<tr>
<td>Screening: anxiety, depression, abnormal behavior (compulsive aggression, eating disorders) or psychosis</td>
<td></td>
</tr>
<tr>
<td>Examine: complete history, appearance, behaviour, speech, mood, thinking, abnormal perceptions</td>
<td></td>
</tr>
<tr>
<td>Management in standard way by psychiatric expert</td>
<td></td>
</tr>
</tbody>
</table>

SARA: Scale for the assessment and rating of ataxia ;
WISC-IV: Wechsler Intelligence Scale for Children, Fourth Edition ; MMSE :Mini Mental State Examination; FAB: Frontal Assessment Battery
# Recommendations for the management of Wolfram Syndrome

## Urological involvement

### Management of urological involvement by urologists, rehabilitation physicians and neurologists

| Baseline investigations | Standardised questionnaire regarding urinary symptoms and voiding diary, clinical examination  
| | Assessment of renal function (blood electrolytes, urea, creatinine, glomerular filtration rate (GFR))  
| | Bladder and renal ultrasound (residual urine), urodynamic testing  
| Yearly assessment :  
| | Questionnaire regarding urinary symptoms and voiding diary  
| | Assessment of renal function (urea, creatinine, GFR)  
| | Bladder and renal ultrasound (PVR)  
| Urodynamic testing : yearly  
| | Clinical exam, questionnaire regarding urinary symptoms and quality of life scale twice a year  
| | Management in standard way according expert’s decision:  
| | +/- Intra-venous urography, retrograde urethrocystography (voiding), renal scintigraphy  
| | +/- treatment (anticholinergic drugs, botulinum toxin, intermittent self-catheterization) …  
| | Electrical stimulation and physiotherapy, surgical intervention when needed  

### Screening urinary infections

- Urine culture if fever or other symptoms

### Intermittent self-catheterization

- Preliminary assessment of the ability to self-catheterize, taking into account ataxia, low vision or cognitive deficiency

### Indwelling urinary catheter

- Risk factors for infection
## Recommendations for the management of Wolfram Syndrome

### Genetics

<table>
<thead>
<tr>
<th>Genetic testing</th>
<th>Genetic counselling</th>
<th>Prenatal Diagnosis (PN)</th>
<th>Preimplantation Genetic Diagnosis (PGD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index case: <em>WFS1</em> +/- <em>CISD2</em> screening if desired by patient or parents</td>
<td>Information about recurrence risk to parents (25%), to adult patients and extended family members.</td>
<td>Available only for families in which the disease-causing mutation has been identified. For 25% recurrence risk (example: parents of an index case)</td>
<td>To discuss with referral centres (may be available for families in which the disease-causing mutation has been identified).</td>
</tr>
</tbody>
</table>
Management of Wolfram Syndrome

Bibliography

1. INTRODUCTION

2. DIABETES

3. NEUROLOGICAL SIGNS

4. GENETICS
Acknowledgements

The development of these guidelines is an outcome of work package 4 of the EURO-WABB project (work package lead Prof V Paquis-Fluckinger)

The following people kindly contributed to this guideline:

Barrett T University of Birmingham, UK
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Lopez de Heredia M CIBERER, Spain
Marshall B Washington University, St Louis, USA
Maffei P University of Padova, Italy
McGee M Birmingham Children’s Hospital, UK
Morrison K University of Birmingham, UK
Orssaud C Georges Pompidou European Hospital, France
Nunes V IDIBELL, Spain
Paquis-Fluckinger V University of Nice, France
Rohayem J Universitätsklinikum Münster, Germany
Tranebjaerg L University of Copenhagen, Denmark
Viallettes B University of Marseille, France
**Information for patients**

**Sources of information and support**

The groups listed below are useful sources of support and information:

- **Association du syndrome de Wolfram** ([http://asso.orpha.net/ASW/](http://asso.orpha.net/ASW/))
  Contact: Tél. +33.2.97.61.42.37  Email. nolwenn.jaffre@voila.fr

- **EURO-WABB project** – [www.euro-wabb.org](http://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](http://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 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](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.

- **Wolfram Syndrome UK** : [www.wolframsyndrome.co.uk](http://www.wolframsyndrome.co.uk)
  The website is run by families affected by this rare genetic disorder and the aim is to raise as much awareness of the syndrome as possible.
Information Request:

Complete this card, detach & post to us.

Name: Mr/Mrs/Miss/Dr……………………………

Address………………………………………

……………………………………………

……………………………………………

Postcode……………………………………

Telephone…………………………………

Email………………………………………

DONATION (if desired) £………………….
(Please make cheques payable to WOLFRAM SYNDROME UK)

Please tick if you would like us to be able to reclaim tax on your donation.*

Wolfram Syndrome UK
9 Church Way
Worthing
West Sussex
BN13 1HD

Tel:01903 211358
Email: admin@wolframsyndrome.co.uk

WSUK are always pleased to hear from families & those affected by the condition.

Donations & contributions of support are always gratefully received so that we may continue to provide information, support & help fund research into trying to find medication to provide the best treatment.

Donations can be made via post or online by going to our website and following one of the links there.

* You must pay an amount of income tax and/or capital gains tax equal to the tax we reclaim on your donations.
How it all started

Wolfram Syndrome is a rare, progressive neurodegenerative condition and Wolfram Syndrome UK (WSUK) is the national charity and support group to help fund research and provide support for those affected by the condition and their families.

The support group and website were started in 2010 by Paul & Tracy Lynch from Worthing, West Sussex after their daughter, then aged eight, was diagnosed with WS. The only website associated with WS then was a worldwide site. There was no easy to read information available & no real support, as many medical professionals had or still have never heard or come across the syndrome.

WSUK became a registered charity in June 2013. Prior to that we had been raising funds for research via WellChild, the national charity for sick children, and our fundraising group ‘The Charity Roadtrip’. WSUK and WellChild continue to work closely together.

About Wolfram Syndrome……….

The first signs of someone being affected by WS are juvenile onset Diabetes Mellitus and Optic Atrophy (reduced vision). Some patients go on to develop hearing loss and Diabetes Insipidus (water diabetes).

These four conditions are the main features of WS, also known as DIDMOAD. There are also other health problems for those with WS which can include irregular breathing, loss of the sense of smell, depression, loss of the gag reflex and impulsive and aggressive behaviour to name but a few. WS affects 1 in 770,000 people in the UK.

What we are doing

There is a dedicated UK telephone line and website giving up to date information on events, research, links to other useful sites, an annual conference, multi disciplinary clinics and a forum via which patients, families and professionals can use to contact each other. We also send out a quarterly newsletter in conjunction with the Wolfram Syndrome families coordinator, Rachel Bates, at WellChild.

WSUK are working in alliance with WellChild and Birmingham Children’s Hospital to raise awareness, bring support to patients and families and to advance research into trying to find a way of halting or slowing down the progression of this syndrome.

Research

Research is being carried out at Birmingham Children’s Hospital and The Queen Elizabeth Hospital in Birmingham, as well as at other hospitals and universities around the world. We currently help to provide funding towards the research carried out here in the UK.

WSUK keeps up to date with the medical research and is in contact with medical experts who can offer advice.

We maintain the only UK database of those affected by this disorder.
Washington University School of Medicine has a long history of pioneering medical research, including the discovery of the Wolfram syndrome gene (WFS1) and its function, led by the late Alan Permutt, MD, and his team of researchers. Today, a collaborative effort by Washington University School of Medicine faculty, led by Fumihiko (Fumi) Urano, MD, the Samuel E. Schechter Professor of Medicine, is advancing the understanding of the progression of Wolfram syndrome with the goal of identifying targets for therapeutic interventions and treatments for Wolfram syndrome.

AT WASHINGTON UNIVERSITY MEDICAL CENTER IN ST. LOUIS, USA

- Identified an enzyme implicated in endoplasmic reticulum stress as a molecular target for Wolfram syndrome treatment.
- Uncovered FDA-Approved drugs that block activation this enzyme and cell death by induced pluripotent stem cells (iPSCs) derived from patient skin cells. These pluripotent stem cells will help in the identification of therapeutics to treat Wolfram syndrome and may eventually be used to replace damaged tissues, including pancreatic β cells, brain cells, and eye cells, resulting from this monogenic disorder.
- Identified potential biomarkers reflecting the progression of the disease using blood samples from patients and their siblings.
- Several biotech and pharmaceutical companies have been identified with overlapping interests in advancing drugs of potential benefit to patients with Wolfram syndrome. With the aid of the Jack and JT Snow Scientific Research Foundation, Dr. Urano and Dr. Timothy Barrett are planning joint clinical trials.

These translational discoveries utilized an important pediatric patient population, combining multiple assessment methods and resources drawn from a dedicated basic science and clinical community working collaboratively to understand the molecular mechanism and identify actionable targets for the treatment of Wolfram Syndrome.

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http://www.erstress.com/
http://wolframsyndrome.blogspot.com/
EURO-WABB
An EU Registry for Wolfram, Alström, Bardet-Biedl and other rare Syndromes

Increasing knowledge, raising awareness and improving the lives of people and families affected by WABB syndromes

The Euro-WABB Project has received funding from the European Union in the framework of the Health Programme
INTRODUCTION

1 An introduction from the coordinator
2 Creating partnerships to build essential resources
3 The Patient Experience

DEVELOPING RESEARCH RESOURCES

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8 Genetic Mutation Databases
9 Patient Registry

IMPLEMENTING BEST PRACTICE

10 Standards of care guidelines
11 Genetic testing network

CATALYZING NEW DEVELOPMENTS

13 Catalyzing new developments
14 The future
15 Acknowledgements
INTRODUCTION

Recent years have seen increasing interest and resources applied to understand rare diseases. Wolfram, Alström, Bardet Biedl and other syndromes are ultra rare genetic diseases sharing the characteristics of loss of vision, loss of hearing, and a predisposition to diabetes mellitus. Other complications may involve almost any organ system in the body. The improving knowledge of basic disease mechanisms has raised hopes for new treatments to slow or stop the progress of these diseases. However, translational research towards new treatments has faced several barriers.

For patients, promising research results have still not been translated into the treatments they hope for, while lack of standardized care guidelines prevents many from receiving optimal care. Sadly, many families still experience delayed diagnosis and lack of access to diagnostic testing.

For the biomedical industry, identifying investigators and sites with the relevant expertise, and accessing the appropriate patient cohorts for clinical trials, is challenging.

For clinicians and researchers, lack of support tools such as validated clinical outcome measures or standard operating procedures for research protocols has held back development of treatments.

EURO-WABB brings together stakeholders in the community, and provides an infrastructure to accelerate research and therapy development, increasing collaboration, improving patient care and providing a platform to support future international clinical trials.

EURO-WABB was initiated on 1st January 2011 with co-funding from the EU within The Health Programme Framework. The general objective of the 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.

Professor Timothy Barrett
EURO-WABB Project Coordinator
CREATING PARTNERSHIPS

Partnering with patient advocacy groups

Close relationships with the major advocacy groups in the field are key to the project’s success. The initial European Union funding for the project was advocated by The Association Syndrome de Wolfram, with the support of The Association Française contre les Myopathies (AFM), and the European Organisation for Rare Diseases (EURORDIS). Researchers and clinicians within EURO-WABB benefit from the knowledge and experience that patient groups can provide.

This association was founded in 2008 by Nolwen LE FLOCH, a teacher, after one of her children was diagnosed with Wolfram Syndrome. The first goal of the association was to initiate research programs on Wolfram syndrome. The association organized the first international workshop on Wolfram syndrome in Paris in 2009. It was decided that a European Registry was absolutely necessary and with a consortium of organizations, EURO-WABB was born. The Association has organized four international workshops of researchers and clinicians; and initiated a research program on gene therapy for the eye, led by a French team, bringing together international collaborators Prof Tanizawa (from Japan), and Profs S Koks and V Tillmann (from Estonia) who agreed to share their resources. The first trials in mice started in April 2013. (http://loeildelynxmonblog.wordpress.com/2012/07/25/cecile-dele terrible-recherche-inserm-sattaque-au-syndrome-de-wolfram/ ). The French Association has also funded a study by an English team with Professor Tim Barrett entitled “Developing personalized therapies for children and adults with Wolfram syndrome”, to address the neurological complications; and a French team led by Prof Karsenty (Marseille) has made a preliminary study about urological affection, disseminated it to all the French families and foreign families (http://www.uorfrance.org/science-et-recherche/base-bibliographique/resultats/affichage/standard/tri/chronologique-inverse.html?tx_axdocdb_pi1%5BSword%5D=karsenty)

The Association du Syndrome de Wolfram also creates information leaflets, flyers and annual newsletters. Each year, the French families are invited to the annual meeting of the association. They can meet clinicians and researchers in the morning to ask all questions they have and in the afternoon can discuss with other families to share advice, experience and to share their contact details to communicate throughout the year. After 4 years, the association counts nearly 40 patients in France who communicate regularly. The Association du syndrome de Wolfram plans to organize a multidisciplinary clinic in France in 2014 and the action of the association gave a dynamic who initiated multidisciplinary consultation in the USA and Spain.
CREATING PARTNERSHIPS cont.

Alström syndrome UK:  
www.alstrom.org.uk
Alström Syndrome UK was founded in 1998 by Kay Parkinson, after her two children were diagnosed aged 15 and 18 with Alström Syndrome. Initially 7 families were known in the UK and through attendance at the yearly Family Conference, ASUK was able to instigate and develop patient led multi-disciplinary clinics which commenced in 2006 and in which AS UK are an equal partner. AS UK were Awarded Third Sector Excellence Award 2007 for the “Best use of the COMPACT” in ensuring the service remained user-led. Patients contact the charity mainly through the web site after receiving a diagnosis. AS UK family support workers visit the patient at home and make referrals to either the children’s clinic if under 16 or the adult clinic. The Alström Service was hailed as a role model for rare disease by EURORDIS and other rare condition clinics followed our model. AS UK produced the first medical handbook on AS in 2004 dedicated to the son of the charity’s founder and later also to her daughter. Both children did not survive heart transplantation. Today the charity supports 60 patients, their families, carers and the professionals who work with them. We produce information leaflets, flyers, quarterly newsletters and hold an Annual Family Conference. We have a dedicated Asian Support worker, supporting families where a culture of cousin marriages has led to increases in affected children. In 2010 ASUK were awarded a Big Lottery Medical and Scientific grant to develop a UK National Database and take skin cells from patients for further research. AS UK were presented with the EURORDIS Patient of the Year Award 2013 for outstanding services to Alström Patients. Please visit the following site for information and an aid to diagnosis: http://youtu.be/mcrHbqHtktg

Laurence-Moon-Bardet-Biedl society:  
www.lmbs.org.uk
The first official meeting of the Laurence-Moon-Bardet-Biedl Society (LMBBS) was held in 1989. Today, The Society supports over 400 families and communicates with over 150 health professionals involved in their care. The Society has produced many leaflets promoting the welfare of those with LMBBS, including a booklet aimed at the medical profession to provide a more in-depth look at the syndrome. The Society’s latest publication ‘Who Are We and How Can We Help You’ is a leaflet about The Society itself and can be used to raise awareness of the syndrome and as a hand out for fundraising. There will soon be a new medical leaflet about genetic inheritance and cilia research. Our thanks go to all the clinicians for their assistance. The Annual Family Conference attracts many eminent and international speakers. The children and young adults benefit hugely from being part of a group where they are no different to anyone else. The newsletters and conference reports are intended to keep its members informed and supported, and hopefully ease the feelings of isolation that can occur with such a rare syndrome. Our helpline is also a lifeline to many, especially for the newly diagnosed, and is a chance to talk to someone who understands. In1999, the society, together with Prof Beales, produced and sent out questionnaires to all its members. Prof Beales used the information from this study to produce the main diagnostic criteria, which are now used worldwide. In April 2010, after a successful bid with the National Commissioning service and input from Professor Phil Beales, the BBS Multi-Disciplinary Clinics commenced. These are held across four centres, and have brought about a major difference in how LMBBS is managed, with a focus on early intervention and good health management.

Wolfram syndrome UK:  
www.wolframsyndrome.co.uk
Paul and Tracy Lynch set up the support group after their daughter Jennifer was diagnosed with Wolfram syndrome in March 2010. The website is monitored by families affected by this rare genetic disorder and the aim is to raise as much awareness of the syndrome as possible. They feel that the more people that know about Wolfram syndrome, the better; and that as many doctors and health professionals as possible should be aware of this site. The charity also supports multidisciplinary clinics for children and adults across 2 hospitals. They have set up a forum to provide contact, support and an exchange of information between families in the UK who are affected by Wolfram syndrome; and an annual meeting for Wolfram syndrome patients.
THE PATIENT EXPERIENCE

DANCING WITH BARDET-BIEDL SYNDROME

This story begins way back when I was 30 weeks pregnant with our oldest child Tom, where a routine scan showed that he had what they described as a kidney abnormality and I was told that this would have to be closely monitored after he was born. Tom arrived safely and was born with an extra finger on his left hand and an extra toe on his right foot. But none of the doctors or nurses seemed to be concerned about it. Tom’s kidney function was monitored for the first few months of his life and we were told that it was fine. He was discharged from the kidney clinic aged 6 months, shortly after his extra digits had been removed.

Tom appeared a little lazy and his development was not as advanced as other children of his age. By the time Tom was 2 and a half he began attending pre-school and it was obvious that developmentally he was way behind his peers, although oblivious and in his own ‘bubble of happiness’.

When Tom was 9 months old I was pregnant with our daughter Katie. Again I had a routine scan at 30 weeks and it showed the same kidney abnormality which Tom’s scan had showed and sure enough she was born with an extra digit on her foot.

When Tom was 7 genetic testing revealed that Tom & Katie had BBS. Diagnosis day was life changing for me as a Mum, I really began to see the world through the eyes of the children and understand them and therefore be able to help them much more effectively, albeit on a rollercoaster journey.

Coping...

The two things which inspire me the most to carry on with strength and determination are Tom & Katie, our beautiful children. Two bright, funny, intelligent, kind and loving young people who are happy and have enriched our lives and made us proud parents. As far as coping is concerned, well there’s not much option. To me it’s not so much ‘do we cope?’ and more ‘how do we cope?’ by this I mean what tools do we use to make living with this thing as good as it can be. For me the answer is contained in one word – acceptance. I have learnt to totally accept Bardet-Biedl Syndrome. I have learnt to make room for it. I can’t change it or make it go away, so I decided to accept it. People talk about fighting illness but to me this implies a winner and a loser. And we can never completely win with BBS and make it go away and losing is not an option, so to me it is like a dance. Sometimes I am not always a willing partner and during those quiet, reflective moments or those times when we are in a bad mood and tired, it would be easier to ‘sit it out’. But if it wants to dance with me, then I must dance with it. I look at each appointment like a new routine, sometimes the steps are harder to learn than other times, but learn them I must if I am are to keep on top of this energetic thing called BBS.

Bardet – Biedl Syndrome never stops dancing... and nor must we

Emma Oates.

(This is an edited version of the full article which can be found at www.euro-wabb.org/en/presentations/euro-wabb-presentations)
THE PATIENT EXPERIENCE

Adorable twins Katie and Hannah were diagnosed with Alström Syndrome when they were 4 years old. Hannah was very ill for the first year of her life. After seeing a cardiologist at Leeds Hospital, the family were told she had a 33% chance of survival, a 33% chance of death and a 33% chance of needing a heart transplant. Both girls were diagnosed with nystagmus at 3 months old and parents noticed they both had an extreme sensitivity to light, after seeing many consultants the parents realised the severity of Katie and Hannah’s sight loss. In 2010 parents Ian and Julie were referred to a geneticist as it was thought Katie and Hannah may have Alström Syndrome, this has now been confirmed. Julie Beck gives her thoughts:

“Since Katie and Hannah were diagnosed with Alström Syndrome, ASUK have provided both medical and emotional support. Without this support the last few years would have been even more difficult. Through ASUK's multi disciplinary clinics, we receive the specialist advice and treatments to enable the girls to lead as normal life as possible. As a family we look forward to the trips and annual conference, where we meet old friends and hope to make many new ones. ASUK gives us continued hope for the future.”

The cheeky twins live life to the full and are always smiling and laughing together as well as keeping the Doctors on their toes!

Julie Beck

When I discovered the disease of my son (Wolfram syndrome), I was alone in front of the screen of my computer. Three days before, life was so beautiful. He was diabetic since 4 years of age but he learnt to live with it and he was so happy. We visited an ophtalmologist and he discovered he had a bilateral optic atrophy.

I understood immediately that it was very serious. I undertook research on the internet and discovered Wolfram syndrome. A genetics consultant confirmed it few weeks later. I already wanted to create an association because I felt there was no research and no hope. I refused to stay and look the disease each day without doing anything.

Since I created The Association Syndrome de Wolfram, we have initiated research programs, The European registry, other studies on Wolfram syndrome ....

But another dimension is very important for the affected people: now they can share their experiences and advice, and they can discuss with other affected people. Some of them told me that they were waiting for this for several years. They felt so alone and not understood before.

Since the association was formed, they feel less alone and have a better life.

I want to continue my fight for all this patients...

Now I can sleep because I know I am doing all possible to help and save them.

Mdm Nolwen LE FLOCH
To inform the development of information resources, EURO-WABB researchers worked with Alström Syndrome UK (Kay Parkinson photographed left), Association Syndrome de Wolfram, the UK Wolfram syndrome association supported by Wellchild, and The Laurence-Moon-Bardet-Biedl Society to record patient experiences and identify the learning and information needs of affected people and their families. The full report can be accessed via the project website.

Feelings Experienced at Diagnosis:

The most commonly reported feelings were those of fear and anxiety, with very few respondents feeling adequately supported. Most respondents felt the diagnosis had been given sympathetically, but a significant proportion wanted more explanation and counselling at the time of diagnosis.

Access to Information at Diagnosis:

‘There wasn’t much information, so I searched on the internet.’

About two thirds of respondents felt that they were not given enough information at diagnosis, with many seeking additional information on the internet. The reported experiences also differed widely with some patients feeling both informed and supported, and others less so. The main training requirements requested by families included: training in visual impairment; genetic counseling; healthy eating, exercise and lifestyle; mobility equipment; and dual sensory loss.

Recommendations for Health Professionals:

‘Speak to each other and share information’
‘Knowing more about the syndrome - we are the experts’
‘Help with emotional / anxiety issues’

Four common areas for improvement have been identified by patients and families: the need to communicate better, both with fellow health professionals and with families; the need to be more knowledgeable about the conditions; to offer more support for psychological symptoms; and to provide more support for specific symptoms such as visual loss.

The EURO-WABB project is addressing these areas by working with family support groups to develop resources for comprehensive information, support and training; and with health professionals to improve coordination of care and communication between health professionals across subspecialties and hospital sites.
The Scientific Advisory Committee is an expert multidisciplinary body that provides the rare disease community (clinicians, researchers, patient advocacy groups and industry) with independent and objective peer review of new research proposals that use data from the EURO-WABB registry.

Its goal is to support studies into the natural history of WABB diseases, genotype phenotype correlation studies, identification and validation of biomarkers, and future early phase intervention studies of new treatments.

Scientific Advisory Committee Members

- Ségolène Aymé, France
- Tim Barrett, UK
- Phil Beales, UK
- Andrew Hattersley, UK
- Chris Humphries, UK
- Nolwen Le Floch, France
- Miguel Lopez de Heredia, Spain
- Pietro Maffei, Italy
- Jan Marshall, USA
- Wojciech Mlynarski, Poland
- Virginia Nunes, Spain
- Richard Paisey, UK
- Véronique Paquis, France
- Kay Parkinson, UK
- Julia Rohayem, Germany
- Richard Sinnott, UK
- Vallo Tillmann, Estonia
- Lisbeth Tranebjaerg, Denmark
- Fumi Urano, USA

Further details are available online at www.euro-wabb.org

EURO-WABB has been designed to facilitate data sharing for maximum patient benefit. Participant consent includes additional optional data sharing with ethically approved national or international registries; agreement to be contacted about future research projects including clinical trials; and that any tissue samples collected or previously stored, may be used for in future ethically approved research projects.

Registry Consent Form

- I agree that my anonymised data can be included in a national disease registry for my condition  YES/NO
- I agree that my anonymised data can be shared with other disease registries and research projects relevant to my condition within Europe  YES/NO
- I agree that my anonymised data can be shared with international disease registries and research projects relevant to my condition that take place outside Europe  YES/NO
Genetic Mutation Database

Led by the University of Birmingham, Euro-WABB researchers and geneticists have established a series of mutation databases for the genes associated with WABB syndromes. These include Bardet-Biedl (18 genes), Alström (1 gene), Wolfram (2 genes), Wolcott-Rollison syndrome (1 gene) and Thiamine responsive megaloblastic anaemia syndrome (1 gene). Mutation data is linked to the citation report and published phenotypic data to allow basic genotype phenotype correlation.

Identified mutations have been compiled into open access databases using the Leiden Open access Variation Database (LOVD) software and are freely available online at: https://lovd.euro-wabb.org.

The databases currently contain information about 118 published ALMS1 mutations, 430 mutations in BBS genes, 230 in Wolfram genes 80 mutations associated with other syndromes, together with the corresponding clinical phenotype where published. The databases are updated on a monthly basis.

Not only do the databases provide a useful resource for clinicians, it also ensures standardized reporting of genetic data into the project’s patient registry increasing accuracy and cross-site analysis.

The mutation databases are registered and recognised by the HGVS and the project is a Human Variome Project Partner.
PATIENT REGISTRY

With nearly 300 participants recruited from more than 10 countries and across many recruitment sites, the Euro-WABB registry captures detailed clinical data about each syndrome. The registry includes data from the affected person and their clinician. All data is held in an anonymous format.

Registry data is split between a ‘Core’ (minimum), ‘Extended’ and ‘Patient Experience’ datasets. The core dataset includes 44 variables, consisting of summary current clinical and demographic data, and capturing the clinical and genetic data necessary to establish diagnosis. A further 370 variables capturing detailed phenotypic data are included in the extended dataset recording disease progression and date of onset of symptoms form the extended dataset. Patient experience records the patient’s journey and their experiences from onset of symptoms, through diagnosis and the subsequent management of their condition.

The Registry allows longitudinal collection of data on individual participants, for instance from annual reviews. It also includes the facility for collection of imaging data.

Clinical diagnostic data across datasets is standardized using The International Classification of Diseases (ICD) coding system version 10. The endocrine subset data is further classified using The European Society for Paediatric Endocrinology (ESPE) Classification of Paediatric Endocrine Diseases. Data records are catalogued using a unique identifier, with only the clinician caring for the patient able to link the data record to the patient. The database offers secure access to, and sharing of, data at local, national and international levels.

- **Project Management**: Associate Partners, Project Management Committee, Scientific Advisory Committee, Stakeholders
- **Clinical Partners**: seek consent from patients to input their data
- **Patient Partners**: register themselves, see own data records, input quality of life data
- **Euro-WABB Registry**: 300 anonymised patient records: clinical, genetic diagnostic, outcomes and quality of life data.
- **Research Partners**: Regulated access to data Platform for clinical trials, No direct access to patients
- **State of the art security with password access restricted by role**
WABB syndromes, like many rare diseases, are often mis-diagnosed or subject to delayed diagnosis. Following diagnosis, clinical management requires the coordinated involvement of many different clinical specialties.

Together with clinical specialists for each syndrome, Euro-WABB has developed clinical management guidelines for health professionals for Wolfram, Alström and Bardet-Biedl syndromes, helping to ensure that patients receive a timely diagnosis and optimal clinical management and care.

These have been developed through multidisciplinary guideline development meetings, contribution and peer review by international experts in the fields, and advice from family support groups. Reassessment of existing and potential patients from The Registry have been used to refine the agreed diagnostic criteria and to facilitate the development of consensus referral, care and management pathways.

The development of these guidelines is identifying knowledge gaps and specific learning needs of healthcare professionals. In partnership with family support groups, educational materials and training tools are being developed to disseminate to target groups such as medical students and primary care professionals.

These guidelines are freely available via the website www.euro-wabb.org
GENETIC TESTING NETWORK

Equal access to genetic diagnostic testing

All three WABB syndromes are autosomal recessive conditions. Two causative genes have been identified for Wolfram, a single gene for Alström and multiple genes for Bardet-Biedl syndrome.

For registry participants who haven’t undergone genetic testing to confirm diagnosis, and where the cost of genetic testing is not met by national health funding, this is provided through the project. Access to diagnostic testing is via clinician referral, to ensure that any resulting diagnosis is coupled with appropriate counseling.

The Project has established a network of EU accredited and research laboratories that are able to offer genetic testing for WABB diseases. Information for each laboratory on the range of genetic tests offered, testing method, and reporting times is available on the EURO-WABB website.

In March 2012, Prof. Tim Barrett joined a team of specialists at the Huercal-Overa Hospital in Almeria, Spain for their multidisciplinary Wolfram syndrome clinic. Coordinated by Dr Gema Esteban-Bueno 16 individuals affected by Wolfram syndrome received specialist guidance for their condition. Dr Esteban Bueno also coordinates the ‘Asociación Nacional del Síndrome de Wolfram’ in Spain. (www.aswolfram.org). Genetic testing for these patients is now offered through the network.

“We got the results from Padova last week. In this way, I would like to thank you for your help with the testing and for the opportunity to join the EUROWABB project.”

Eszter Hegyi, MD
University Children`s Hospital, Bratislava, Slovakia

Latest addition:
Wilhelm Johannsen Centre of Functional Genomics, University of Copenhagen
CATALYZING NEW DEVELOPMENTS

In bringing together a wide range of people with so many different disciplines, EURO-WABB is becoming a catalyst for new research proposals and spin-off projects, all of which can take advantage of the translational research platform provided by the Project. The following three examples of projects using the EURO-WABB resources contribute to international efforts to identify new treatments for these diseases:

**Wolfram syndrome**

Association Syndrome de Wolfram is supporting a drug repurposing project to identify licensed medicines which may slow down or halt the neurodegeneration in Wolfram syndrome. They also initiated a research program on gene therapies for the eye, led by a French team and bringing together international collaborators. At the same time Professor Fumi Urano is establishing a consortium to commence clinical trials; and both groups have identified similar classes of drugs. The EURO-WABB Registry will be the portal of entry for recruitment of European patients to an international clinical trial of new treatments for Wolfram syndrome.

**Alström syndrome**

A European Union Innovative Medicines Initiative (IMI) grant has been awarded to a consortium of European researchers and pharmaceutical companies to develop stem cells developing novel drugs for common diseases (STEM cells for Biological Assays of Novel drugs and predictive toxicology). This includes a work package developing stem cell models of diabetes. There is an opportunity within this work package to develop stem cell models for Alström syndrome as a monogenic model of insulin resistant diabetes (and Wolfram syndrome as insulin dependent diabetes). The ethics approval for EURO-WABB is allowing early collection of skin biopsies from participants into biorepositories for de-differentiation to iPSCs.

**Bardet-Biedl syndrome**

Professor Beales (UCL, London, UK) is leading current research efforts with an industrial partner to develop clinical trials of gene editing technology. This is of particular relevance to about one third of Bardet-Biedl patients who carry premature stop mutations in their genes. There is also ongoing interest in new treatments for the kidney disease. The development of the EURO-WABB registry of over 100 consenting participants offers a unique resource from which to invite participants to clinical trials.
The platform EURO-WABB has established for establishing the natural history of these diseases, developing international cohorts, consensus management guidelines, open access genetic databases, and improved access to genetic testing, is accelerating translational research. The Project is providing a platform to support new developments across the field, and is proving its value to the rare diseases community. Its coordinator, associate and collaborating partners are committed to sustaining this project in the long term.

The future will see the Project further develop this essential infrastructure, playing an increasing role in areas such as long term assessment of clinical care pathways, validation of disease monitoring tools, lobbying activities to advocate on behalf of affected people, and updating and implementing of care standards across the spectrum of these diseases. We will support benchmarking of service delivery against care standards, supporting idea generation from leaders in the field, and supporting training and education to develop new care and trial sites with the expertise to treat these rare diseases.

We hope that our efforts will ensure that the rare disease community can move forward together to develop the treatments for which affected people, their families and their health professionals have waited for so long.

A number of local investigators have recruited participants for the registry. We are immensely grateful to:

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- Eszter Hegyi, Slovakia
- Kaire Heilman, Estonia
- Olga Liaugaudiene, Lithuania
- Pietro Maffei, Italy
- Shehla Mohammed, UK
- Veronique Paquis-Flucklinger, France
- Julia Rohayem, Germany
- Vallo Tillmann, Estonia
- Donald Whitelaw, UK
- Agnieszka Zmyslowska, Poland
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PROJECT MANAGEMENT TEAM

The following partners receive funding from the European Union though the Euro-WABB project.

CNRS, FRANCE (Ségolène Aymé)
INSERM, FRANCE (Véronique Paquis)
University of Tartu, ESTONIA (Vallo Tillmann)
University of Birmingham, UK (Timothy Barrett)
Alström Syndrome UK, UK (Kay Parkinson)
Medical University of Lodz, POLAND (Wojciech Mlynarski, Agnieszka Zmysłowska)
University of Padua, ITALY (Pietro Maffei)
University of Glasgow, UK (Richard Sinnott, Susan McCafferty)
IDIBELL, Spain (Virginia Nunes)

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COLLABORATING PARTNERS

Bispebjerg Hospital, DENMARK (Lisbeth Tranejaerg)
University of Münster, GERMANY (Julia Rohayem)
Association Syndrome de Wolfram, FRANCE (Virginie Picard & Nolwen LE FLOCH)
CIBERER, SPAIN (Miguel Lopez de Heredia)
University of Central London, UK (Philip Beales)
LMBBS, UK (Chris Humphries)
South Devon Healthcare NHS FT, UK (Richard Paisey)
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University of Washington, USA (Fumi Uramo)
The Jackson Laboratory, USA (Jan Marshall)
Spanish association for the research and help of Wolfram’s syndrome, SPAIN (Gema Esteban Bueno & Luisa Maria Botelli)
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