DIAGNOSTIC TOOLKIT

for **Medical Comorbidities** in **Autism Spectrum Disorders**

A GUIDE FOR PARENTS & HEALTHCARE PROFESSIONALS

Many medical conditions are significantly over-represented in autism and are a frequent contributing factor to morbidity and lower quality of life. These include diseases of nervous, circulatory, respiratory, immune and digestive systems. The severity of these conditions most often correlates with the severity of autism.

Premature mortality is significantly increased in autism. The average life expectancy of a person with severe autism is only 39.5 years. The average life expectancy in individuals with high-functioning autism/Asperger syndrome was is around 58 years. Early mortality is higher across variety of medical conditions, with epilepsy being the single most common cause of premature death in severe autism.

Individuals with autism may not show clear and typical signs and symptoms but may instead express their discomfort and distress through unusual or challenging behaviours - it is important to note that diseases may present atypically in autism as our knowledge on diseases presentation is based on general population. Therefore lack of usual disease presentation and symptoms only lowers the possibility of the disorder in a patient with autism, but does not exclude it.

This document is a work in progress – this is is a sample 'taster' version.

● *research suggests increased prevalence in autism* ■ *symptoms may overlap with autism* ✦ *frequently found in autism, published evidence*

Condition/ disorder		Overview and general information	Possible presentation & symptoms *Note: the list is not exhaustive*	Diagnostics/tests *Note: the list is not exhaustive* *Note: the availability of each test will depend on country/location*	Treatments *Note: the list is not exhaustive*	References *Note: full list of references will be supplied in a separate document*
GASTROINTESTINAL (GI) DISORDERS						
	● ■	A high index of suspicion of GI disorders should be maintained, and especially in individuals who are more severely affected and/or not able to communicate. Presence of gastrointestinal dysfunction in individuals with autism is in most cases NOT associated with dietary habits or medication status, and parental reporting of any GI dysfunction in their children is highly concordant with later clinical diagnosis of that dysfunction. Individuals presenting with more severe forms of autism are likely to suffer from more severe GI symptoms and disorders	Abdominal distension; constipation/diarrhea; individual pointing to or self-harming GI area/s; selective 'picky' eating and food refusal; crying/irritability around feeding times; regurgitation; undigested food in stool; weight loss and or/growing retardation; atopy and allergies; over-eating, constant hunger; aggressive, oppositional and self-injurious behaviours; dysregulated sleep; sensory overresponsitivity; rigid–compulsive behaviours; strange posturing or movements incl. toe-walking; mood disorders incl. withdrawal, anxiety, irritability/ tantrums; seizure disorders.			

GASTROESOPHAGEAL REFLUX DISEASE GERD	● ■	GERD is a condition in which the liquid content of the stomach regurgitates into the esophagus. The liquid contains acid, digestive enzymes and bile, which can inflame and damage the esophagus lining (signs of inflammation occur and are visible only in a minority of patients. Children with neurologic impairment are at higher risk of GERD. GERD may increase the risks of subsequent pneumonia, depression, anxiety, and sleep disorders.	Typical symptoms*: a burning sensation in the chest (heartburn), usually after eating, which might be worse at night; hoarseness after sleeping; chest pain; difficulty swallowing; regurgitation of food or sour liquid; sensation of a lump in the throat; nausea; vomiting; bad breath; painful and/or constant cough or throat clearing; dysregulated sleep including sleep apnoea. Possible: GERD manifestations include: dental erosions, and proposed associations include pharyngitis, sinusitis, and recurrent otitis media/ ear infections, headache.✦ Respiratory symptoms, including cough and laryngitis, as well as wheezing in infancy. **not all may be present*	Clinical diagnosis Esophageal pH monitoring Endoscopy UK NICE clinical guidelines recommends to: *"Arrange a specialist hospital assessment for infants, children and young people for a possible upper GI endoscopy with biopsies in presence of unexplained distress in children and young people with communication difficulties."*	Antacids Proton pump inhibitors (PPIs) H2 blockers Food elimination diet Elevated sleeping position Antireflux surgery	Davies et al. 2015; Johnson 2005; Lee et al. 2017; Martami et al. 2017; Papachrisanthou & Davis 2016; You et al. 2015
LARYNGOPHARYNGEAL REFLUX LPR ('SILENT REFLUX')	● ■	In LPR, stomach acid flows back into the esophagus and irritates the throat. It is called 'silent reflux' because patients do not show the typical symptoms associated with acid reflux, such as heartburn and regurgitation. If left untreated complications can include: long-term irritation, tissue scarring, damage to vocal cords, ulcers, and increased risk for certain cancers. In rare cases, LPR may also cause growth issues.	Heartburn /burning sensation in the chest is absent in LPR. Typical symptoms*: a bitter taste in throat; a sore throat or a burning sensation in throat; difficulty swallowing; hoarseness; constant clearing of throat; postnasal drip (sensation drainage dripping from nose into throat), respiratory problems including asthma; swelling and irritation of vocal cords; dysregulated sleep including sleep apnoea. In young children or communication-impaired individuals symptoms can manifest as 'feeding behaviours', also as noisy breathing/aspiration, self harming behaviours.✦ Possible: LPR manifestations include: dental erosions, and proposed associations include allergic rhinitis / rhinosinusitis, pharyngitis, nasal polyps, and recurrent otitis media/ ear infections. ✦ **not all may be present*	Physical examination Barium X-ray Laryngoscopy	Antacids Proton pump inhibitors (PPIs) H2 blockers Food elimination diet Elevated sleeping position Antireflux surgery Antimicrobials, in cases of suspected infectious etiology Surgery for obstructive sleep apnea, if present	Kim et al. 2017; Martinucci et al. 2013; Nation et al. 2014; Oridate et al. 2006; Youssef & Ahmed 2010.
EOSINOPHILIC OESOPHAGITIS EOE	● ■	EoE is a chronic inflammatory disorder that manifests in reflux-type symptoms that do not respond to standard anti-reflux medication. EoE is a distinct form of food allergy. Immunoglobulin E (IgE)-mediated food allergies are common in EoE patients. Strongly suspected to be linked to autoimmune and allergy-related mechanisms. Untreated EoE is usually associated with persistent symptoms and inflammation, leading to esophageal remodeling resulting in stricture formation and functional abnormalities. There is some evidence that effective anti-inflammatory treatment may limit progression.	See list of possible GI symptoms above, especially: **feeding disorders**✦; vomiting, **abdominal pain**, dysphagia, and food impaction✦; **asthma**✦, **eczema**✦, **allergic rhinitis** and food allergies✦, classic symptoms of reflux not responsive to PPI. There is a strong overlap of symptoms common in autism and those experienced by typical children suffering from EoE, including social difficulties, anxiety, sleep difficulties and depression. *"Clinical symptoms of EoE are nonspecific, and easily overlooked. If further evaluation, incl. endoscopy, is omitted, pathological causes of feeding disorders such as EoE can be overlooked or inappropriately categorized as behavioral in origin."*	Absolute eosinophil count, along with additional atopic diagnoses, may be predictive of EoE and may prove to be helpful in stratifying the need for endoscopy. Inflammatory changes in EoE are frequently patchy and may not be present in all biopsies, it is therefore recommended that at least 6 biopsies should be obtained from at least two different locations in the esophagus. Currently, noninvasive biomarkers are not accurate to diagnose or monitor EoE. Symptoms do not correlate accurately with histologic disease activity, so histology currently continues to be necessary to monitor the disease.	Dietary changes: targeted or empiric food elimination, amino acid–based formula. Elemental diet induces histologic remission in up to 90% of pediatric and adult EoE patients. Food allergy testing-based elimination diet induces histologic remission in one third of adult patients. The rate may be higher in pediatric patients. Prolonged avoidance of triggering foods may lead to drug-free sustained clinical and histological remission of EoE. An empiric six-food group elimination diet (SFED) induces histologic remission in around three quarters of pediatric and adult patients. In patients who respond to PPI, long-term therapy is effective in maintaining remission. Systemic steroids are not	Heifert et al. 2016 Harris 2013 Jarocka-Cyrta et al. 2011 Lucendo et al. 2017 Markowitz & Clayton 2018 Mukkada et al. 2010 Pelz et al. 2016

					recommended in EoE. In topical-steroids responsive patients, long-term therapy is effective in maintaining remission in a proportion of patients. Immunomodulators azathioprine and 6-mercaptopurin are effective in maintaining remission in a small proportion of patients.	
EOSOPHAGEAL ACHALASIA	●	Disease of the muscle of the lower esophageal body and the lower esophageal sphincter that prevents relaxation of the sphincter and an absence of contractions, or peristalsis, of the esophagus. Strongly suspected to be autoimmune in origin.	See list of possible GI symptoms above but especially: **dysphagia** (difficulty swallowing), **regurgitation**, coughing (esp when lying down), weight loss and/or growth failure, **aggressive** and **self-harming** behaviours, crying during meals, sleep disturbances, frequent recurrence of pneumonia, symptoms of gastroesophageal reflux such as **chest pain** unresponsive to PPI therapy. *"Regurgitation of indigested food … may be confused with food selectivity or generically related to the behavior disturbance of these patients."*	Barium swallow. High-resolution manometry and peroral endoscopic myotomy Eosophagogastroduodenoscopy, with or without endoscopic ultrasound.	Sublingual nifedipine significantly improves outcomes in 75% of people with mild or moderate EA. Other treatment options: pneumatic dilatation, surgery (Heller myotomy), Botox, endoscopic myotomy.	Betalli et al. 2013 Francis & Katzka 2010 Sato et al. 2017
SMALL INTESTINAL BACTERIAL OVERGROWTH SIBO	● ■	SIBO is defined as the presence of excessive bacteria in the small intestine. It can result from failure of the gastric acid barrier, failure of small intestinal motility, anatomic alterations, or impairment of systemic and local immunity. It is believed to be significantly underdiagnosed due to the non-specific nature of symptoms, asymptomatic individual, or because symptoms are often confused with functional bowel disease - the nonspecific nature of complaints makes SIBO difficult to distinguish clinically from other disease entities, such as IBS, lactose intolerance, or fructose intolerance. No study has evaluated the specificity of these symptoms; therefore, objective testing is recommended.	See list of possible GI symptoms above, especially: **bloating, distention, cramping, abdominal discomfort; diarrhea, fatigue, and weakness, diarrhea, nutritional deficiencies** (incl. vitamins A, D, E, vitamin B12 and iron) due to malabsorption; weight loss; metabolic bone disorders/osteoporosis✦, IBD and IBS, celiac disease. Note: A person with SIBO does not need to have all of these symptoms. The frequency and severity of symptoms likely reflect both the degree of bacterial overgrowth along with the extent of mucosal inflammation.	Microbial investigation of jejunal aspirate. Non-invasive, indirect methods: hydrogen and methane breath testing (using either glucose or lactulose as a substrate). Low sensitivity. Interpretations of breath tests vary, no universally accepted standard at present. Empiric treatment in patients with suspected SIBO with a trial of antibiotics with subsequent evaluation of symptomatic response and normalization of breath testing.	The recommended management strategies for SIBO are: correcting underlying causes, eradicating overgrowth, and address associated nutritional deficiencies. Antibiotics. Some evidence of efficacy for probiotics, herbal therapy, guar gum.	Dukowicz et al. 2007 Furnari et al. 2010 Sachdev & Pimentel 2013 Wang et al. 2017
CELIAC DISEASE CD	● ■	CD is defined as a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten. The prevalence of CD in general Western population is close to 1%, but the true prevalence is suspected to be higher. In addition to typical form of CD with GI symptoms (see next column), two asymptomatic forms have been described: Silent CD characterized by positive serology and histology, and Potential CD with positive serology and compatible Human Leukocyte Antigen (HLA) alleles but negative histology. Untreated CD is associated with several	Typical symptoms*: diarrhoea, abdominal pain, bloating, flatulence, weight loss, anorexia, constipation. *Clinical manifestations of CD, especially in children, are **not limited to typical GI symptoms** (see above), but include other common or atypical manifestations potentially affecting any organ or body system, including abnormal liver function tests, iron deficiency anemia, bone disease, skin disorders, and many other protean manifestations. Known manifestations of celiac disease and gluten sensitivity include various types of neurological dysfunction, which can occur in the absence of full CD or gut involvement, possibly via systemic immune	The confirmation of a diagnosis of CD should be based on a combination of findings from the medical history, physical examination, serology, and upper endoscopy with histological analysis of multiple biopsies of the duodenum. Blood tests: antibodies (IgA anti-tissue transglutaminase); total IgA ; In patients in whom low IgA or selective IgA deficiency is identified, IgG-based testing is recommended. Genetic susceptibility HLA test. Upper endoscopy with small-bowel biopsy. Multiple biopsies of the duodenum are recommended. **Note: if the suspicion of CD is high, intestinal biopsy should be pursued even if serologies are negative.** • *Patients with symptoms, signs, or laboratory evidence*	Dietary – gluten exclusion. Steroids (in cases of inflammatory damage to small intestine).	Butwicka et al. 2017; Calderoni et al. 2016; Campagna et al. 2016; Genuis & Bouchard 2010; Hadjivassiliou et al. 2014; Jericho et al. 2016; Jorge et al. 2014; Lau et al. 2013; Ludvigsson et al. 2013; † Rubio-Tapia et al. 2013. *Further references coming soon, see: medscape.com/viewarticle/889005*

		complications, and an increased risk of overall mortality has been observed Recent population-based research indicates that children with CD are at increased risk for most psychiatric disorders, including autism. Studies indicate higher rates of both celiac disease and non-celiac gluten sensitivity in autism compared to controls, even in absence of any gastrointestinal complaints. Small-scale studies and case reports have noted abatement of autistic presentation where a gluten-free and/ or casein-free diet is installed in cases of dual autism and coeliac disease or NCGS diagnoses.	activation caused by translocation of microbial and dietary components. These include but are not limited to: **seizure disorders**✦, **ataxia**✦, **neuropathy**, **migraine, mood and anxiety disorders**✦. High index of suspicion of CD or NCGS in autism is recommended, especially in those presenting with the aforementioned types of neurological dysfunction. *** Many individuals with celiac disease may have no symptoms at all*	*suggestive of malabsorption, steatorrhea (presence of fat in stool), abdominal pain after meals, and bloating, should be tested for CD. (Strong recommendation, high level of evidence)* • *Patients with symptoms, signs, or laboratory evidence for which CD is a treatable cause should be considered for testing for CD. (Strong recommendation, moderate level of evidence)* • *Consider testing of asymptomatic relatives with a first-degree family member who has a confirmed diagnosis of CD. (Conditional recommendation, high level of evidence)* • *CD should be sought among the explanations for elevated serum aminotransferase levels when no other etiology is found. (Strong recommendation, high level of evidence)†* Both serology and biopsy should be performed on a gluten-containing diet.		

NON-CELIAC GLUTEN SENSITIVITY NCGS, BACTERIAL DYSBIOSIS, IRRITABLE BOWEL SYNDROME IBS, INFLAMMATORY BOWEL DISEASE IBD… -- COMING SOON --

SEIZURE DISORDERS ● ■

EPILEPSY (SEIZURE DISORDER SD) & SUBCLINICAL EPILEPTIFORM DISCHARGES SED	● ■	Epilepsy occurs as a result of abnormal electrical activity originating in the brain, which produces seizures. This activity may be within a specific part of the brain or be generalized, depending on the type of epilepsy. Seizure Disorder is a general term that it is often used in place of the term ''epilepsy." The prevalence of epilepsy is significantly higher in people with autism. Epilepsy and autism likely share common aetiology. Individuals with autism and epilepsy are more likely to have severe social impairments and life-long dependency than those diagnosed solely with autism. At the same time individuals with epilepsy are 10 times more likely to develop autism compared to general population. Even in the absence of a learning disability patients with both autism and seizures frequently display more aberrant behaviours including irritability, inattention, hyperactivity, impulsivity, and aggression towards self and others. The occurrence of seizures may lead to changes in brain function that impact core autism symptoms and associated maladaptive behaviours.	Typical signs and symptoms of epilepsy: convulsions, uncontrollable jerking movements of the arms and legs, loss of consciousness or awareness, temporary confusion, staring spells, psychic symptoms such as fear, anxiety or deja vu. Some behaviours commonly attributed to 'autism' may in some cases be due to epileptic activity itself. Those include: unprovoked outbursts of aggression, irritability, crying, laughing for no reason, screaming or self-harming, tics and unusual facial and body movements and postures, staring spells, covering ears with hands, drooling, severe anxiety and panic attacks. The prevalence of epilepsy in autism increases with age, but seizure onset can happen at any time. Employing a high level of clinical suspicion is therefore of paramount importance at any time in patient's life. Children and adults with autism who display symptoms indicative of seizure activity should be referred for full investigation. Screening for early subclinical EEG abnormalities and treating subclinical epileptic spikes may be neuroprotective prospectively, and may improve cognitive behaviour in some patients.	EEG/sleep EEG 24 hour sleep EEG 48 hour sleep EEG videoEEG MEG (info: megcommunity.org) Prolonged studies and those including the sleep state are more sensitive in picking up abnormalities, and investigative strategies of choice include a 24-hour slow wave sleep EEG. A magnetoencephalography (MEG) investigation should also be included, whenever available. A normal routine EEG investigation lasting less than 2 hours will often give false-negative results and miss important abnormalities such as electrical status epilepticus in sleep. Detailed investigations utilizing both prolonged overnight EEG and MEG have revealed that subclinical epileptiform abnormalities, in particular nocturnal epileptiform discharges, are present in a large majority of individuals with autism, even in total absence of clinical seizures. All types of EEG abnormalities are found in autism including: epileptiform abnormalities which are focal, multifocal, or generalized; generalized or focal slowing; excessive fast activity; and the absence of normal wakefulness or sleep patterns. The epileptiform abnormalities are focal in the majority of cases, and localization varies.	AEDs, e.g. valproic acid, especially their early use Neurosurgical intervention Vagus nerve stimulation Dietary therapy: ketogenic diet, modified Atkins diet Immunomodulatory treatments: high dose steroid therapy, intravenous immunoglobulin, plasma exchange Adrenocorticotropic hormone Neurofeedback There is emerging evidence that treating SED is beneficial in autism. The management of seizure waves in patients with autism may result in improved function and reduction of autistic symptoms - successful treatment of both convulsive seizures as well as SED can lead to a reduction in aberrant behaviours and improvement in psychosocial function. Treatment of SED may also prevent subsequent development of epilepsy.	Altunel et al. 2017; Chez et al. 2006; Couthino et al. 2016; Deona et al. 1995; El Achkar et al. 2015; Golla et al. 2014; Frye et al. 2013; Hollander et al. 2001; Kasteleijin-Nolst et al. 1995; Ko et al. 2016; Kokoszka et al. 2016; Lewine et al. 1999; Munoz-Yunta et al. 2007; Nickels et al. 2008; Pressler et al. 2005; Swatzyna et al. 2016; Viscidi et al. 2014; Wang et al. 2017; Yasuhara et al. 2010.

ALLERGIES / IMMUNE DISORDERS ● ■

MAST CELL ACTIVATION DISORDER (CUTANEOUS AND SYSTEMIC MASTOCYTOSIS, MAST CELL ACTIVATION SYNDROME)	■	Mast cell activation disorders are characterized by accumulation of genetically altered mast cells and/or abnormal release of mast cells' mediators, affecting functions in potentially every organ system. In most cases of mast cell activation disease, diagnosis is possible by relatively non-invasive investigation, while trigger avoidance and pharmacological treatment ameliorates or reduces the symptoms. The prevalence of ASDs in children with mastocytosis appears to be 10-fold higher than the general population	Constitutional or multisystem symptoms consistent with aberrant mast cell mediator release, typically: Skin: flushing, pruritus, urticaria (hives), angioedema, urticarial pigmentosa Cardiovascular: hypotension Respiratory: wheezing, throat swelling GI: diarrhea Naso-ocular: pruritus Presentation can include neurological and psychiatric symptoms: Neurological: headache (esp. migraine), presyncope and/or syncope, peripheral (usually distal) sensory and/or motor neuropathies with paresthesias, tics, tremors , chronic inflammatory demyelinating polyneuropathy, seizure disorders (can be "treatment-refractory"), pseudoseizures, dysautonomia Psychiatric: mood disturbances (e.g., anger, depression), bipolar affective disorder, attention deficit-hyperactivity disorder, post-traumatic stress disorder, anxiety and panic, psychoses, memory problems, word finding difficulties, other cognitive dysfunction, wide variety of sleep disruptions Symptoms can be low grade, chronic, episodic or fluctuant.	Serum tryptase 24-hr urinary measurements: methyl histamine, PGD2, 11-β-prostaglandin F2α level Repeated testing and testing during symptoms flare may be required. D816V KIT mutation in peripheral blood or bone marrow biopsy, kin biopsy – if systemic or cutaneous mastocytosis is suspected Response to mast cell targeting treatment.	H1 and H2 histamine receptor antagonists, various mast cell stabilizing drugs e.g. sodium cromoglicate. Symptomatic treatment Cytoreductive therapy in aggressive systemic mastocytosis.	Afrin et al. 2015; Afrin & Molderings 2014; Molderings et al. 2016; Molderings et al. 2011; Picard 2013; Theoharides et al. 2015.
PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME PANS / PANDAS (WHEN ASSOCIATED WITH STREPTOCOCCAL INFECTIONS)	■	PANS is a clinical condition defined by the unusually abrupt onset of obsessive-compulsive symptom and/or severe eating restrictions and additional cognitive, behavioral, or neurological symptoms as a result from a variety of disease mechanisms. Evidence of post-infectious autoimmunity and/or neuroinflammation is found in more than 80% of PANS cases. There is currently no evidence that PANS/ PANDAS is overrepresented in autism, however it can be difficult to diagnose due to overlapping symptoms.	Foudroyant (lightning-like) onset of obsessive–compulsive disorder (OCD) or eating restrictions. Other symptoms: anxiety (particularly separation anxiety), emotional lability or depression, irritability, aggression, and/or severely oppositional behaviors; deterioration in school performance [related to attention-deficit/hyperactivity disorder (ADHD)-like behaviors, memory deficits, and cognitive changes], sensory or motor abnormalities, somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency	PANS is a diagnosis based on clinical criteria and can be confirmed if symptoms are not better explained by a known neurological or medical disorder. Laboratory testing/imaging is required to rule out Sydenham chorea, autoimmune encephalitis, neuropsychiatric lu- pus, central nervous system vasculitis, and others if relevant. PANDAS diagnosis requires the evidence of streptococcal infection. Laboratory tests recommended at first presentation: throat swab for GAS rapid test and/or culture ASO, ADB (repeat in 2–6 weeks for antibody rise or fall), throat or nasopharyngeal swab for M. pneumoniae PCR, M. pneumoniae IgG, IgM (confirmatory IgM fluorescent antibody if positive), tests for other infections, immune, autoimmune conditions suspected on the basis of history and physical examination, 25OH vitamin D level. Clinical usefulness of Cunningham Panel (Molecular Panel, a set of tests cross-reactive antineuronal antibodies associated with dopaminergic neurotransmission) is not clearly established.	Symptomatic treatment with psychoactive medications, psychotherapies (particularly cognitive behavioral therapy), and supportive interventions. Antimicrobials. Immuno- modulatory and/or anti-inflammatory therapies.	Chang et al. 2015; Cooperstock et al. 2017; Frankovich et al. 2017; Swedo et al. 2017; Thienemann et al. 2017.

METABOLIC/ MITOCHONDRIAL DISORDERS

		Autism is associated with several metabolic and genetic syndromes in which at least some of the pathophysiology is known, and which are often amenable to treatment. Treating these underlying disorders—for example inborn errors of metabolism—can often lead to reduction in comorbid conditions such as epilepsy or motor impairments as well as reduction in autism symptoms and improved cognition and functioning. When a patient is presenting with autism and seizures and/or motor and cognitive impairments it is of crucial importance to always rule out metabolic conditions such as mitochondrial disease and dysfunction and abnormalities in cerebral folate metabolism, disorders of creatine, cholesterol, pyridoxine, biotin, carnitine, -aminobutyric acid, purine, pyrimidine, and amino acid metabolism and urea cycle disorders and others				
NEUROMETABOLIC DISORDERS	● ■	Heterogeneous group of more than 90 disorders which feature failure of important metabolic pathways, either inherited or occuring as the result of spontaneous mutation. IEMs occur in 1 in 2500 births. Although they are sometimes viewed as disorders of in infancy, 50% of all IEMs manifests outside of the neonatal period and symptoms can occur at any age. In a number of treatable IEMs autism core symptoms are a part of a disease presentation. Core autism symptoms can be the leading or the only presentation in a number of IEMs (phenyloktonuria, creatine deficiency syndromes, biotinidase deficiency, histidinemia, disorders of purine and pyrimidine metabolism, cholesterol biosynthesis syndromes (see Smith-Lemli-Opitz syndrome, organic acidemias, dihydropyrimidine dehydrogenase deficiency)	Neurological: developmental delay, loss of milestones, poor muscle tone, seizures, motor abnormalities (taken together they can be found in about 80% of IEMs cases) Gastrointestinal symptoms: vomiting, hepatomegaly, food intolerance, diarrhea, food aversion Recurrent feeding issues, failure to thrive Behavioral or learning issues, including autism core symptoms and intellectual disability Others: exercise intolerance, autonomic instability www.treatable-id.org digital tool can be used for symptoms assess symptoms	Screening in children with autism of no obvious etiology: Blood: (phenylalanine [usually performed as a part of routine neonatal screening for IEM – is it better to mention this], histidine, biotinidase activity, cholesterol and 7-dehydrocholesterol, Urine: purines and pyrimidines histidine, organic acid, creatine metabolites Brain MR spectroscopy and/or genetic testing can be used to diagnose creatine deficiency syndromes Screening in children with autism + intellectual disability or global developmental delay: Blood: ammonia, lactate, plasma amino acids, total homocysteine, acylcarnitine profile, copper, ceruloplasmin. Urine: organic acids, purines and pyrimidines, creatine metabolites, oligosaccharides, glycosaminoglycans. Screening tests can identify ~60% of potentially treatable IEMs in ID and are offered by most biochemical genetics laboratories around the world with reasonable turn-around times and affordable prices. Careful interpretation of results is crucial. Findings might be subtle in attenuated disease variants. Primary gene analysis can enhance the diagnostic yield in conditions with unspecific clinical and biochemical presentation. Further, detailed evaluation and specific investigations based on the patient's signs and symptoms should be consider at specialist center in case of IEMs suspicion and negative result of first-tier screening tests.	Dietary restriction or supplementation of co-factor/enzyme, vitamin, substrate inhibition, substrate reduction, enzyme replacement, bone marrow and hematopoietic stem cell transplant and gene therapy Therapeutic effects include improvement or stabilization of psychomotor and cognitive development, behavior or psychiatric disturbances, seizures, neurologic and systemic manifestations	GGogou et al. 2016; Sayson et la. 2015; Schulze 2016; Spilioti et al. 2013; van Karnebeek et al. 2014; van Karnebeek & Stockler 2012; van Karnebeek et al. 2012
MITOCHONDRIAL DYSFUNCTION/DISEASES, DISORDERS OF FOLATE METABOLISM -- COMING SOON --						

OTHER / VARIOUS

AUTONOMIC DYSFUNCTION / POTS, CHIARI SYNDROME, NEUROTRANSMITTERS DISORDERS, THYROID AND OTHER ENDOCRINE DISORDERS, SLEEP APNOEA / SLEEP DISORDERS … -- COMING SOON --