

Autism research: progress and future directions

Healthy Development Adelaide, 20 October 2011

Brain, Behaviour & Development: *the future looks bright!*

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Progress....

- What is autism?
- What causes autism?
- Is autism prevalence increasing?
- How is DSM-V different from DSM-IV?
- What interventions work?

Future directions....

- Subtyping
- National autism register
- Service improvement framework



What is autism?

- Autism spectrum disorder (ASD) is a neurodevelopmental condition characterised by impairments in reciprocal social interaction and communication and the presence of stereotyped behaviours.
- Differences exist in the degree of severity of the three core symptoms as well as other co-occurring mental health and physical conditions.



What causes ASD?

- ASD manifests from a complex interaction between genetic, epigenetic and environmental factors
- A strong genetic component has been identified as shown by family and twin studies
 - 90% concordance rates in monozygotic twins compared with 1-10% in dizygotic twins.
- Heritability of ASD is estimated to be >90%.



Sibling recurrence

- Sibling recurrence risk previously estimated to be 6-8%
- A very recent prospective study reported that if there was an older sibling with ASD, the likelihood of subsequent offspring having autism was 18.7% overall and 32.2% if the child had more than one older sibling with autism.

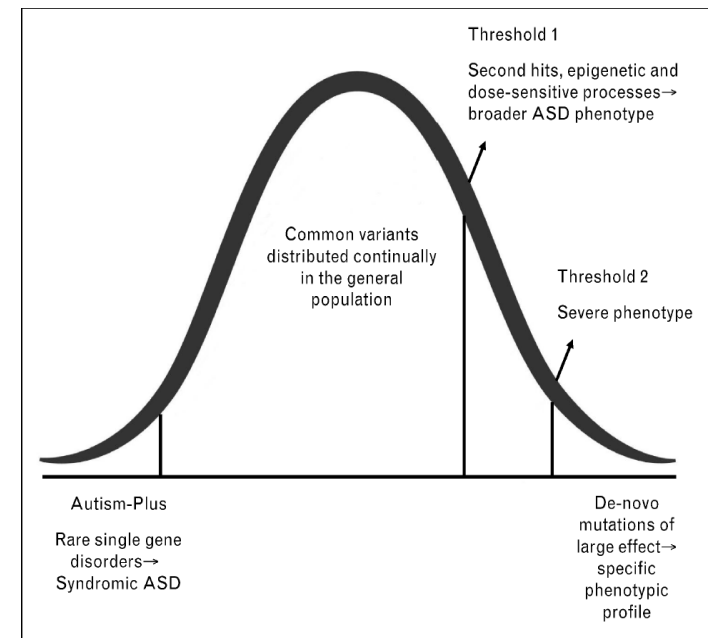
Ozonoff et al. 2011

- Prospective parents should be fully informed of
 - the heritability of ASD
 - the risk of autism recurring if planning subsequent children.



The genetic basis of ASD

- The current literature highlights the presence of genetic and phenotypic heterogeneity in ASD with at least three phenotypic presentations with distinct genetic underpinnings:
 - autism plus phenotype characterised by syndromic ASD caused by rare, single-gene disorders;
 - broad autism phenotype caused by genetic variations in single or multiple genes, which are present in the general population, but resulting in varying clinical phenotypes when it reaches a certain threshold; and
 - severe and specific phenotype caused by ‘de-novo’ mutations in the patient or transmitted through asymptomatic carriers of such mutation.



Eapen 2011



The environment and autism

- Environmental factors play a role in both the onset and outcome of the disorder and include:
 - Advanced parental age,
 - Oxidative stress,
 - Neuroinflammation,
 - Mitochondrial dysfunction,
 - GI disturbance, and
 - Environmental pollutants
 - air pollution, organophosphates and heavy metals



Epigenetics and autism

- Epigenetic mechanisms may play a role in other neurobehavioral phenotypes.
- New molecular technologies allowing whole-genome screening for DNA methylation and chromatin alterations will enable identification of epigenetic determinants of ASD.
- The characterisation of specific epigenetic determinants for ASD will shed light on its aetiology.
- As epigenetic marks are modifiable with environmental factors, targeting them is an excellent strategy for developing new therapeutic interventions in ASD

Grafodatskaya et al. 2010

- Disturbances in the folate/methionine cycle have been shown to present in autism

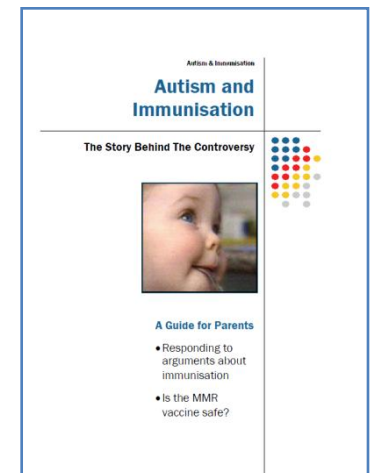
Main PAE, Angley MT, Thomas P, O'Doherty CE, Fenech M, (2010) 'Folate/methionine metabolism and autism: a systematic review.' *American Journal of Clinical Nutrition*. 91:1–26.



Vaccination DOESN'T cause autism

- Although an array of epidemiological studies do not support causality the alleged link between autism and vaccination continues to be debated extensively.
- Many parents and parent advocacy groups continue to suspect that vaccines cause autism.
- Free booklet discussing autism and immunisation issues available at:

<http://marac.com.au/assets/88392%20Autism%20%20Immunisation%20Booklet.pdf>



Is autism prevalence increasing?

- In the last 20 years, the number of people diagnosed with ASD in **Australia** has increased ten-fold with a current incidence of approximately 1 in 160 among primary school children.

Williams et al, 2008

- Further analysis of additional FaHCSIA/Centrelink data shows
 - Steady annual growth in ASD diagnoses from 2004 to 2009
 - Australian ASD prevalence exceeded 1 in 100 (or 1%) in 2009

Buckley, 2009 and Wray, 2011, personal communications

- A recent UK study found essentially the same prevalence of ASD in adults in the UK as children i.e. 1 in 100

Brugha et al., 2011



Is autism prevalence increasing?

- When epidemiological studies from several countries are summarised for prevalence of ASD “a best estimate of 60 to 70/10,000or one child in about 150 children...”
- “..broadening of the concept, the expansion of diagnostic criteria, the development of services, and improved awareness of the condition have played a major role in explaining this increase, although it cannot be ruled out that other factors might have also contributed to that trend”.

Fombonne, 2009



How is DSM-V different from DSM-IV?



American Psychiatric Association
DSM-5 Development

Home About DSM-5 Meet Us Research Background General Resources Proposed R

Home / Proposed Revisions / Proposed Revision

A 09 Autism Spectrum Disorder

Proposed Revision Rationale Severity DSM-IV

Revised January 26, 2011

Autism Spectrum Disorder

Must meet criteria A, B, C, and D.

- A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:
1. Deficits in social-emotional reciprocity, ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction.
 2. Deficits in nonverbal communicative behaviors used for social interaction; ranging from poorly integrated verbal and nonverbal communication, through abnormalities in eye contact and body-language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.
 3. Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends, to an apparent absence of interest in people.
- B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following:
1. Stereotyped or repetitive speech, motor movements, or use of objects; (such as simple motor stereotypies, echolalia, repetitive use of objects, or idiosyncratic phrases).
 2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change; (such as motoric rituals, insistence on same route or food, repetitive questioning or extreme distress at small changes).
 3. Highly restricted, fixated interests that are abnormal in intensity or focus; (such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
 4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment; (such as apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).
- C. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities).
- D. Symptoms together limit and impair everyday functioning.



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New name for category, ASD, which includes autistic disorder (autism), Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified

How is DSM-V different from DSM-IV?

The screenshot shows the American Psychiatric Association's website for DSM-5 Development. The page title is "A 09 Autism Spectrum Disorder". Below the title are tabs for "Proposed Revision", "Rationale", "Severity", and "DSM-IV". The page is dated "Revised January 26, 2011". The criteria are listed as follows:

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D. Symptoms together limit and impair everyday functioning.

- Social/communication deficits collapsed into one domain.
- More accurately considered as a single set of symptoms with contextual and environmental specificities
- Improves **specificity** without impairing **sensitivity**

How is DSM-V different from DSM-IV?



Home / Proposed Revisions / Proposed Revision

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Unusual sensory behaviours are explicitly included expanding the specification of different behaviours that can be coded within this domain

Reorganisation of sub-domains increases clarity and continues to provide adequate sensitivity while improving specificity through provision of examples from different age ranges and language levels.

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Severity

A 09 Autism Spectrum Disorder

Proposed Revision	Rationale	Severity	DSM-IV
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Revised January 26, 2011

Severity Level for ASD	Social Communication	Restricted interests & repetitive behaviors
<p>Level 3</p> <p>'Requiring very substantial support'</p>	<p>Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning; very limited initiation of social interactions and minimal response to social overtures from others.</p>	<p>Preoccupations, fixated rituals and/or repetitive behaviors markedly interfere with functioning in all spheres. Marked distress when rituals or routines are interrupted; very difficult to redirect from fixated interest or returns to it quickly.</p>
<p>Level 2</p> <p>'Requiring substantial support'</p>	<p>Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions and reduced or abnormal response to social overtures from others.</p>	<p>RRBs and/or preoccupations or fixated interests appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress or frustration is apparent when RRB's are interrupted; difficult to redirect from fixated interest.</p>
<p>Level 1</p> <p>'Requiring support'</p>	<p>Without supports in place, deficits in social communication cause noticeable impairments. Has difficulty initiating social interactions and demonstrates clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions.</p>	<p>Rituals and repetitive behaviors (RRB's) cause significant interference with functioning in one or more contexts. Resists attempts by others to interrupt RRB's or to be redirected from fixated interest.</p>



What interventions work?

- There are many proposed interventions that are currently used to manage autism but few have evidence for efficacy. The lack of useful interventions stems from a lack of understanding of what is causing autism.
- A range of behavioural interventions have evidence for efficacy
 - Antecedent Package
 - Behavioural Package
 - Comprehensive Behavioural Treatment for Young Children
 - Joint Attention Intervention
 - Modelling
 - Naturalistic Teaching Strategies
 - Peer Training Package
 - Pivotal Response Treatment
 - Schedules
 - Self-management
 - Story-based Intervention Package



Psychotropics

- Pharmacotherapy in ASD lacks a solid, reliable neurobiological basis and is mainly directed at associated behavioural symptoms, with limited relevance to core symptoms. Canitano & Scandurra 2011
- 55% of individuals with autism receive psychotropic medications regardless of the fact evidence for efficacy is limited. Aman et al. 2003
- More randomised controlled trials (RCT) are needed to establish efficacy.
- The long-term safety and tolerability are unknown and cause for serious concern..



Management of autism with psychotropic medications

- Medications should generally be initiated by a specialist, such as a developmental paediatrician, child neurologist or child psychiatrist
- Primary strategies are understanding, environmental modification and behavioural interventions.
- Combined with these, medications can be helpful in the overall management of autism
- Psychostimulants, antidepressants and antipsychotics are used to manage symptoms of ASD



Antipsychotics

- Many conventional antipsychotics have approval for use in children with severe behavioural disorders (not specifically autism)
- Conventional antipsychotics have a high tendency for extra pyramidal side effects (EPSEs)



Risperidone

- Risperidone is the most studied new generation antipsychotic in autism.
- Reduction of maladaptive behaviours (aggression, self-injury, stereotypies and tantrums) has been repeatedly observed with its use.
- Adverse effects reported in autism are: weight gain, increased appetite, fatigue, drowsiness, drooling, dizziness, constipation, tremor and tachycardia.
- Risperidone has TGA approval and is listed on the PBS for management of maladaptive behaviours in ASD



Women's and Children's Health Network (WCHN) antipsychotic monitoring program

- Physical health and adverse effect monitoring chart
- Abbreviated guidelines
- Comprehensive guidelines
- Consumer leaflets

All resources available at:

<http://www.wch.sa.gov.au/services/az/other/pharmacy/antipsychotic.html>

- WCHN package currently being revised

Grzeskowiak L et al (2008) 'Implementation of a chart and guidelines for monitoring physical health and adverse effects in children and adolescents prescribed antipsychotics.' JPPR vol. 38 no.1 pp.9-13.

Ellis D et al (2008) 'Development of a novel program to facilitate monitoring physical health and adverse effects in children and adolescents prescribed antipsychotic medication.' Australasian Psychiatry. Vol 16 no.2 pp 368-369.



Government of South Australia

Children, Youth and Women's
Health Service



UniSA

Sansom
Institute

Complementary and alternative medicine (CAM) products

- <http://www.intechopen.com/books/show/title/autism-spectrum-disorders-from-genes-to-environment>
- Semple S, Hewton C, Paterson F, Angley M, (2011) Complementary medicine products used in autism: evidence for rationale. In: Autism Spectrum Disorders: from Genes to Environment (ISBN 978-953-307-558-7)
<http://www.intechopen.com/articles/show/title/complementary-medicine-products-used-in-autism-evidence-for-rationale>
- Semple S, Hewton C, Paterson F, Angley M, (2011) Complementary medicine products used in autism: evidence for efficacy and safety. Autism Spectrum Disorders: From Genes to Environment (ISBN 978-953-307-558-7)
<http://www.intechopen.com/articles/show/title/complementary-medicine-products-used-in-autism-evidence-for-efficacy-and-safety>
- Currently working on a consumer resource



Level of Evidence Grade

Natural Standard Research Collaboration Grading Rationale

- **A** Strong scientific evidence
- **B** Good scientific evidence
- **C** Unclear or conflicting scientific evidence
- **D** Fair negative scientific evidence
- **F** Strong negative scientific evidence

Natural Standard Research Collaboration, 2010.



Results - Evidence for the efficacy of selected CAMs in treating autism

Complementary Medicine	Natural Standard Research Collaboration Rating
Vitamin B6 + magnesium	C
Vitamin B12	C
Multivitamins/minerals (Spectrum Support)	C
Dimethylglycine (DMG)	C
Vitamin C	C
Probiotics	C
Digestive enzymes	D
Secretin	F
Polyunsaturated fatty acids	C
Melatonin	B
All others	Lack of scientific evidence



Major adverse effects observed during trials of selected CAMs in people with autism

Complementary medicine	Most prevalent adverse effects
Vitamin B6 + magnesium	Loose stools, URTI symptoms, nausea, excitability
Vitamin B12	Hyperactivity and increased mouthing of objects
Dimethylglycine (DMG)	Agitation, hyperactivity
Vitamin C	None mentioned
Iron	GI irritation, stained teeth
Probiotics	Rash, diarrhoea, weight loss
Digestive enzymes	Hyperactivity, aggression, diarrhoea, increased self-stimulatory behaviours, loose stools, provocation or red ears and cheeks, increased hunger and cessation of eating.
Secretin	Rash, hyperactivity, fever, tachycardia, vomiting, photosensitivity, increased irritability and generalised flushing.
Polyunsaturated fatty acids	GI irritation, hyperactivity, behavioural worsening, increase the risk of bleeding
Melatonin	Tiredness, headache, dizziness, diarrhoea, agitation
Thiamine tetrahydrofuryl disulphide (TTFD)	Unpleasant odour
DMSA	Sleep problems, increased tantrums



Future directions.....

- Subtyping
- National autism register
- Service improvement framework



Subtyping

- There is a need for research to be targeted to defining the causes underpinning the different autism subgroups.
- “Development of targeted therapies based on pathophysiologically and etiologically defined subtypes of ASD remains an important and achievable goal of current research.” Geschwind 2009



Development of a laboratory test to diagnose/subtype autism

- Currently, diagnosis of autism is based on a cluster of behaviours
- Diagnosis of autism is problematic, as there are currently no validated laboratory tests to diagnose autism and/or identify subtypes



Urinary Metabolic Phenotyping Differentiates Children with Autism from Their Unaffected Siblings and Age-Matched Controls

Ivan K. S. Yap,[†] Manya Angley,^{†,‡} Kirill A. Veselkov,[†] Elaine Holmes,[†] John C. Lindon,[†] and Jeremy K. Nicholson^{*,†}

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Received December 22, 2009

Autism is an early onset developmental disorder with a severe life-long impact on behavior and social functioning that has associated metabolic abnormalities. The urinary metabolic phenotypes of individuals (age range=3–9 years old) diagnosed with autism using the DSM-IV-TR criteria ($n = 39$; male = 35; female = 4), together with their nonautistic siblings ($n = 28$; male = 14; female = 14) and age-matched healthy volunteers ($n = 34$, male = 17; female = 17) have been characterized for the first time using ¹H NMR spectroscopy and pattern recognition methods. Novel findings associated with alterations in nicotinic acid metabolism within autistic individuals showing increased urinary excretion of *N*-methyl-2-pyridone-5-carboxamide, *N*-methyl nicotinic acid, and *N*-methyl nicotinamide indicate a perturbation in the tryptophan–nicotinic acid metabolic pathway. Multivariate statistical analysis indicated urinary patterns of the free amino acids, glutamate and taurine were significantly different between groups with the autistic children showing higher levels of urinary taurine and a lower level of urinary glutamate, indicating perturbation in sulfur and amino acid metabolism in these children. Additionally, metabolic phenotype (metabotype) differences were observed between autistic and control children, which were associated with perturbations in the relative patterns of urinary mammalian-microbial cometabolites including dimethylamine, hippurate, and phenylacetylglutamine. These biochemical changes are consistent with some of the known abnormalities of gut microbiota found in autistic individuals and the associated gastrointestinal dysfunction and may be of value in monitoring the success of therapeutic interventions.

Keywords: autism • microbial co-metabolites • metabonomics • metabolic profiling • metabolic phenotype • gut microbiota • NMR • pattern recognition

Introduction

Autism spectrum disorders (ASD) represent a series of related highly complex socio-psychological and neurodevelopmental problems with associated metabolic and gastrointestinal abnormalities of poorly defined etiology. ASD typically develop during the first 3 years of life and are characterized by a myriad of deficits in language/communication skills, social detachment as well as repetitive and stereotypic behaviors.^{1,2} The etiopathology of ASD is multifactorial and has been linked to genetic abnormalities^{3,4} and inborn errors of metabolism but there are many postulated, largely ill-defined, triggers including infectious agents and environmental toxins.⁵ Autism has been shown to have strong associations with various metabolic abnormalities, immunological function and gastrointestinal dysfunction.⁶ Although the precise mechanisms of these associations

In addition to the panel of neurodevelopmental problems associated with ASD, a range of gastrointestinal disorders have been reported, and recent studies have found that the condition is associated with abnormal gut microbiota.⁹ There is also the possibility of previously unrecognized etiologic connections between microbiome disorder and childhood developmental problems, given the importance of the microbiome in mammalian metabolism, for example, bile acid metabolism.¹⁰ Individuals with ASD are commonly exposed to repeated courses of multiple antibiotic therapies and this may contribute to the complex relationships between gastrointestinal dysbiosis and ASD by altering the composition or stability of their microbiota.^{11–13} Abnormal sulfur metabolism has also been shown to typify individuals with ASD.¹⁴ Waring et al. showed that individuals with autism have lower levels of plasma sulfate

Autism Finding Could Lead to Simple Urine Test for the Condition

[Autism Info For Parents](#)

Informative Workshops for Parents Of Children with ASD. Find Out More


[Kids Development](#)

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Ads by Google

Children with autism have a different chemical fingerprint in their urine than non-autistic children, according to new research published tomorrow in the print edition of the Journal of Proteome Research.

The researchers behind the study, from Imperial College London and [the University of South Australia](#), suggest that their findings could ultimately lead to a simple urine  test to determine whether or not a young child has autism.

Autism affects an estimated one in every 100 people in the UK. People with autism have a range of different symptoms, but they commonly experience problems with communication and social skills, such as understanding other people's emotions and making conversation and eye contact.

People with autism are also known to suffer from gastrointestinal disorders and they have a different makeup of bacteria in their guts from non-autistic people.

Today's research shows that it is possible to distinguish between autistic and non-autistic children by looking at the by-products of gut bacteria and the body's metabolic processes in the children's urine. The exact biological significance of gastrointestinal disorders in the development of autism is unknown.

The distinctive urinary metabolic fingerprint for autism identified in today's study could form the basis of a non-invasive test that might help diagnose autism earlier. This would enable autistic children to receive assistance, such as advanced behavioural therapy, earlier in their development than is currently possible.

At present, children are assessed for autism through a lengthy process involving a range of tests that explore the child's social interaction, communication and imaginative skills. Early intervention can greatly improve the progress of children with autism but it is currently difficult to establish a firm diagnosis when

**Imperial College
London**

[Teach Autistic Toddlers](#)

Language Learning
Tools for your Autistic
or language delayed
child

www.BabyBumbleBee.com



Ads by Google

GI Disturbance in autism

- Gut problems are common in children with autism
 - abdominal pain, constipation, diarrhoea
- May give insight into the cause of autism or influences on phenotype
 - Altered gut bacteria
 - Wang LV, Christophersen CT, Sorich MJ, Gerber CP, Angley MT, Conlon MA, (2011) Low Relative Abundances of the Mucolytic Bacterium *Akkermansia muciniphila* and *Bifidobacterium* spp. in Feces of Children with Autism. *Applied and Environmental Microbiology* Vol. 77 (18) pp. p. 6718–6721, doi:10.1128/AEM.05212-11v
 - Altered bowel fermentation product profiles
 - Wang L, Christophersen CT, Sorich MJ, Gerber JP, Angley MT & Conlon MA (2010). Gut bacterial and fermentation profiles are altered in children with autism. *J Gastroenterol Hepatol* 25: A116
 - Leaky gut?



National autism register

- 2007 election promise
- 2009 funding allocated to develop a proposal
- Development is currently on hold



A national autism register

- Will enable accurate determination of the prevalence of autism within Australia and longitudinal data collection.
- Will provide a platform for workforce planning and service needs projections.
- Will contain demographic/diagnostic information
 - Can be enhanced with further clinical and biological information
- Has potential for data linkage with accompanying research opportunities
- Can inform practice regarding the range of interventions available and responsiveness of individuals to interventions.



Ultimately...

- can establish an evidence base for the range of autism interventions
- rationalisation of resources in autism management that focuses on efficient use of evidence based approaches.



SA service improvement framework for ASD

- The Department for Families and Communities (DFC) has committed funding for a statewide autism project (SWAP) to develop a service system improvement framework for people with ASD.
- The framework will be structured to reflect key phases of the 'ASD' journey
 - diagnosis and assessment, early intervention, education, employment/day options, long-term care and care in advanced age.
- Mental health
- Family support
 - Adaptation to diagnosis
 - Transitions



- The intention of the framework is to drive improvements in the service system to achieve optimal outcomes for all South Australians with ASD through the provision of equitable, timely and effective services and support.
- It is also an aim to reduce variations in support by outlining the services that all people with ASD should expect to receive from the SA health, disability and education sectors, across the continuum of the condition.
- Implementation strategies will be embedded that reflect current best practice.



Stakeholder surveys to investigate experiences with autism services in SA

- Data will be used to inform development of the SA service system improvement framework for ASD
- Survey links:
 - consumers
<http://www.surveymonkey.com/s/DH6B2WR>
 - professionals
<http://www.surveymonkey.com/s/8PBXJ3D>



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- Caregivers



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