Thinking through the Causes for Changes in Cognition in Adults with Down Syndrome: Clinical Problem Solving

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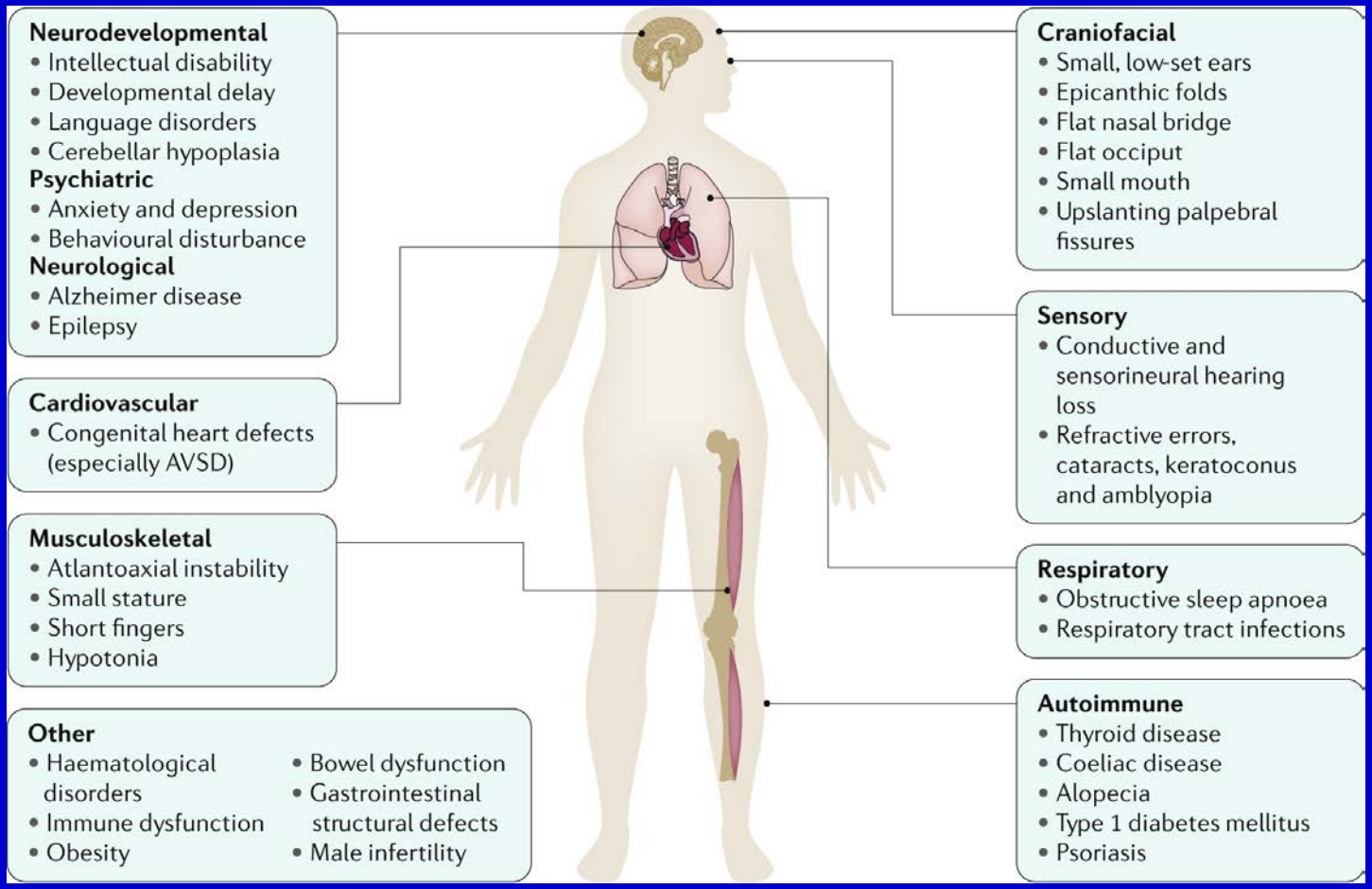
Disclosures

- Co-inventor on patent applications for γ-secretase modulators.
- SAB Member for Alzheon Inc, Promis Inc., and Samumed Inc.
- Consultant for Cortexyme and Annovis-Bio and received stock.

Caring for Adults with DS in Neurology Clinic

- Adults with DS experience a number of clinical challenges
- Changes in brain function are not infrequent, leading to evaluation in the Neurology Clinic
- Clinicians with experience in the management of adults with DS are aware of a number of conditions that can impact learning, memory, mood and overall brain function
- Caregivers turn to these physicians for defining the problems and their solutions.
- Clinicians must carefully consider the possible causes of neurologic dysfunction, including memory loss.

Adverse Impacts of DS on Health



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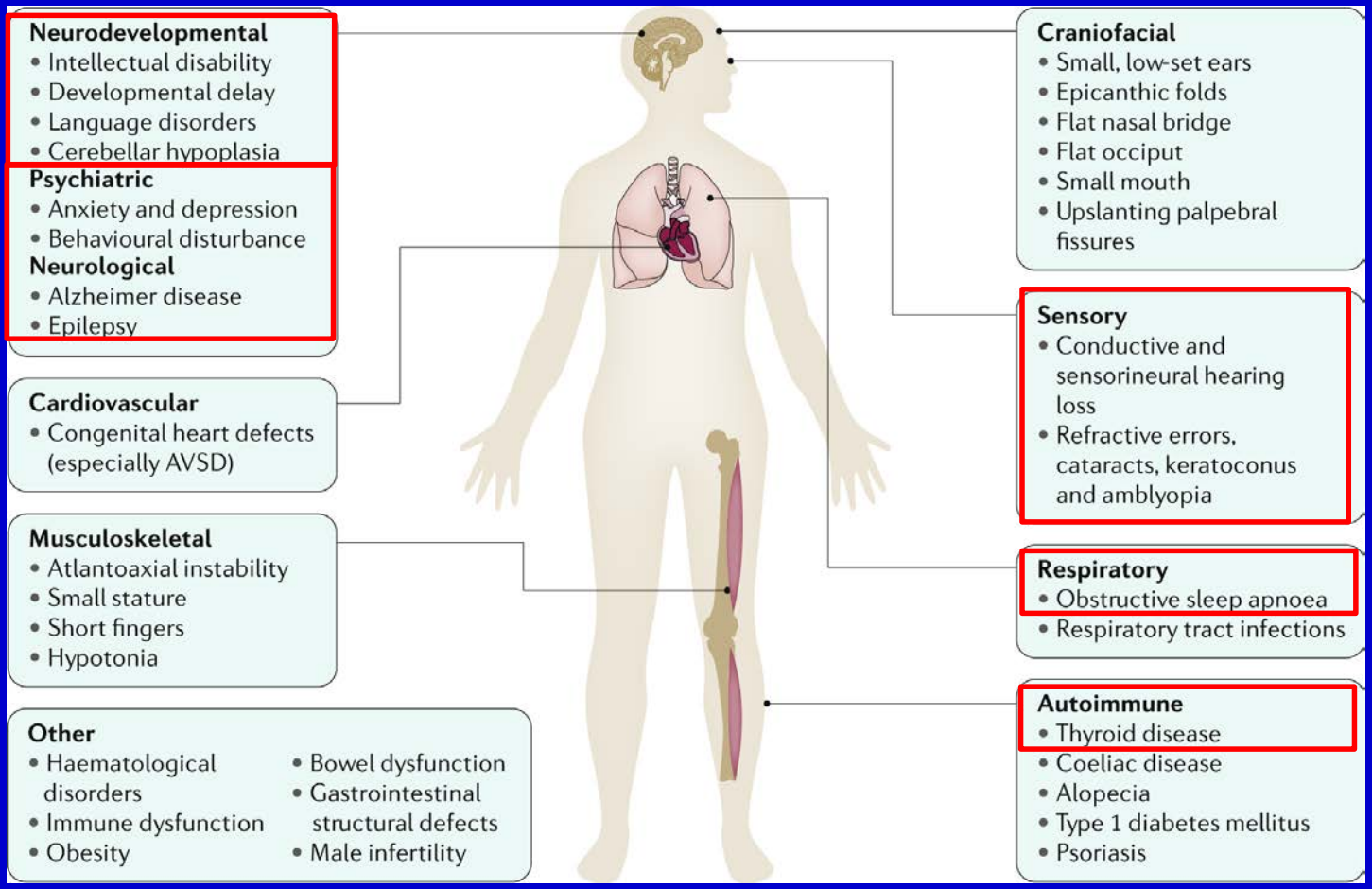
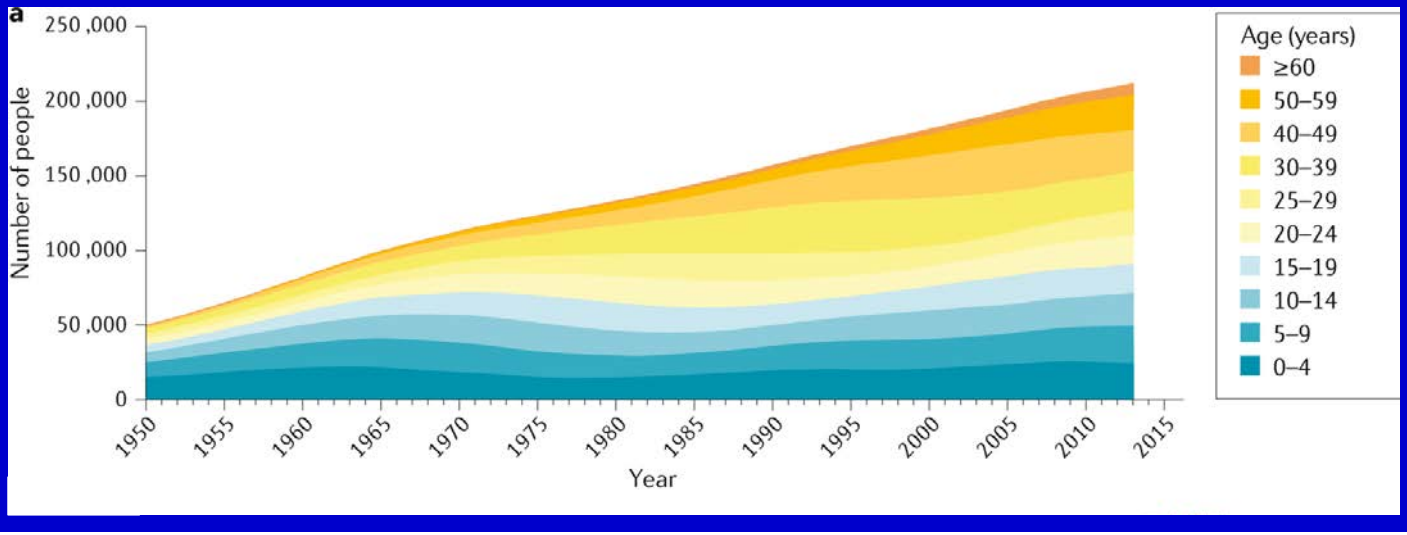


Increasing Longevity and Size of DS Population in US

Life expectancy of individuals with DS in the USA:

- 1950: mean of 26 years; median of 4 years
- 2010: mean of 53 years; median of 58 years

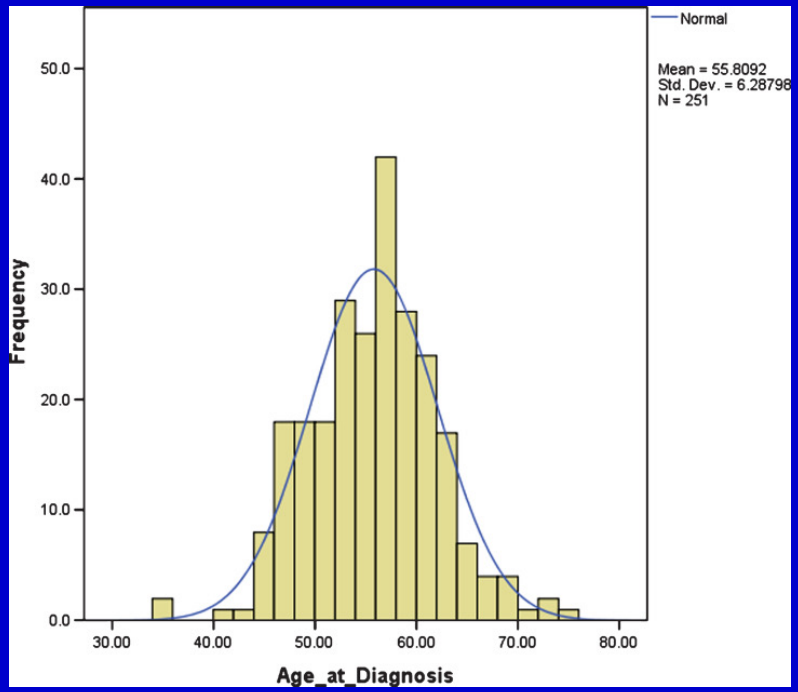


Antonarakis et al, Nature Rev, 2020

Alzheimer Disease(AD) in DS (AD in DS)

- More frequent and earlier in adults with DS (incidence may exceed 90% beyond age 65).
- Dementia: cognitive or behavioral symptoms in two domains that: 1) interfere with the ability to function normally; and 2) represent a decline from a previous level of functioning and performing. AD typically includes memory loss.
- Dementia occurs at a median age of ~55 years.
- Genetics: a third copy of HSA 21
- Neuropathological changes very similar if not identical to typical AD, and found in essentially all by age 40.

DS Markedly Increases Risk of AD



Sinai et al., JAD, 2018

Cumulative risk by age 65 is estimated to be 90%.

McCarron et al., J Intellect Disabil Res, 2014.

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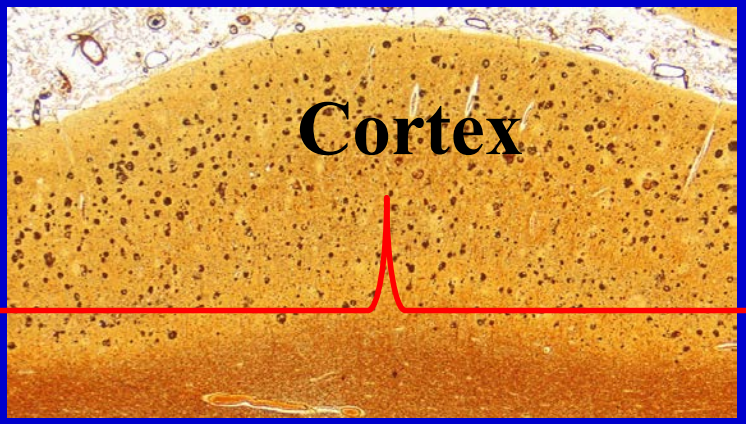
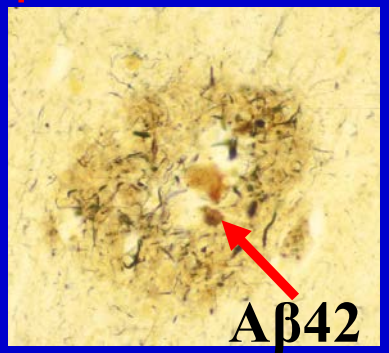
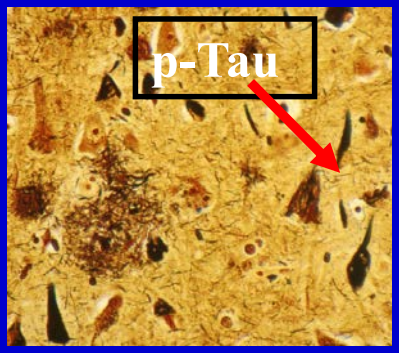
Neuropathology: AD-DS

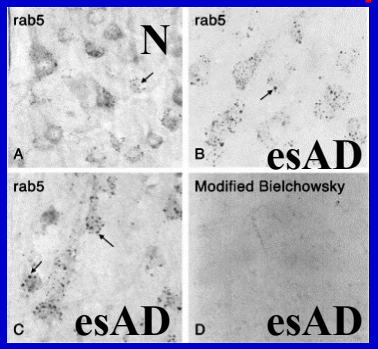




Amyloid plaque



Neurofibrillary tangle



Enlarged Endosome

(Cataldo et al., N'biol Aging, 2004)

Caring for Adults with DS in Neurology Clinic

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- Changes in brain function are not infrequent, leading to evaluation in the Neurology Clinic
- Clinicians with experience in the management of adults with DS are aware of a number of conditions that can impact learning, memory, mood and overall brain function
- Caregivers turn to these physicians for defining the problem(s) and the solution.
- Clinicians must carefully consider the possible causes of neurologic dysfunction, including memory problems.

Possible Causes of Memory Problems

Condition	Presentation
Sensory deficits	Hearing loss Vision loss, low vision, depth perception changes
Metabolic disturbances	Electrolyte abnormalities Hypoglycemia/hyperglycemia B_{12} or folate deficiencies Undetected thyroid dysfunction Anemia Toxic levels of antiepileptic or psychoactive medications Toxic adverse effects of certain medications (eg, hyperammonemia in chronic valproic acid use)
Coexisting mood disorder	Either newly detected or subacute worsening of baseline mood disorder Note: Depression can cause symptoms that seem similar to dementia

Possible Causes of Memory Problems

Condition	Presentation
Sleep problems	Sleep apnea and other undetected sleep disorders
Seizures	Undetected or worsening seizure disorders
Pain	Undiagnosed pain or undertreated pain
Mobility problems	Mobility disorders and loss of functionality
Psychosocial or environmental stressors	Changes in routines, death or impairment of family members or close acquaintances, new regimen at home or in the workplace, reactions to threatening situations
Others	Conditions that may be associated with cognitive deficit (stroke, chronic subdural hematoma, brain tumors, multiple sclerosis, human immunodeficiency virus, and cryptococcal infection)
Additional considerations: prevalent conditions in adults with Down syndrome	Vision impairment :cataracts and keratoconus

Case Study: Mary Visits the Clinic

Mary is a 45 year old, right handed, Caucasian female with Down syndrome referred to the Neurology Clinic for concern about recent changes from normal in her interests, mood and behavior. She is accompanied by her mother and younger sister. The mother and sister are aware of the increased risk of AD and quite concerned. They give a history of a very normal young woman with DS whose only medical problem was hypothyroidism, now treated, until about 6-18 months ago there was decreased interest in carrying out her normal daily activities. Appetite decreased at about this time. Mom says that while in the past Mary was quite engaging with others, there is less of this now. She sometimes seems distant and stares. Her self-talk is now more often and is sometimes more negative.

Case Study: Mary Visits the Clinic

During the last two months Mom says she often finds Mary crying in her bedroom. She also says that Mary sometimes wanders about the house during the night. The next morning she is noticeably less active and seems tired. When questioned about memory, Mom and sister suspect perhaps a slight decrease in her ability to remember her favorite TV shows. Mary does continue to perform the activities of daily living and if encouraged will participate in chores around the house. Due to Covid she has not been able to attend the day care program in which she was enrolled. No concern for physical or sexual abuse in her program activities.

Case Study: Mary Visits the Clinic

- Should Mary be diagnosed with Alzheimer Disease?
- If not, why not?
- What alternative diagnoses should be considered?
- What would you like to do to further evaluate her problems?

Case Study: Mary Visits the Clinic

Steps in the evaluation:

History – from knowledgeable source

- review of medical and psychiatric issues, cardiovascular disease, head injury, sleep disorders, thyroid disease, vitamin B12/ folate deficiency, metabolic syndrome (obesity, diabetes) hypertension
- baseline and current levels of function (? past formal evals)
- review of systems (HEENT, GI, Heart, Lungs, Urologic, M-skel, Neuro
- medications
- family history
- Psychosocial and social environment

Examination – general (esp. HEENT, Thyroid, GI, M-skel, back, Neurologic (Mental status, Cranial nerves, fundus, motor and sensory, reflexes, Cbl, Gait)

Case Study: Mary Visits the Clinic

- Steps in the evaluation: filling in the blanks to determine what has changed, how marked and over what time period. Careful review of:
  - attention, orientation, judgement
  - memory (short term, names, word finding, problem solving, track of time, recognition of familiar people, object use
  - behavior (aggressiveness, irritability, self injurious, self talk)
  - Mood (overall demeanor, social engagement, depression, apathy)
  - Psychiatric (hallucinations, delusions)
  - Speech (understanding, speaking, communication skill)

Case Study: Mary Visits the Clinic

- Steps in the evaluation:
  - neurologic function (seizures, motor and sensory function, stroke, falls, head injury, neck injury)
  - vision and audition (status, when last formally evaluated)
  - sleep (waking and wandering at night, symptoms of apnea, daytime somnolence)
  - activities of daily living (eating, dressing, bathing, grooming, toileting)
  - skills, schooling, employment (reads, writes, math, money management, jobs held, day care activities, type of living environment)
  - social (status, recent changes in significant others, history of abuse)

Case Study: Mary Visits the Clinic

Your history taking further reveals:

1) The mother and sister are confident the changes in mood have been present for no more than 18 months. On reflection, they note that the sister moved out of the family home at this same time. On careful questioning, they do not think Mary's memory is worse.
2) They deny hallucinations, pain, problems with vision or hearing, seizures, head trauma. The only change in speech is that it is less frequent.
3) The night wandering started about the same time as the change in behavior. They note that she occasionally snores.
4) No other problems elicited in the history from mom and sister.
5) Mary identifies mom and sister, understands questions and responds. She says she has no pain, and no problems with seeing and hearing. She speaks about favorite TV programs. She misses her friends and think she might be sad.
6) Review of systems: negative.
7) Medications: Synthroid. No family history of dementia or mood disorders.

Case Study: Mary Visits the Clinic

Steps in the evaluation:

History – from knowledgeable source

- review of medical and psychiatric issues, cardiovascular disease, head injury, sleep disorders, thyroid disease, vitamin B12/ folate deficiency, metabolic syndrome (obesity, diabetes) hypertension
- baseline and current levels of function (? past formal evals)
- review of systems (HEENT, GI, Heart, Lungs, Urologic, M-skel, Neuro
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Examination – general (esp. HEENT, Thyroid, GI, M-skel, back, Neurologic (mental status, cranial nerves, fundus, motor and sensory, reflexes, coor, gait)

Case Study: Mary Visits the Clinic

Your examination reveals:

1) An alert cooperative woman with DS.
2) She follows instructions.
3) No abnormal findings on the general exam.
4) Neurologic and Psychiatric exams show normal orientation, speech, memory for three words after 3 minutes, normal eye movements, vision, audition, normal movement, normal strength and tone, normal reflexes, normal coordination, normal gait.

Case Study: Mary Visits the Clinic

Steps in the evaluation:

Formulating the differential diagnosis

synthesize all the data

consider all possible causes of her problems

-what diagnoses are you considering now?

- what would you like to do to support them?

Case Study: Mary Visits the Clinic

Steps in the evaluation:

Formulating the differential diagnosis

synthesize all the data

consider all possible causes

1) depression in the context of a change in social environment

2) possible obstructive sleep apnea

3) doubt seizures

Formulate a plan to support your diagnoses.

Case Study: Mary Visits the Clinic

Steps in the evaluation:

Plan for additional evaluations:

F/U visit – in 3 months

-screening laboratory studies – e.g. CBC, Metabolic panel, thyroid function tests, +/- B12 and folate

-others as appropriate – sleep studies, EEG, vision/hearing, EKG, MRI

- baseline formal psychometric/behavioral/functional testing (e.g. cognition:Dementia Scale for DS, DS Mental Status Exam [DS-MSE], Cambridge Examination for Mental Disorders of Older People with DS, Severe Impairment Battery, Dementia Questionnaire for People with Learning Disabilities [DLD]; function:Vineland 3; mood/behavior: Neuropsychiatric Inventory).

Case Study: Mary Visits the Clinic

Treatment: 1) Counsel Mary's mother and sister about your tentative diagnosis.

2) Discuss the possible impact of sister leaving the family home. Offer suggestions to enhance their connection.

3) Review study results and treat as indicated.

4) Consider an antidepressant (SSRI) after baseline testing.

3) Results of sleep study may indicate utility of CPAP for combatting obstructive sleep apnea

4) Inquire about staring at F/U visit

Regression Syndrome

- Adolescents and young adults with DS. (Females:Males: 2:1).
- Subacute onset of mood lability, decreased participation in activities of daily living, new-onset insomnia, social withdrawal, autistic-like regression, language regression (from lack of fluency to mutism), delusions, hallucinations, and changes in motor function.
- Regression for about 6 months, then stable, then possible recovery.
- No well established diagnostic standards.
- Possible causes: autoimmune disorders, psychological stress, underlying predisposition for a psychiatric disorder.
- Treatment: none proven.

Alzheimer Disease vs Regression

What is similar?

- Both involve decline in skills
- Both are neurological conditions that often have psychological symptoms
- Both are challenging for the individual and families
- Both need more research, including ways to support the individual and family

What is different?

- Alzheimer's disease
  - Age of onset = > 40
  - Not reversible
- Regression syndrome
  - Age of onset = teens, early 20s
  - Sometimes reversible
- Not all decline in skills in those age ranges is either Alzheimer's disease or regression

Brian Chicoine

Adult DS Care Guidelines

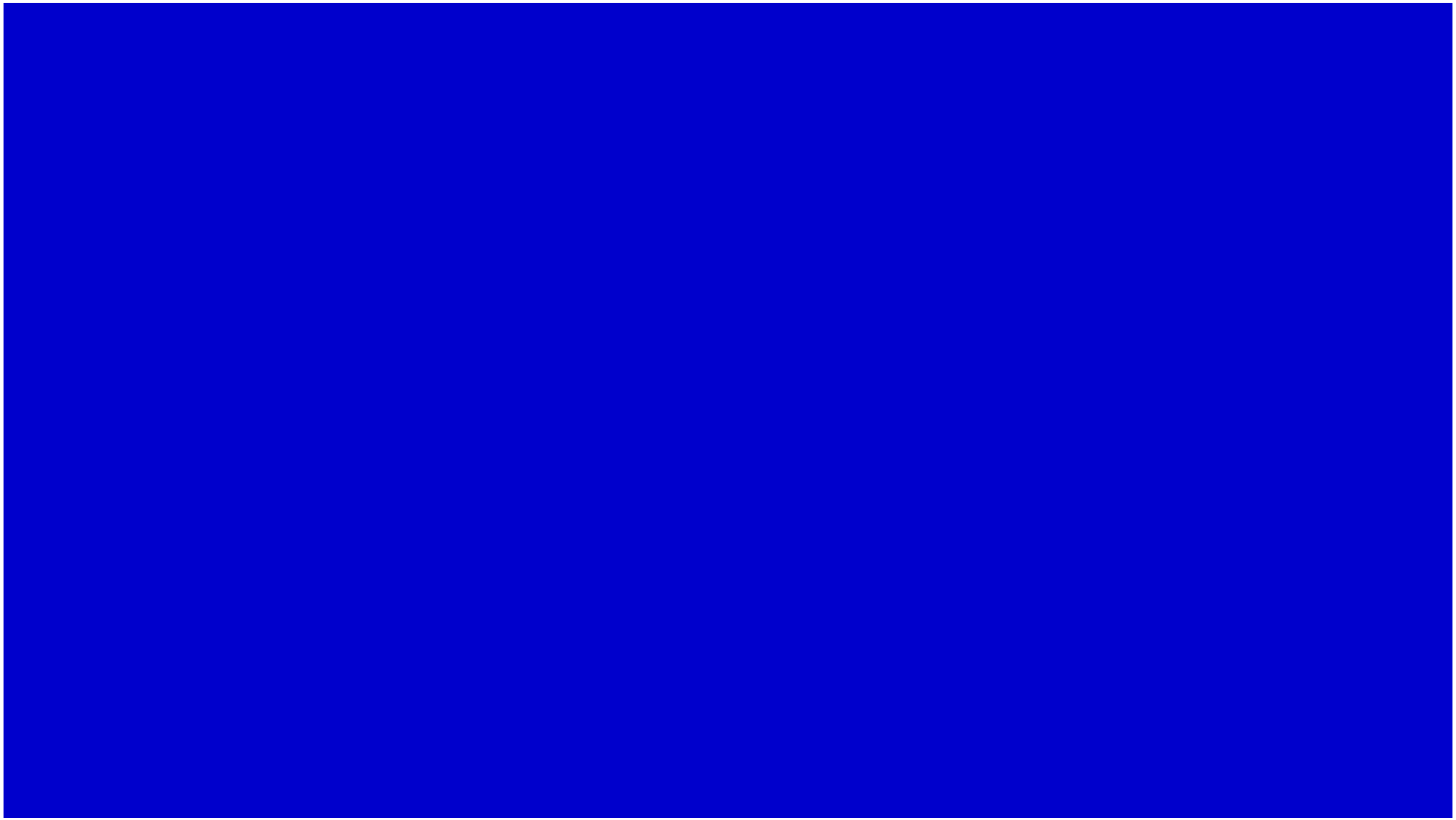
Table 1. Recommendations and Statements of Good Practice

Recommendation/statement of good practice	Strength of recommendation	Confidence in quality of evidence
Recommendations		
Behavior		
Recommendation 1. When concern for a mental health disorder in adults with Down syndrome is present, medical professionals should refer to a clinician knowledgeable about the medical, mental health disorders, and common behavioral characteristics of adults with Down syndrome	Weak	Very low
Recommendation 2. When concern for a mental health disorder in adults with Down syndrome is present, medical professionals should follow guidelines for diagnosis in the *DSM-5*[37]; the *DM-ID-2*[38] also may be used to adapt diagnostic criteria from the *DSM-5*	Weak	Very low
Dementia		
Recommendation 3. Caution is needed when diagnosing age-related, Alzheimer-type dementia in adults with Down syndrome younger than 40 y because of its low prevalence before this age	Weak	Low
Recommendation 4. Medical professionals should assess adults with Down syndrome and interview their primary caregivers about changes from baseline function annually beginning at age 40 y; decline in the following 6 domains as per the NTG-EDSD[39] should be used to identify early-stage age-related Alzheimer-type dementia and/or a potentially reversible medical condition: • Cognition, memory, and executive function • Behavior and personality • Communication • Adaptive functioning • Ambulation and motor skills • General decline in established skills	Strong	Moderate

Tsou et al., JAMA. 2020

Caring for Adults with DS in Neurology Clinic

- Adults with DS experience a number of changes in brain function.
- Clinicians with experience in the management of adults with DS are aware of conditions that can impact learning, memory, and mood.
- Clinicians carefully consider the possible causes of neurologic dysfunction.
- Though AD is more common in those with DS, a thorough evaluation is indicated to rule out other, often treatable, causes for changes in cognition and behavior.



Studies Employed in Life-DSR

Cognitive measures:

- Severe Impairment Battery (SIB) with the Shoebox test. If the participant achieves a score 60 or above on the SIB, the Down Syndrome Mental Status Examination (DS-MSE) will also be administered.

Functional measures:

- Vineland-3

Behavioral measures:

- Dementia Questionnaire for Persons with Learning Disabilities (DLD)
- Neuropsychiatric Inventory (NPI)