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Medical Care of Adults With Down Syndrome
A Clinical Guideline

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IMPORTANCE Down syndrome is the most common chromosomal condition, and average life expectancy has increased substantially, from 25 years in 1983 to 60 years in 2020. Despite the unique clinical comorbidities among adults with Down syndrome, there are no clinical guidelines for the care of these patients.

OBJECTIVE To develop an evidence-based clinical practice guideline for adults with Down syndrome.

EVIDENCE REVIEW The Global Down Syndrome Foundation Medical Care Guidelines for Adults with Down Syndrome Workgroup (n = 13) developed 10 Population/Intervention/Comparison/Outcome (PICO) questions for adults with Down syndrome addressing multiple clinical areas including mental health (2 questions), dementia, screening or treatment of diabetes, cardiovascular disease, obesity, osteoporosis, atlantoaxial instability, thyroid disease, and celiac disease. These questions guided the literature search in MEDLINE, EMBASE, PubMed, PsychINFO, Cochrane Library, and the TRIP Database, searched from January 1, 2000, to February 26, 2018, with an updated search through August 6, 2020. Using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology and the Evidence-to-Decision framework, in January 2019, the 13-member Workgroup and 16 additional clinical and scientific experts, nurses, patient representatives, and a methodologist developed clinical recommendations. A statement of good practice was made when there was a high level of certainty that the recommendation would do more good than harm, but there was little direct evidence.

FINDINGS From 11 295 literature citations associated with 10 PICO questions, 20 relevant studies were identified. An updated search identified 2 additional studies, for a total of 22 included studies (3 systematic reviews, 19 primary studies), which were reviewed and synthesized. Based on this analysis, 14 recommendations and 4 statements of good practice were developed. Overall, the evidence base was limited. Only 1 strong recommendation was formulated: screening for Alzheimer-type dementia starting at age 40 years. Four recommendations (managing risk factors for cardiovascular disease and stroke prevention, screening for obesity, and evaluation for secondary causes of osteoporosis) agreed with existing guidance for individuals without Down syndrome. Two recommendations for diabetes screening recommend earlier initiation of screening and at shorter intervals given the high prevalence and earlier onset in adults with Down syndrome.

CONCLUSIONS AND RELEVANCE These evidence-based clinical guidelines provide recommendations to support primary care of adults with Down syndrome. The lack of high-quality evidence limits the strength of the recommendations and highlights the need for additional research.

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Supplemental content

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Down syndrome is the most common chromosomal condition[1] and in 2010-2014 occurred in 1 of every 700 live births in the US.[1] Individuals with Down syndrome have a significantly lower risk for some conditions, including solid malignancies, but a higher risk for other conditions, including congenital cardiac conditions, autoimmune diseases, and Alzheimer disease. Average life expectancy for people with Down syndrome has substantially increased, from 25 years in 1983[2] to 60 years in 2020.[3] According to one estimate, the number of people with Down syndrome living in the US was approximately 206 000 in 2010,[4] although exact and current prevalence is unknown because of lack of data, changing survival rates across decades, and trends in live births vs termination rates.

Because individuals with Down syndrome are living longer, guidance is needed to support high-quality care. Although guidelines based on expert opinion exist,[5,6] evidence-based clinical practice guidelines (CPGs) for adults with Down syndrome have not been developed. This Special Communication presents a clinical guideline with recommendations to support high-quality primary care for adults with Down syndrome.

Methods

The Global Down Syndrome Foundation (GLOBAL), a nonprofit in the US dedicated to improving the lives of people with Down syndrome through research, medical care, education and advocacy, recruited expert Down syndrome clinicians, many of whom are members of the Down Syndrome Medical Interest Group–USA, and the ECRI (originally the Emergency Care Research Institute) Evidence-based Practice Center to form the Global Medical Care Guidelines for Adults with Down Syndrome Workgroup (Workgroup) and create an evidence-based CPG for clinicians, adults with Down syndrome, and families/caregivers.

In 2017, the 13-member Workgroup (11 Down syndrome experts, 1 ECRI guideline methodologist, and 1 parent representative/advocacy leader and expert from GLOBAL) convened a 29-member committee, including all 13 members of the Workgroup plus 16 volunteers (listed at the end of this article). There was consensus among Workgroup members that these guidelines should provide guidance to support primary care clinicians in caring for adults with Down syndrome. The 29 experts were assigned to 9 committees representing the 9 topic areas prioritized for inclusion in these guidelines: behavior, dementia, diabetes, cardiac disease, obesity, atlantoaxial instability, osteoporosis, thyroid disease, and celiac disease. Workgroup members prioritized clinical topics for consideration and developed 10 questions using the standardized Population/Intervention/Comparator/Outcome (PICO) format (summaries of the full-length PICO questions are reported in **Box 1**).

Clinicians caring for adults with Down syndrome must often decide in what situations "standard" guidelines for adults without Down syndrome (such as US Preventive Services Task Force [USPSTF]recommendations) should be followed. For most of the key questions, the Workgroup anticipated that limited published research would include adults with Down syndrome. Thus, several PICO questions sought to identify differences in disease prevalence between adults with Down syndrome and the

Box 1. Population/Intervention/Comparator/Outcome (PICO) Questions[a]

Behavioral Health (PICO 1 and PICO 2)

PICO 1: In adults with Down syndrome, do clinical symptoms of depression, OCD, mood disorder, catatonia, GAD, and regression/disintegrative disorder differ from the general population?

PICO 2: In adults with Down syndrome, does performing a psychosocial assessment (by clinical assessment or by caregiver or patient questionnaire) to screen for mental health disorders (such as depression, anxiety, OCD, psychosis/regression/disintegrative disorder) improve recognition and diagnosis of medical conditions or health outcomes?

Dementia (PICO 3)

What is the prevalence of dementia in adults with Down syndrome by decade?

Diabetes (PICO 4)

A. What is the prevalence of diabetes (type 1 or 2) in adults with Down syndrome compared with the general population (by decade)?
B. Does screening asymptomatic adults with Down syndrome for diabetes improve cardiovascular outcomes, diabetic comorbidities, and functional outcomes?
C. Does screening adults with Down syndrome and obesity (BMI ≥30) more often improve outcomes (cardiovascular, diabetic comorbidities, and functional outcomes?

Cardiovascular Disease (PICO 5)

A. What is the prevalence of coronary artery disease and stroke secondary to atherosclerosis in adults with Down syndrome (compared with the general population)?
B. In adults with Down syndrome and hyperlipidemia, does treatment of total cholesterol, LDL-C, or triglycerides improve clinical outcomes?

Obesity (PICO 6)

A. Are treatments for obesity safe and effective for reducing complications of obesity (obstructive sleep apnea, joint pain, heart disease, diabetes, mental health problems) or improving quality of life in adults with Down syndrome?
B. What target BMI is optimal for reducing comorbidities of obesity in adults with Down syndrome?

Atlantoaxial Instability (PICO 7)

A. What is the prevalence of atlantoaxial instability in asymptomatic adults with Down syndrome (compared with the general population)?
B. Does screening with imaging (radiography, CT, MRI) asymptomatic (ie, no symptoms or examination findings) adults with Down syndrome for atlantoaxial instability improve outcomes?

Osteoporosis (PICO 8)

A. What is the prevalence of osteopenia, osteoporosis, spinal compression, hip or femur fractures in Down syndrome (by decade of life) compared to general population?
B. What is the clinical utility of screening asymptomatic adult patients with Down syndrome with DEXA (to detect osteopenia or osteoporosis)?
C. In adults with Down syndrome and no known history of low bone density, do lifestyle factors or serum markers (vitamin D, calcium, PTH, or thyrotropin) predict diagnosis of osteopenia, osteoporosis or fracture?
D. What pharmacological treatments are effective for prevention of osteoporotic fractures in adults with Down syndrome?

(continued)

Box 1. (continued)

Thyroid (PICO 9)

A. What is the prevalence of hypothyroidism in adults with Down syndrome by decade?
B. What is the diagnostic accuracy of thyrotropin, free thyroxine, and antithyroid antibodies for hypothyroidism in asymptomatic adults with Down syndrome?
C. Does treating elevated thyrotropin levels in asymptomatic adults with Down syndrome improve clinical or functional outcomes?
D. What is the clinical utility of using antithyroid antibodies to screen for thyroid disease in adults with Down syndrome and autoimmune disease (celiac disease, rheumatoid arthritis, lupus, alopecia areata)?

Celiac Disease (PICO 10)

A. What is the accuracy of tTG-IgA or total IgA (compared with duodenal biopsy) for diagnosing celiac disease in adults with Down syndrome?
B. What is the clinical utility of screening asymptomatic adults with Down syndrome for celiac disease using tTG-IgA or total IgA?
C. Does HLA antigen haplotype DQ2 or DQ8 predict risk of developing celiac disease in adults with Down syndrome?
D. Does a gluten-free diet improve symptoms in adults with Down syndrome and celiac disease?

Abbreviations: BMI, body mass index; CT, computerized tomography; DEXA, dual-energy x-ray absorptiometry; GAD, generalized anxiety disorder; HLA, human leukocyte antigen; IgA, immunoglobulin A; LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; OCD, obsessive-compulsive disorder; PTH, parathyroid hormone; tTG-IgA, tissue transglutaminase IgA.

[a] Questions presented here are an abbreviated summary of full-length PICO questions developed for the systematic review.

general population to inform where existing clinical recommendations might warrant modification. The PICO format was used for all questions; however, for questions focused on prevalence, the PICO category of "intervention" was not applicable. Questions targeting prevalence did include population and outcome, along with a comparator if the comparative prevalence was addressed.

Using these PICO questions, ECRI performed a systematic review. A medical librarian performed a comprehensive literature search in MEDLINE, EMBASE, PubMed, PsycINFO, the Cochrane Library, and the TRIP database from January 1, 2000, to February 26, 2018. Titles and abstracts were screened, followed by a full-text assessment based on predefined inclusion/exclusion criteria. Detailed PICO questions, search strategies, and selection criteria are reported in eMethods 1 and eMethods 2 in Supplement 1. An updated literature search was performed on August 6, 2020; 2 additional articles were identified and included.

To conduct the literature review, a "best evidence" approach was used, which has previously been used for systematic reviews underpinning CPGs.[7,8] For each PICO question, we identified any relevant previously published English-language systematic reviews rated as good quality as per USPSTF criteria.[9] If multiple relevant systematic reviews were identified, the most recent, relevant, and comprehensive (eg, the review with the most high-quality studies) was selected for inclusion to avoid multiple ratings of a similar evidence base. If no relevant systematic reviews met those criteria, relevant studies were identified with the highest-quality study designs (eg, randomized clinical trials for intervention PICOs). If no studies were identified that focused on a specific question, lower-quality studies (eg, observational studies) were considered for inclusion. For example, for PICOs that addressed prevalence (prevalence addressed varies by PICO question), observational studies with 300 or more adults with Down syndrome were sought. However, if no studies met these criteria, studies with fewer patients (eg, $n \geq 100$) were included.

Data regarding study design, population characteristics, intervention(s), prevalence estimates, and outcome measures were extracted from all included studies, and a narrative synthesis (qualitative synthesis of evidence) was performed. Study quality for individual studies was assessed using USPSTF methods except for prevalence studies, which were assessed using prespecified items (see eMethods 2 in Supplement 1). Overall quality of evidence for each outcome was assessed using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.[10]

The 13-member Workgroup participated in a 3-day in-person meeting from January 23 to 25, 2019. A patient advocate and families (n = 3) were also present for selected sessions. Workgroup members reviewed evidence from the systematic review and used the GRADE Evidence-to-Decision framework to formulate recommendations.[11,12] This framework uses 4 domains to determine a recommendation's strength (strong or weak): (1) balance of desirable and undesirable outcomes, (2) confidence in evidence quality, (3) patient values and preferences, and (4) other implications (including equity, feasibility, and subgroup considerations).[10] A strong recommendation indicates a high or moderate confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, and similar values and preferences, along with consideration of other implications.

If the Workgroup had less confidence after assessment across these domains and determined that additional evidence could change the recommendation, it generally assigned a weak recommendation. A statement of good practice (SOGP) was made when there was a high level of certainty, based on clinical assessment of anticipated benefits and harms, that the recommendation would do more good than harm but there was little direct evidence.[13] The Workgroup's consideration of each domain for every recommendation included in this guideline is reported in eTable 1 in Supplement 1.

After recommendations were drafted, Workgroup members voted with verbal assent (or dissent) to adopt (or reject) the recommendation. If unanimous consent was not present, objections and suggested modifications to the recommendation were discussed and another vote was taken. In the event unanimous consent could not be reached, a two-thirds majority of Workgroup members was required for the recommendation to be adopted. Disclosures and potential conflicts of interest for all Workgroup members were obtained and updated throughout the process.

For key questions for which no direct evidence was identified in the patient population (ie, adults with Down syndrome),

Workgroup members considered additional indirect evidence from other patient populations (eg, children with Down syndrome, people with intellectual disability) and arrived at consensus regarding whether evidence was "direct enough" to inform care for adults with Down syndrome. This approach has been used to develop evidence-based CPGs in contexts with limited direct evidence.[14]

To obtain input from patients and caregivers, a 7-day online focus group was conducted in October 2019 and included 7 adults with Down syndrome and 27 caregivers (including parents and siblings), to solicit feedback on draft recommendations, usability, importance, and areas requiring clarification. In addition, the draft guidelines were reviewed by 7 members of the American Academy of Developmental Medicine and Dentistry. All feedback was reviewed, and updates were incorporated by the Workgroup. The full guidelines, complete methods, systematic review, and implementation tools are available in eAppendix 1 in Supplement 2 or at https://www.globaldownsyndrome.org/global-adult-guidelines/.

Since creation of these guidelines did not involve human participants in research, this project was determined to be exempt from institutional review board (IRB) approval as confirmed by the Colorado Multiple IRB.

Results

Searches identified 11 295 citations, of which the systematic review included 20 studies (3 systematic reviews[15-17] and 17 primary studies, including 1 randomized clinical trial,[18] 4 cohort studies,[19-22] 11 cross-sectional studies,[23-33] and 1 case series).[34] An updated literature search on August 6, 2020, identified 2 additional cross-sectional studies[35,36] relevant to recommendations (eFigure 1 and eTable 2 in Supplement 1). No studies addressing PICO 2 (efficacy of psychosocial assessment for recognition of mental or health conditions) were identified. Fourteen recommendations and 4 SOGPs were formulated (**Table 1**). A 1-page checklist tool summarizing all recommendations and SOGPs for families/caregivers to easily track care and support adherence with the guideline recommendations was also created (eFigure 2 in Supplement 1).

Diagnosis and Treatment of Behavioral Health Conditions

Recommendation 1

When concern for a mental health disorder in adults with Down syndrome is present, medical professionals should refer the patient to a clinician knowledgeable about the medical, mental health disorders, and common behavioral characteristics of adults with Down syndrome.

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 *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*).[37] The *Diagnostic Manual–Intellectual Disability 2: A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability* (*DM-ID-2*)[38] also may be used to adapt diagnostic criteria from the *DSM-5*.

Evidence Summary

No studies directly compared symptoms in adults with Down syndrome with the general population. However, 1 systematic review[15] included 3 cross-sectional studies that described symptoms of unipolar depression. Individuals with Down syndrome who met criteria for major depressive episodes had common symptoms (anhedonia, depressed mood, and disturbed sleep) but also hallucinations, and a subset presented with a "deficit" syndrome (apathy, abulia, anhedonia, and mutism) without obvious mood changes or psychosis. A case series (n = 30) reported that symptoms of patients with Down syndrome with regression included changes in mood, behavior, and psychotic symptoms.[34] Confidence in the quality of evidence was very low.

Rationale for Recommendation 1

Behavioral and mental health conditions are common in Down syndrome and many clinicians are not familiar with distinctive behaviors in this population, which differ from those in the general population. Thus, despite very low confidence in quality of evidence, the potential benefits, including identifying salient psychosocial issues requiring attention, avoiding misdiagnosis of adaptive behavior as a disorder, and limiting unnecessary use of psychotropic medications, warranted a weak recommendation for referral to medical professionals familiar with the common behaviors and presentation of medical and mental health conditions in adults with Down syndrome.

Rationale for the Recommendation 2

In the absence of tools validated specifically for Down syndrome, given distinctive challenges of diagnosing mental health disorders, clinicians should use the *DSM-5* complemented by the *DM-ID-2*, an expert consensus tool helpful in recognizing mental health disorders in people with intellectual and developmental disabilities.

Statements of Good Practice 1 and 2 and Rationale

A review of behavioral, functional, adaptive, and psychosocial factors should be performed as part of an annual history that clinicians obtain from all adults with Down syndrome, their families, and caregivers (SOGP 1).

When concern for a mental health disorder in adults with Down syndrome is present, medical professionals should evaluate patients for medical conditions that may present with psychiatric and behavioral symptoms (SOGP 2).

Diagnosis of Dementia

Recommendation 3

Caution is needed when diagnosing age-related, Alzheimer-type dementia in adults with Down syndrome younger than 40 years because of its low prevalence before this age.

Recommendation 4

Medical professionals should assess adults with Down syndrome and interview primary caregivers about changes from baseline function annually, beginning at age 40 years. Decline in 6 domains specified by the National Task Group–Early Detection Screen for Dementia (NTG-EDSD)[39] should be used to identify early-stage age-related Alzheimer-type dementia, a potentially reversible medical condition, or both.

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
Diabetes		
Recommendation 5. For asymptomatic adults with Down syndrome, screening for type 2 diabetes using HbA1c or fasting plasma glucose should be performed every 3 y beginning at age 30 y	Weak	Moderate
Recommendation 6. For any adult with Down syndrome and comorbid obesity, screening for type 2 diabetes using HbA1c or fasting plasma glucose should be performed every 2-3 y beginning at age 21 y	Weak	Moderate
Cardiovascular disease		
Atherosclerotic cardiovascular disease		
Recommendation 7. For adults with Down syndrome without a history of ASCVD, the appropriateness of statin therapy should be assessed every 5 y starting at age 40 y and using a 10-y risk calculator as recommended for adults without Down syndrome by the USPSTF[40]	Weak	Low
Stroke		
Recommendation 8. For adults with Down syndrome, risk factors for stroke should be managed as specified by the American Heart Association/American Stroke Association guidelines for the primary prevention of stroke[41]	Weak	Very low
Recommendation 9. In adults with Down syndrome with a history of congenital heart disease, given the elevated risk of cardioembolic stroke, a periodic cardiac evaluation and a corresponding monitoring plan should be reviewed by a cardiologist	Weak	Very low
Obesity		
Recommendation 10. Monitoring for weight change and obesity should be performed annually by calculating BMI in adults with Down syndrome; the USPSTF behavioral weight loss interventions to prevent obesity-related morbidity and mortality in adults should be followed[42]	Weak	Very low
Atlantoaxial instability		
Recommendation 11. In adults with Down syndrome, routine cervical spine radiographs should not be used to screen for risk of spinal cord injury in asymptomatic individuals; instead, annual screening of adults with Down syndrome should include signs and symptoms of cervical myelopathy using targeted history and physical examination	Weak (against)	Very low
Osteoporosis		
Recommendation 12. For primary prevention of osteoporotic fractures in adults with Down syndrome, there is insufficient evidence to recommend for or against applying established osteoporosis screening guidelines, including fracture risk estimation; thus, good clinical practice would support a shared decision-making approach to this issue	Neither for nor against	NA
Recommendation 13. All adults with Down syndrome who sustain a fragility fracture should be evaluated for secondary causes of osteoporosis, including screening for hyperthyroidism, celiac disease, vitamin D deficiency, hyperparathyroidism, and medications associated with adverse effects on bone health	Weak	Very low
Thyroid		
Recommendation 14. Screening adults with Down syndrome for hypothyroidism should be performed every 1-2 y using a serum thyrotropin test beginning at age 21 y	Weak	Moderate

(continued)

Table 1. Recommendations and Statements of Good Practice (continued)

Recommendation/statement of good practice	Strength of recommendation	Confidence in quality of evidence
Statements of good practice[a]		
Behavior		
Statement 1. A review of behavioral, functional, adaptive, and psychosocial factors should be performed as part of an annual history that clinicians obtain from all adults with Down syndrome, their families, and caregivers		
Statement 2. When concern for a mental health disorder in adults with Down syndrome is present, medical professionals should evaluate for medical conditions that may present with psychiatric and behavioral symptoms		
Obesity		
Statement 3. Healthy diet, regular exercise, and calorie management should be followed by all adults with Down syndrome as part of a comprehensive approach to weight management, appetite control, and enhancement of quality of life		
Celiac disease		
Statement 4. Adults with Down syndrome should receive an annual assessment for gastrointestinal and nongastrointestinal signs and symptoms of celiac disease using targeted history, physical examination, and clinical judgment of good practice		

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; *DM-ID-2*, *Diagnostic Manual-Intellectual Disability 2: A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability*; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); HbA_{1c}, glycated hemoglobin; NTG-EDSD, National Task Group—Early Detection Screen for Dementia; USPSTF, US Preventive Services Task Force.

[a] Statements of Good Practice are made when there is a high level of certainty a recommendation will do more good than harm but there is little supporting direct evidence. As per GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology, statements of good practice are not assigned a formal strength rating.

Evidence Summary

One moderate-quality Dutch study[23] (n = 506 adults with Down syndrome) found dementia prevalence of 8.9% (95% CI, 5%-12%) in 45- to 49-year-olds; prevalence increased every 5 years to 32.1% (95% CI, 22%-42%) in 55- to 59-year-olds and decreased to 25.5% (95% CI, 12%-40%) in patients 60 years or older. An additional study (n = 878 adults with Down syndrome)[35] reported increasing prevalence of dementia in adults with Down syndrome older than 45 years and 40% prevalence after age 45, but dementia diagnosis was based on administrative data. One low-quality study from Spain and the UK[36] (n = 388) also reported increasing prevalence rates for dementia in adults with Down syndrome after age 40 years, with rates rising from approximately 10% (for 40- to 45-year-olds) up to 90% to 100% (for 65- to 70-year-olds).

Three studies assessed prevalence in patients younger than 40 years.[19,24,36] However, only 1 study[36] (n = 388) used a validated measure for diagnosis and reported 0% prevalence in adults with Down syndrome aged 30 to 39 years. Two additional large studies (n > 5000 adults with Down syndrome)[19,24] did not confirm diagnosis based on validated tests but found similar low prevalence in younger adults (18-39 years). Confidence in the quality of evidence was low for prevalence in patients younger than 40 years but moderate for those older than 45 years.

Rationale for Recommendation 3

Because clinicians may attribute symptoms of Down syndrome to Alzheimer-type dementia without adequately considering alternative causes, a weak recommendation suggests that clinicians should exercise caution when attributing symptoms to Alzheimer-type dementia in adults with Down syndrome younger than 40 years. Benefits of considering other causes, including treatable conditions (eg, hypothyroidism, sleep apnea), significantly outweighed potential harms (underdiagnosis of true Alzheimer-type dementia).

Rationale for Recommendation 4

Because dementia prevalence increases after age 40 years, adults with Down syndrome and primary caregivers should be interviewed annually beginning at age 40 to establish a baseline and identify changes in baseline function in the adult with Down syndrome, which could suggest potential Alzheimer-type dementia. The justification was based on the benefits of early identification of dementia, treatment of potentially reversible causes of cognitive decline, or both, which outweigh potential harms associated with more testing.

Despite absence of disease-modifying dementia treatments, most adults with Down syndrome and their families/caregivers place high value on early diagnosis, accurate diagnosis, or both to modify existing supports and allow for additional resource planning. Individuals with mild to moderate dementia will typically have changes across multiple domains (memory and executive function, behavior and personality, language and communication, gait and motor skills, activities of daily living, continence, and sleep patterns) as described in the NTG-EDSD,[39] which was developed for dementia diagnosis in individuals with intellectual disability.

Diabetes

Recommendation 5

For asymptomatic adults with Down syndrome, screening for type 2 diabetes using glycated hemoglobin or fasting plasma glucose levels should be performed every 3 years beginning at age 30 years.

Recommendation 6

For any adult with Down syndrome and comorbid obesity, screening for type 2 diabetes using glycated hemoglobin or fasting plasma

glucose level should be performed every 2 to 3 years beginning at age 21 years.

Evidence Summary

One population-based study in the UK[19] (n = 3808) found that diabetes prevalence was higher in adults with Down syndrome compared with general population–matched controls (3.5% vs 0.7%, respectively, for ages 16 to 30 years and 5.5% vs 2.7%, respectively, for 30 years or older). Confidence in the quality of evidence was rated moderate.

Rationale for Recommendations 5 and 6

The American Diabetes Association (ADA) recommends screening for abnormal blood glucose level and type 2 diabetes in all adults beginning at age 45 years.[43] Given risks associated with premature aging in adults with Down syndrome (with increased risk for cataracts and kidney and peripheral nervous system damage),[44-46] screening should be initiated earlier, beginning at age 30 years and to be repeated every 3 years if results of blood glucose screening are normal (weak recommendation).

The ADA recommends that individuals who are overweight or obese (body mass index [BMI] ≥25, calculated as weight in kilograms divided by height in meters squared) and with 1 additional risk factor begin screening for abnormal blood glucose levels every 3 years and for type 2 diabetes after puberty.[43] Because obesity is common in Down syndrome and associated with increased risk for diabetes, for adults with Down syndrome and obesity, screening should be initiated at age 21 years and repeated every 2 to 3 years with or without the presence of an additional risk factor outlined by the ADA (weak recommendation). Benefits of earlier identification and management of diabetes were judged to outweigh potential harms of obtaining laboratory testing and potential for overtreatment (eg, hypoglycemia).

Cardiovascular Disease Prevention

Recommendation 7

For adults with Down syndrome without a history of atherosclerotic cardiovascular disease (ASCVD), the appropriateness of statin therapy should be assessed every 5 years starting at age 40 years and using a 10-year risk calculator as recommended by the USPSTF for adults without Down syndrome.[40]

Evidence Summary

No studies assessed whether treatment to reduce levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), or triglycerides improve clinical outcomes. However, an Australian study[20] that compared hospitalized patients with Down syndrome (n = 1706) with age-matched controls (n = 6828) found that in patients 50 years or younger myocardial infarction events were similar, but in patients 51 years or older (n = 1845) events were reduced in adults with Down syndrome (8.1% for those with Down syndrome vs 13.3% for controls). A second UK study[19] (n = 3808) also reported a mildly lower incidence of ischemic heart disease in adults with Down syndrome compared with controls (absolute annual incidence per 100 person-years for Down syndrome of all ages was 0.19 [95% CI, 0.15-0.25] with an incidence rate ratio of 0.9 compared with matched controls). For those older than 30 years (50.5% of the study population) the absolute rate was 0.28 (95% CI, 0.21-0.38), with an incidence rate ratio of 0.8 and an overall prevalence of 1.5% for adults with Down syndrome 30 years or older.[19] True incidence of ASCVD may be even lower because the study did not distinguish between atherosclerotic ischemia vs nonatherosclerotic ischemia due to conditions such as sleep apnea, congenital heart disease, and pulmonary hypertension, all of which the study found were more common in Down syndrome. Confidence in the quality of the evidence was low.

Rationale for Recommendation 7

No studies evaluated if elevated lipid levels are predictive of ASCVD for adults with Down syndrome. While limited available evidence suggests a reduced risk of ASCVD, given very low certainty in effect size estimates, there was insufficient justification to recommend adults with Down syndrome be treated differently. Altogether, benefits of treating potential atherosclerotic events slightly outweighed potential harms including adverse events associated with statin therapy and polypharmacy. Thus, USPSTF guidance (using a 10-year risk calculator and personalizing lipid goals) should be followed (weak recommendation).

The American Board of Internal Medicine Choosing Wisely campaign, in cooperation with the AMDA—The Society for Post-Acute and Long-Term Care Medicine (2017), recommends against routinely prescribing lipid-lowering medications in individuals with limited life expectancy.[47] Weighing the ideal time to discontinue screening and treatment for individuals with Down syndrome may also involve consideration of shorter average life expectancy (60 years) for adults with Down syndrome.[48]

Stroke Prevention

Recommendation 8

For adults with Down syndrome, risk factors for stroke should be managed as specified by the American Heart Association/American Stroke Association's (AHA/ASA) Guidelines for the Primary Prevention of Stroke.[41]

Recommendation 9

In adults with Down syndrome with a history of congenital heart disease, given the elevated risk of cardioembolic stroke, a periodic cardiac evaluation and a corresponding monitoring plan should be reviewed by a cardiologist.

Evidence Summary

One Australian study[20] compared strokes in hospitalized adults with Down syndrome (n = 1706) with those in matched controls (n = 6828). Adults with Down syndrome had more strokes across both age groups: 1.8% vs 0.5% (ages 19-50 years) and 9.8% vs 4.9% (age ≥51 years) ($P < .05$ for both comparisons). On average, strokes occurred at a younger age in adults with Down syndrome compared with controls (mean age, 41.8 vs 57.1 years), with cardioembolic strokes being most common. Confidence in the quality of the evidence was very low.

Rationale for Recommendations 8 and 9

Given increased risk of cardioembolic stroke in adults with Down syndrome, the established guidelines for risk factor management for stroke prevention should be followed as specified in the AHA/ASA guidelines (weak recommendation). Typical risk factors such as hypertension are uncommon in Down syndrome,[19] while moyamoya

disease,[49] obstructive sleep apnea,[50,51] and congenital heart disease are more common. As many as 50% of children with Down syndrome are born with congenital heart disease, which increases the risk of cardioembolic stroke.[52,53] Thus, all patients with a history of congenital heart disease should receive a cardiac evaluation and monitoring plan reviewed by a cardiologist (weak recommendation).

Obesity Screening and Management

Recommendation 10

Monitoring for weight change and obesity should be performed annually by calculating BMI in adults with Down syndrome. The USPSTF recommendation for behavioral weight loss interventions to prevent obesity-related morbidity and mortality in adults should be followed.[42]

Evidence Summary

Three randomized clinical trials (RCTs) from 2 systematic reviews[16,17] assessed exercise interventions in obese adults with Down syndrome (n = 84). Mentored physical activity had no effect on weight or waist circumference at 9 weeks,[16] and aerobic exercise and progressive resistance exercise had no effect on weight at 9 to 12 weeks (Cohen d, 0.09; $P = .37$).[17] Quality of evidence was rated very low. Studies excluded patients with orthopedic conditions, cardiac disease, or metabolic disease, further limiting applicability. These studies reported no adverse effects from physical activity[16] and no abnormal electrocardiogram findings (aerobic exercise or progressive resistance exercise). Quality of evidence for safety outcomes was rated moderate.

No studies assessed other interventions for obesity or the effect of various BMI targets for reducing comorbidities of obesity.

Rationale for Recommendation 10

USPSTF guidelines recommend referring obese adults to intensive, multicomponent behavioral interventions.[42] These trials in people with Down syndrome[16,17] did not provide sufficient justification to warrant differing from USPSTF guidance. First, trials did not assess multicomponent interventions but only exercise alone (potentially limiting efficacy). Second, many factors may contribute to obesity in Down syndrome, including medication adverse effects, conditions (hypothyroidism, obstructive sleep apnea), poor appetite-satiety control, and lack of physical activity. Because obesity is common, clinicians may not consider obesity a modifiable condition. However, weight loss or stabilization is possible through activity interventions such as swimming, dancing, or working with a personal trainer and through diet management, portion control, and consistency of mealtimes. Although trials failed to demonstrate benefit, they reported no adverse effects. Thus, given long-term harms of obesity, the benefits of monitoring for obesity with annual BMI and adhering to USPSTF guidance for adults outweighed potential harms.

Statement of Good Practice 3 and Rationale

Healthy diet, regular exercise, and calorie management should be followed by all adults with Down syndrome as part of a comprehensive approach to weight management, appetite control, and enhancement of quality of life (SOGP 3).

Although no interventions reviewed demonstrated effects on weight, obesity is a common concern in adults with Down syndrome. Adults with Down syndrome, families, and clinicians should support generally accepted practices for overall wellness.

Screening for Atlantoaxial Instability

Recommendation 11

In adults with Down syndrome, routine cervical spine radiographs should not be used to screen for risk of spinal cord injury (SCI) in asymptomatic individuals. Instead, annual screening of adults with Down syndrome should include a review of signs and symptoms of cervical myelopathy, such as altered gait, new incontinence, brisk reflexes, or clonus, using targeted history and physical examination.

Evidence Summary

No studies assessed utility of screening for atlantoaxial instability (AAI) with cervical spine radiographs. However, 2 cross-sectional studies reported prevalence of AAI. An Australian registry-based survey (n = 197) found that 8.1% (95% CI, 4.35%-11.9%) of adults with Down syndrome younger than 30 years had AAI.[25] A similar prevalence (11% [95% CI, 2.7%-19.5%]) was reported by a Spanish chart review (n = 144).[27] Neither study provided criteria used to establish AAI or presence of signs or symptoms of myelopathy. Confidence in the quality of evidence was very low.

Rationale for Recommendation 11

Cervical spine radiographs have been used to identify individuals with Down syndrome at risk for SCI with physical activity. Although AAI prevalence is approximately 10% in adults younger than 30 years,[25,27] no studies have assessed if radiographs are effective for identifying at-risk individuals or preventing SCI. While avoiding potential SCI is important, restricting asymptomatic individuals with AAI from participating in physical activities is also undesirable for reasons related to physical and psychological health. Additional indirect evidence has suggested that SCI from AAI is uncommon. A 1995 review from the American Academy of Pediatrics Committee on Sports Medicine noted only 41 well-documented, published cases of symptomatic AAI in adults with Down syndrome.[54] In addition, Special Olympics organizers report no spinal cord injuries from more than 50 000 individuals with Down syndrome who participated in Special Olympics activities over 20 years.[55]

Because the true risks of SCI are unknown, the benefits of allowing physical activity slightly outweighed the potential harms of SCI. Cervical radiographs should not be used to screen for AAI in asymptomatic individuals; instead, targeted history and physical examination should be used for evaluation of signs or symptoms of myelopathy (weak recommendation).

Adults with Down syndrome, and their families/caregivers, may differ in preferences to avoid risk of SCI; thus, a shared decision-making approach is endorsed that considers potential benefits and harms of restricting participation in high-risk activities, including but not limited to gymnastics, diving, skiing, and horseback riding.

Screening for Osteoporosis

Recommendation 12

For primary prevention of osteoporotic fractures in adults with Down syndrome, there is insufficient evidence to recommend for

or against applying established osteoporosis screening guidelines, including fracture risk estimation; thus, good clinical practice would support a shared decision-making approach.

Recommendation 13

All adults with Down syndrome who sustain a fragility fracture should be evaluated for secondary causes of osteoporosis, including screening for hyperthyroidism, celiac disease, vitamin D deficiency, hyperparathyroidism, and medications associated with adverse effects on bone health.

Evidence Summary

Only 6 small, poor-quality studies (total n = 796) reported prevalence for osteopenia, osteoporosis, or osteoporotic fracture in adults with Down syndrome, with wide-ranging prevalence estimates for osteoporosis (1.4% to 45.1%).[28-33]

No studies assessed utility of dual-energy x-ray absorptiometry (DEXA) screening or efficacy of pharmacological treatments for osteoporotic fracture prevention.

Rationale for Recommendations 12 and 13

Although the Fracture Risk Assessment Tool (FRAX) is typically used to assess fracture risk,[56] this model may not be applicable to adults with Down syndrome because it was derived from epidemiologic data from the general population. Populations with small body size or constitutionally short stature may require volumetric bone mineral density measurement or other adjustments for bone characteristics relevant to fracture risk.[57] Based on the available evidence, standard DEXA is not helpful for assessing risk of osteoporotic fracture in Down syndrome. Furthermore, reduced bone formation, rather than excessive bone resorption, may drive skeletal dynamics in adults with Down syndrome,[58] although this has not been consistently observed.[59] If true, bisphosphonates, which reduce bone resorption, may not be effective for individuals with Down syndrome. Given the absence of studies demonstrating benefit of DEXA screening and concerns regarding applicability of DEXA, to acknowledge the uncertainty, the recommendation is neither for nor against osteoporosis screening, noting that a shared decision-making approach should be used to incorporate patient and family preferences.

The 2016 American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guideline[60] for postmenopausal women with osteoporosis recommended evaluation for secondary causes of osteoporosis, some of which are common in Down syndrome. Given the low harms associated with testing, potential benefits of avoiding fragility fractures, and additional health benefits of treating relevant diseases, adults with Down syndrome who sustain a fragility fracture should receive an evaluation for secondary causes of osteoporosis such as hyperthyroidism, celiac disease, vitamin D deficiency, hyperparathyroidism, and medications with adverse effects on bone health (weak recommendation).

Screening for Thyroid Disease

Recommendation 14

Screening adults with Down syndrome for hypothyroidism should be performed every 1 to 2 years using a serum thyrotropin test beginning at age 21 years.

Evidence Summary

Three studies reported a similar high prevalence of hypothyroidism in adults with Down syndrome. A study from the UK[19] (n = 3808) found a prevalence of 39% (95% CI, 36%-42%) in adults with Down syndrome aged 18 to 29 years and 51% (95% CI, 49%-53%) in those 30 years or older. Two additional clinic-based studies performed in Spain[27] (n = 144) and the US[31] (n = 141) reported similar rates: 43% (ages 18-29 years) and 57% to 61% (age ≥30 years)[27]; 39% (ages 18-49 years) and 42% (age ≥50 years).[31] Confidence in the quality of evidence was moderate.

No studies assessed treating elevated thyrotropin levels in asymptomatic patients, the diagnostic accuracy of thyrotropin, free thyroxine or antithyroid antibodies, or the clinical utility of antithyroid antibodies to screen for thyroid disease in adults with Down syndrome and autoimmune disease.

Rationale for Recommendation 14

Symptoms of hypothyroidism are challenging to distinguish because weight gain and constipation are common in Down syndrome. Furthermore, adults with Down syndrome may have difficulty communicating fatigue or cold intolerance.

Prevalence of hypothyroidism in adults with Down syndrome is substantially higher (approximately 50% in adults older than 30 years[19]) compared with prevalence in US adults without Down syndrome,[61] and treatment may improve cognitive function and weight management. Thus, adults with Down syndrome should be screened for hypothyroidism every 1 to 2 years (weak recommendation).

Screening for Celiac Disease

Statement of Good Practice 4

Adults with Down syndrome should receive an annual assessment for gastrointestinal and nongastrointestinal signs and symptoms of celiac disease using targeted history, physical examination, and clinical judgment of good practice (SOGP 4).

Rationale for Statement of Good Practice 4

Celiac disease is more common in individuals with Down syndrome, with an estimated prevalence of 11% among people with Down syndrome.[27] However, diagnosis presents unique challenges because gastrointestinal and nongastrointestinal symptoms can be difficult to recognize. In addition, some gastrointestinal problems (eg, constipation, loose stools, and cramping) are common in Down syndrome. These may also be more challenging to identify, depending on communication skills. No studies assessed utility of screening asymptomatic adults with Down syndrome or efficacy of a gluten-free diet, and studies assessing diagnostic accuracy of tissue transglutaminase IgA and biopsy had significant flaws.[21,22]

Discussion

Providing care for the increasing number of adults with Down syndrome can be challenging, given their broad phenotypic variation in health and function. As the first, to our knowledge, evidence-based guideline for adults with Down syndrome, these recommendations provide guidance across a wide range of clinical conditions and support clinicians in providing high-quality medical care for adults with Down syndrome.

Table 2. Recommendations Compared With Existing Guidance

Recommendation	Existing guideline
Recommendations in Down syndrome guidelines concur with existing guidance for the general population	
Recommendation 7. Statin therapy for lowering cardiovascular risk for adults with Down syndrome	Agrees with USPSTF guidance for the general population, statin use for the primary prevention of cardiovascular disease in adults: preventive medication[40]
Recommendation 8. Managing risk factors for stroke prevention for adults with Down syndrome	Agrees with AHA/ASA guidelines for primary prevention of stroke[41] for the general population
Recommendation 10. Obesity screening for adults with Down syndrome	Agrees with USPSTF guidance for the general population, Behavioral Weight Loss Interventions to Prevent Obesity-Related Morbidity and Mortality in Adults[42]
Recommendation 13. Evaluating secondary causes of osteoporosis for adults with Down syndrome	Agrees with American Association of Clinical Endocrinologists/ American College of Endocrinology (2016) guideline,[60] Diagnosis and Treatment of Postmenopausal Osteoporosis for the General Population
Recommendations in Down syndrome guidelines differ from existing guidance for the general population	
Recommendation 5. Diabetes screening in asymptomatic individuals with Down syndrome	Recommendation (screen starting at age 30 y [instead of 45] every 3 y[43]) differs from ADA guidance for the general population
Recommendation 6. Diabetes screening in adults with Down syndrome and obesity	Recommendation (screen starting at age 21 y and every 2-3 y [instead of every 3 y] without requiring any additional risk factors[43]) differs from ADA guidance for the general population
Recommendation in Down syndrome guidelines neither for or against existing guidance for the general population	
Recommendation 12. Screening for primary prevention of osteoporosis for adults with Down syndrome	Neither for or against osteoporosis risk prediction tools (FRAX) for the general population
New recommendations in Down syndrome guidelines	
Recommendations 1 and 2. Diagnosis of behavioral health conditions for adults with Down syndrome	
Recommendations 3 and 4. Diagnosis and screening for Alzheimer-type dementia for adults with Down syndrome	
Recommendation 9. Refer adults with Down syndrome and history of congenital heart disease for cardiac evaluation and monitoring plan for adults with Down syndrome	
Recommendation 11. Screening for atlantoaxial instability for adults with Down syndrome	
Recommendation 14. Screening for hypothyroidism for adults with Down syndrome	

Abbreviations: ADA, American Diabetes Association; AHA/ASA, American Heart Association/American Stroke Association; FRAX, Fracture Risk Assessment Tool; USPSTF, US Preventive Services Task Force.

The process for developing these guidelines adhered to standards for trustworthy guidelines established by the Institute of Medicine[62] and used the Evidence-to-Decision framework[12] (eTable 1 in Supplement 1) to formulate 14 clinical recommendations along with 4 SOGPs. As anticipated, evidence was limited for many PICO questions. To address this challenge, a pragmatic approach was utilized, using evidence of differences in prevalence and age of onset in adults with Down syndrome to consider if changes to existing guidance for the general population were justified.

Half of the recommendations (n = 7) pertained to guidance for the general population from existing CPGs (**Table 2**). Four recommendations (managing cardiovascular risk [recommendation 7], stroke prevention [recommendation 8], screening for obesity [recommendation 10], and evaluation for secondary causes of osteoporosis [recommendation 13]) agreed with existing guidance. Conversely, for diabetes screening (recommendations 5 and 6), earlier and more frequent screening was recommended based on studies demonstrating high prevalence and earlier onset in adults with Down syndrome.

Regarding optimal screening for osteoporosis, based on clinical experience, the existing tools (FRAX) for predicting fracture risk are likely poor predictors in adults with Down syndrome. There is concern that patients estimated to be at increased risk for fracture based on FRAX, perceived to have osteoporosis on the basis of DEXA measurement, or both, often receive bisphosphonates, which have potential adverse effects. If causes of osteoporosis in Down syndrome differ from those in the general population, it is possible bisphosphonates may not be effective. Thus, these concerns were highlighted by making a recommendation neither for nor against current osteoporosis risk prediction tools.

Remaining recommendations addressed evaluation for mental health disorders (recommendations 1 and 2), screening and diagnosis of Alzheimer-type dementia (recommendations 3 and 4), cardiology referrals for adults with history of congenital heart disease (recommendation 9), screening for AAI (recommendation 11), and screening for hypothyroidism (recommendation 14). Because rates of dementia increase after age 40 years from approximately 10% to 20% (ages 45-50 years)[23,36] to as high as 50% (ages 55-59 years),[36] a strong recommendation to initiate screening for behavioral changes at age 40 years was made (recommendation 4). In these guidelines, age 40 years was chosen because dementia prevalence is low (<1%) in patients younger than 40 years,[19,24,36] and initiating screening at this age allows a baseline to be established. Since dementia is rare in patients younger than 40 years, caution is required in making a dementia diagnosis in this age group, a recommendation intended to prevent inaccurate attribution of cognitive symptoms to dementia. The high prevalence of hypothyroidism in adults with Down syndrome (50% in adults aged ≥30 years)[19] was also the basis for recommending screening for hypothyroidism every 1 to 2 years.

Adults with Down syndrome benefit from receiving care from clinicians familiar with common behaviors, which might otherwise

Box 2. Future Research Priorities (Abbreviated)[a]

Behavior

Create a standardized assessment tool specific to people with Down syndrome to help further evaluate co-occurring medical conditions associated with psychiatric and behavioral issues

Review if existing tools validated in and treatments effective for people with IDD are useful in people with Down syndrome

Identify potential mental health risk factors, protective factors, or both in adults with Down syndrome

Dementia

Research prevalence and clinical emergence of age-related dementia symptoms in adults with Down syndrome

Expand and validate the use of available biomarkers into clinical practice to help inform diagnosis and decision-making

Further validate and refine existing dementia screening tools for adults with IDD, including expanding their repertoire of application and usefulness in different settings

Diabetes

Research whether early treatment of type 2 diabetes reduces the extent of tissue and end-organ damage to reduce or prevent long-term complications in Down syndrome

Determine the prevalence of type 1 and type 2 diabetes in adults with Down syndrome

Identify genetic and/or immunological risk factors for diabetes in Down syndrome

Cardiovascular Disease

Evaluate modifiable risk factors for atherosclerotic disease in adults with Down syndrome and better understand which risk factors identified are relevant for this population regarding disease prevention

Identify strategies to prevent stroke in adults with congenital heart disease and the potential impact of lowering lipid levels for stroke prevention

Determine the prevalence of atherosclerotic cardiovascular disease and myocardial infarctions in people with Down syndrome

Obesity

Study impact of leptin and ghrelin hormonal circuitries, whose dysregulation could affect appetite control in Down syndrome

Determine what weight loss strategies (including medications) are effective in people with Down syndrome, including what modifications or adaptations to existing fitness strategies better manage weight and appetite regulation

Identify the effects of obesity in people with Down syndrome and the potential health benefits of weight

Atlantoaxial Instability

Research the symptomatic true incidence of AAI in adults with Down syndrome, what factors are predictive of the future development of symptoms, and what interventions are best at preventing spinal cord injury

Determine the comparative impact on morbidity and mortality of conservative (watchful waiting) vs surgical intervention of AAI

Study compliance of medical professionals to universal precaution of proper neck positioning for people with Down syndrome during medical procedure, treatment, or recovery

(continued)

Box 2. (continued)

Osteoporosis

Describe the unique epidemiology of skeletal fracture in people with Down syndrome and determine optimal prevention, screening, and treatment strategies

Review the comparative effectiveness of medications and other interventions for prevention and treatment of osteoporotic fracture in adults with Down syndrome

Create a screening tool or test for assessing risk for skeletal fracture in people with Down syndrome

Thyroid Disease

Determine the precise thyrotropin level at which problems manifest and over what time frame these can be corrected with treatment

Research the clinical application of predictive biologic markers (antithyroid antibodies) and the discovery of new markers (proteomic and molecular DNA) that predate disease in people with Down syndrome

Explore the role of autoimmune thyroid disease and the clustering effect of autoimmune conditions seen in people without Down syndrome to determine if hypothyroidism in Down syndrome could potentially indicate a higher risk of other autoimmune conditions more common in this population

Celiac Disease

Describe specific HLA antigen types and risks for developing autoimmune disorders in adults with Down syndrome

Correlate HLA antigen type with tTG-IgA levels and small-bowel biopsy results in adults with Down syndrome

Compare magnitudes of tTG-IgA values to help define cutoffs more appropriate for adults with Down syndrome. Formalize a diagnostic protocol for celiac disease in Down syndrome

Abbreviations: AAI, atlantoaxial instability; HLA, human leukocyte antigen; IDD, intellectual and developmental disability; tTG-IgA, tissue transglutaminase IgA.

[a] For a complete list of all future research priorities, see eTable 3 in Supplement 1.

be mistaken as indicative of pathology. Recommendations 1 and 2 highlight the importance of referral to an experienced clinician and use of tools designed for individuals with intellectual and developmental disabilities if concerns for mental health disorders such as depression, anxiety, or regression arise.

Although prevalence of AAI was found to be approximately 10%, no studies assessed whether screening using cervical radiographs allows identification of otherwise asymptomatic individuals at risk for SCI. Participation in physical activities offers highly desirable, potential physical and psychological benefits. In the absence of other evidence, reports from Special Olympics organizers of no SCI over the past 20 years was considered. After considering the potential benefits and harms (including SCI), a weak recommendation was made against cervical spine radiography for screening asymptomatic individuals, reasoning that no evidence suggests that cervical spine radiographs are helpful, whereas restricting patients from physical activity has known harms.

In some cases for which no evidence was identified, aspects of care many would consider standard were highlighted. To accomplish this, 4 SOGPs were formulated pertaining to mental health

disorders (SOGP 1 and SOGP 2), healthy practices for obesity (SOGP 3), and assessment for signs/symptoms of celiac disease at annual examinations (SOGP 4) (Table 1). Based on identified evidence gaps, key priorities for future research across each clinical domain were identified (**Box 2**; eTable 3 in Supplement 1).

Limitations

The guideline development process had several limitations. First, limited evidence meant recommendations were often based on little, indirect, or low-quality evidence. However, it is important to provide guidance where possible, despite very low-quality evidence, as others have affirmed.[63] Second, recommendations for screening interventions would ideally be based on clinical trials that demonstrated that screening resulted in better clinical outcomes. However, because it was anticipated that the evidence would be limited, PICO questions were formulated to identify whether sufficient evidence justified alterations to existing guidance for the general population (eg, initiating screening earlier based on higher prevalence at earlier age). Although the Evidence-to-Decision framework is typically used for interventions, using this framework provided a transparent, systematic process for considering benefits, harms, and other important factors in drafting clinical guidance.

Conclusions

These evidence-based practice guidelines provide recommendations to support primary care of adults with Down syndrome. The lack of high-quality evidence limits the strength of the recommendations and highlights the need for additional research.

ARTICLE INFORMATION

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