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GLOBAL DOWN SYNDROME FOUNDATION

MEDICAL CARE GUIDELINES
for ADULTS WITH DOWN SYNDROME

Written by the Global Down Syndrome Foundation Medical Care Guidelines for Adults with Down Syndrome Workgroup

ECRI

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INTRODUCTION

The Global Down Syndrome Foundation Medical Care Guidelines for Adults with Down Syndrome Workgroup (GLOBAL Workgroup) formed in 2016 to create evidence-based and updated guidelines for medical professionals and adults with Down syndrome and their families or caregivers, intended to improve health outcomes for this population. Consensus-derived clinical practice guidelines (CPG) for children with Down syndrome, birth through age 21, have existed since 1994[1] and continue to be regularly revised based on emerging evidence.[2] Such pediatric guidelines are substantially different from standard health care guidelines provided to children without Down syndrome.

Health management guidelines for adults with Down syndrome based on clinical practice observations were written in 1999[3] and 2001[4] but have not been updated since their initial dissemination despite many research and medical advancements in the field of Down syndrome. Other more recent reports that highlight co-occurring medical conditions in adults with Down syndrome were largely informed by clinical experience and supported by existing literature, but used somewhat less-rigorous protocol before formulating recommendations.[5, 6] Clinical convenience samples ascertained through specialty clinics have also been used to estimate the prevalence and variety of medical conditions in adulthood.[7] It is also important to note that people with Down syndrome have a different disease spectrum than those without Down syndrome in that they are highly predisposed to, and highly protected from, many diseases and conditions. This disease spectrum also changes with age but has not been adequately researched and annotated for adults with Down syndrome.

In 2014, the Global Down Syndrome Foundation (GLOBAL) established an Adult Down Syndrome Task Force (Global Task Force) made up of over 60 adults with Down syndrome, family members, and professional experts to, "assist the Global Down Syndrome Foundation and the Anna and John J. Sie Foundation to establish a world-class interdisciplinary medical care center for adults with Down syndrome." Over time, the Global Task Force recommendations grew to include the following action items: (1) conduct a national survey of families about their needs for, access to, and quality of medical care; (2) research available and comparable medical guidelines; and (3) with the conclusions from steps one and two, manage and fund the creation of evidence-based adult medical care guidelines. During this same time period, the Down Syndrome Medical Interest Group-USA (DSMIG-USA) began a systematic review of medical literature on adults with Down syndrome, and their results helped identify gaps in evidence, in addition to a need for evidence-based guidelines for this population.[8] Acting on the recommendations of the Global Task Force, GLOBAL funded and organized the GLOBAL Workgroup (n=13) composed of 11 Down syndrome experts, 1 ECRI guideline methodologist, and 1 parent representative/ advocacy leader and expert from GLOBAL.

These CPG are the first evidence-based guidelines for adults with Down syndrome. Such guidelines will provide an important tool in a primary care setting, augmenting both evaluation and care previously based solely on a person's age, gender, clinical symptoms, or the presence of known risk factors and other comorbidities.

BACKGROUND

1. What Is Down syndrome

The three types of Down syndrome are:

- **Trisomy 21.** About 95% of people with Down syndrome have trisomy 21[9] – a condition in which a person is born with three copies of chromosome 21 instead of the usual two copies in every cell.
- **Translocation Down syndrome.** Translocation Down syndrome accounts for 3% of people with Down syndrome[9] and occurs when a portion of chromosome 21 or a complete chromosome 21 becomes attached (translocated) onto another chromosome.
- **Mosaic Down syndrome.** Mosaic Down syndrome accounts for approximately 2% of people with Down syndrome[9] and occurs when a person has only some cells, but not all cells, with an extra copy of chromosome 21.

Down syndrome is the most commonly occurring chromosomal condition[10] and cause of developmental delay in the United States, occurring in approximately 1 of every 691 live births.[11] Most cases of Down syndrome are random and not hereditary.[12] While neither the exact cause nor the complete implications of this chromosomal trisomy are fully understood, due to its involvement of every organ-system, people with Down syndrome have a unique disease spectrum that differs from both people without Down syndrome and those with other intellectual and developmental disabilities (IDD), and requires specialized medical care.

People with Down syndrome have an increased risk for some medical conditions, such as congenital cardiac and gastrointestinal anomalies, autoimmune conditions, diverse leukemias, respiratory infections, sleep disorders, hearing and vision loss, and early development of Alzheimer's-type dementia. We recognize that some people with Down syndrome do not have any of these conditions. Furthermore, predisposition does not equate to certainty of disease and therefore may provide an opportunity for early intervention through vigilance and screening. If such conditions are managed properly, the majority of people with Down syndrome can lead healthy lives.[13]

While some medical ill-effects of Down syndrome may be evident during fetal development or early childhood, other comorbidities may not develop until later in adolescence or adulthood.[14] Conversely, people with Down syndrome are much less likely to develop solid malignancies than those without Down syndrome and may be less likely to suffer from atherosclerotic cardiovascular disease.[15, 16] Most people with Down syndrome function in the mild to moderate range of intellectual disability.[2] Down syndrome's common features present to varying degrees depending on the individual and may or may not include limited expressive language skills, complex medical comorbidities, delayed motor skill development, intellectual disability, and reduced executive functioning capacity compared with a person without Down syndrome. These features, compounded with inequitable access to care, guardianship arrangements, and social stigma, contribute to the vulnerability of adults with Down syndrome and should be considered when providing medical and social care.

2. Prevalence and Life Course

The life expectancy of people with Down syndrome has increased dramatically in the last half century from 25 years in 1983[17] to an average of 60 years.[18] Live births of individuals with Down syndrome have also increased from 1 in 1,000 in 2002[19] to 1 in 691 in 2006.[11] Such gains in life expectancy reflected in the United States are largely due to improvement in the ability to treat congenital heart disease, hypothyroidism and lung disease, as well as deinstitutionalization, which led to access to medical care, education, community, family supports, and more.

The census does not track the number of people with Down syndrome living in the United States; therefore, prevalence estimates vary widely. A recent publication using data from 2008 to 2010 estimates the population to be approximately 206,000, with the number of adults over the age of 18 with Down syndrome living in the United States approaching or exceeding 125,000.[20] However, using the current adjusted birthrate and most recent census data, Down syndrome's prevalence could exceed 350,000 in the United States.

Despite the increased prevalence and longevity of adults with Down syndrome, relatively little is known regarding the optimal prevention and etiology of common diseases that occur more frequently in this population. While many people with Down syndrome enjoy meaningful inclusion in their communities, as well as more physically active and longer lives, more needs to be accomplished in preventive healthcare to support healthier aging. Specific medical problems may go unnoticed—in part as a result of limited access to care, diagnostic overshadowing, and decreased ability to articulate needs. Thus, screening guidance becomes necessary to inform clinical decision-making for this vulnerable population with high medical complexity.

ABOUT THIS CLINICAL PRACTICE GUIDELINE

1. Scope

This clinical practice guideline focuses on people with Down syndrome due to Trisomy 21, not partial translocation or mosaicism, as even less literature and expertise exist for these latter two subgroups. The biggest challenges for guideline development relate to their intended scope, breadth and depth, and lack of evidence. Down syndrome is not itself a disease, but rather a complex genetic condition involving every major organ-system and life-stage experience.[21] Thus, comprehensive adult guidelines would need to address all concerns and involve every major organ-system.

The first set of key questions addressed by the GLOBAL Workgroup does not cover all systems, all questions, or all health conditions. In this first iteration, the topic areas covered are:

1. Behavior
2. Dementia
3. Diabetes
4. Cardiovascular Disease
5. Obesity
6. Atlantoaxial Instability
7. Osteoporosis
8. Thyroid
9. Celiac Disease

A previous review identified eight of these nine topics as being of high public health importance for this population[8] due to the increased prevalence of these conditions, their impact on morbidity and mortality, and the potential for guidelines to improve clinical practice within these areas.

While a CPG reviewing all major systems and health topics is beyond the scope of this initial effort, the GLOBAL Workgroup is committed to updating the guidelines every five to six years to: (1) further expand upon the breadth and depth of the focus areas and key questions in this initial guideline, and (2) add important focus areas and questions that were identified as key determinants of health in adults with Down syndrome. Such additional areas to be covered include obstructive sleep apnea, cancer, autoimmune disorders beyond thyroid disease and celiac disease, autism, and prevention of respiratory infections.

The timing of this guideline purposefully coincides with unprecedented increases in Down syndrome research funding at the National Institutes of Health (NIH). With the establishment of the trans-NIH INCLUDE (**IN**vestigation of **C**o-occurring conditions across the **L**ifespan to **U**nderstand **D**own syndrom**E**) Project, the Down syndrome research budget at NIH has increased from $27M in FY2016 to an estimated $113M in FY2020. Due to advocacy, excellent initial scientific results, and a focus on translational research at NIH, this trend is likely to continue. Over the next five years, it is the goal of the GLOBAL Workgroup to ensure that the Down syndrome research community is galvanized to submit INCLUDE grant applications associated with adult care that supports our existing and future guidelines. To this end, the

"Future Research" section found in each medical topic covered in this guideline provides an important roadmap for transformative grants that address biomarkers, prevalence, comorbidity, diagnostics, screening, intervention, and treatment. Finally, the GLOBAL Workgroup is dedicated to ensuring our future adult research takes into account sex differences and racial disparities. For example, confirming if, in fact, African Americans with Down syndrome have a significantly shorter lifespan than their Caucasian counterparts and why would be of great importance.

2. Limitations and Challenges

As these guidelines make evident, lack of research posed the greatest challenge to development, and the need for additional research to support guideline recommendations was noted for nearly every question. In children with Down syndrome, the estimated prevalence of comorbidities (e.g., congenital heart defect, thyroid disease, obstructive sleep apnea) is sufficiently high so that routine screening is recommended even for asymptomatic individuals.[2] In adults with Down syndrome, questions about the prevalence and severity of comorbid health conditions and the respective risk factors are both underappreciated and not well understood. Presently, the current efficacy, risks, and benefits of screening asymptomatic adults with Down syndrome for the same conditions currently recommended for those without Down syndrome have been called into question. Future research needs are included for each individual guideline topic. However, in this guideline, the GLOBAL Workgroup used existing evidence from a systematic literature review and employed a standardized and transparent methodology to develop clinical practice recommendations to create the first evidence-based guideline for adults with Down syndrome.

3. Methods

To develop an evidence-based clinical practice guideline for use by families, caregivers, adults with Down syndrome and community providers who care for adults with Down syndrome, the GLOBAL Workgroup adhered to standards for trustworthy guidelines.[22] To inform the systematic literature review, GLOBAL Workgroup members identified high priority key questions around providing care for adults with Down syndrome. The GLOBAL Workgroup also provided direction on inclusion and exclusion criteria for the evidence review, assessed the level and quality of the evidence, and used this information to develop clinical practice recommendations. Appendix A provides detailed description of each of the tasks carried out as part of the guideline development process.

The guideline development process for the 2020 CPG consisted of the following steps:

1. Forming and prioritizing key questions.
2. Conducting the systematic evidence review.
3. Convening a face-to-face meeting with GLOBAL Workgroup members to review the evidence, craft evidence-based recommendations, and develop decision-making algorithms.
4. Drafting a CPG on the health care management of adults with Down syndrome.
5. Convening a focus group of adults with Down syndrome and their family members to provide feedback on guideline recommendations.
6. Soliciting feedback from other clinicians.
7. Incorporating focus group and clinician feedback to draft the final CPG.

A. Grading Recommendations

The GLOBAL Workgroup used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system Evidence to Decision framework to assess the quality of the evidence base.[23] The GRADE system uses the following four domains to assess each recommendation's strength:[24]

- Balance of desirable and undesirable outcomes
- Confidence in the evidence's quality
- Values and preferences
- Other implications, as appropriate—for example:
    - » Resource use
    - » Equity
    - » Acceptability
    - » Feasibility
    - » Subgroup considerations

Using these four domains, the GLOBAL Workgroup determined each recommendation's strength ("Strong" or "Weak"). A "Strong" recommendation generally indicates a high confidence in the quality of the available scientific evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar values and preferences, and understood influence of other implications (e.g., resource use, feasibility). If the GLOBAL Workgroup has less confidence after the assessment across these domains and believes that additional evidence may change the recommendation, it generally assigns a "Weak" recommendation. It is important to note that the GRADE terminology (i.e., "Strong" versus "Weak") used to indicate the assessment across the four domains should not be confused with the recommendation's clinical importance. A weak recommendation may still be important to clinical care. A statement of good practice (SOGP) 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.

Using these elements, each recommendation's grade is presented as part of a continuum:

- Strong for (or "We recommend offering this option …")
- Weak for (or "We suggest offering this option …")
- No recommendation for or against (or "There is insufficient evidence…")
- Weak against (or "We suggest not offering this option …")
- Strong against (or "We recommend against offering this option …")

GLOBAL Workgroup members initially developed all recommendations for this CPG using the GRADE framework's standard language ("suggest" and "recommend" for corresponding strong and weak recommendations), however such language was modified into actionable statements in order to conform to JAMA's editorial style for publications.

Medical professionals providing care for adults with Down syndrome are often faced with deciding in what situations "standard" CPGs developed for the general population (such as United States Preventive Services Task Force guidelines (USPSTF)) should be followed. For most key questions, the GLOBAL Workgroup anticipated a paucity of published research performed

in adults with Down syndrome. Thus, several key questions were oriented towards identifying epidemiologic evidence of differences in age of disease onset or disease prevalence between adults with Down syndrome and adults without Down syndrome to guide whether existing clinical recommendations could warrant modification.

Similarly, for several key questions, if no direct evidence (i.e. performed in adults with Down syndrome) was identified, GLOBAL Workgroup members considered evidence from other patient populations (e.g. children with Down syndrome, adults with IDD) and arrived at consensus regarding whether evidence was 'direct enough' to inform care of adults with Down syndrome. This approach has successfully been employed to develop evidence-based clinical practice guidelines using GRADE methodology in contexts with a paucity of direct evidence.[25]

The grade of each recommendation made in the GLOBAL Guidelines can be found in the Recommendations section. Additional information regarding use of the GRADE system can be found in Appendix A.

4. Intended Audience

The intended audience for this guideline includes community-based primary health care providers (physicians, nurses, nurse practitioners, behavioral health providers, and physician assistants) who provide direct care to adults. Other critical stakeholder groups include self-advocates (adults with Down syndrome), their caregivers (parents, siblings, and agency workers), and advocacy organizations (national and regional parent groups) who will use this information to advocate for quality health care locally and nationally.

This CPG is based on the best information available at the time of publication and designed to provide information and assist decision-making. It is not intended to define a standard of care and should not be construed or interpreted as prescribing an exclusive management course.

5. Health Promotion and Person-Centered Care

Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to their community, institution, or type of practice. Every health care professional using this CPG is responsible for evaluating the appropriateness of applying this CPG to the individual adult, in the setting of any particular clinical situation.

6. Affiliations

The following GLOBAL Workgroup authors are affiliated with the institutions/clinics as set forth as follows: University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (Bulova); Down Syndrome Clinic and Research Center, Johns Hopkins School of Medicine, Baltimore, Maryland (Capone); Advocate Medical Group Adult Down Syndrome Center, Park Ridge, Illinois (Chicoine); Global Down Syndrome Foundation, Denver, Colorado (Gelaro); Department of Pathology and Laboratory Services and Department of Internal Medicine, Division of Hematology University of Arkansas for Medical

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7. Conflict of Interest and Disclosures

M. S. Whitten and B. Gelaro are currently employed by the Global Down Syndrome Foundation. During the development of the guidelines, Dr McGuire was a paid consultant for the Global Down Syndrome Foundation.

Dr Bulova, Dr Capone, Dr Chicoine, Dr Harville, Dr McKelvey, Dr Martin, Dr McGuire, Dr Peterson, ECRI (Dr Amy Tsou, Dr Joann Fontanorosa, Allison Gross, Gina Giradi, and Dr Karen Schoelles), Dr Tyler, and M. Wells received a fee from the Global Down Syndrome Foundation for their time and work associated with the guidelines.

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Dr Capone serves on the steering committee for the Down Syndrome International Health Guideline Project and is a current board member of the Down Syndrome Medical Interest Group-USA (DSMIG-USA). Dr Chicoine is the current Treasurer of the Down Syndrome Medical Interest Group-USA (DSMIG-USA). Dr Capone and Dr Chicoine both currently serve on the Clinical Advisory board for the National Down Syndrome Society and on the Executive Committee of the LuMind Down Syndrome-Clinical Trials Network.

Dr Esbensen reports the following conflicts of interest: NIH R21 HD082307 – Principal Investigator on government supported research (8/6/2015-6/30/2018), Lejeune Foundation – Principal Investigator on foundation supported research (12/27/2016-12/26/2017), ProPhase LLC – consulting work involved Roche Pharmaceuticals and Janssen (2011-present), Ovid LLC – consulting (2018-present), and Roche – consulting (2016).

Dr Tyler and Dr Keller currently serve on the board for the American Academy of Developmental Medicine and Dentistry. Dr Keller is an author of the National Task Group Early Detection Screen for Dementia (NTG-EDSD).

Dr Barnhill is author of the Diagnostic Manual-Intellectual Disability (DM-ID) and the Diagnostic Manual-Intellectual Disability 2 (DM-ID 2).

Dr Eckel reports personal fees from Sanofi/Regeneron, Merck, Novo Nordisk, and Kowa, outside the submitted work.

GLOBAL Workgroup members and volunteer committee member/contributors not named here have reported no conflicts of interest.

8. Summary of Focus Groups

Within the disability community, many advocacy organizations champion the motto, "Never for us without us," highlighting the importance of including the perspectives and voices of people with IDD in every discussion. Although GLOBAL Workgroup members weighed perceived preferences of adults with Down syndrome, their families, and caregivers throughout

the guideline development process, to provide further opportunities for input, the GLOBAL Workgroup solicited guideline feedback from adults with Down syndrome and their family members through a seven-day focus group as the guideline was nearing completion.

The focus group began on October 14, 2019 and was conducted via an online survey platform by Corona Insights, an expert in market research design. Participants were recruited by the Global Down Syndrome Foundation through a national network of local Down syndrome organizations. Twenty-seven caregivers or family members and seven adults with Down syndrome participated in the focus group for a total of 34 participants.

The focus group's goal was to determine whether these guidelines appropriately reflected the needs, values, and perspectives of adults with Down syndrome, their families, and caregivers. The focus group gauged initial reactions to the guideline, including feedback regarding usability, appealing elements of the guidelines, and sections requiring further clarification. Further details regarding focus group methods can be found in Appendix C.

The chart below represents the three key findings from the focus group. The GLOBAL Workgroup carefully considered these findings during the manuscript finalization to ensure the completed manuscript was appropriately understandable and useful for adults with Down syndrome, their families, and caregivers. Additional details of the methodology and findings can be found in Appendix C.

Medical Care Guidelines for Adults with Down Syndrome Focus Group Key Findings
1. Adults with Down syndrome and families strongly prefer recommendation statements that avoided complex terminology and provided concrete, actionable steps.
2. Families want the most background information and evidence for recommendation statements that differ from previous recommendations or that suggest care for an adult with Down syndrome is different from standard care for adults without Down syndrome.
3. Additional toolkits and checklists provided in layman's terms will help families and adults with Down syndrome feel more in control of their healthcare and increase usability.

9. Summary of Peer Review

Given the comparatively few medical providers in the United States with extensive experience working with adults with Down syndrome, the GLOBAL Workgroup sought peer review from providers who work outside this patient population since they are whom many adults must rely on for care. The GLOBAL Workgroup reached out to the American Academy of Developmental Medicine and Dentistry (AADMD), and their board approved its members to participate in the review. Eight members volunteered to participate, seven of whom completed the peer review. The seven members of the AADMD Board who participated in the review received the introduction, the near-final manuscript recommendation narratives, and the checklist tool. The peer reviewers were not incentivized for their contributions, and they agreed to be acknowledged as an organization. The peer reviewers were given 10 days to read the three manuscript components outlined above.

Comments were compiled and presented to the GLOBAL Workgroup who had the opportunity to either accept, reject, or respond to each comment based on the guideline protocol, the evidence available, and the expert consensus. The guidelines were updated as a result of the peer-review process.

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The Family of Rya Gracyn Pierce

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Kern Down Syndrome Network
Red River Valley Down Syndrome Society
Rio Grande Valley Down Syndrome Association
Sampson Collaborative Law
S.M.I.L.E. on Down Syndrome
Southern Arizona Network for Down Syndrome
The UpSide of Downs of Northeast Ohio
Wisconsin Upside Down

Recommendation Table

	Recommendations	Strength of Recommendation
	Behavior	
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 For
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 (5th Ed; DSM-5).[26] The Diagnostic Manual-Intellectual Disability 2 (DM-ID-2)[27] also may be used to adapt diagnostic criteria from the DSM-5.	Weak For
	Dementia	
3.	Caution is needed when diagnosing age-related, Alzheimer's-type dementia in adults with Down syndrome younger than age 40 due to its low prevalence before this age.	Weak For
4.	Medical professionals should assess adults with Down syndrome and interview their primary caregivers about changes from baseline function annually beginning at age 40. Decline in the following six domains as per the National Task Group – Early Detection Screen for Dementia (NTG-EDSD),[28] should be used to identify early-stage age-related Alzheimer's-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 For
	Diabetes	
5.	For asymptomatic adults with Down syndrome, screening for type 2 diabetes mellitus (T2DM) using hemoglobin A1c (HbA1c) or fasting plasma glucose should be performed every 3 years beginning at age 30.	Weak For
6.	For any adult with Down syndrome and comorbid obesity, screening for T2DM using HbA1c or fasting plasma glucose should be performed every 2—3 years beginning at age 21.	Weak For

	Cardiovascular Disease	
	Atherosclerotic Cardiovascular Disease	
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 and using a 10-year risk calculator as recommended for adults without Down syndrome by the U.S. Preventive Services Task Force.[29]	Weak For
	Stroke	
8.	For adults with Down syndrome, risk factors for stroke should be managed as specified by the American Heart Association/American Stroke Association's *Guidelines for the Primary Prevention of Stroke*.[30]	Weak For
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 For
	Obesity	
10.	Monitoring for weight change and obesity should be performed annually by calculating body mass index (BMI) in adults with Down syndrome. The U.S. Preventive Services Task Force (USPSTF) Behavioral Weight Loss interventions to Prevent Obesity-Related Morbidity and Mortality in Adults should be followed.[31]	Weak For
	Atlantoaxial Instability	
11.	In adults with Down syndrome, routine cervical spine X-rays 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 a review of signs and symptoms of cervical myelopathy using targeted history and physical exam.	Weak Against
	Osteoporosis	
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
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 For

	Thyroid	
14.	Screening adults with Down syndrome for hypothyroidism should be performed every 1—2 years using a serum thyroid-stimulating hormone test beginning at age 21.	Weak For

Statements of Good Practice

	Behavior
1.	*Statement of Good Practice 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.
2.	*Statement of Good Practice 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
3.	*Statement of Good Practice 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
4.	*Statement of Good Practice 4:* Adults with Down syndrome should receive an annual assessment for gastrointestinal and non-gastrointestinal signs and symptoms of celiac disease using targeted history, physical examination, and clinical judgement of good practice.

BEHAVIOR

Statement of Good Practice 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.

Discussion

Adults with Down syndrome should have access to medical care that is equitable to the quality of care available to adults without Down syndrome. This should include an annual review of all relevant behavioral (mood, attention, and activity level), functional-adaptive (social, communication, and daily living skills), and psychosocial (major life events, bereavement, and trauma) factors that may affect physical and mental well-being. Because limitations of expressive language and intellectual functioning may significantly affect self-report and the presentation of physical or emotional problems, the history must include any observed changes in mood and behavior by knowledgeable family members, caregivers, and significant others, especially those who are a regular part of the adult's daily life. If no significant reported behavioral changes occur, an annual review may allow clinicians to establish a functional baseline to which future potential change or decline could be compared.

Statement of Good Practice 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.

Discussion

Behavior and mental health conditions are common in adults with Down syndrome[32] and a cause for concern among most families and caregivers. When confronted with a report of change in behavior or function, further medical and mental health evaluation is best accomplished by understanding the differential diagnosis of such symptoms as expressed in adults with Down syndrome. Sleep apnea, hypothyroidism, celiac disease, seizures, chronic pain, dysphagia, vision or hearing loss, and other systemic medical illnesses should also be considered.[33-36]

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.

[**Strength of Recommendation:** Weak For]

Discussion

The recommendation is based on the following considerations:

- Behavior and mental health conditions are common in adults with Down syndrome[32] and are cause for concern among most families and caregivers.
- The benefits of making an accurate diagnosis include avoiding misdiagnosis of medical and psychiatric conditions, avoiding misdiagnosing adaptive behavior as a disorder and identifying salient psychosocial issues that require attention.
- Assessment for underlying medical conditions, such as hypothyroidism, celiac disease, or obstructive sleep apnea (OSA), significantly improves understanding of contributing causes to behavior or mental health changes and improves treatment.
- Most or all adults with Down syndrome, their families, and caregivers would place high value on identifying medical conditions contributing to mental health conditions, especially if this is used to improve diagnosis and treatment outcomes.

No studies directly comparing symptoms of behavioral and mental health conditions in adults with Down syndrome to adults without Down syndrome were identified. However, small cross-sectional studies and case series describing depression and functional decline in adults with Down syndrome were identified.[35, 37] Symptoms of depression and functional decline have also been associated with untreated moderate to severe OSA.[33] Such a connection, if further substantiated, could have direct implications for both preventing and treating depression and other mental health disorders in this population. Similarly, a case series of 30 children and adults with Down syndrome experiencing functional regression described comorbid psychiatric and medical conditions seen in their cases; co-morbid medical problems described included thyroid disease, sleep apnea, and epilepsy.[35]

While adults with Down syndrome and family members usually welcome the prospect of treating concurrent medical conditions or a major mental health disorder, medical professionals unfamiliar with caring for adults with Down syndrome may find it challenging to fully implement such treatments. For example, medications with anti-cholinergic side effects tend to be less well-tolerated in this population. Treatment is improved with an understanding of the unique tolerance and intolerance of medications for many people with Down syndrome and the need to balance those differences with the higher rate of a variety of comorbid conditions. Access to a specialist knowledgeable about Down syndrome may be limited in many U.S. regions, and additional discussions of access to care are critical to address this shortage. Appendix E provides links to an abbreviated list of national Down syndrome and IDD resources, and to Down syndrome clinics by state.

Future Research

Future research is needed to better understand the effects of co-occurring medical conditions on behavior and mental health in adults with Down syndrome. Evidence is needed to determine the most effective approaches to treatment when multiple concurrent conditions are present.

In addition, regression, which can be debilitating for both the person with Down syndrome and families, requires better phenotyping, identification of biomarkers, and psychosocial stressors that can contribute to regression. Furthermore, identification of potential mental health risk factors and/or protective factors in adults with Down syndrome would be beneficial.

Given the large body of literature demonstrating chronic peripheral inflammation and neuroinflammation in Down syndrome,[38-45] research is also needed to understand the role of immune dysregulation in diverse behavior and mental health in 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 (5th Ed; DSM-5).[26] The Diagnostic Manual-Intellectual Disability 2 (DM-ID-2)[27] also may be used to adapt diagnostic criteria from the DSM-5.

[**Strength of Recommendation:** Weak For]

Discussion

The recommendation is based on the following considerations:

- Behavior and mental health conditions in adults with Down syndrome are common concerns among most families and caregivers.
- Rather than relying on self-report of emotional distress from the adult with Down syndrome, it is important for clinicians to recognize that observable, maladaptive behavior may be highly informative.
- Certain types of behavior may be common in adults with Down syndrome (e.g., self-talk), while other behaviors may indicate a treatable mental health condition (e.g., agitation, irritability).
- The benefits of making an accurate diagnosis significantly outweigh the harms of making an incorrect or no diagnosis.
- Most or all adults with Down syndrome, their families, and caregivers would place high value on having this information, especially when used to improve diagnosis and treatment outcomes.

Behavior changes and mental health conditions in adults with Down syndrome are common causes for concern but can be challenging to diagnose due to differences in clinical presentation from adults without Down syndrome. Differences may include limited verbal language skills, increased maladaptive behaviors, a high incidence of confounding medical comorbidities, and lack of access to experts familiar with mental health, specifically in adults with Down syndrome. Assessing and treating medical conditions should improve accuracy of mental health diagnosis and better inform care management.

In the GLOBAL Workgroup's experience, common behavioral characteristics to be aware of in adults with Down syndrome include frequent self-talk, blurring between fantasized and actual

individuals or events, and strict adherence to certain routines. Clinicians interpreting behaviors that present during a history or mental status examination should account for, rather than pathologize, common behavioral characteristics of adults with Down syndrome. Such behaviors alone do not necessarily indicate a major psychiatric or mental health disorder.[46] These behaviors may be heightened during times of emotional-physical stress or discomfort and may serve an adaptive purpose. However, these behaviors may also become maladaptive, particularly during times of high or persistent stress. In addition, as noted in the literature and consistent with the GLOBAL Workgroup's experience, stressful life events are often reported as possible triggering events for behavior changes.[35] The GLOBAL Workgroup agreed that highly maladaptive behavior and reports by caregivers indicating a demonstrable change from a previous level of function often suggests a medical and/or psychiatric disorder.

Although no studies directly comparing symptoms in adults with Down syndrome to adults without Down syndrome were identified, one systematic review that examined three smaller studies described the clinical presentation of depression in adults with Down syndrome.[37] These symptoms included anhedonia, psychomotor slowing, sleep disturbance, depressed mood, and functional decline. Other case series have reported that self-report of guilt and low self-esteem is less likely in adults with Down syndrome, while observable behavioral symptoms, such as a lack of interest or participation in previously enjoyed activities, social withdraw, and psychomotor slowing or agitation, may be more reliable symptoms of depression in this population.[47] This is also consistent with the GLOBAL Workgroup's experience.

Regression of previously acquired skills in adults with Down syndrome is another finding that should prompt a high level of concern. General decline in function may be a distinguishing feature of either a medical or mental health disorder in this population. OSA, hypothyroidism, seizures, chronic pain, and other systemic medical illnesses should be suspected and ruled out. In a large French case series, functional regression occurred in adults with Down syndrome independent of previous cognitive level.[35] Salient aspects included prominent psychiatric symptoms, maladaptive behaviors, and loss of or decline in previously acquired daily living skills.

It seems likely that adults with Down syndrome may be at increased risk for certain mental health disorders based on preexisting behavioral characteristics, such as cognitive inflexibility and internalizing symptoms.[48-50] With the caveats discussed above regarding common behaviors, and in the absence of valid diagnostic tools specifically for adults with Down syndrome, we recommend using DSM-5[26] complemented by the DM-ID-2,[27] which is helpful for recognizing mental health disorders in people with intellectual and developmental disabilities (IDD).[51] The DM-ID uses modified DSM criteria, takes a developmental perspective, and emphasizes observable behaviors in the absence of self-report from individuals with IDD.[51, 52]

Future Research

Future research is needed to better understand the prevalence of specific mental health conditions, their predisposing risk factors, and the unique vulnerabilities of adults with Down syndrome. A standardized assessment tool to help further evaluate medical conditions associated with psychiatric and behavioral issues should be developed. Down syndrome's behavioral phenotype has been extensively researched among young children, but more research is needed

to characterize this phenotype into adolescence and through adulthood. Of the few Down syndrome specialty clinics in the U.S., very few have mental health providers, and little is known about the condition prevalence. Clearly more quantitative and qualitative data is needed.

Reviewing existing tests, screenings, therapies, and interventions validated in adults with IDD for appropriateness/usefulness in adults with Down syndrome should be a priority. For example, while many clinicians refer for Applied Behavior Analysis (ABA), most widely recognized and studied in the Autism community, there has yet to be a study for its effectiveness in people with Down syndrome.

Future research should also aim to identify the metabolic, physiological, and immune processes underlying the etiology of specific mental health conditions in adults with Down syndrome, with a focus on processes that may affect levels and/or action of diverse neurotransmitters (e.g., serotonin, norepinephrine, GABA, glutamate).[41, 53-58] These efforts could illuminate novel diagnostics and therapeutic strategies for improved mental health in adults with Down syndrome.

DEMENTIA

Recommendation

3. Caution is needed when diagnosing age-related, Alzheimer's-type dementia in adults with Down syndrome younger than age 40 due to its low prevalence before this age.

[**Strength of Recommendation:** Weak For]

Discussion

The recommendation is based on the following considerations:

- The prevalence of age-related, Alzheimer's-type dementia increases with age in adults with Down syndrome.
- Age-related dementia is uncommon or rarely observed in those under age 40.
- Potential benefits to adults with Down syndrome are high if providers avoid inaccurate attribution of symptoms to Alzheimer's-type dementia; considering alternative causes may lead to diagnosis of treatable medical conditions.
- Most adults with Down syndrome, their families, and caregivers will place high value on having this information to provide additional support and for resource planning.

This recommendation is intended to decrease the misdiagnosis of age-related, Alzheimer's-type dementia in this population. One moderate quality population based Dutch study of 506 adults with Down syndrome demonstrated increased prevalence of dementia after the age of 45.[59] A second, large population based study[60] reported similar findings, although the diagnosis of dementia appeared to be based on administrative data.

Three studies assessed prevalence in patients <40 years.[61-63] However, only one study[63] (n=388) used a validated measure for diagnosis and reported 0% prevalence in adults with Down syndrome aged 30-39. Two additional large studies (n >5,000 adults with Down syndrome)[61, 62] did not confirm diagnosis based on validated tests but found similar low prevalence in younger adults (18 to 39 years).

Misdiagnosis of age-related dementia in adults with Down syndrome may occur if medical providers do not carefully evaluate for other medical conditions as a possible cause or contributing factor for the adult's functional decline. Without careful attention to differential diagnosis and proper management of existing medical and mental health conditions, the potential benefits of the correct interventions or treatment become unnecessarily restricted. Thus, the GLOBAL Workgroup supports careful assessment and thorough medical evaluation for other possible medical etiologies at all ages, especially in those under 40 years old.

The potential benefits of making an accurate diagnosis of dementia and/or evaluating for treatable comorbid medical conditions (such as hypothyroidism or sleep apnea) significantly outweigh the potential harms of under-diagnosis of Alzheimer's-type dementia in individuals younger than 40 years old. If both a medical condition and mental health disorder are found to

be present, adults with Down syndrome, their families, and caregivers typically welcome the prospect of concurrent treatment for both conditions.

Future Research

Medications for dementia approved for use in adults without Down syndrome have not been found to be helpful in adults with Down syndrome.[64-67] Efforts are underway to better understand the prevalence and clinical emergence of age-related dementia symptomology in adults with Down syndrome.[68] Improved understanding of the multisystem physiologic changes experienced by aging adults with Down syndrome requires further study, as do the medical conditions that contribute to or accelerate the dementia process itself. Disentangling the pathogenic mechanisms of such conditions and expanding the use of available biomarkers into clinical practice should help inform decision-making and guide future treatment approaches when they become available.[69]

Further research is needed to validate biomarkers that can be used to support (or refute) a diagnosis of Alzheimer's disease dementia in the clinic. This would allow a clinician who is evaluating a symptomatic adult with Down syndrome to confidently rule-in or rule-out Alzheimer's disease as the underlying etiology. We are now able to non-invasively visualize (and quantify) the presence of the two key pathological hallmarks of Alzheimer's disease: amyloid plaques and neurofibrillary tangles, as there are four amyloid Positron Emission Tomography (PET) tracers and one tau PET tracer which are Food and Drug Administration (FDA) approved. Although the clinical utility of amyloid PET is limited given that it is uniformly positive by age 40 in Down syndrome, tau PET has emerged as a strong candidate for predicting cognitive decline due to Alzheimer's disease. It has been shown to be a more proximal indicator of Alzheimer's disease-related cognitive decline both in people without Down syndrome[70] as well as in people with Down syndrome.[71] Tau PET may likely allow for staging of people with Down syndrome who are in the symptomatic phase of Alzheimer's disease (i.e., mild cognitive impairment or dementia) while presence of elevated brain amyloid as visualized by amyloid PET will define preclinical Alzheimer's disease, where pathology is present without the manifestation of symptoms. By identifying the stage of Alzheimer's disease for each individual with Down syndrome, clinical trials can be more efficiently designed, and a more accurate prognosis can be provided to patients and their families in the clinic.

The NIH-funded Alzheimer's Biomarker Consortium Down Syndrome (ABC-DS)[72] and the European Horizon 21 Consortium[73] are collecting critical information on the natural history of Alzheimer's disease biomarkers in adults with Down syndrome including amyloid PET and tau PET and their relationship to clinical diagnosis. Recently, plasma levels of the protein neurofilament light (NF-L) have been shown to strongly correlate with clinical status[74] as well as Alzheimer's disease biomarkers.[75] This blood-based biomarker seems to provide an excellent measure of neurodegeneration and shows strong correlation with brain atrophy and hypometabolism as assessed with magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG) PET, respectively. Results regarding the correlation of plasma NF-L and longitudinal cognitive decline and relationship to and clinical diagnosis and Alzheimer's disease biomarkers in over 500 ABC-DS participants are expected later this year but results thus far indicate both sensitivity and specificity above 90%.

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. Decline in the following six domains as per the National Task Group – Early Detection Screen for Dementia (NTG-EDSD),[28] should be used to identify early-stage age-related Alzheimer's-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

[**Strength of Recommendation:** Strong For]

Discussion

The recommendation is based on the following considerations:

- The prevalence of age-related dementia increases with age in adults with Down syndrome.
- The benefit of early identification and treatment of potentially reversible causes of cognitive decline outweighs the potential harms (obtaining additional tests and false positives).
- Most adults with Down syndrome, their families, and caregivers place high value on early and accurate diagnosis of irreversible age-related dementia to modify existing supports and for additional resource planning.

Age related cognitive decline is a common concern for most families and caregivers of adults with Down syndrome due to its increased prevalence, early development, and impact on quality of life. However, other medical and mental health conditions that affect both cognitive and adaptive function are also common in this population and merit ongoing vigilance and monitoring. Prevalence of dementia has been shown to increase after age 40,[59, 63] thus, we recommend starting screening at age 40 to support identification of potential future changes.

Evidence for increased prevalence comes primarily from two studies. A Dutch study (n= 506 adults with Down syndrome)[59] found high prevalence of age-related dementia in individuals with Down syndrome 45 years and older; specifically, prevalence was 8.9% for individuals 45—50 years old and increased with age to 32% in 55—59 year-olds. Prevalence estimates from this study were based on validated clinical measures combined with caregiver interviews. Additionally, one low quality study using non-population based samples from Spain and U.K.[63] also reported exponentially increasing prevalence rates for dementia in adults with Down syndrome per

five-year age brackets, from about 10% for individuals ages 40—45 years, up to 90-100% for individuals ages 65—70 years. Many older or smaller studies have assessed prevalence using a range of sampling frames and diagnostic standards.[76-81] While studies reported a range of prevalence estimates for different age groups, all studies consistently found rising prevalence after age 45.

A high incidence in older adults is consistent with the clinical experience of GLOBAL Workgroup members. However, as GLOBAL Workgroup members have not found symptomatic age-related Alzheimer's-type dementia to be universal (i.e., the rate is less than 100%), consideration of other possible causes remains important. Reports of pseudodementia in adults with Down syndrome due to cerebrovascular disease, severe sleep apnea, catatonia, hypothyroidism, metabolic disturbances, sensory impairments, and medication effects have been noted.[28, 82]

The GLOBAL Workgroup feels strongly that establishing a working diagnosis of age-related Alzheimer's-type dementia requires more than just changes in behavior or personality. Typically, individuals with mild-moderate dementia will show changes in multiple domains, including memory and executive function, behavior and personality, language and communication, gait and motor skills, activities of daily living, continence, and sleep patterns. These domains come from the National Task Group-Early Detection Screen for Dementia (NTG-EDSD) manual, which was developed by experts in the field[28] and reflects the workgroup's clinical experience.

In the Workgroup's experience, additional neurologic findings that may accompany age-related Alzheimer's-type dementia in adults with Down syndrome include new-onset seizures or myoclonus, extrapyramidal movements (Parkinsonism), and gait dyspraxia.

Future Research

In addition to the NTG-EDSD manual,[28] several other dementia screening tools specifically for adults with Down syndrome or IDD are available, including the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities.[83] Dementia could be detected earlier and more accurately with further validation and refinement of these existing tools, including expanding their repertoire of application and usefulness in different settings.

There is a critical need for practical, standardized and validated assessment tools for use in the clinic to diagnose and stage Alzheimer's disease in individuals with Down syndrome across a spectrum of baseline intellectual abilities. The ABC-DS study is evaluating a battery of nearly a dozen cognitive tests, some of which can be readily used in the clinic as potential screening tools to evaluate for Alzheimer's disease-related cognitive decline. By correlating cognitive decline with new and innovative biomarkers, clinical staging will be grounded in Alzheimer's disease pathology and will allow for efficient clinical trial designs.

Beyond the further development of biomarkers such as amyloid PET, Tau PET and plasma NF-L in staging Alzheimer's disease in Down syndrome, as well as valid cognitive assessment tools linked to these biomarkers, more work is needed to understand the pharmacokinetic and pharmacodynamic features of compounds being tested for Alzheimer's disease in people without Down syndrome. In addition, other drugs that target different aspects of the amyloid cascade, including modulation amyloid precursor protein (APP) expression , apolipoprotein e protein or

tau will need to be considered and developed, as well as drugs aimed at modifying the immune status in Down syndrome, which is also thought to contribute to development of Alzheimer's disease-related brain pathology. Identification of sensitive and accurate tests that quantify the earliest signs of Alzheimer's disease-related cognitive decline in adults with Down syndrome, across all ranges of intellectual function will also be extremely helpful for diagnosis and prognosis as well as in the design of preclinical Alzheimer's disease trials.

DIABETES

Recommendation

5. For asymptomatic adults with Down syndrome, screening for type 2 diabetes mellitus (T2DM) using hemoglobin A1c (HbA1c) or fasting plasma glucose should be performed every 3 years beginning at age 30.
6. For any adult with Down syndrome and comorbid obesity, screening for T2DM using HbA1c or fasting plasma glucose should be performed every 2—3 years beginning at age 21.

[**Strength of Recommendation:** Weak For]

Discussion

The recommendations are based on the following considerations:

- Diabetes is a common concern for adults with Down syndrome, their families, and caregivers due to obesity's high prevalence in Down syndrome, a known risk factor for diabetes in adults without Down syndrome.
- The potential benefits of making an early diagnosis, such as reducing the development of neuropathy, retinopathy, and kidney disease associated with T2DM, likely outweigh the potential harms associated with diabetes treatment (such as hypoglycemia, medication side effects).
- Most or all adults with Down syndrome, their families, or caregivers would place high value on having this information when used to improve diagnosis and treatment outcomes.

One large high quality U.K. study including over 3,800 individuals found the prevalence of diabetes was significantly higher in adults with Down syndrome compared to adults without Down syndrome, although the study did not distinguish between Type 1 and Type 2 diabetes mellitus (DM).[61] Prevalence of diabetes for ages 16—30 years and ≥30 years was 3.5% and 5.5% for adults with Down syndrome, compared to 0.7% and 2.7% in matched controls from the general population. Another small Canadian study[84] also directly compared diabetes prevalence, but found no difference; however, the GLOBAL Workgroup felt this study's small sample size, and lack of clear population-based sampling frame rendered the data not applicable.

In people without Down syndrome, chronic hyperglycemia secondary to uncontrolled diabetes is associated with retinopathies, neuropathies, nephropathies, and cardiovascular/vessel damage.[85] Early detection and prompt effective treatment may reduce the burden of the disorder and long-term complications.[86] However, the evidence report identified no studies assessing whether screening asymptomatic adults with Down syndrome for diabetes was associated with improved clinical outcomes. Of note, even the most recent U.S. Preventive Services Task Force (USPSTF) guidelines for diabetes screening concluded that evidence is inadequate to determine the direct benefits and harms of screening versus no screening in people without Down syndrome.[85] Despite the absence of studies demonstrating direct benefit in adults with Down syndrome, given

the potential benefits of avoiding long-term complications, the GLOBAL Workgroup supports screening for adults with Down syndrome.

The American Diabetes Association (ADA) recommends screening for abnormal blood glucose and T2DM in all adults beginning at age 45.[87] However, due to the premature aging in adults with Down syndrome, the earlier onset of some conditions (e.g., cataracts), which can also be increased in diabetes, and the higher prevalence of impaired function in organ systems affected by diabetes (e.g., peripheral nervous system and kidneys), the GLOBAL Workgroup concluded that earlier screening is warranted.[88- 90] Thus, we recommend screening every 3 years beginning at age 30 for all adults with Down syndrome. The ADA also recommends individuals who are who are overweight or obese (BMI ≥25) with one additional risk factor begin screening for abnormal blood glucose every 3 years and T2DM after puberty.[87] Due to the high prevalence of obesity and the benefit of earlier detection, for adults with Down syndrome and obesity, screening should be initiated at age 21 and repeated every 2—3 years with or without the presence of an additional risk factor outlined in the ADA.

In addition to potentially identifying pre-diabetes, screening may alleviate concerns for those with positive family histories of T1DM or T2DM who may be concerned about the development of diabetes. Potential harms associated with earlier screening include temporary discomfort due to the related blood draw and overtreatment of diabetes after diagnosis, which can lead to stringent control of blood sugars, severe dietary restrictions, and the potential use of nonbeneficial medications leading to hypoglycemia and other side effects. Despite these potential harms, the GLOBAL Workgroup recognizes that potential benefits likely outweigh the possible harms. In addition, knowledge of the risks of and /or the presence of diabetes can motivate the adult to improve his or her overall lifestyle. As for any individual, the goals of glycemic control need to be individualized and should be made in discussion with the adult with Down syndrome, their families, and caregivers. It is important to note that childhood cancer and use of antipsychotics, both known risk factors for diabetes,[91, 92] are more common in people with Down syndrome.[2, 61]

Future Research

Additional research is needed to determine whether the macro-/microvascular complications, tissue damage, and end-organ damage in adults with Down syndrome associated with untreated T2DM parallel those observed in individuals without Down syndrome. Since altering diet and adhering to exercise programs can be difficult and because glycemic control medication treatment can be challenging and result in complications, it is important to study whether early treatment of T2DM reduces the extent of tissue and end-organ damage to reduce/prevent treatment-associated complications. Specific genetic risk factors have not been proven for T2DM's development in adults with or without Down syndrome. Multiple genes might possibly be involved to some extent. Limited studies indicate that obesity, along with environmental factors, appear to provide the greatest risk for T2DM in adults with Down syndrome.[93] Future research is needed to confirm the risk association with obesity and to determine specific contributions of the extra genes from chromosome 21 regarding T2DM's development. Understanding which genes on chromosome 21 may be contributing to disease could result in future targeted therapies regarding T2DM.

Research is also needed to define the true prevalence of and risk factors for T1DM in adults with Down syndrome. Several publications document increased rates of T1DM in children with Down syndrome,[94-96] but definitive figures are not available for adults, and genetic and/or immunological risk factors remain to be identified.

CARDIOVASCULAR DISEASE -ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

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 and using a 10-year risk calculator as recommended for adults without Down syndrome by the U.S. Preventive Services Task Force.[29]

[**Strength of Recommendation:** Weak For]

Discussion

The recommendation is based on the following considerations:

- Heart disease is the leading cause of death in the United States, and coronary artery disease is the leading cause of heart disease.[97]
- The limited available data show a moderately reduced, but not low, risk of ischemic heart disease in people with Down syndrome.
- Most adults with Down syndrome, their families, and caregivers will place high value on having this information to understand their risk and consider modifying risk factors.

Evidence from two trials suggests adults with Down syndrome may have a reduced risk of ischemic heart disease. Sobey et al.[98] directly compared atherosclerotic events in hospitalized Australian adults with Down syndrome compared to matched controls without Down syndrome. The number of myocardial infarction events was similar for patients <50 years, but significantly lower in adults with Down syndrome compared to adults without Down syndrome for patients >50 years (8.1% vs. 13.3%). Since this study only captured hospitalized patients, these likely represent overestimates for prevalence of events, but nevertheless could suggest lower comparative prevalence in adults with Down syndrome. A second large study of U.K. patients reported a mildly lower incidence of heart disease in adults with Down syndrome compared to adults without Down syndrome (incidence rate ratio 0.9) with an overall prevalence of 1.5% for adults with Down syndrome ≥ 30 years.[61] Although the prevalence estimate in Alexander et. al[61] is only mildly lower for adults with Down syndrome, we believe the findings might overestimate the incidence because in the GLOBAL Workgroup's experience, the prevalence of coronary artery disease in adults with Down syndrome is even lower. In addition, the Alexander study did not distinguish between atherosclerotic ischemia versus nonatherosclerotic ischemia from conditions such as sleep apnea, congenital heart disease, and pulmonary hypertension, all of which are more common in this population[61] and have been noted in the GLOBAL Workgroup's experience to cause ischemic heart disease in adults with Down syndrome.

The 2016 USPSTF guidance recommends screening for hyperlipidemia in all adults aged 40—75 as part of assessing cardiovascular risk and use of a 10-year risk calculator as a starting point for consideration of pharmacotherapy.[29] While screening and treatment of hyperlipidemia is

beneficial in adults without Down syndrome, no studies have evaluated whether elevated lipid levels are similarly predictive of atherosclerotic cardiovascular disease (ASCVD) for adults with Down syndrome. The clinical experience of GLOBAL Workgroup members suggests ASCVD is less common in adults with Down syndrome, but given the limitations of existing research, the GLOBAL Workgroup felt there was not sufficient justification to recommend adults with Down syndrome be treated differently than adults without Down syndrome. Thus, we recommend using a 10-year risk calculator, personalizing the goals for lipid management, and discussing with the adult with Down syndrome, their family, and caregivers.

USPSTF does not recommend treating hyperlipidemia in adults without Down syndrome over age 75. Similarly, the American Board of Internal Medicine Choosing Wisely campaign recommends against routinely prescribing lipid-lowering medications in individuals with a limited life expectancy.[99] Older observational evidence suggests there may be an association between lower cholesterol levels and an increased risk of mortality with advanced age, after adjusting for other risk factors.[100, 101] Some recent data, however, suggest there may be a benefit in treating hyperlipidemia in older individuals without Down syndrome.[102-104] 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.[105]

Potential benefits to screening include reduction of cardiovascular events. In addition, the GLOBAL Workgroup notes that families, especially those with positive family histories for ischemic heart disease, are concerned that ischemic heart disease may develop in their adult with Down syndrome and often express interest in screening as recommended by USPSTF. To date, no data indicate whether family history is a risk factor for atherosclerotic disease similar to those without Down syndrome.

In addition to these potential benefits, the GLOBAL Workgroup considered potential harms including issues cooperating with phlebotomy, the unknown side-effect profile of cholesterol-lowering medications in adults with Down syndrome, this population's limited ability to articulate discomfort (including side effects), and the potential for polypharmacy.

The potential for memory impairment (which has been raised as a suspected side effect of statins) is of particular concern for adults with Down syndrome over age 40 as Alzheimer's disease is more common and occurs at a younger age in this population. Although the specific impact of statins on cognitive function in adults with Down syndrome has not been studied, well done studies such as, Chou et al. have found no clear increase in risk observed in those without Down syndrome.[106]

Future Research

Further studies to assess the incidence of atherosclerotic disease in people with Down syndrome is warranted. Additional studies should be done to evaluate modifiable risk factors for atherosclerotic disease in adults with Down syndrome and to better understand which risk factors identified are relevant for this population regarding disease prevention. Further study is needed regarding the effect of early aging and a shorter life expectancy in this population and the implications for screening and treating atherosclerotic risk factors. Future research to address

the prevalence of and risk factors for atherosclerotic and nonatherosclerotic cardiac ischemia by decade of life would also be useful to help identify best practices for the timing and frequency associated with screening and potential therapeutics.

Additional research is needed regarding the interplay between liver function, cholesterol metabolism, vascular biology, and immune function to elucidate why adults with Down syndrome do not show increased rates of atherosclerotic disease despite the presence of risk factors associated with atherosclerosis in adults without Down syndrome, such as obesity and increased inflammatory markers. This may provide important information as it relates to treatment of atherosclerosis in people with and without Down syndrome.

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 *Guidelines for the Primary Prevention of Stroke*.[30]
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.

[**Strength of Recommendation:** Weak For]

Discussion

The recommendations are based on the following considerations:

- Stroke is a leading cause of death in the United States.
- Congenital heart disease is more common in people with Down syndrome.
- Adults with Down syndrome with a history of congenital heart disease have an elevated risk of cardioembolic stroke.
- Most adults with Down syndrome, their families, and caregivers will place high value on having this information to understand their risk and take appropriate health measures.

Only one study[98] compared the number of strokes in adults with Down syndrome to adults without Down syndrome. Compared to the matched controls, the number of strokes were higher for adults with Down syndrome for both the 19—50 and >51 age groups (9.8% vs. 4.9% for adults ≥51 years). Mean age at first cerebrovascular event was 41.8 (SD 22.8) years in those with Down syndrome and 57.1 (SD 17.9) years in those without Down syndrome. Cardioembolic strokes were the most common stroke type. Of note, this study compared only hospitalized patients with and without Down syndrome and did not delineate between ischemic and hemorrhagic stroke. Furthermore, the study provided no details about microangiopathic disease, a potential cause of stroke related to amyloid accumulation, which is associated with Alzheimer's disease and is more common in people with Down syndrome.[107] No prevention for this type of stroke is currently available.

An increased number of strokes in adults with Down syndrome is consistent with known risk factors. Interestingly, hypertension (a common stroke risk factor), is less common in adults with Down syndrome. One study by Alexander et al. reported an incidence rate ratio of 0.3 (for adults with Down syndrome compared to adults without Down syndrome).[61] However, in the GLOBAL Workgroup's clinical experience, the incidence of hypertension is likely even lower. Several common co-morbidities in adults with Down syndrome increase stroke risk including previous and/or persistent congenital heart disease, moyamoya disease,[108] and obstructive sleep apnea.[8, 109] A large Canadian study found that among adults without Down syndrome with congenital heart disease, which increases stroke risk by altering flow and rhythm disturbance, 1 in 11 men and 1 in 15 women experienced a stroke between 18 and 64 years.[110] The CDC reports that about 50% of children with Down syndrome are born with congenital heart disease.[111] Although data is lacking regarding the

prevalence of adults with Down syndrome with congenital heart disease, it would be expected to rise along with increasing survival and life expectancy. In addition, deep vein thrombosis in individuals with septal defects and persistent patent foramen ovale can result in strokes. Based on the GLOBAL Workgroup's clinical experience, appropriate assessment, monitoring, and treatment of these conditions should be considered, although studies have not yet been performed to assess whether this will reduce stroke risk.

Assessment for hyperlipidemia is recommended (see Recommendation 7). The AHA/ASA *Guidelines for Primary Prevention of Stroke* offer guidance including a risk assessment tool for risk of first stroke, and addressing other risk factors such as physical inactivity, obesity and body fat distribution, atrial fibrillation, and other cardiac conditions.[30]

Each individual undergoing the assessments and interventions for conditions discussed above have unique abilities to tolerate testing, whether due to a difference in risk of complications or the need for sedation to undergo testing. This is particularly true for adults with Down syndrome, and these factors should be included in the discussion with the adult with Down syndrome, their family, and caregivers as part of a monitoring plan. In addition, access to a cardiologist familiar with congenital heart disease and caring for adults with Down syndrome may affect the monitoring plan. We recommend a cardiologist determine the appropriate monitoring plan and schedule, based on a review of the type of congenital heart disease, the type of surgery performed, and other clinical factors, in addition to considering guidelines such as the AHA/ASA *Guidelines for the Primary Prevention of Stroke*[30] and the American Heart Association/American College of Cardiology *Guideline for the Management of Adults With Congenital Heart Disease*.[112]

Future Research

Future research to address the prevalence of and risk factors for thromboembolic and hemorrhagic stroke by decade of life would be useful, including understanding the impact of microangiopathic disease. In addition, research regarding the benefit of modifying risk factors will improve future guideline recommendations. As per the GLOBAL Workgroup's recommendations for atherosclerotic cardiac disease, limited data guide recommendations for screening and treating risk factors for atherosclerosis. The benefit of lowering lipid levels in adults with Down syndrome to prevent stroke is not known, and further study is warranted. In addition, further study is needed to understand screening and prevention of potential long-term complications for adults who have had congenital heart disease.

Future research is also needed to define the lifelong multidimensional impacts of congenital heart disease, even if repaired by surgery, on metabolism, cardiovascular function, immune responses (especially in cases involving thymectomy during heart surgery) and how these events may modify the risk of stroke, pulmonary hypertension, autoimmune disorders and other comorbidities.[113-115] Future research will also be needed to better understand difference in the thrombosis and coagulation cascades in Down syndrome[116] and how these may impact the risk of stroke.

OBESITY

Statement of Good Practice 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.

Discussion

The statement of good practice is based on the following considerations:

- Obesity is common in adults with Down syndrome; thus, overweight-obesity and health-related consequences are common concerns for adults with Down syndrome, their families, and caregivers.
- Most or all adults with Down syndrome, their families, and caregivers would highly value being able to reduce health-related consequences of overweight-obesity.

In the GLOBAL Workgroup's experience, overweight-obesity and health-related consequences are frequently identified as issues of concern by adults with Down syndrome, their families, and caregivers. Maintaining a healthy diet, controlling appetite, monitoring portion control, having consistent mealtimes and exercising regularly are generally recognized approaches to maintaining good health and quality of life.

The GLOBAL Workgroup's experience supports building fitness into daily routines and encouraging a focus on activities that foster socialization and limit sedentary behavior. The GLOBAL Workgroup recommends shared decision-making in diet and activity choices. Structured exercise and nutrition programs require deliberate planning and engagement of the adult, family members, and caregivers including those at day programs, group homes, and schools.

Recommendation

10. Monitoring for weight change and obesity should be performed annually by calculating body mass index (BMI) in adults with Down syndrome. The U.S. Preventive Services Task Force (USPSTF) Behavioral Weight Loss interventions to Prevent Obesity-Related Morbidity and Mortality in Adults should be followed.[31]

[**Strength of Recommendation:** Weak For]

Discussion

The recommendation is based on the following considerations:

- Obesity is common in adults with Down syndrome; thus, overweight-obesity and health-related consequences are common concerns for adults with Down syndrome, their families, and caregivers.
- The benefits of maintaining an optimal weight and BMI appear to outweigh the potential harms of monitoring for obesity and recommending appropriate treatments.

- Most or all adults with Down syndrome, their families, and caregivers would place high value on being able to reduce health-related consequences of overweight-obesity.

No literature reviewed reported on the effect of a healthy diet, regular exercise, and/or calorie management on medical complications of obesity in adults with Down syndrome. The quality of evidence for weight loss interventions in this population was low, with multiple small studies of short duration and large confidence intervals showing no statistically significant change in BMI or body fat composition.[117, 118] These studies also excluded adults with Down syndrome who had other co-occurring medical conditions, including orthopedic issues, cardiac problems, or metabolic disease, which dramatically limits its generalizability to the adult Down syndrome population. Adults with Down syndrome 40 years of age or older already exhibit multiple medical issues typically seen in the geriatric population.[119]

The absence of weight loss reported in these studies is not surprising because the programs studied focused on exercise intervention only, without a calorie restriction or dietary component. Programs with combined exercise and dietary components have been more effective in obese adults without Down syndrome but have not yet been studied in adults with Down syndrome.[120] In terms of other outcomes, statistically significant improvement occurred in cardiovascular fitness in select studies of adults with Down syndrome, while other studies showed that exercise improved balance, muscle strength, and endurance.[121] Despite the absence of group effect, benefits were limited for some individuals – for example, in one case series of 6 adults with Down syndrome, after a swim intervention, one adult no longer required insulin for diabetes.[122]

Several factors identified in the literature and supported by the GLOBAL Workgroup's clinical experience may predispose this population to weight gain, including lack of control over their environments, exposure to poor food choices, and lack of nutritional guidance. Medical conditions such as hypothyroidism, obstructive sleep apnea, and certain medications such as oral estrogens and psychotropics used to treat depression or other mental illness may contribute to weight gain.[123, 124] The GLOBAL Workgroup also noted that poor appetite-satiety control and a preference for unhealthy foods also contribute to obesity.

Adults with Down syndrome face several barriers to sustained physical activity. Physiologic differences in autonomic function, including low heart rate and low blood pressure, may make exercise less efficient or poorly tolerated.[125] The GLOBAL Workgroup also noted that mental health disorders, such as depression, fatigue, and low motivation, can create barriers to sustained physical activity. The presence of joint hyper flexibility, low muscle tone (hypotonia), and issues with balance (likely associated with documented cerebellar atrophy), may impose additional obstacles for some types of physical activity. Having multiple medical comorbidities (neurologic, musculoskeletal, cardiac, and pulmonary) is another challenging and common barrier to achieving physical fitness in this population.

Despite obesity's high prevalence and the multiple barriers discussed, the GLOBAL Workgroup notes that not all adults with Down syndrome will become obese. Clinical inertia and the above-mentioned barriers may lead clinicians to ignore or minimize viewing obesity as a modifiable condition in adults with Down syndrome. It may be difficult to overcome prevalent attitudes that question whether obesity can be treated once present, but the GLOBAL Workgroup noted

that weight gain may be driven primarily by a lack of physical activity and/or unhealthy eating habits. Families that take decisive action may help their family member with Down syndrome stabilize or lose weight. In the GLOBAL Workgroup's experience, adults have achieved success when participating in highly social group activities (e.g., dance, Zumba), working with a personal trainer, or participating in team sports through Special Olympics.

Despite the lack of reliable data reporting effects from comprehensive programs combining diet and exercise in this population, we believe adherence to USPSTF guidelines, including intensive behavioral intervention as appropriate, would also benefit adults with Down syndrome.[126] Evidence suggests exercise is generally safe in this population, with the caveat that most studies did not report comorbid medical illnesses which may require exclusion or limited participation.[121]

To remain vigilant about obesity, accurate and timely weight measures and BMI monitoring are imperative. The GLOBAL Workgroup's experience finds that rapidly changing weight and BMI may be reasons for concern and intervention even if not yet in the range of obesity (BMI >30 kg/m2).

Future Research

Future research could focus on the physiologic regulation of weight, energy metabolism, and appetite regulation in adults with Down syndrome. Special emphasis should be devoted to known pathways regulating these processes, such as leptin and ghrelin hormonal circuitries, whose dysregulation could affect appetite control in people with Down syndrome.[127] Additional studies should focus on the impact of other comorbidities such as obstructive sleep apnea and hypothyroidism, which are known to affect these physiological processes in people without Down syndrome.[128, 129] Studies of liver function, adipose tissue biology, and the oral and gut microbiome would likely reveal additional information in this regard. Recent studies have shown increased prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) in children with Down syndrome,[130] but the impacts of these findings on health outcomes into adulthood remains to be defined.

Studies on the health consequences of overweight and obesity in adults with Down syndrome would also help guide future health care recommendations. Mental health issues, such as depression and the specific medical conditions that create barriers to maintaining fitness and sustained physical participation in exercise, need to be better understood in this population. Further modification and adaptation to existing fitness strategies should continue in an effort to remove existing barriers whenever feasible, including studies of different exercise modalities that could address the issue of joint hyperflexibility, hypotonia, and decreased cerebellar function.[131-133]

ATLANTOAXIAL INSTABILITY

Recommendation

11. In adults with Down syndrome, routine cervical spine X-rays 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 a review of signs and symptoms of cervical myelopathy using targeted history and physical exam.

[**Strength of Recommendation:** Weak Against]

Discussion

The recommendation is based on the following considerations:

- Atlantoaxial instability (AAI) by radiographic criteria occurs in about 10% of adults with Down syndrome; however, spinal cord injury resulting directly from radiographic AAI appears to be uncommon among adults with Down syndrome.
- No studies have examined whether a correlation between AAI detected on X-rays and incidence of spinal cord injury exists.
- Screening asymptomatic individuals with X-rays not only contributes to potentially unnecessary costs but may result in unnecessary restriction of individuals in participation from physical activities.
- Looking for signs of myelopathy using a targeted history and physical exam is low cost and low risk.
- A shared decision-making approach highlighting potential benefits and harms of restricting participation in high risk activities should be employed.

AAI, as identified by cervical spine X-rays, occurs in about 10% of adults with Down syndrome.[7, 134] One cross-sectional study of 197 individuals with Down syndrome in Australia ages 16—31 years found the incidence of AAI to be 8.1%.[134] A Spanish retrospective chart review assessed prevalence of atlantoaxial subluxation in all people with Down syndrome 17—65 years old followed by a large tertiary referral center.[7] In 144 individuals, the prevalence of atlantoaxial subluxation on radiographs was 11% in individuals ages 17—35 years, 2% in those ages 30—39 years, and 0% in those age 40 years or older. Notably, neither study stated whether the individuals in the normal or instability/subluxation groups had any signs or symptoms of myelopathy.

Using cervical X-ray to identify AAI is intended to identify individuals at risk for spinal cord injury with physical activity. However, aside from these moderate quality studies reporting on prevalence of AAI, evidence regarding how to manage AAI remains sparse. For instance, no studies have assessed whether screening asymptomatic adults with Down syndrome using cervical X-ray impacts risk of spinal cord injury. Similarly, no studies have assessed whether individuals for whom AAI is identified on cervical spine X-rays are at higher risk of progression to spinal cord injury.

The GLOBAL Workgroup noted reported cases of spinal cord injury in people with Down syndrome resulting from AAI are relatively uncommon. The 1995 American Academy of Pediatrics (AAP) Committee on Sports Medicine's publication *Atlantoaxial Instability in Down Syndrome: Subject Review* noted only 41 well-documented cases of symptomatic AAI that had been described in the published literature.[135] In addition, Special Olympics organizers report no spinal cord injuries from over 50,000 individuals with Down syndrome participating in Special Olympics activities over 20 years.[136]

Avoiding spinal cord injury is important, given the potential for significant morbidity and even death. However, the benefits of screening asymptomatic individuals using cervical X-ray are uncertain. Potential burdens of obtaining cervical X-rays include additional cost and radiation exposure, as well as the restriction of individuals identified as having AAI from participation in physical activities, which can be beneficial for physical and psychological health. GLOBAL Workgroup members acknowledge that adults with Down syndrome and families/caregivers may differ in their preferences for risk. Thus, a shared decision-making approach highlighting potential benefits and harms of restricting participation in high risk activities should be employed.

If common symptoms or signs of spinal cord compromise are identified, an appropriate workup (including X-rays and further imaging) is indicated. Common symptoms of spinal cord compromise noted by the GLOBAL Workgroup include altered gait, weakness in the legs, weakness in the hands (dropping objects), new incontinence, or difficulty with holding the head up. Additional signs present on physical exam include weakness in one or both arms and/or legs, abnormal tendon stretch reflexes, clonus, or an abnormal plantar reflex.

Future Research

Research is needed to better understand symptomatic AAI's true incidence 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. Research is also needed to better understand whether screening for myelopathy with a targeted history and physical exam have good predictive value for pathology. For symptomatic individuals, there could be huge benefit in studying the comparative impact on morbidity and mortality of a conservative approach (watchful waiting) versus surgical intervention. The practice of universal precautions would support medical providers practicing proper neck positioning for all people with Down syndrome during all medical procedures or treatments and a future study on compliance related to this practice could underscore opportunities to improve medical education. In addition, further review is needed on the impact of activity restriction as a preventative measure and on overall wellbeing.

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.

[**Strength of Recommendation:** Neither for nor against]

Discussion

The recommendation is based on the following considerations:

- Evidence is inadequate regarding osteoporosis prevention in adults with Down syndrome, including when to screen for osteoporosis, how to interpret bone mineral density (BMD) values, what the thresholds should be for initiating pharmacotherapy, and how to choose pharmacotherapy agents.
- There is no evidence comparing effectiveness of preventive measures in people with Down syndrome versus without Down syndrome.
- Available fracture risk estimate models have been derived from epidemiologic data of adults without Down syndrome.
- Epidemiology of fragility fractures in adults with Down syndrome is poorly understood but likely differs significantly from adults without Down syndrome.
- A shared decision-making discussion should include potential risks, benefits, and uncertainties around osteoporosis screening and potential preventive measures, including medications, exercise and vitamin D supplementation.

Osteoporosis is an age-associated metabolic bone disease characterized by altered skeletal microarchitecture and abnormal bone mineral turnover, leading to increased fracture risk. Clinical decisions relating to osteoporosis screening, diagnosis, prevention, and treatment are predicated on knowledge of a population's epidemiology of skeletal fractures.

The most commonly utilized fracture risk model, the Fracture Risk Assessment Tool (FRAX), was derived from studies involving 60,000 men and women without Down syndrome.[137] Since adults with Down syndrome in general bear a lower life expectancy, lower bone mineral density, and greater risks for secondary causes of osteoporosis, the FRAX model would not be expected to accurately predict fracture risk in adults with Down syndrome.

Additionally, interpreting standard BMD data is complicated in clinical populations whose phenotypes are associated with small body size and/or short stature, (e.g., adults with Down syndrome) and may require volumetric BMD measurement or other ways of measuring bone characteristics relevant to fracture risk rather than relying on BMD.[138] Carfi et al. compared BMD of 234 Italian adults with Down syndrome, mean age 37 years with comparative data derived from United States National Health and Nutrition Survey 2009—2010 dataset. Stratifying for age, femoral neck adjusted BMD was significantly lower for the cohort with Down syndrome age 40

years and older; lumbar spine adjusted BMD was significantly lower for the cohort with Down syndrome for age all groups except those over age 60.[138] It is impossible to interpret and clinically apply these study findings without corresponding knowledge of this population's epidemiology of fragility fractures.[138, 139] In addition, no studies have critically examined the clinical utility of Dual-energy X-ray absorptiometry (DEXA) screening for osteoporosis in adults with Down syndrome.

Bisphosphonates are the most common drug prescribed for preventing and treating osteoporosis. Preliminary data based on post-mortem histologic assessment of a single individual with Down syndrome[140] and a small study examining bone turnover markers[141] have suggested that reduced bone formation, rather than excessive bone resorption, may drive the skeletal dynamics observed in adults with Down syndrome; however these findings have not been consistently observed.[142] Non-bisphosphonate medications may eventually prove to be the most efficacious treatment for osteoporosis in adults with Down syndrome.[143] However, no data are available on the comparative safety or efficacy of bisphosphonates or any other osteoporosis therapy in adults with Down syndrome. Serious adverse effects of bisphosphonates include esophageal ulceration from tablets lodged in the esophagus; this is of particular concern in adults with Down syndrome, who have high rates of esophageal dysmotility.[144] There is significant potential for overuse of bisphosphonate therapy in adults with Down syndrome solely based on low BMD values without clarity about therapeutic benefit or potential harm.

The GLOBAL Workgroup was concerned that applying diagnostic and treatment algorithms developed and validated for adults without Down syndrome at average risk for osteoporosis could lead to over-diagnosis and potentially ineffective and/or harmful treatment in adults with Down syndrome. Thus, given the present state of inadequate evidence to support osteoporosis screening in adults with Down syndrome, in individuals without a history of fragility fracture, we recommend a shared decision-making model to frame discussions about potential risks, benefits, and uncertainties around osteoporosis screening, relevant nutritional intake (e.g., calcium and vitamin D) and preventive medications in adults with Down syndrome.[144] Such discussion should include the potential value of weight-bearing exercise on bone health; evidence suggests this is generally safe in this population, with the caveat that most studies did not report comorbid medical conditions, which may require exclusion or limited participation.[121]

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.

[**Strength of Recommendation:** Weak For]

Discussion

The recommendation is based on the following considerations:

- Potential secondary etiologies of osteoporosis are more prevalent in adults with Down syndrome than in adults without Down syndrome.

- Many of these conditions are treatable without significant burdens to the adult with Down syndrome.
- Recognizing and ameliorating secondary etiologies of osteoporosis in adults with Down syndrome may lead to health benefits beyond the potential impact on fracture risk.

In adults with Down syndrome, potential risk factors for osteoporotic fracture include physical inactivity[145] and medical conditions associated with secondary osteoporosis, such as hypogonadism,[146] premature menopause,[147] hyperparathyroidism[148] and disorders associated with malabsorption, such as celiac disease.[149] All of these risk factors for secondary osteoporosis appear to be more prevalent in individuals with Down syndrome when compared to their prevalence in adults without Down syndrome.[150] No studies have assessed the impact of identifying and treating secondary causes of osteoporosis in adults with Down syndrome on clinical outcomes. However, given the higher prevalence of these secondary causes of osteoporosis, and the fact that many of these conditions can be corrected with accrual of health benefits in addition to improved bone health, the GLOBAL Workgroup recommends pursuing a medical evaluation for secondary causes of osteoporosis.

In adults without Down syndrome, the role of vitamin D supplementation for preventing and treating osteoporosis is undergoing critical review and reassessment.[151] Vitamin D deficiency and insufficiency are common in adults with Down syndrome. In addition, low-quality evidence suggests that secondary hyperparathyroidism due to vitamin D deficiency, a secondary cause of osteoporosis, may be more prevalent in adults with Down syndrome, and that vitamin D supplementation may normalize elevated parathyroid hormone levels and improve bone turnover markers.[152] In these studies, it appears that vitamin D supplementation in adults with Down syndrome was not associated with harm.[148, 152]

In addition to considerations related to vitamin D intake, the GLOBAL Workgroup advises a comprehensive approach to preventing osteoporosis and its complications, including assuring an adequate dietary intake of calcium, fall risk reduction measures, optimizing vision, and promoting weight-bearing physical activity, as is recommended for adults without Down syndrome.[153]

Future Research

Research priorities related to bone health in adults with Down syndrome must begin with a core understanding of the epidemiology of skeletal fracture and identification of risk factors specific to this population. From this information, fracture predictive models specific to Down syndrome can be derived. The predictive role and value of BMD or other measures of bone quality need to be clarified. The comparative effectiveness of medications and other interventions for prevention and treatment of osteoporotic fracture in adults with Down syndrome requires careful study.[143] Future research is also needed to determine if people with Down syndrome show difference in the activity of osteoblast and osteoclasts across the lifespan, whether bone mineralization and turnover rates vary in adults with Down syndrome, as well as the role of genes on chromosome 21 on these processes.[154, 155] Results from this research could lead to more immediate diagnostics and treatments specific to individuals with Down syndrome.

THYROID

Recommendation

14. Screening adults with Down syndrome for hypothyroidism should be performed every 1—2 years using a serum thyroid-stimulating hormone (TSH) test beginning at age 21.

[**Strength of Recommendation:** Weak For]

Discussion

The recommendation is based on the following considerations:

- Hypothyroidism's prevalence is elevated in adults with Down syndrome and continues to rise throughout the individual's life.
- Screening based solely on symptoms is difficult. Fatigue, weight gain, and constipation are common in adults with Down syndrome. This likely decreases the diagnostic accuracy of medical history and examination.
- Serum TSH is the best single screening test for hypothyroidism for the vast majority of outpatient clinical situations.
- In the opinion of some GLOBAL Workgroup members, also testing to measure free T4 levels may help guide treatment decisions.[156] This may be performed concomitantly with the TSH (for practical reasons) or subsequently (if TSH is abnormal).
- In the GLOBAL Workgroup's experience, identifying hypothyroidism with subsequent treatment produces better clinical outcomes than waiting to begin treatment after overt signs and symptoms present.
- Treatment with thyroid hormone supplementation is inexpensive and safe with individualized monitored follow-up.
- Given the myriad potential complications and organ systems involved in hypothyroidism, adults with Down syndrome, their families, and caregivers are likely to agree that the potential benefits of laboratory screening outweigh the risks.

Three studies (ranging from low to high quality) all demonstrate that the prevalence of hypothyroidism is higher in adults with Down syndrome compared to adults without Down syndrome.[7, 61, 157] Collectively, these studies captured over 4,000 individuals and identified hypothyroidism prevalence from 39—61%. This rate is substantially higher compared to prevalence in adults without Down syndrome in the United States: about 5.9% in women and 2.3% in men over age 60 years.[158] Furthermore, studies that reported prevalence by age suggest prevalence increases with age. For instance, a large U.K. study[61] of over 3,800 individuals found prevalence increased from 39% for adults with Down syndrome <30—51% in adults ⩾ 30 years. Importantly, although hypothyroidism is more common among females in people without Down syndrome, this sex bias is not observed in people with Down syndrome, with both sexes being at high risk for hypothyroidism.[159, 160]

Identifying hypothyroidism in adults with Down syndrome presents distinctive challenges. Symptoms such as weight gain and constipation which are commonly associated with hypothyroidism in adults are common regardless of thyroid status. In the GLOBAL Workgroup's experience, no symptoms are pathognomonic of hypothyroidism. In addition, adults with Down syndrome may have difficulty recognizing or clearly verbalizing symptoms such as fatigue and temperature intolerance, which may complicate recognition of truly symptomatic individuals. For these reasons, relying solely on symptoms and signs to prompt screening is inadequate. The GLOBAL Workgroup concluded that to identify this treatable condition for adults with Down syndrome requires routine laboratory screening every 1—2 years based on the discretion of the clinician after taking individual patient risk, harms, and preferences into account.

No studies have assessed whether screening with TSH or T4 levels improve clinical outcomes in adults with Down syndrome. However, given hypothyroidism's high prevalence, the GLOBAL Workgroup felt screening serum TSH offers more benefits than risks. Additionally, some but not all GLOBAL Workgroup members felt measurement of free T4 levels may also help guide treatment decisions.[156] This may be performed concomitantly with the TSH (for practical reasons) or subsequently (if TSH is abnormal). Potential burdens associated with testing include issues with phlebotomy, such as anxiety and time. However, accurate identification of hypothyroidism offers significant benefits. Hypothyroidism can cause mental changes and weight gain which, once present, may be devastating and difficult to correct. Treatment of hypothyroidism, when monitored, is safe and may ameliorate some of the challenges adults with Down syndrome experience like constipation, dry skin and fatigue. Therefore, testing asymptomatic adults with Down syndrome is very likely to produce more benefit than harm.

Future Research

Research is needed to identify adverse medical outcomes as well as potential social and psychological impacts of untreated hypothyroidism. Studies are needed to determine the precise TSH level at which problems manifest and over what time frame these can be corrected with treatment. Detailed characterization of the immune system by decade of life is necessary to better characterize normal cutoff values and the range of antibodies present in adults with Down syndrome. A better understanding of normal values with clinical correlation may be significant not only for thyroid disease, but also the spectrum of autoimmunity (systemic lupus erythematosus, celiac, dermatologic conditions) more common in Down syndrome. Research regarding the clinical application of predictive biologic markers (antithyroid antibodies) and the discovery of new markers (proteomic and molecular DNA) that predate disease are specifically apropos in this population.

In addition, there is strong evidence to support the notion that hypothyroidism in people with Down syndrome is caused by autoimmune thyroid disease (AITD). Many studies have documented that autoantibodies targeting the thyroid gland associate with the severity of hypothyroidism in Down syndrome,[159-162] and both Grave's disease and Hashimoto's disease are more prevalent in Down syndrome.[163] Given that autoimmune disorders tend to cluster in people without Down syndrome, a diagnosis of hypothyroidism in a person with Down syndrome could potentially indicate a higher risk of other autoimmune conditions more common in this population, such as celiac disease or various autoimmune skin disorders more common in Down syndrome (e.g., atopic dermatitis, alopecia areata, psoriasis, hidradenitis suppurativa, vitiligo).[163]

CELIAC DISEASE

Statement of Good Practice 4

> Adults with Down syndrome should receive an annual assessment for gastrointestinal and non-gastrointestinal signs and symptoms of celiac disease using targeted history, physical examination, and clinical judgement of good practice.

Discussion

The statement of good practice is based on the following considerations:

- Studies have found celiac disease is more common in people with Down syndrome than in people without Down syndrome.
- Signs and symptoms may be difficult to detect in some adults with Down syndrome due to communication difficulties, and signs and symptoms may be overlapping with other common comorbidities.
- Clinicians should annually assess for the gastrointestinal, dermatologic, behavioral, neurologic, and rheumatologic features of celiac disease via a history and physical examination.
- While human leukocyte antigen (HLA) type determination has been demonstrated to be useful in identifying risk for celiac disease in people without Down syndrome and in children with Down syndrome, the utility in adults with Down syndrome has not yet been fully established.
- Although serum Immunoglobulin A (IgA) and IgA anti-tissue transglutaminase (tTG) are clinically useful in people without Down syndrome, the routine cutoff value for positive does not appear to correlate well with the symptoms of celiac disease and intestinal biopsy results in those with Down syndrome, based on the observations from the GLOBAL Workgroup, and inferred from publications cited.
- If history and physical examination raise concerns for celiac disease, consider referral to clinicians more familiar with the specific testing for confirming the diagnosis of celiac disease in adults with Down syndrome.

Studies demonstrate that celiac disease is more prevalent in children with Down syndrome.[164, 165] However, prevalence or treatment of celiac disease in adults with Down syndrome is not well studied. Thus, the GLOBAL Workgroup's consensus is for a minimum of annual targeted history and physical examination regarding celiac disease's features. Based on the results, further evaluation and testing may be warranted to confirm the diagnosis. Referral to clinicians familiar with celiac disease in adults with Down syndrome should be considered, specifically regarding evaluating, testing, and interpreting test results. Diagnosing celiac disease in adults with Down syndrome is challenging for many reasons. First, celiac disease can cause a range of gastrointestinal and non-gastrointestinal symptoms (such as loose stools, diarrhea and abdominal cramps), and individuals may only exhibit a subset of the symptoms. Eliciting these signs and symptoms may be particularly

difficult to detect in adults with Down syndrome due to limitations in communication skills. Furthermore, many of these signs and symptoms are common in this population, even for individuals without celiac disease. For example, abdominal complaints in adults with Down syndrome may be due to chronic constipation, which is a common issue in those with (and without) hypothyroidism. Yet, the underlying autoimmune risks for hypothyroidism may also provide risks for celiac disease, so that evaluation for celiac disease may still be warranted.

In people with symptoms of celiac disease, diagnostic testing for celiac disease involves laboratory testing (IgA anti-tTG) and confirmation with small bowel biopsy. However, in the GLOBAL Workgroup's experience, mild elevation of IgA anti-tTG (based on the routine laboratory ranges) is common in Down syndrome and does not necessarily correlate with disease as it does in those without Down syndrome. The exact cut-off for a "normal" range in people with Down syndrome is not known. Obtaining a small bowel biopsy (used as a confirmatory test) is challenging not only from the procedure, but also the anesthesia, which presents unique risks for individuals with Down syndrome.

Data from children with Down syndrome who have celiac disease indicate that HLA analysis and sufficiently elevated serum IgA anti-tTG levels are helpful for establishing the diagnosis only when a variety of symptoms are present, including gastrointestinal (GI), behavioral, rashes, and other autoimmune disease features. Thus, the GLOBAL Workgroup recommends targeted history with special attention to GI symptoms, behavioral changes, rashes, and symptoms of other possible autoimmune disorders to screen for the possibility of celiac disease. Screening for clinical features of celiac disease is the first step, to be followed by appropriate laboratory testing, as necessary, to confirm the diagnosis. In some instances, the GLOBAL Workgroup suggests it may be appropriate to perform a gluten-free diet at home.

Many still consider small bowel biopsy the gold standard for diagnosing celiac disease. As Uibo et al. reported, the presence of symptoms, with positive IgA anti-tTG, and expression of the HLA-DQA1*05:01/DQB1*02:01 heterodimer, correlates exactly with the biopsy results and therefore may be considered in lieu of a biopsy for diagnosing celiac disease in children with Down syndrome.[166] Husby et al. have suggested a higher laboratory cutoff value for IgA anti-tTG levels may be useful for diagnosing celiac disease in children in lieu of a small bowel biopsy.[167] It remains unclear whether detecting an elevation in IgA anti-tTG levels, with negative biopsy results, could be a harbinger of future disease, especially in those expressing the specific HLA-DQ2 celiac disease risk factors.

Csizmadia et al. found 8% of children with Down syndrome screened and evaluated for celiac disease ultimately received the diagnosis (about eight times the ~1% prevalence in individuals without Down syndrome).[164] The positive predictive value (PPV) was 31% for association of children with Down syndrome who express the HLA-DQA1*05:01/DQB1*02:01 heterodimer and celiac disease. Further, there was absence of celiac disease, with 100% negative predictive value (NPV) in those who do not express the celiac disease HLA risk factors. Thus, testing for HLA may have clinical benefit in people with Down syndrome who express the HLA-DQA1*05:01/DQB1*02:01 heterodimer being at risk for disease, but it is not a definitive diagnostic tool without clinical assessment.

Clinical decisions regarding need for small bowel biopsy and gluten avoidance are complex. The data from children suggest celiac disease can be diagnosed without a small bowel biopsy, so that the procedure's risks should be discussed on a case-by-case basis. Evidence-based data in the reports cited indicate gluten-free diet benefits adults with Down syndrome who have celiac disease, and the GLOBAL Workgroup suggests that a trial of a gluten-free diet with regard to changes in symptoms can be a useful clinical tool in some cases.

Future Research

Future research will be needed to better define the predictive value of autoantibodies and HLA-typing results to assess the risk of developing celiac disease in adults with Down syndrome. In GLOBAL Workgroup discussion, serum IgA anti-tTG values are reported higher in those with Down syndrome than in those without, but correlation with symptoms is not always present. This could be explained by the presence of other immune factors contributing to disease severity beyond the autoantibodies, such as dysregulation of T cell lineages important in control of autoimmunity.[38] Future studies comparing the magnitudes of IgA anti-tTG values may help define "cut-offs" more appropriate for adults with Down syndrome. Additionally, further longitudinal studies are also needed to determine whether those with detected elevated IgA anti-tTG, but negative small bowel biopsy results, may be at future risk of disease development, especially in those with inherited high-risk HLA-DQ2 alleles as identified in people without Down syndrome. The potential value of once-per-lifetime HLA-type identification to improve risk stratification should be carefully evaluated both from a clinical and economic perspective, since it may have important merit for diagnosis and treatment options in adults with Down syndrome. Given that trisomy 21 is a stochastic event of improper chromosome segregation during gametogenesis, the frequency of the high-risk HLA alleles encoded on chromosome 6 would not be different among those with and without Down syndrome. Instead, the increased rate of autoimmunity is likely driven by the immune dysregulation caused by the extra copy of chromosome 21, which would affect the predictive value of HLA testing. Thus, overall correlation of HLA type, IgA anti-tTG levels, other immune markers, and small bowel biopsy results in adults with Down syndrome requires more study.

APPENDIX A: EVIDENCE REVIEW METHODOLOGY

A. Developing the Key Questions

The GLOBAL Workgroup was tasked with identifying key questions (KQs) to guide the systematic review of the literature on treating patients with Down syndrome (DS). These questions were developed in consultation with the ECRI Evidence-based Practice Center and addressed clinical topics of the highest priority for patients with DS. Due to resource constraints, all developed KQs could not be included in the systematic evidence review. The KQs follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 provides a brief overview of the PICOTS typology. The final KQs are listed in Table A-2.

Table A-1. PICOTS [168]

PICOTS Element	Description
Population, Patients, or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
Setting, if applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

a. Population(s)

- Adults 18 years or older with a diagnosis of DS.

b. Interventions

The table below lists the interventions, diagnostic factors, and prognostic factors covered in this systematic review. The interventions and factors are listed according to the KQs they address.

Table A-2. PICOTS used for evidence review

Key Question	Intervention(s) or Factor(s)
1	Clinical symptoms of depression, OCD, mood disorder, catatonia, anxiety and regression/ disintegrative disorder in adults with DS (vs. symptoms in adults without DS)
2	Psychosocial assessment tools: • PHQ-9 • Reiss Screen • "Has there been a change in behavior/function compared to prior year?" • Caregiver or patient questionnaire
3	Prevalence of dementia in adults with DS
4	Prevalence of diabetes (type 1 or 2) in adults with DS
	• Hemoglobin A1c (when used in asymptomatic patients) • Fasting glucose • Oral glucose tolerance test
	Obesity (BMI ⩾30 kg/m^2)
5	Prevalence of coronary artery disease and stroke (secondary to atherosclerosis) in adults with DS
	Hyperlipidemia treatments: • Statins • Aspirin 81 mg/day
6	Obesity treatments, such as: • Counseling on diet and exercise by clinician • Exercise programs • Dietary counseling • Phentermine • Xenical® (orlistat) • Other alternative medications
	Various BMI cutoffs
7	Prevalence of atlantoaxial instability in asymptomatic adults with DS
	• X-ray • CT • MRI • Other imaging modalities

Key Question	Intervention(s) or Factor(s)
8	Prevalence of osteoporosis, osteopenia, spinal compression fractures, and hip and femur fractures in adults with DS
	DEXA
	Lifestyle factors: • Non-ambulatory Serum markers: • Vitamin D • Calcium • Parathyroid hormone • Thyroid stimulating hormone
	Treatments for osteoporosis: • Bisphosphonates • Vitamins • Raloxifene • Hormone replacement therapy • Other supplements
9	Prevalence of hypothyroidism in adults with DS
	Diagnostic tests for hypothyroidism: • Thyroid stimulating hormone • Free T4 • Anti-thyroid peroxidase antibody (Anti-TPO) • Anti-thyroglobulin
	Levothyroxine
	Anti-TPO Anti-thyroglobulin
10	(TTG IgA Total IgA
	TTG IgA Total IgA
	HLA type DQ2 or DQ8
	Gluten-free diet

ADL: Activities of daily living; CT: Computed tomography; BMI: Body mass index; DEXA: Dual-energy x-ray absorptiometry DS: Down syndrome; IgA: Immunoglobulin A; MRI: Magnetic resonance imaging; OCD: Obsessive-compulsive disorder; TTG: Tissue transglutaminase; TSH: Thyroid stimulating hormone

c. Outcomes

Table A-3lists the outcomes of interest for this systematic review. The outcomes are listed by the KQ they address.

Table A-3. Outcomes

Key Question	Outcomes(s)
1	• Symptoms of depression, OCD, mood disorders, catatonia, generalized anxiety disorder, and regression/disintegrative disorder
2	• Accurate diagnosis of medical (e.g. hypothyroidism) vs. mental health disorder • Improvement in functional outcomes, such as: » ADLs » Assisted living/Nursing home placement
3	• Prevalence of dementia in DS adults <45 vs. ⩾45 years old
4	• Difference in prevalence of diabetes (DS vs. general population) Outcomes of screening for diabetes in DS population • Cardiovascular outcomes (coronary artery disease, stroke) • Diabetic comorbidities (neuropathy, macular degeneration, kidney disease) • Functional outcomes (ADLs, assisted living/nursing home placement)
5	• Difference in prevalence of atherosclerotic coronary artery disease (DS vs. general population) • Difference in prevalence of stroke secondary to atherosclerotic disease (DS vs. general population) • Decreased coronary artery disease, dementia, or myocardial infarction • Changes in functional outcomes, including: » Assisted living, nursing home placement » ADLs
6	• Adverse treatment-related events • Improved obstructive sleep apnea • Pain (including joint pain) • Osteoarthritis • Heart disease • Diabetes • Mental health • Changes in functional status, including: » ADLs » Assisted living, Nursing Home placement » Caregiver support » Ambulatory ability • Quality of Life

Key Question	Outcomes(s)
7	• Difference in prevalence of atlantoaxial instability in asymptomatic adults (DS vs. general population) • Clinical outcomes including: » Neck pain » Cervical myelopathy » Ability to ambulate » Weakness » Other neurological deficits » Number of surgeries » Surgical complications • Adverse events related to imaging
8	Difference in Prevalence (DS vs. general population) • Osteoporosis, osteopenia, fractures (spinal compression, hip or femur), diagnostic accuracy Clinical utility of DEXA screening for osteoporosis: • Clinical yield • Time to treatment • Fracture rate Predictive value of risk factors for: • Osteopenia, osteoporosis, fracture Clinical outcomes after treatment: • Number of compression, hip, and femur fractures • Falls • Quality of life • Pain • Changes in functional status, including: » ADLs » Assisted living, nursing home placement » Ambulatory status
9	• Prevalence of hypothyroidism in adults with DS • Diagnostic accuracy of TSH, free T4, anti-thyroid antibodies • Clinical outcomes after treatment: » Fatigue, weight changes, constipation » Functional outcomes (ADLs, ambulatory ability) • Clinical utility of anti-thyroid antibodies to detect thyroid disease in patients with other autoimmune disease (celiac disease, rheumatoid arthritis, lupus, alopecia areata) » Diagnostic yield » Time to diagnosis » Time to treatment » Improved functional outcomes

Key Question	Outcomes(s)
10	• Diagnostic accuracy of TTG IgA and total IgA in symptomatic patients • Clinical utility of TTG IgA or total IgA for screening asymptomatic patients » Diagnostic yield » Time to diagnosis » Time to treatment » Improvement in functional outcomes (ADLs) • Lifetime risk for biopsy proven celiac disease • Clinical outcomes after gluten free diet » Abdominal pain, bloating, flatulence, rash, diarrhea, reflux disease, weight loss

ADL: Activities of daily living; DEXA: Dual-energy x-ray absorptiometry; DS: Down syndrome; IgA: Immunoglobulin A; OCD: Obsessive- compulsive disorder; TTG: Tissue transglutaminase; TSH: Thyroid stimulating hormone

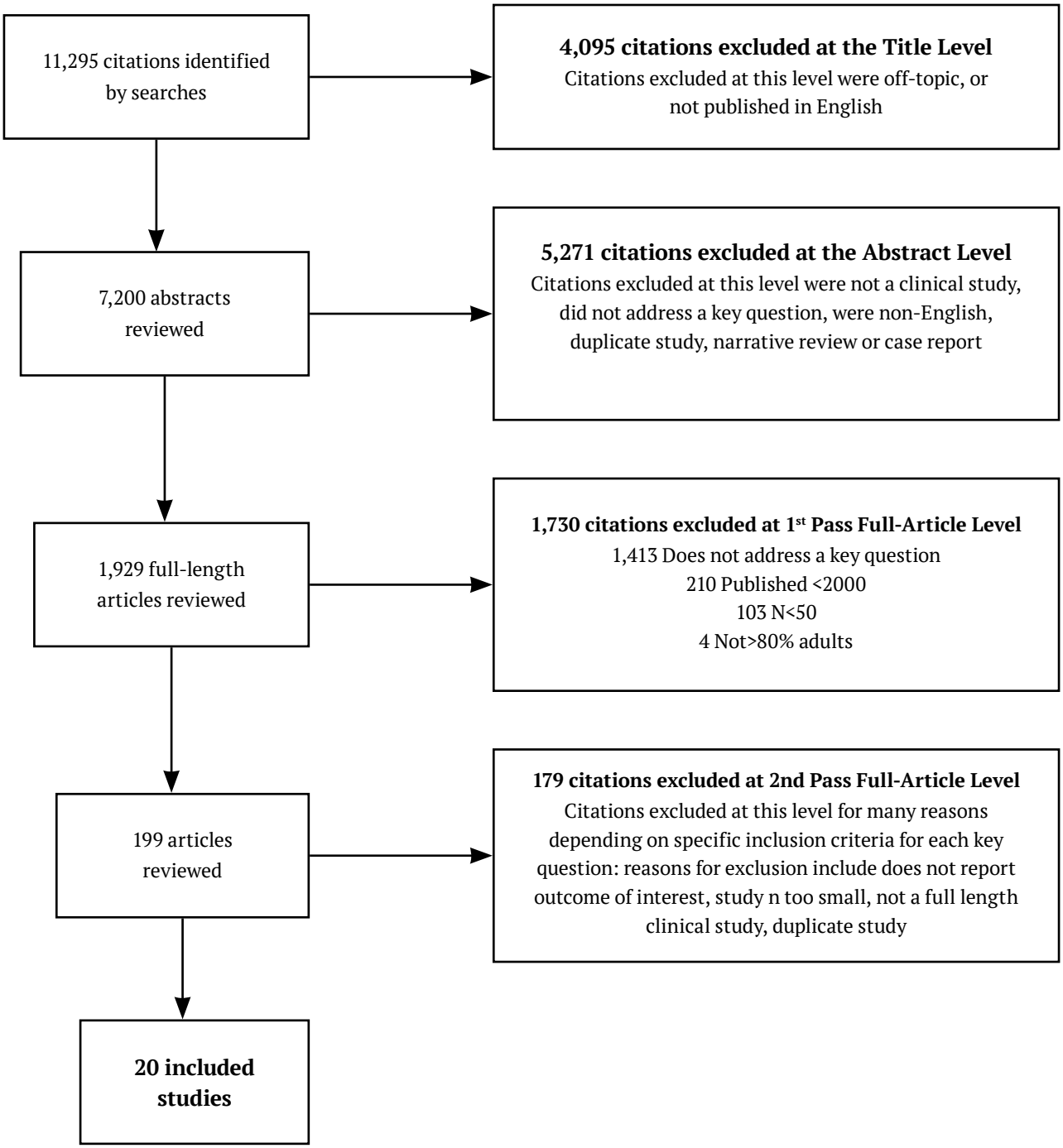
B. Conducting the Systematic Review

Based on the decisions made by the GLOBAL Workgroup regarding the scope, KQs, and PICOTS statements, the ECRI Evidence-based Practice Center produced a systematic review protocol before conducting the review. The GLOBAL Workgroup approved the protocol. It described in detail the final set of KQs, the methodology to be used during the systematic review process, and the inclusion/exclusion criteria to be applied to each potential study, including study type, sample size, and PICOTS criteria.

a) Evidence base

Literature searches identified 11,295 citations. Of these, 4,095 were excluded at the title review level for being off-topic or non-English studies. The remaining 7,200 citations were reviewed at the abstract level, and 5,271 were excluded for not being a clinical study, not addressing a KQ, non-English study, duplicate study, narrative review, or case report. A further 1,730 citations were excluded after initial review of the full-text article; a subsequent 179 articles were excluded after further review for a variety of reasons, including failure to report the outcome of interest, too few patients, or duplicate study. Reasons for exclusion are also summarized in Figure 1. Twenty articles* were included as evidence for this review (see Table A-4 below).

a) Evidence base (Cont.)



*An updated literature search was performed on August 6, 2020; 2 additional articles were identified and included.

Table A-4. Evidence Base for Key Questions

Number of Question	Question	Number of Studies
1	In adults with DS, do clinical symptoms of depression, OCD, mood disorder, catatonia, GAD, and regression/disintegrative disorder differ from the general population?	1 SR, 1 study
2	In adults with DS, does performing a psychosocial assessment (by clinical assessment, 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?	0 studies
3	What is the prevalence of dementia in adults with DS by decade?	5 studies*
4	What is the prevalence of diabetes (type I or II) in adults with DS compared to the general population (by decade)? Does screening asymptomatic adults with DS for diabetes improve clinical outcomes? Should adults with DS and obesity (BMI ⩾30 kg/m2) be screened more often?	3 studies
5	What is the prevalence of coronary artery disease and stroke secondary to atherosclerosis in adults with DS (compared to the general population)? In adults with DS and hyperlipidemia, does treatment of total cholesterol, LDL, or triglycerides improve clinical outcomes?	2 studies
6	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 DS? What target BMI is optimal for reducing comorbidities of obesity in adults with DS?	2 SRs
7	What is the prevalence of atlantoaxial instability in asymptomatic adults with DS (compared to the general population)? Does screening asymptomatic (ie, no symptoms or exam findings) adults with DS for atlantoaxial instability with imaging (x-ray, CT, MRI) improve outcomes?	2 studies

Number of Question	Question	Number of Studies
8	(a) What is the prevalence of osteopenia, osteoporosis, spinal compression, and hip or femur fractures in DS (by decade of life) compared to general population? (b) What is the clinical utility of screening asymptomatic adult patients with DS with DEXA (to detect osteopenia or osteoporosis)? (c) In adults with DS and no known history of low bone density, do lifestyle factors or serum markers (vitamin D, calcium, PTH, or TSH) predict diagnosis of osteopenia, osteoporosis, or fracture? (d) What pharmacologic treatments are effective for preventing osteoporotic fractures in adults with DS?	7 studies
9	(a) What is hypothyroidism's prevalence in adults with DS by decade? (b) What is the diagnostic accuracy of TSH, free T4, and anti-thyroid antibodies for hypothyroidism in asymptomatic adults with DS? (c) Does treating elevated TSH in asymptomatic adults with DS improve clini-cal or functional outcomes? (d) What is the clinical utility of using anti-thyroid antibodies to screen for thy-roid disease in adults with DS and autoimmune disease (celiac disease, rheumatoid arthritis, lupus, alopecia areata)?	3 studies
10	(a) What is the accuracy of TTG IgA or total IgA (compared to duodenal biopsy) for diagnosing celiac disease in adults with DS? (b) What is the clinical utility of screening asymptomatic adults with DS for celiac disease using TTG IgA or total IgA? (c) Does HLA type DQ2 or DQ8 predict risk of developing celiac disease in adults with DS? (d) Does a gluten-free diet improve symptoms in adults with DS and celiac disease?	2 studies

BMI: Body mass index; CT: Computed tomography; DEXA: Dual-energy x-ray absorptiometry; DS: Down syndrome; GAD: Generalized anxiety disorder; IgA: Immunoglobulin A; LDL: Low-density lipoprotein; MRI: Magnetic resonance imaging; OCD: Obsessive-compulsive disorder; PTH: parathyroid hormone; SR: Systematic review; TTG: Tissue transglutaminase; TSH: Thyroid stimulating hormone

* An updated literature search was performed on August 6, 2020; 2 additional articles were identified and included for a total of 22 articles.

b) General Inclusion Criteria

- Clinical studies or systematic reviews published January 1, 2000, to February 26, 2018, in a peer-reviewed journal. If no studies were identified for particular KQs, we considered inclusion of studies with earlier publication dates. If multiple systematic reviews addressed a KQ, we selected the most recent and/or comprehensive review. Systematic reviews were supplemented with clinical studies published afterward. An updated literature search was performed on August 6, 2020; additional articles were identified and included.
- Studies were required to be published in English.
- Publications were required to be a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.
- Intervention studies prioritized studies with an independent control group (see Key Question Specific Criteria below). The ideal diagnostic study compares clinical outcomes after diagnostic technology evaluation versus clinical evaluation or compares clinical outcomes linked to different diagnostic technologies. However, noncomparative diagnostic studies reporting a change in management strategy or patient outcomes (e.g. evidence of organic-based disease patterns) were included.
- Study must have enrolled at least 50 patients (25 per study group) unless otherwise noted (see Key Question Specific Criteria below). If no studies were identified, we included smaller studies (e.g. n ≥20).
- Study must have reported on an outcome of interest. Study must have enrolled a patient population in which at least 80% of patients were adults with DS. If the percentage is less than 80%, then data must have been reported separately for this patient subgroup.

c) Key Question Specific Criteria

- For KQs assessing prevalence (KQs 3, 4, 5, 7, 8, 9), we included observational studies with large populations (n ⩾300) of adults with DS; if no studies were identified, we considered including studies with fewer patients (n ≥100). For comparison, prevalence of these conditions in the general population was identified by searching for prevalence statistics provided by the Centers for Disease Control and Prevention, National Institutes of Health, or specialty professional societies.
- For KQs addressing treatment, screening, diagnostic interventions (KQs 2, 4, 5, 6, 7, 8, 9, 10), or risk factors (KQs 8, 10), acceptable study designs included systematic reviews of acceptable study designs, randomized controlled trials, observational cohort studies, and diagnostic cohort studies. We considered case-control studies for KQs addressing treatments and risk factors but not for screening and diagnostic interventions. If no studies were identified, we considered inclusion of trials with before-and-after study designs.

- For KQ1, acceptable trials included any comparative study design describing clinical symptoms of specified mental health disorders in adults with DS compared to the general population. If no studies performing a direct comparison were identified, we included studies that described clinical symptoms in patients with DS alone. For comparison, clinical symptoms in the general population were ascertained from a standardized description provided in the Diagnostic and Statistical Manual of Mental Health Conditions, 5th Edition.

d) Search strategy and databases searched

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table A-5, below.

Table A-5. Bibliographic Database Information

Name	Search Dates	Platform/Provider
Centers for Disease Control and Prevention	May 25, 2018	www.cdc.gov
Cochrane Library	January 1, 2000, through August 6, 2020	John Wiley & Sons, Ltd.
EMBASE (Excerpta Medica)	January 1, 2000, through August 6, 2020	Embase.com
MEDLINE	January 1, 2000, through August 6, 2020	OVID Technologies, Inc.
National Guideline Clearinghouse (NGC)	December 1, 2017	Agency for Healthcare Research and Quality (AHRQ)
National Institute for Health and Care Excellence (NICE)	December 1, 2017	National Institute for Health and Care Excellence
PsycINFO	January 1, 2000, through August 6, 2020	OVID Technologies, Inc.
PubMed (In-process and Publisher records)	Last searched August 6, 2020	National Library of Medicine (NLM)
TRIP Database	August 6, 2020	

Hand Searches of Journal and Gray Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Non-journal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included feedback and recommendations from Workgroup members and review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

Topic-specific Search Terms

The vocabulary presented in this table includes controlled vocabulary and free-text keywords for bibliographic database searches performed in EMBASE, Medline, Cochrane Library and PsycINFO. Strategies for selected databases follow this table.

EMTREE, Medical Subject Headings (MeSH), PsycINFO, and Keywords

The strategies below are presented in Embase.com and OVID syntaxes. Embase.com was used to search for EMBASE (EMTREE) records. OVID was used to search PsycINFO and Medline records.

Specific search strings were used to capture studies based on the Key Questions identified by the GLOBAL Workgroup. Unique strategies were structured for each concept addressed by the key questions. These search results were further refined to capture specific study designs, publication types, date ranges, English language studies, and to exclude out-of-scope citations.

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Patient Population		
Adults with Down Syndrome (18 years and older)	**EMBASE** 'down syndrome'/exp 'trisomy 21'/exp 'adult'/exp **MeSH** "adult"[mh] "down syndrome"[mh] **PsycINFO** Exp down's syndrome/ exp adult development/ exp aging/ exp elder care/ exp emerging adulthood/ exp geriatric patients/ exp geriatrics/	Down* AND syndrome 'down* syndrome' downsyndrome Trisomy AND 21 'trisomy 21' Adult Adulthood Adults Elder* Geriatric* 'middle age' 'middle aged' Middle AND age* Older AND adult* 'young adult' Young AND adult*

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
		NOT (child* OR infan* OR prenatal OR fetus OR teen* OR adolescen* OR baby OR babies OR birth* OR newborn OR pediatric* OR paediatric* Or preschool OR trisomy* OR sonogram* OR youth* OR son* OR daughter* OR chromosom* OR DNA OR fetal OR gestat* OR marker* OR nuchal) NOT (child* OR newborn* OR toddler* OR child* OR neonat* OR baby OR babies)

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Audiology	**EMBASE** 'audiology'/exp **MeSH** "audiology"[mh] "hearing"[mh] **PsycINFO** Exp audiology/	Auditory Balance Dizziness dizzy Ear* Eye* Hear* vestibular
Behavioral and Mental health, including ADHD, depression, aggression, neurology, dementia, alzheimer's disease, seizures, psychiatry	**EMBASE** 'alzheimer disease'/exp 'behavior disorder'/exp 'dementia'/exp 'disorders of higher cerebral function'/exp 'mental disease'/exp 'mental health'/exp 'mood disorder'/exp 'psychiatry'/exp **MeSH** "aggression"[mh] "Alzheimer disease"[mh] "attention deficit disorder with hyperactivity"[mh] "behavior"[mh] "behavioral symptoms"[mh] "dementia"[mh] "mental disorders"[mh] "mental health"[mh] "nervous system diseases"[mh] **PsycINFO** Exp aggressive behavior/ Exp Alzheimer's disease/ Exp attention deficit disorder/ Exp attention span/ Exp behavior disorders/ Exp behavior problems/ Exp bullying/ Exp cognitive impairment/ Exp dementia/ exp impulsiveness/ exp major depression/ Exp mental disorders/ exp mental health/ exp mental health programs/	ADHD Aggression Aggressive Alzheimer* 'attention deficit' dementia Depression Neurolog* Psych*

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	exp mental health services/ exp neurology/ exp nervous system disorders/ exp primary mental health prevention/ exp psychiatry/ exp seizures/ exp well being/	
Cardiology, including heart disease and valvular disorders	**EMBASE** 'cardiology'/de 'cardiovascular disease'/exp 'congenital heart malformation'/exp 'heart atrium'/exp **MeSH** "blood pressure"[mh] "cardiovascular diseases"[mh] "cerebrovascular disorders"[mh] **PsycINFO** Exp blood pressure disorders/ Exp cardiology/ Exp cardiovascular disorders/ Exp heart/ Exp heart auricles/ Exp heart disorders/ Exp heart valves/ Exp heart ventricles Exp myocardium/	"atrioventricular septal defect" Cardiac Cardiolog* ductus Endocardial* "endocardial cushion defect" fallot Heart* "persistent ductus arteriosus" Septal "tetralogy of fallot" Valve* Valvular "ventricular septal defect" ((cardio* OR pressure OR cerebrovascular OR heart) AND (disease* OR disorder*))
Dental	**EMBASE** 'dental health'/exp 'dentistry'/exp 'jaw'/exp 'mouth'/exp 'mouth disease'/exp 'temporomandibular joint disorder'/exp 'tongue'/exp 'tooth'/exp **MeSH** "mouth"[mh] "mouth diseases"[mh] "temporomandibular joint disorders"[mh]	cheek Dental Dentist enamel Gums Jaw* Lip* Mouth Orthodont* Taste Teeth tongue

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	PsycINFO exp dentistry/ facial muscles/ masticatory muscles/ exp mouth/ exp oral health/ pharynx/ jaw/ salivary glands/ exp temporomandibular joint/ exp tongue/ teeth/	
Endocrinology, including thyroid disorders, diabetes	**EMBASE** 'diabetes mellitus'/exp 'endocrine disease'/exp 'endocrine system'/exp 'endocrinology'/exp **MeSH** "endocrine gland neoplasms"[mh] "endocrine system"[mh] "endocrine system diseases"[mh] **PsycINFO** Exp adrenal gland disorders/ Exp endocrine disorders/ Exp endocrine glands/ Exp endocrinology/ Exp thyroid disorders/ exp thyroid hormones/	Adrenal* Diabet* Endocrin* Goiter* Hyperthyroid* Hypothyroid* Para-thyroid* 'para thyroid*' Pituitary Thyroid*
Hematology, bordering immunology	**EMBASE** 'anemia'/exp 'blood cell'/exp 'hematologic disease'/exp 'hematology'/exp 'preleukemia'/exp **MeSH** "blood"[mh] "hematologic diseases"[mh] "hematology"[mh] "lymphatic diseases"[mh] **PsycINFO** Exp blood/ Exp blood and lymphatic disorders/ Exp blood platelets/	Polycythemia Erythrocytosis Macrocytosis Thrombocytopenia Thrombocytosis Leucopenia "leukemoid reactions" "transient myeloproliferative disorder Leukemia Platelet* Red adj1 cell* White adj 1 cell* Blood adj 1 cell*

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
Muscular, Skeletal, and Spine including physical therapy, exercise	**EMBASE** 'musculoskeletal disease'/exp 'musculoskeletal system'/exp 'adult'/exp **MeSH** "exercise"[mh] "muscular diseases"[mh] "musculoskeletal diseases"[mh] "physical therapy modalities"[mh] **PsycINFO** Chronic fatigue syndrome/ Exp movement disorders/ Exp movement therapy/ Exp muscular disorders/ Exp musculoskeletal disorders/ Exp musculoskeletal system/ Exp neuromuscular disorders/ Occupational therapy/ Physical therapy/	Spinal Joint* Bone* Skeletal Hip* Knee* Neck Foot AND (disorder* OR disease* OR limitation* OR malform* OR deform* OR abnormal* OR delay* OR instability OR condition*)
Nutrition, including gastrointestinal conditions, celiac disease, obesity	**EMBASE** 'digestive system disease'/exp 'metabolic disorder'/exp 'nutritional disorder'/exp **MeSH** "digestive system diseases"[mh] "gastrointestinal tract"[mh] "metabolic diseases"[mh] "nutrition disorders"[mh] "nutritional and metabolic diseases"[mh] **PsycINFO** Exp body weight/ Exp celiac disease/ Exp digestive system/ Exp digestive system disorders/ exp gastrointestinal system/ exp metabolism disorders/ exp nutritional deficiencies/	Bowel Celiac Digestion Digestive gastrointestinal Gastro-intestinal Intestinal Intestine Malnutrition Metabolic Nutrition* Obesity
Ophthalmology	**EMBASE** 'ophthalmology'/exp 'vision'/exp 'visual disorder'/exp	Amblyopia astigmatism Brusfield* Cataract* Eye*

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	MeSH "eye diseases"[mh] "vision disorders"[mh] "vision, ocular"[mh] **PsycINFO** Exp eye disorders/ Exp ophthalmology/ Exp optometry/ Exp vision/ Exp vision disorders/	Eyelid* Farsight* focus Glasses Hyperopia Iris Myopia Nearsight* Nystagmus Ptosis Stereopsis Strabismus Tear-duct Tearduct Vision Visual
Sexuality, including gynecology, fertility, pregnancy	**EMBASE** 'birth control'/exp 'genital system function'/exp 'gynecology'/exp 'reproductive health'/exp 'sex'/exp 'sexual behavior'/exp 'sexual health'/exp 'urogenital system function and reproduction'/exp **MeSH** "contraception"[mh] "genital diseases, female"[mh] "genital diseases, male"[mh] "menstrual cycle"[mh] "reproductive medicine"[mh] "sexual behavior"[mh] **PsycINFO** Affection/ Exp birth control/ Exp genital disorders/ Exp gynecological disorders/ Gynecology/ Exp infertility/ Exp menstruation/ Exp obstetrics/ Exp pregnancy/ Exp psychosexual behavior/ Reproductive health/	Contraception Contraceptives Fertility Fertile Genital* Gynecolog* Menstruat* Ovulat* puberty Reproductive Sex* Sexuality

Concept	Controlled Vocabulary	Keywords/PubMed Concepts
	Exp sex/ Exp sexual reproduction/ Exp sexuality/	
Sleep, including pulmonary, sleep apnea, atlanto-axial instability, spinal cord compression	**EMBASE** 'apnea'/exp 'polysomnography'/ 'sleep deprivation'/ 'sleep disordered breathing'/exp 'sleep disorder'/exp **MeSH** "apnea"[mh] "sleep wake disorders"[mh] **PsycINFO** Exp apnea/ Polysomnography/ Exp sleep/ sleep apnea/ Exp sleep disorders/ Exp sleep wake cycle/	Apnea* Apneic 'atlanto-axial instability' Gasp* OSA Polysomnogra* 'pulmonary hypertension' Restless adj2 sleep 'sleep disorder*' 'sleep disordered breathing' 'sleep study' Sleepiness Snor*

PsycINFO/Medline Search Strategies conducted using OVID Syntax

Set #	Concept	Search Statement
1	Adults with Down Syndrome	Exp down's syndrome/ OR ('down syndrome' OR downsyndrome OR (down* adj1 syndrome)).ab,ti. OR (trisomy adj1 "21").mp. OR 'trisomy 21'.mp.
2		Exp adult development/ OR exp aging/ OR exp emerging adulthood/ OR exp geriatrics/ OR exp geriatric patients/ OR exp elder care/
3		('middle aged' OR (middle adj1 age*) OR 'young adult*' OR (young adj1 adult*) OR (older adj1 adult*) OR adult OR adulthood OR adults OR geriat-ric* OR 'middle age' OR elder).mp.
4		Exp pediatrics/ OR exp prenatal development/ OR exp prenatal diagnosis/ OR infan*.mp. OR prenatal*.mp. OR fetus.mp. OR baby.mp. OR babies.mp. OR newborn.mp. OR pediatric*.mp. OR paediatric.mp. OR preschool.mp. OR sonogra*.mp. OR fetal.mp. OR gestat*.mp. OR marker*.mp. OR nuchal.mp.

Set #	Concept	Search Statement
5	Audiology	Exp audiology/ OR exp hearing/ OR ear*.ab, ti. OR hear*.ab,ti. OR auditory.ab,ti.
6		((ear OR vestibular) AND (balance OR eye* OR dizzy OR dizziness)).mp.
7	Behavioral and mental	Exp aggressive behavior/ OR exp alzheimer's disease/ OR exp attention deficit disorder/ OR exp attention span/ OR exp behavior disorders/ OR exp behavior problems/ OR exp bullying OR exp cognitive impairment/ OR exp dementia/ OR exp impulsiveness/ OR exp major depression/ OR exp mental disorders/ OR exp mental health/ OR exp primary mental health prevention/ OR exp psychiatry/ OR exp seizures/ OR exp well being/
8		exp attention deficit disorder with hyperactivity/ OR exp behavior/ OR exp behavioral symptoms/ OR exp nervous system diseases/
9		(depression OR aggressive OR aggression OR psych* OR dementia OR Alzheimer* OR neurology* OR ADHD OR 'attention deficit').mp.
10	Cardiology	Exp cardiology/ OR exp heart/ OR cardiac.ab, ti. OR heart*. ab, ti. OR valve*.ab, ti. OR valvular.ab,ti. OR cardiolog*.ab, ti. OR ("atrioventricular septal defect" OR "endocardial cushion defect" OR "ventricular septal defect" OR "persistent ductus arteriosus" OR "tetralogy of fallot").mp.
11		Exp cardiovascular disorders/ OR exp cardiovascular diseases/ OR exp blood pressure/ OR exp blood pressure disorders/ OR exp cerebrovascular disorders/ OR exp heart disorders/ OR exp heart auricles/ OR exp heart valves/ OR exp heart ventricles/ OR exp myocardium
12		((cardio* OR pressure OR cerebrovascular OR heart).ab, ti. AND (disease* OR disorder*).ab,ti.)
13	Dental	Exp dentistry/ OR exp mouth/ OR exp oral health/ OR pharynx/ OR jaw/ OR salivary gland/ OR exp temporomandibular joint/ OR exp tongue/ OR teeth/ OR facial muscles/ OR masticatory muscles/
14		Exp mouth diseases/ OR exp temporomandibular joint disorders/

Set #	Concept	Search Statement
15		Cheek OR dental OR dentist OR enamel OR gums OR jaw* OR lip* OR mouth OR orthodont* OR taste OR teeth OR tongue
16	Endocrinology	exp adrenal gland disorders/ OR exp endocrine disorders/ OR exp endocrine glands/ OR exp endocrinology/ OR exp thyroid disorders/ OR exp thyroid hormones/ OR exp endocrine gland neoplasms/ OR exp endocrine system/ OR exp endocrine system diseases/
17		(endocrin* OR diabet* OR thyroid* OR para-thyroid* OR parathyroid* OR adrenal* OR pituitary OR goiter* OR hyperthyroid* OR hypothyroid).mp.
18	Hematology	Exp blood/ OR Exp blood and lymphatic disorders/ OR Exp blood platelets/ OR exp hematologic diseases/ OR exp hematology OR exp lymphatic diseases
19		"leukemoid reactions" OR "transient myeloproliferative disorder OR leukemia OR platelet* OR Red adj1 cell* OR White adj 1 cell* OR Blood adj 1 cell* OR polycythemia OR erythrocytosis OR macrocytosis OR thrombocytopenia OR thrombocytosis OR leucopenia
20	Musculoskeletal	Chronic fatigue syndrome/ OR Exp movement disorders/ OR Exp muscular disorders/ OR Exp musculoskeletal disorders/ OR Exp musculoskeletal system/ OR Exp neuromuscular disorders/ OR Occupational therapy/ OR Physical therapy/ OR exp muscular diseases/ OR exp musculoskeletal diseases/ OR exp physical therapy modalities/ OR exp exercise/ OR exp movement therapy/
21		(Musculoskeletal OR Muscle OR Muscular OR Spine OR Spinal OR Joint* OR Bone* OR Skeletal OR Hip* OR Knee* OR Neck OR Foot) AND (disorder* OR disease* OR limitation* OR malform* OR deform* OR abnormal* OR delay* OR instability OR condition*)

Set #	Concept	Search Statement
22	Nutrition	Exp body weight/ OR Exp celiac disease/ OR Exp digestive system/ OR Exp digestive system disorders/ OR exp gastrointestinal system/ OR exp metabolism disorders/ OR exp nutritional deficiencies/ OR exp digestive system diseases/ OR exp gastrointestinal tract/ OR exp metabolic diseases/ OR exp nutrition disorders/ OR nutritional and metabolic diseases/
23		Bowel OR Celiac OR Digestion OR Digestive OR gastrointestinal OR Gastro-intestinal OR Intestinal OR Intestine OR Malnutrition OR Metabolic OR Nutrition* OR Obesity
24	Ophthalmology	Exp eye disorders/ OR Exp ophthalmology/ OR Exp optometry/ OR Exp vision/ OR Exp vision disorders/ OR exp eye diseases/ OR exp vision disorders OR exp vision, ocular/
25		Amblyopia OR astigmatism OR Brusfield* OR Cataract* OR Eye* OR Eyelid* OR Farsight* OR focus OR Glasses OR Hyperopia OR Iris OR Myopia OR Nearsight* OR Nystagmus OR Ptosis OR Stereopsis OR Strabismus OR Tear-duct OR Tearduct OR visual OR vision
26	Sexuality	Affection/ OR Exp birth control/ OR Exp genital disorders/ OR Exp gynecological disorders/ OR Gynecology/ OR Exp infertility/ OR Exp menstruation/ OR Exp obstetrics/ OR Exp pregnancy/ OR Exp psychosexual behavior/ OR Reproductive health/ OR Exp sex/ OR Exp sexual reproduction/ OR Exp sexuality/ OR exp contraception/ OR exp genital diseases, female/ OR exp genital diseases, male/ OR exp menstrual cycle/ OR exp reproductive medicine/ OR exp sexual behavior/
27		Contraception OR Contraceptives OR Fertility OR Fertile OR Genital* OR Gynecolog* OR Menstruat* OR Ovulat* OR puberty OR Reproductive OR Sex* OR Sexuality
28	Sleep	Exp apnea/ OR Polysomnography/ OR Exp sleep/ OR sleep apnea/ OR Exp sleep disorders/ OR Exp sleep wake cycle/ OR exp apnea/ OR exp sleep wake disorders/
29		Apnea* OR Apneic OR 'atlanto-axial instability' OR Gasp* OR OSA OR Polysomnogra* OR 'pulmonary hypertension' OR Restless adj2 sleep OR 'sleep disorder*' OR 'sleep disordered breathing' OR 'sleep study' OR Sleepiness OR Snor*

Set #	Concept	Search Statement
30	Publication type limits	NOT (book* or dissertation* or comment* or editorial* or letter*)
31		AND (exp randomized controlled trial/ or observational study/ OR exp observational studies as topic/ or exp case-control studies/ or exp cohort studies/) OR ((RCT or random$ or 'randomized controlled' or 'case series' or 'case control$' or observation$ or cohort$).mp)
32	Additional limits	NOT (mice or mouse or postmortem or post-mortem)
33		NOT (infan* or newborn* or neonat* or toddler*).mp.

OVID Conventions:

* (within or following a term) = truncation character (wildcard)

.ab. = limit to abstract

ADJn = search terms within a specified number (n) of words from each other in any order

exp/ = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.ti,ab. = limit to title and abstract fields

e) Items for Reporting Study Quality in Prevalence Studies

Table 1. Items for Rating Quality of Studies of Prevalence or Incidence of a Health Problem

Items
1. Random sample or whole population
2. Unbiased sampling frame (i.e. census data)
3. Adequate sample size (>300 subjects)
4. Use of standard measures (objective, suitable, and standard criteria used for measurement of health outcomes)
5. Adequate response rate (>70%), refusers described
6. Confidence intervals provided
7. Study subjects described (sufficient details provided to allow audience to determine if population is comparable to another population of interest)

Table 2. Items not applicable to this population

Items	Rationale
Outcomes measured by unbiased assessors	Not feasible to blind assessors to diagnosis of Down syndrome

Drawn from Loney et al. 1998, *Critical Appraisal of the Health Research Literature: Prevalence or Incidence of a Health Problem.*[169]

C. Convening the Face-to-face Meeting

In consultation with the Global Down Syndrome Foundation and the GLOBAL Workgroup, the ECRI Evidence-based Practice Center convened a three day face-to-face meeting of the GLOBAL Workgroup on January 23-25, 2019, to develop and draft the clinical recommendations. The ECRI Evidence-based Practice Center presented findings from the evidence review to facilitate recommendations development and moderated the process.

The GLOBAL Workgroup was charged with interpreting results of the evidence review and developing clinical practice recommendations. As the GLOBAL Workgroup drafted clinical practice recommendations, it also graded each recommendation based on a modified GRADE methodology. Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

D. Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a strength for each recommendation. The GRADE system uses the following four domains to assess each recommendation's strength:[170]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate—for example:
    - » Resource use
    - » Equity
    - » Acceptability
    - » Feasibility
    - » Subgroup considerations

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g. increased longevity, reduction in morbid event, resolution of symptoms, improved quality of life,

decreased resource use) and harms (e.g. decreased longevity, immediate serious complications, adverse events, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that most clinicians will offer patients therapeutic or preventive measures as long as the intervention's advantages exceed the risks and adverse effects. The clinician's confidence level of the risk-benefit balance will greatly influence the recommendation's strength.

Discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects greater than undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects each study's methodologic quality for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review ECRI used to develop recommendations assessed the confidence in the evidence base's quality using GRADE methodology and assigned a rating of "High," "Moderate," "Low," or "Very Low." The outcomes judged to be critical were used to determine the overall quality of evidence

Questions to determine confidence in the quality of the evidence include:

- Does high- or moderate-quality evidence exist that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term "values" has the closest connotation to these processes. For others, the connotation of "preferences" best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. When the risk-benefit balance is uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having "similar values," "some variation," or "large variation" in typical values and preferences between patients and the larger populations of interest.
Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences, and are they similar across the target population?

- What are the patient's values and preferences?
- Are the assumed or identified relative values similar across the target population?

Other implications consider the recommendation's practicality, including resource use, equity, acceptability, feasibility, and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example, statin use in the frail elderly and others with multiple co-occurring conditions may not be effective and, depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the recommendation's practicality.

The GLOBAL Workgroup used the framework below (Table A-6) to guide discussions on each domain.

Table A-6. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Balance of desirable and undesirable outcomes	• Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? • Are the desirable anticipated effects large? • Are the undesirable anticipated effects small? • Are the desirable effects large relative to undesirable effects?	• Benefits outweigh harms/burden • Benefits slightly outweigh harms/burden • Benefits and harms/burden are balanced • Harms/burden slightly outweigh benefits • Harms/burden outweigh benefits
Confidence in the quality of the evidence	• Is there high or moderate quality evidence that answers this question? • What is the overall certainty of this evidence?	• High • Moderate • Low • Very low
Values and preferences	• Are you confident about the typical values and preferences and are they similar across the target population? • What are the patient's values and preferences? • Are the assumed or identified relative values similar across the target population?	• Similar values • Some variation • Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	• Are the resources worth the expected net benefit from the recommendation? • What are the costs per resource unit? • Is this intervention generally available? • Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? • Is there lots of variability in resource requirements across settings?	• Various considerations

A recommendation's strength is defined as the extent to which one can be confident that an intervention's desirable effects outweigh its undesirable effects and is based on the framework above, which combines the four domains.[170] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence), instances may arise in which strong recommendations are warranted even when the quality of evidence is low.[170] In these instances in which the balance of desirable and undesirable outcomes and values and preferences played large roles in determining a recommendation's strength, see the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The recommendation's relative strength is based on a binary scale: "Strong" or "Weak." A strong recommendation indicates the GLOBAL Workgroup is highly confident that desirable outcomes outweigh undesirable outcomes. If the GLOBAL Workgroup is less confident of the balance between desirable and undesirable outcomes, it presents a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates the undesirable consequences outweigh the desirable consequences.

Occasionally, instances may occur when the Workgroup feels insufficient evidence exists to make a recommendation for or against a therapy or preventive measure. This can occur when there is an absence of studies on a particular topic that met evidence review inclusion criteria, studies included in the evidence review report conflicting results, or studies included in the evidence review report inconclusive results regarding the desirable and undesirable outcomes.

Using these elements, each recommendation's grade is presented as part of a continuum:

- Strong For (or "We recommend offering this option …")
- Weak For (or "We suggest offering this option …")
- No recommendation for or against (or "There is insufficient evidence…")
- Weak Against (or "We suggest not offering this option …")
- Strong Against (or "We recommend against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based on patient values and preferences, the resources available, or the setting where the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

APPENDIX B: ABBREVIATIONS

AAI	Atlantoaxial instability
ABC-DS	Alzheimer's Biomarker Consortium Down Syndrome
AAP	American Academy of Pediatrics
ADA	American Diabetes Association
AHA/ASA	American Heart Association/American Stroke Association
AITD	Autoimmune thyroid disease
APP	Amyloid precursor protein
ASCVD	Atherosclerotic cardiovascular disease
BMD	Bone mineral density
BMI	Body mass index
CAD	Coronary artery disease
DEXA	Dual-energy x-ray absorptiometry
DM-ID-2	Diagnostic Manual-Intellectual Disability, 2nd Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSQIID	Dementia Screening Questionnaire for Individuals with Intellectual Disabilities
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FRAX	Fracture Risk Assessment Tool
GI	Gastrointestinal
HbA1c	Hemoglobin A1C
HLA	Human leukocyte antigen
IDD	Intellectual and developmental disabilities
IgA	Immunoglobulin A
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NAFLD	Nonalcoholic Fatty Liver Disease
NF-L	Neurofilament light

NPV	Negative predictive value
NTG-EDSD	National Task Group-Early Detection Screen for Dementia
OSA	Obstructive sleep apnea
PET	Positron emission tomography
PPV	Positive predictive value
TSH	Thyroid-stimulating hormone
tTG	Tissue transglutaminase
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
USPSTF	United States Preventive Services Task Force

APPENDIX C: PATIENT FOCUS GROUP METHODS & FINDINGS

A. Methods

On October 14th 2019, Corona Insights, under the guidance and leadership with the Global Down Syndrome Foundation, conducted and online focus groups for adults with Down syndrome, their family members, and caregivers to provide insight and feedback on the near-final manuscript of the GLOBAL Medical Care Guidelines for Adults with Down Syndrome. The focus groups consisted of 27 family members or caregivers and 7 adults with Down syndrome, of which 17 family members and caregivers and 4 self-advocates participated in at least 90% of the online discussion.

The goal of the focus groups was to determine if the guidelines appropriately reflected the needs, values and perspectives of adults with Down syndrome, their families and caregivers. The focus group allowed us to gauge initial reactions to the guidelines, to determine usability, and to identify appealing elements of the guidelines, as well as opportunities for further clarification or explanation.

Global Down Syndrome Foundation and Corona Insights collaboratively developed two sets of survey questions based on the near-final guideline manuscript, one set for the family and caregivers, and one set for the adults with Down syndrome. Between the two sets of survey questions, there were questions that over lapped, but the adults with Down syndrome were provided multiple choice questions whereas the family members and caregivers were provided open ended response questions. They were all given the same material to respond to: the guideline introduction, the recommendation statements, and the checklist. The online survey was conducted on HatchTank discussion board and monitored by Corona Insights. The online discussion board was open for 7 days.

Focus group participants were recruited by the Global Down Syndrome Foundation, with assistance from 10 local and 1 national Down syndrome organization(s) from 9 different states through "snowball" sampling. Snowball Sampling, also called chain sampling, is a non-probability sampling technique whereby existing participants reach out to their networks to recruit other participants. The GLOBAL Workgroup acknowledges the limits of using snowball sampling, including limited generalizability. Additionally, the focus group's feedback was limited to their review of the near-completed guideline manuscript they were provided, which prevented broader consideration for other potential topics or conditions affecting the care and wellbeing of adults with Down syndrome.

Efforts were made to recruit participants of different age ranges, race, gender, and relationship to Down syndrome. For the focus group consisting of only adults with Down syndrome, some self-selection happened, especially as the participants needed to be skilled in reading and typing, which are not skills developed by all adults with Down syndrome. And for the focus group consisting of family members and caregivers, it was difficult recruiting relatives of a person with Down syndrome over the age of 50, not just because of the shorter live span of adults with Down syndrome, but also, this survey took place on a computer and required an email address. None of the participants were incentivized for their participation.

Findings from family members and caregivers were analyzed separately from findings from adults with Down syndrome. These findings were carefully considered by the GLOBAL Workgroup during the finalization of the manuscript to ensure the completed manuscript was understandable and useful for adults with Down syndrome, their families, and caregivers.

B. Findings

1. **Highly preferred recommendation statements use clear and consistent language and provide actionable steps.**
    a. Strong evidence preferred to weak or insufficient evidence.
    b. Lists increase understandability.
    c. Executable steps or options are useful.
2. **Families want the most background information and evidence supporting recommendation statements that recommend/suggest a course of action that differ from a previous made recommendation or that suggest care for an adult with Down syndrome is different from standard care for adults without Down syndrome.**
3. **Additional toolkits and checklists help families and self-advocates feel more in control of their healthcare and increase usability.**
    a. Symptom checklists are desirable.
    b. Develop a comparable document with families as key audience.
    c. Include a well-organized glossary of terms.

APPENDIX D: GLOBAL MEDICAL CARE GUIDELINES FOR ADULTS WITH DOWN SYNDROME CHECKLIST (2020)

This checklist is intended to support the health of adults with Down syndrome directly or through their caregivers. We encourage this checklist to be shared with your medical professionals. Statements in blue represent our recommended, periodic health screenings/assessments that should begin at a specific age. Below each blue screening/assessment recommendation, there are blank boxes. Caregivers or individuals with Down syndrome can check off, date, or initial each blank box when the screening/assessment is completed. For screening/assessment recommendations with a time range (e.g. 1-2 years), the box size represents the longer possible time frame, such as 2 years versus 1. Statements in gray represent advisory recommendations that individuals with Down syndrome and caregivers should follow throughout adulthood.

Screening/Assessment | Advisory | Checkbox | No Recommendations

	21-29 Years	30-39 Years	40-49 Years	50-59 Years	60+ Years
Behavior	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. *(Boxes below represent 1 year increments)*				
	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐
	When concern for a mental health disorder in adults with Down syndrome is present medical professionals should: a) Evaluate for medical conditions that may present with psychiatric and behavioral symptoms and b) Refer to a clinician knowledgeable about the medical, mental health disorders, and common behavioral characteristics of adults with Down syndrome.				
	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 (DSM 5). The Diagnostic Manual-Intellectual Disability 2 (DM-ID-2) also may be used to adapt diagnostic criteria from the DSM-5.				
Dementia	Caution is needed when diagnosing age-related, Alzheimer's Type Dementia in adults with Down syndrome less than age 40.		Medical professionals should assess adults with Down syndrome and interview their primary caregivers about changes from baseline function annually beginning at age 40. Decline in the six domains as per the National Task Group – Early Detection Screen for Dementia (NTG-EDSD) should be used to identify early-stage age-related Alzheimer's-type dementia and/or a potentially reversible medical condition. *(Boxes below represent 1 year increments)*		
			☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐
Diabetes		For asymptomatic adults with Down syndrome, screening for type 2 diabetes using HbA1c or fasting plasma glucose should be performed every 3 years beginning at age 30. *(Boxes below represent 3 year increments)*			
		☐☐☐	☐☐☐	☐☐☐	☐☐☐
	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 years beginning at age 21. *(Boxes below represent 3 year increments)*				
	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐
Cardiac			For adults with Down syndrome without a history of atherosclerotic cardiovascular disease, the appropriateness of statin therapy should be assessed every 5 years starting at age 40 and using a 10-year risk calculator as recommended for adults without Down syndrome by the U.S. Preventive Services Task Force. *(Boxes below represent 5 year increments)*		
			☐☐	☐☐	☐☐
	For adults with Down syndrome, risk factors for stroke should be managed as specified by the American Heart Association/American Stroke Association's Guidelines for the Primary Prevention of Stroke.				
	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.				
Obesity	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 .				
	Monitoring for weight change and obesity should be performed annually by calculating Body Mass Index in adults with Down syndrome. The U.S. Preventive Services Task Force Behavioral Weight Loss Interventions to Prevent Obesity-Related Morbidity and Mortality in Adults should be followed. *(Boxes below represent 1 year increments)*				
	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐
Atlantoaxial Instability	In adults with Down syndrome, routine cervical spine x-rays should not be used to screen for risk of spinal cord injury in asymptomatic individuals.				
	Annual screening for adults with Down syndrome should be based on a review of signs and symptoms of cervical myelopathy using targeted history and physical exam. *(Boxes below represent 1 year increments)*				
	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐
Osteoporosis	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 would support a shared decision-making approach to this issue.				
	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.				
Thyroid	Screening adults with Down syndrome for hypothyroidism should be performed every 1-2 years using a serum thyroid-stimulating hormone (TSH) test beginning at age 21. *(Boxes below represent 2 year increments)*				
	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
Celiac Disease	Adults with Down syndrome should receive an annual assessment for gastrointestinal and non-gastrointestinal signs and symptoms of celiac disease using targeted history, physical examination and clinical judgement of good practice. *(Boxes below represent 1 year increments)*				
	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐☐☐☐☐

This checklist is not intended to be diagnostic. Presentation of medical and mental health conditions for people with Down syndrome may be atypical. Similar signs and symptoms may be a consequence of multiple reasons, including different disease processes. Thus, the patient evaluation should include considerations of additional causes for any detected sign or symptom. The development of new and/or changes in signs or symptoms should prompt a comprehensive evaluation with your clinician.

APPENDIX E: DOWN SYNDROME RESOURCES

Global Down Syndrome Foundation

The Global Down Syndrome Foundation (GLOBAL) is the largest non-profit in the U.S. working to save lives and dramatically improve health outcomes for people with Down syndrome. GLOBAL established the first Down syndrome research institute supporting over 400 scientists and over 2,000 patients with Down syndrome from 28 states and 10 countries. Working closely with Congress and the National Institutes of Health, GLOBAL is the lead advocacy organization in the U.S. for Down syndrome research and care. GLOBAL has a membership of over 100 Down syndrome organizations worldwide and is part of a network of Affiliates. For more information visit our website: https://www.globaldownsyndrome.org/.

Global Down Syndrome Foundation Medical Care Guidelines for Adults with Down Syndrome:
https://www.globaldownsyndrome.org/global-adult-guidelines/
Down syndrome medical care centers in the U.S. by state:
https://www.globaldownsyndrome.org/research-medical-care/medical-care-providers/
Local Down syndrome organizations in the U.S. by state:
https://www.globaldownsyndrome.org/about-down-syndrome/resources/local-organizations/
Linda Crnic Institute for Down Syndrome, the world's leading Down syndrome research institute:
https://medschool.cuanschutz.edu/linda-crnic-institute
Anna and John J. Sie Center for Down Syndrome, one of the world's largest Down syndrome medical care centers:
https://www.globaldownsyndrome.org/our-story/anna-and-john-j-sie-center-for-down-syndrome/

The following resources are listed in alphabetical order:

American Academy of Developmental Medicine and Dentistry
https://www.aadmd.org/
Down Syndrome-Autism Connection
http://www.ds-asd-connection.org/
Down Syndrome Medical Interest Group-USA
https://www.dsmig-usa.org/
DS Connect® An important registry and portal connecting people with Down syndrome, clinicians, and researchers
https://dsconnect.nih.gov/
International Mosaic Down Syndrome Association
https://www.imdsa.org/mosaic-down-syndrome
National Down Syndrome Congress
https://www.ndsccenter.org/
National Down Syndrome Society
https://www.ndss.org/
National Institutes of Health Down Syndrome Consortium
https://downsyndrome.nih.gov/
National Task Group on Intellectual Disabilities and Dementia Practices
https://www.the-ntg.org/
Special Olympics
https://www.specialolympics.org/
The Arc
https://thearc.org/

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