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RESEARCH REVIEW

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Co-occurring medical conditions in adults with Down syndrome: A systematic review toward the development of health care guidelines

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Adults with Down syndrome (DS) represent a unique population who are in need of clinical guidelines to address their medical care. The United States Preventive Service Task Force (USPSTF) has developed criteria for prioritizing conditions of public health importance with the potential for providing screening recommendations to improve clinical care. The quality of existing evidence needed to inform clinical guidelines has not been previously reviewed. Using the National Library of Medicine (NLM) database PubMed, we first identified 18 peer reviewed articles that addressed co-occurring medical conditions in adults with DS. Those conditions discussed in over half of the articles were prioritized for further review. Second, we performed detailed literature searches on these specific conditions. To inform the search strategy and review process a series of key questions were formulated a priori. The quality of available evidence was then graded and knowledge gaps were identified. The number of participating adults and the design of clinical studies varied by condition and were often inadequate for answering all of our key questions. We provide data on thyroid disease, cervical spine disease, hearing impairment, overweight-obesity, sleep apnea, congenital heart disease, and osteopenia-osteoporosis. Minimal evidence demonstrates massive gaps in our clinical knowledge that compromises clinical decision-making and management of these medically complex individuals. The development of evidence-based clinical guidance will require an expanded clinical knowledge-base in order to move forward.

KEYWORDS
adult health conditions, aging, clinical practice guidelines, Down syndrome, evidence-based medicine, literature review, trisomy 21

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1 | INTRODUCTION

According to recent estimates, the number of persons with DS living in the United States (2008–2010) is between 200,000 and 250,000 (de Graaf, Buckley, & Skotko, 2017; Presson et al., 2013). A marked increase in the number of persons aged 35–60 years can be explained by the baby boom (1946–1964) and increased life expectancy for older individuals (Presson et al., 2013). The total population prevalence of DS in the United States as of 2010 was estimated to be 6.7/10,000 inhabitants. The age-adjusted prevalence is estimated at 8.6/10,000 for 20- to 24-year-olds; 6.4/10,000 for 30- to 36-year-olds; and 1.9/10,000 for 60- to 69-year olds (de Graaf et al., 2017). Thus, the number of adults (>18 yr) with DS living in the United States approaches or exceeds 125,000 individuals (de Graaf et al., 2017). Further, the life expectancy of persons with DS has increased dramatically in the last half century and now approaches an average of 60 years in many developed countries (Bittles & Glasson, 2004; Glasson et al., 2002).

Consensus-derived health supervision guidelines for children with Down syndrome (DS) (birth-21 yr) have existed since 1994 (AAP, 1994) and continue to be revised on a regular basis based on emerging evidence (AAP, 2011). Consensus-based guidelines for adults with DS over 21 years do not exist. There is, however, a growing literature published in peer-reviewed medical journals addressing screening and/or evaluation for co-occurring medical conditions seen in adults with DS. Many of the reports that highlight co-occurring medical conditions in adults with DS are largely informed by clinical experience and supported by existing literature when available (Chicoine, McGuire, Hebein, & Gilly, 1994; Galley, 2005; Jensen & Bulova, 2014; Malt et al., 2013; Martin, 1997; Pueschel, 1990; Smith, 2001; Steingass, Chicoine, McGuire, & Roizen, 2011; Wilson, Jones, Weedon, & Bilder, 2015). Clinical convenience samples ascertained through specialty clinics focused on DS or intellectual and developmental disabilities (IDD) have also been used to estimate the prevalence and variety of medical conditions in adulthood (Henderson, Lynch, Wilkinson, & Hunter, 2007; Jensen, Taylor, & Davis, 2013; Jones, 2009; Real de Asua, Quero, Moldenhauer, & Suarez, 2015; van Allen et al., 1999; Van Buggenhout et al., 1999). Occasionally IDD population-based databases have been utilized to compile this information using survey methods (Maatta et al., 2011; Wong, 2011).

In a primary care setting, the impetus to initiate screening or evaluation may be based on a person's age, gender, clinical suspicion, existing guidelines, and/or the presence of risk-factors and other co-morbidities. In children with DS the estimated prevalence of certain co-morbidities (e.g., thyroid disease, obstructive sleep apnea) is sufficiently high that routine screening is recommended in asymptomatic individuals (AAP, 2011). In adults questions about the prevalence and severity of co-morbid health conditions and their respective risk-factors has not been fully elucidated. Likewise the efficiency, financial costs, and risk/benefit of routine screening have not been well studied. Nor has the question of whether such screening actually results in measurably improved health outcomes.

The risk of manifesting any particular medical condition varies with the life-stage of an individual (Esbensen, 2010). Several authors have focused on these age-related comorbidities (Glasson, Dye, & Bittles, 2014), reasons for hospitalization (Tenenbaum, Chavkin, Wexler, Korem, & Merrick, 2012), and causes of death (Bittles, Bower, Hussain, & Glasson, 2007). Given the absence of clinical guidance for medical conditions in adults there is sufficient reason to believe that the medical and mental health needs of this adult population also remain largely underserved (Carfi, Brandi, Zampino, Mari, & Onder, 2015; Jensen et al., 2013). Such questions have taken on greater importance as adults with DS are living longer (Presson et al., 2013) and typically experience an increased burden of chronic medical conditions associated with high morbidity or mortality (Bittles et al., 2007; Esbensen, 2010; Glasson et al., 2014; Tenenbaum et al., 2012).

In November 2007, a meeting held at the Centers for Disease Control entitled, "Setting a Public Health Research Agenda for Down Syndrome" was convened to review current knowledge, identify gaps, and develop priorities for future public health research related to Down syndrome (Rasmussen, Whitehead, Collier, & Frias, 2008). Participants from clinical medicine and public health were asked to identify key public health research questions and to discuss potential strategies to address those questions. A subset of topics focused on the provision of health care, including the identification of risk and preventive factors for various health outcomes; understanding of comorbid conditions, including their prevalence, clinical variability, natural history, and optimal means of evaluation and treatment; identification of mental health comorbidities; and improved methods for the diagnosis and treatment of Alzheimer disease.

Since 2010, the Down Syndrome Medical Interest Group in the United States of America (DSMIG-USA) has met annually to focus on health care and related topics at their annual symposium. Beginning in 2014, adult health topics started to receive special priority within DSMIG-USA which in turn has catalyzed interest in further assessing the quality of existing evidence. During this time many of the authors participated in the DSMIG-USA symposia where a portion of this information has been presented. Under the auspices of DSMIG-USA an Adult Health Workgroup was created to present and discuss annually, the emerging evidence in the adult health literature. This article summarizes those efforts and the findings of the Workgroup.

The goals of this review are as follows:

Goal 1: Using the National Library of Medicine (NLM) database PubMed (MEDLINE) identify review articles in peer-reviewed journals that discuss co-occurring medical conditions and their relative frequency in adults with DS

Goal 2: Use PubMed to identify original research articles that address the prevalence, severity and methodologies for screening or evaluation of adults with DS

Goal 3: Guided by key questions formulated a priori determine the quality of the available evidence

Goal 4: Identify critical areas of deficit in our clinical knowledge

Goal 5: Discuss the implication of these findings for the development of practice guidelines and the direction of future clinical research.

2 | MATERIALS AND METHODS

2.1 | Survey of resources on health conditions

Using the National Library of Medicine (NLM) PubMed database (NCBI, 1946–2015), we undertook a survey of review articles that discussed the co-occurrence of medical conditions in adults with DS. Many of the 18 articles contained recommendations for routine screening or evaluation, but only a portion contained original, clinical data in support of their recommendations (Henderson et al., 2007; Jensen et al., 2013; Jones, 2009; Maatta et al., 2011; Real de Asua et al., 2015; van Allen et al., 1999; Van Buggenhout et al., 1999). Additional sources of reference not indexed in PubMed included books and book chapters (Chicoine & McGuire, 2010; Pueschel, 2006; Pueschel & Pueschel, 1992; Rubin & Dwyer, 1989) guidance documents prepared for health providers (Cohen & Group, 1999; Sullivan et al., 2006; Van Cleve et al., 2006), several journal articles (Kerins, Petrovic, Bruder, & Gruman, 2008; Prasher, 1994), and websites (Forster-Gibson & Berg, 2011). See Table 1a for a summary of the resources about general health that were consulted.

2.2 | Survey of review articles

The 18 review articles identified through PubMed were reviewed in detail to determine the types of medical condition that were considered and discussed. Review articles were classified according to study design and the source of patient data as either "literature review/expert opinion," "clinic chart review/original data," "cohort survey/original data." See Table 1b for a summary of data classification.

The frequency at which specific conditions were discussed was totaled across all the articles, and thereby served as a "post hoc consensus" of informed expert-opinion regarding the clinical significance of these conditions in adults with DS. This information was then used to inform the next stage of our review. See Table 2 for the frequency and rank order of medical conditions discussed in the review articles.

The conditions discussed in the publications in rank-order included ophthalmologic-vision, age-related dementia, behavior-mental health, thyroid disease, otolaryngology-hearing, cardiac disease, musculoskeletal-cervical spine, overweight-obesity, respiratory-sleep apnea, dermatologic concerns, seizures, dental concerns, gastrointestinal disorders, vaccination-infectious disease, gynecology-women's health, autoimmune disorders, type II diabetes and various cancers. Fewer, than one-third of articles discussed urologic-renal disorders, hematologic conditions, movement disorders, medication use, hyperlipidemia, gout, chronic pain, and syncope. None of the review articles discussed hospitalizations, end of life care, or cause of death.

2.3 | Topic selection

Our Workgroup agreed that those conditions appearing in greater than 50% of the review articles warranted priority for further review. We prioritized those conditions that met criteria outlined by the United States Preventive Service Task-Force (USPSTF) because of (1) public health importance (i.e., burden of suffering and expected effectiveness of the preventive service to reduce that burden) and (2) the potential for recommendations to impact clinical practice (based on existing controversy or the belief that a gap exists between evidence and practice) (USPSTF, 2008). It was the consensus of the Workgroup to proceed with review of the following medical topics initially, thyroid disease, hearing impairment, congenital heart disease, cervical spine disease, osteopenia-osteoporosis, overweight-obesity, and sleep apnea. The Workgroup continues to evaluate the literature on visual impairment, behavior-mental health, age-related dementia, pulmonary disease, dermatology, gastrointestinal problems, dental problems, infectious disease, and women's health to be included in future manuscripts.

TABLE 1 Health information gathered on adults with Down syndrome by resource type and health information from PubMed review articles

(a) Health information gathered on adults with Down syndrome by resource type

	Review article, *N* = 18	Review article, *N* = 2	Book or chapter, *N* = 4	Medical interest groups, *N* = 3	Website, *N* = 1
Source	PubMed	Not in PubMed	Not in PubMed	Not in PubMed	Not in PubMed
Original data	10 (55%)	2	2	No	No
Guidance provided	13 (72%)	No	3	3	1

(b) Health information from PubMed review articles

	All review articles, *N* = 18	Literature review-expert opinion, *N* = 9	Clinic chart review, *N* = 7	Survey of IDD or DS cohort, *N* = 2
Number of subjects	748 adults	na	554 adults	194 adults
Ages covered	18–70+ years	Adults	18–60+ years	18–70+ years
Original data	10 (55%)	1	7 (100%)	2 (100%)
Guidance provided	13 (72%)	9 (100%)	3 (43%)	1 (50%)

TABLE 2 Frequency and rank-order of co-occurring medical conditions discussed in at least two of the review articles

Topic	Number of articles citing the condition	Frequency (%)	Rank order
Vision/ophthalmology	18	100	1
Thyroid disease	17	94	2
Behavior/mental health	17	94	2
Age related dementia	17	94	2
Hearing/ear-nose-throat	16	88	3
Cardiac	16	88	3
Musculoskeletal/cervical-spine	16	88	3
Overweight-obesity	14	77	4
Respiratory/sleep apnea	14	77	4
Dermatologic	12	67	5
Seizures	11	61	6
Gastrointestinal	10	55	7
Dental	10	55	7
Infectious disease/vaccination	9	50	8
Women's health/gynecology	8	44	9
Metabolism (lipids, glucose)	8	44	9
Autoimmune disorders	8	44	9
Cancer	7	39	10
GU/renal	5	28	11
Hematology	3	17	12
Medication use	2	11	13
Movement disorder/parkinsonism	2	11	13
Lifestyle/activity	2	11	13

Special diets, chronic pain, gout, autonomic dysfunction, syncope, tobacco/alcohol use, sexual activity are each discussed in one article only.

2.4 | Key questions

In accordance with USPSTF practice, we next formulated a series of key questions. The formulation of key questions is an integral part of the approach to conducting systematic literature reviews. Along with the analytic framework, these questions specify the logic and scope of the topic and become critical in guiding the literature search, abstraction, and analysis process (USPSTF, 2008). By consensus, the Workgroup agreed that key questions needed to pertain to the clinical prevalence, severity, risk-factors, screening or evaluation methods, and potential benefits and/or harms in an adult population of persons with DS.

By consensus, the following key questions were formulated:

1. Is the prevalence of (condition) in adults with DS known?
2. Is the clinical severity of (condition) in adults with DS known?
3. Among adults with DS can those at ultra-high risk (for condition) be identified?
4. What are the screening or evaluation methods utilized?
5. Does screening or evaluation lead to reduced morbidity or mortality?
6. What are the financial costs, potential benefits, or harms of screening or evaluation?

2.5 | PubMed literature search

A second phase of topical literature searches were conducted in 2015–2016 also using the National Library of Medicine (NLM) biomedical literature database PubMed (MEDLINE) (NCBI, 1946–2013) to identify original research manuscripts addressing our prioritized topics. We used the Medical Subject Headings (MeSH) (the NLM controlled vocabulary thesaurus for indexing) to capture related entry terminology in our searches. For example, the MeSH term "Down syndrome" included the search entry terms: Downs syndrome, Down's syndrome, Mongolism, Trisomy 21, Partial Trisomy 21.

The MESH term "Down syndrome" was combined with one or more MeSH main heading terms to capture literature (unfiltered) about specific conditions in our search. Then, the limiters "Human," ">19 years" were applied to narrow the scope of the search (filtered). Abstracts from Medline were reviewed and excluded according to their relevance in pertaining to key questions. Whenever an abstract made mention of any key question (or there was doubt) the full article was procured. The sections 2 and 3 were then reviewed to determine which articles met inclusion or exclusion criteria. A single reviewer from our group was chosen to conduct the literature searches then individual reviewers performed the data review and extraction process. See Table 3 for results of PubMed searches.

2.6 | Article inclusion criteria

Study sample includes those >19 years, data addresses at minimum one key question, supporting data are original (not previously published), case series includes >5 participants, or uses a cohort, case-series or case-control research design or randomized clinical trial.

2.7 | Exclusion criteria

Study sample includes those <18 years (exclusively), data do not address at least one key question, study uses an uninterpretable methodology, data have been previously published or does not provide supporting data.

2.8 | Data extraction by condition

Using only the PubMed articles meeting inclusion, data pertaining to key questions were extracted from the Abstract section, sections 2 and 3, and entered into a preformatted Excel data template for analysis. See Table 4 for a summary of the articles used for the data extraction.

TABLE 3 PubMed searches, MeSH terms, article inclusion, and exclusion by condition

Condition	MeSH main heading	Search entry terms included	Unfiltered search hits	Filtered search hits	Excluded from review	Included in review
Thyroid disease	Thyroid disease	Thyroid neoplasms; euthyroid sick syndromes; goiter; hyperthyroidism; hyperthyroxinemia; hypothyroidism; thyroid dysgenesis; thyroiditis	426	175	156	19
Cervical spine disease	Cervical vertebrae; spondylosis	Axis, cervical vertebrae; cervical atlas; cervical spondylosis	120	39	23	16
Hearing impairment	Hearing impairment	Hearing loss; hypoacuisis	134	51	41	10
Overweight-obesity	Obesity	Obesity abdominal; obesity, metabolically benign; obesity, morbid;obesity, pediatric	151	61	56	5
Congenital heart disease	Congenital heart defects	Abnormality, heart; congenital heart defect; congenital heart defects; defects, congenital heart; heart abnormalities; heart defect, congenital; heart defects, congenital heart; malformation of heart	947	234	230	4
Sleep apnea	Sleep apnea syndromes	Apnea, sleep; hypersomnia with periodic respiration; mixed central and obstructive sleep apnea; sleep apnea syndromes; sleep apnea, mixed; sleep apnea, mixed central and obstructive; sleep hypopnea; sleep-disordered breathing	140	33	29	4
Osteopenia-osteoporosis	Osteoporosis	Age-related osteoporosis; bone loss, age-related; osteoporosis; osteoporosis, age-related; osteoporosis, involutional; osteoporosis, post-traumatic; osteoporosis, senile; senile osteoporosis	25	16	8	8

2.9 | Evidence ratings by condition

Next a critical appraisal of each of the included articles was performed by reviewers to determine the type of research design used, subject ascertainment, total number of study subjects, source of control subjects, and the extent of internal validity and external validity. The grading of *internal validity* considers study design factors such as ascertainment and selection bias, test procedures and consideration of confounding variables; while *external validity* considers the generalizability of findings to a broader (more representative) population (USPSTF, 2008). See appendix VII in the USPSTF report for criteria on research design hierarchy, and the grading system used for scoring internal and external validity. See Table 5 for summary of evidence rating.

3 | RESULTS

3.1 | Thyroid disease

Of the nineteen articles reviewed, five used a case-control design (II-2) (Hestnes et al., 1991; Kanavin, Aaseth, & Birketvedt, 2000; Kinnell, Gibbs, Teale, & Smith, 1987; Murdoch, Ratcliffe, McLarty, Rodger, & Ratcliffe, 1977; Percy et al., 1990) while the remaining fourteen were cohort studies (II-2) (Baxter et al., 1975; Dinani & Carpenter, 1990; Kohen & Wise, 1992; Korsager, Chatham, & Ostergaard Kristensen, 1978; Percy et al., 2003; Prasher & Haque, 2005; Van Buggenhout et al., 1999) or case series (III) (Feingold, 2004; Jensen et al., 2013; Mani, 1988; Percy et al., 2003; Prasher, Ninan, & Haque, 2011; Real de Asua et al., 2015; Tenenbaum et al., 2012) focused exclusively on individuals with DS. From the case-control studies, one study used controls with psychiatric disease from a residential facility (Murdoch et al., 1977), two studies used controls with other intellectual disabilities (ID) (Hestnes et al., 1991; Kanavin et al., 2000), and two studies used typically developing controls (Kinnell et al., 1987; Percy et al., 1990). The cumulative number of DS subjects studied appears sufficient ($N = 1426$) having been ascertained from residential institutions (44%), community samples (45%) and clinics or unspecified sources (11%). Eleven of the articles were published prior to the year 2000 (Table 4).

The scope of evaluation included standard thyroid function tests and/or anti-thyroid antibody titers. The medical comorbidities assessed in the studies included treatment with thyroxine (Baxter et al., 1975; Feingold, 2004; Mani, 1988; Prasher et al., 2011), presence of anti-thyroid antibodies, other autoimmune conditions (Real de Asua et al., 2015; Tenenbaum et al., 2012), or dementia (Percy et al., 1990; Tenenbaum et al., 2012; Van Buggenhout et al., 1999).

The prevalence of thyroid disease, including both hypothyroidism and subclinical hypothyroidism, appears to be higher in adults with DS (27% across studies) compared to those in the general population. There is only limited evidence regarding the prevalence of hyperthyroidism (estimated 3% across studies) (Hestnes et al., 1991; Kinnell et al., 1987; Percy et al., 1990; Real de Asua et al., 2015;

TABLE 4 Articles used for data extraction by condition

	Publications (N) dates	Subjects (N)	Age range	Source of subjects	Methods	Study designs
Thyroid dysfunction	(19) 1977–2015	DS = 1,426; ID CTR = 68; PD CTR = 82; CTR = 103	17–76 yr	Community homes, clinics, residential facility	(Thyroid function tests) TBG, thyroid antibodies	Cohort/case series (14), case-control (5)
Cervical spine disease	(16) 1985–2014	DS = 1,561; CTR = 308	18–70 yr	Community and residential	(ADI, disc/bone height); plain films	Cohort/case series (13), case-control (3)
Hearing impairment	(10) 1981–2011	DS = 1,201; CTR = 1,461	15–80 yr+	Clinic or center based	pure tone audiometry, sound field testing, speech audiometry, ABR, tympanogram, bone/air conduction	Cohort/case series (6), case-control (3), epidemiologic (1)
Overweight-obesity	(5) 1992–2011	DS = 1,495; ID CTR = 6,095	15–76 yr	Family or community homes	(BMI) calculated	Cohort/case series (2), case-control (3)
Congenital heart disease	(4) 1999–2013	DS = 10,334; CTR = 69,705	18–68 yr	Residential facilities, hospitals	Echocardiogram	Cohort/case series (3), case-control (1)
Sleep apnea	(4) 2002–2013	DS = 71; CTR = 48	14–56 yr	Clinic	(AHI) Laboratory based PSG	Cohort/case series (3), case-control (1)
Osteopenia-osteoporosis	(8) 1999–2008	DS = 406; CTR = 186	18–60 yr+	Community and clinics	(BMD or BMM) DEXA	Case-control (6), chart review (2)

ABR, auditory brainstem response; ADI, atlas-dens interval; AHI, apnea-hypopnea index; BMD, bone mineral density; BMI, body mass index; BMM, bone mass measurement; CTR, control (typical); DS, Down syndrome; ID, Intellectual disability; PD, Psychiatric disease; PSG, polysomnography; TBG, thyroxine-binding globulin.

Van Buggenhout et al., 1999). Data on severity of thyroid disease in adults with DS are limited, but the case-control studies suggest significant differences in thyroid function test values compared to controls. Overall, a high burden of thyroid disease is evident in this population, and is further supported by the high prevalence of thyroid disease in children with DS (Roizen et al., 2014).

Although conditions such as autoimmune disease are common in people with DS, there is a lack of studies exploring the relationship of these conditions with thyroid disease. One study noted a prevalence of thyroid disease in 74% of a sample of 136 children with diabetes and DS (Aitken et al., 2013), but studies about the co-occurrence of thyroid disease and other autoimmune conditions in adults are limited (Prasher, 1999).

We assigned *internal validity* ratings of good to 15 and fair to 4 of the studies based upon design considerations. Seven studies received *external validity* ratings of good, four were fair while eight were rated as poor. *External validity* was limited in several of the studies whenever participants were recruited from institutional settings which increased the likelihood for more serious comorbid medical conditions (Table 5).

3.2 | Cervical spine

Of the articles reviewed, 15 addressed atlanto-axial instability (AAI) and 5 addressed degenerative disease of the cervical spine. The total number of adults with DS studied was large (*N* = 1,561), but only three studies utilized controls. Thirteen of the studies used a cohort or case series design (III), while three used a case-control design (II-2) (Alvarez & Rubin, 1986; Burke, French, & Roberts, 1985; Cooke & Lansdall-Welfare, 1991; El-Khouri et al., 2014; Elliott, Morton, & Whitelaw, 1988; Ferguson et al., 1997; French, Burke, Roberts, Whitecloud, & Edmunds, 1987; MacLachlan et al., 1993; Miller, Capusten, & Lampard, 1986; Miller, Grace, & Lampard, 1986; Morton, Khan, Murray-Leslie, & Elliott, 1995; Pueschel et al., 1987; Pueschel, Scola, & Pezzullo, 1992; Roy, Baxter, & Roy, 1990; Tangerud, Hestnes, Sand, & Sunndalsfoll, 1990; Van Dyke & Gahagan, 1988) (Table 4).

The scope of evaluation included measurement of the atlanto-dens interval (ADI) or bone height taken from plain films without consideration of co-morbid medical conditions. Although there was some variation in the measures used to define increased ADI, most studies used distances between 4.5 and 5 mm.

The prevalence of AAI in adults with DS (2–20%) appears to be decreased compared to children with DS (15–20%) but higher than typical age-matched controls (Alvarez & Rubin, 1986; Burke et al., 1985; Cooke & Lansdall-Welfare, 1991; El-Khouri et al., 2014; Elliott et al., 1988; Ferguson et al., 1997; French et al., 1987; Miller, Capusten, et al., 1986; Pueschel et al., 1987; Roy et al., 1990; Tangerud et al., 1990). The article with the highest prevalence of AAI (20%) used a cut off of 4 mm which may in part explain the findings (Miller, Capusten, et al., 1986). The presence of os odontoideum and/or ossicles appears to be a marker of high-risk in adults as it is in children (Burke et al., 1985; El-Khouri et al., 2014). Males and females appear to have similar risk; however, periods of inflammation may increase risk (Pueschel et al., 1987).

TABLE 5 Evidence ratings by condition

	Key Qs addressed (maximum = 6)	Research design hierarchy	Internal validity rating	External validity rating
Thyroid dysfunction	3	II-2/III	Fair (4), good(15)	Poor (8), fair (4), good (7)
Cervical spine	3	II-2/III	Fair (3), good (13)	Fair (10), good (6)
Hearing impairment	4	II-2/III	Fair (2), good (8)	Fair (8), good (2)
Overweight-obesity	5	II-2	Fair (1), good (4)	Fair (1), good (4)
Congenital heart disease	6	II-2/III	Poor (1), fair (1), good (2)	Fair (3), good (1)
Sleep apnea	4	II-2/III	Poor (2), fair (2)	Poor (2), fair (2)
Osteopenia-osteoporosis	3	III	Poor (7)	Poor (7)

Research design hierarchy: II-2, well designed cohort or case-control study; III, descriptive studies or case series, expert opinion.

The prevalence of spondylosis or degenerative change of the cervical spine appears to be increased (33–64%) among adults with DS compared to the general population (Burke et al., 1985; MacLachlan et al., 1993; Miller, Capusten, et al., 1986; Tangerud et al., 1990; Van Dyke & Gahagan, 1988). These changes often localize to higher levels of the cervical spine and appear to increase in severity with age (Miller, Capusten, et al., 1986; Tangerud et al., 1990).

Three studies received *internal validity* ratings of fair and thirteen were rated as good based on design considerations. Ten studies received *external validity* ratings of fair, while six received a good rating. These assignments reflect the frequent ascertainment of samples from institutionalized settings (Table 5).

3.3 | Hearing impairment

Four of the articles on hearing loss focused exclusively on persons with DS. Five articles also used non-DS controls with intellectual disability (ID), and one included healthy individuals from the general population. Six articles were cohort studies (II-2) (Lavis, 1997; Evenhuis, van Zanten, Brocaar, & Roerdinkholder, 1992; Keiser, Montague, Wold, Maune, & Pattison, 1981; Maatta et al., 2011; Van Buggenhout et al., 1999; van Schrojenstein Lantman-de Valk et al., 1994), three were case control (II-2) (Buchanan, 1990; Hassmann, Skotnicka, Midro, & Musiatowicz, 1998; Lowe & Temple, 2002), and one was a cross sectional study (III) (Meuwese-Jongejeugd et al., 2006). The cumulative number of DS subjects studied appears large (*N* = 1,201). Seven of the articles were published prior to the year 2000 (Table 4).

The scope of evaluation entailed using standard audiologic methods such as pure tone audiometry or sound field testing (80%), however, various other methods were also used across studies suggesting variability in the approach to screening and evaluation. No consideration was given to other medical comorbidities.

The prevalence of any hearing impairment in adults with DS is up to 73% which is increased compared to both the general population and those with other forms of ID (Lavis, 1997; Meuwese-Jongejeugd et al., 2006). Disease severity appears to increase with age and up to 100% of DS adults experience hearing loss by 60 years, which indicates a high burden of disease in this population. Further support is evident from the high prevalence of middle ear disease and hearing impairment in children with DS (Roizen et al., 2014).

Eight studies received an *internal validity* rating of good and two were rated as fair. Good ratings on *external validity* was assigned to two studies while eight were rated as fair, based largely upon the consistently increased rates of hearing impairment in DS individuals when compared to those without DS across all studies (Table 5).

3.4 | Overweight-obesity

Three of the studies on overweight-obesity were based on a case-control design (II-2), two were case-series studies (II-2). Two of the studies were limited only to persons with DS, while three employed contemporaneous non-DS controls with other forms of ID. All of the studies utilized large study samples (range 183–6,429). The cumulative number of subjects with DS studied was large (*N* = 1,426). Three of the articles were published prior to the year 2000. The scope of evaluation focused exclusively on measures of obesity itself, calculated body mass index (BMI) with no emphasis on comorbid medical conditions. Four studies received an *internal validity* rating of good, and one was rated as fair (Table 4).

Each of the studies utilized BMI as weight (kg)/height (m^2) as the preferred method of evaluation for obesity (Bell & Bhate, 1992; Melville, Cooper, McGrother, Thorp, & Collacott, 2005; Prasher, 1995; Rubin, Rimmer, Chicoine, Braddock, & McGuire, 1998; Stancliffe et al., 2011). In four of the studies, participants were living in their home or community and recruited through a regional hospital or center-based medical clinic. A total of 412 males and 377 females with DS (total = 789), and 201 male and 171 female control subjects (total = 372) with other ID were studied. All subjects were between the ages of 15 and 76 years. Across these four studies 38% of DS subjects were classified as obese and 34% as overweight. Females were more likely than males (43% vs. 33%) to be obese, and about as likely to be overweight (32% vs. 35%). Thus 75% females and 68% males with DS were classified as overweight or obese. In the two studies that utilized ID control subjects (Bell & Bhate, 1992; Melville et al., 2005) 60% of females and 50% of males with ID were classified as overweight or obese. Additionally, in two of the studies a decline in

BMI was noted with advancing age beyond 35 years (Prasher, 1995; Rubin et al., 1998).

In the one study that utilized an existing database of individuals with ID, that included persons with DS (*N* = 706), and those with non-specified ID (*N* = 5,627), 73% of both men and women with DS were classified as overweight or obese, compared to 65% of those with other ID (Stancliffe et al., 2011). Among those with DS women were more likely to be obese than men (48% vs. 41%); which was higher than women and men with non-specified ID (40% vs. 31%).

The *external validity* or generalizability of these findings to the larger population of adults with DS warrants a rating of good in four of the studies; and receives further support from the large number of community-residing persons who participated (Table 5). Additional support for generalizability stems from the consistently high prevalence of overweight-obesity (60–75%) across all studies, and the finding that obesity is often present by adolescence in youth with DS (Tenenbaum et al., 2011).

3.5 | Congenital heart

Three of the studies on adult outcome of CHD were based on chart reviews of a DS cohort without controls (II-2) (Majdalany et al., 2010; van Allen et al., 1999; Vis et al., 2010). The largest study, also retrospective used a case-control design and included a large numbers of participants with CHD both with/without DS (Baraona, Gurvitz, Landzberg, & Opotowsky, 2013). Information about financial costs, hospital LOS, non-cardiac comorbidities, and mortality was presented. A single study employed prospective cardiac screening in a subset of their participants ascertained retrospectively (Vis et al., 2010). Participants were ascertained through convenience samples including, medical clinics, hospitals and residential facilities. The cumulative number of subjects with DS reviewed was large (*N* = 10,472). All articles were published between 1999 and 2013 (Table 4).

The data included standard measures of cardiac function (echocardiography) or in one study morbidity (hospitalization, length of stay, medical conditions, and need for cardiac procedure) and mortality. Non-cardiac medical conditions were considered in only two studies.

Up to 17% of patients residing in a residential setting (the Netherlands) had undiagnosed CHD in addition to the 16% with previously CHD (33%). Regurgitation of the mitral, aortic, and tricuspid valves was present in 75% of subjects (Vis et al., 2010). In patients with AVSD repair left AV valve insufficiency and left ventricle outflow tract obstruction are the most frequently reported long-term complications requiring surgical repair (Martinez-Quintana, Rodriguez-Gonzalez, Medina-Gil, Agredo-Munoz, & Nieto-Lago, 2010). Hospitalized patients with DS and CHD had an increase prevalence of pulmonary hypertension, cyanosis and secondary erythrocytosis compared to those without the condition (Baraona et al., 2013). Among all hospitalized patients with CHD, mortality was higher for those with DS. Bacterial and aspiration pneumonia were exclusively associated with higher mortality in DS. Cardiac procedures, however, were less often performed in patients with DS.

Two studies received an *internal validity* rating of fair one was rated as good and another as poor. The *external validity* or generalizability of the findings received a rating of fair in three studies and one as poor (Table 5). Further support for these findings derives from the large number of participants surveyed, and the known prevalence (40–50%) of CHD in newborns with DS (Roizen et al., 2014).

3.6 | Sleep apnea

Three of the studies of sleep apnea (OSA) focused on persons with DS exclusively, and just a single study employed non-DS (historical) controls also suspected of having OSA. One of the studies used a case-control design (II-2) (Trois et al., 2009), and two were small case series (III) of between 6 and 12 subjects (Andreou, Galanopoulou, & Gourgoulianis, 2002; Resta et al., 2003). Another utilized DS subjects, with/without comorbid depression as a within-syndrome case-control design (Capone, Aidikoff, Taylor, & Rykiel, 2013). The cumulative number of DS subjects studied is quite small (*n* = 71) having been ascertained primarily as clinic convenience samples. All of the articles were published after the year 2000 (Table 4).

The scope of evaluations focused on objective findings (apnea-hypopnea index [AHI], 02% saturation) taken from overnight polysomnogram, with some emphasis on co-occurring medical conditions, such as obesity, thyroid disease and depression. The apparent increased prevalence (85%) and high symptom severity (mean AHI = 25.9/hr) reported across these studies suggests a high disease burden in adults with DS.

Two studies were given an *internal validity* rating of poor and two fair. Because adult persons with DS constitute a special population in the United States, the *external validity* or generalizability of these findings must be made to a larger community-based population of adults with DS. Thus, two studies warrant an *external validity* rating of poor and two are rated as fair. These ratings reflect the small sample sizes and selection bias inherent to clinically ascertained samples (Table 5). However, additional support derives from the high prevalence of OSA in children with DS (Churchill, Kieckhefer, Landis, & Ward, 2012; Hoffmire, Magyar, Connolly, Fernandez, & van Wijngaarden, 2014).

3.7 | Osteopenia-osteoporosis

Six of the articles on bone density utilized a case-control design focusing on adults with DS, and controls with ID (II-2) (Angelopoulou et al., 1999, 2000; Baptista, Varela, & Sardinha, 2005; Guijarro, Valero, Paule, Gonzalez-Macias, & Riancho, 2008; Sakadamis, Angelopoulou, Matziari, Papameletiou, & Souftas, 2002; Tyler et al., 2000). Two studies relied on a retrospective chart review (III) (Schrager, Kloss, & Ju, 2007; van Allen et al., 1999). The cumulative number of DS subjects studied was (*N* = 342). The articles were published between 1999 and 2008 (Table 4).

The prevalence of osteopenia-osteoporosis appears increased among adults with DS compared to adults in the general population

and those with other forms of ID. It is unclear if there is a corresponding increase in bone fracture, but some studies suggest this. Risk factors for low bone-mass density (BMD) were identified in five of the studies and included immobility, inactivity, low calcium and vitamin D, low sunlight exposure, hypogonadism, and seizure disorders. Interestingly males and females appear to be equally affected. Most of the studies measured BMD on dual energy X-ray absorptiometry (DXA) scan as the preferred method of evaluation. The DXA method for screening is widely available and without need of modification in the DS population.

Three studies were retrospective medical clinic chart reviews and the remainder utilized community-based samples. Two studies received an *internal validity* rating of fair and six were rated as poor. The *external validity* or generalizability of the findings was rated as fair in two studies and poor in six of the studies (Table 5).

3.8 | Evidence gaps

There is only limited published evidence available to answer our key questions for each of the co-occurring conditions under review in the adult DS population. Many older studies are descriptive, utilizing small convenience samples and either typical controls or those with IDD as a comparison group for DS. Rarely were persons with DS, without the target condition, used as controls for determining possible risk factors or associated co-morbidities within a larger DS sample. Indeed, there is scant information about risk factors or the direct physiologic impact of other medical co-morbidities on target disease prevalence or severity. No studies have addressed the financial costs or risks/benefits of screening in asymptomatic individuals. A single study addressed morbidity, mortality, and the financial costs associated with the specified medical condition (CHD). Due to the absence of longitudinal, prospective cohort data, we are unable to determine the natural history of disease progression in asymptomatic individuals who eventually become symptomatic, especially those presenting with severe disease. Studies about the use of standard versus alternative methodologies for screening were also generally unavailable.

3.9 | Condition specific considerations and emerging knowledge

3.9.1 | Thyroid disease

An increased frequency of thyroid disease is evident in adults with DS compared to members of the general population (Helfand & Force, 2004). An older USPSTF report reviewed the published evidence on screening for subclinical thyroid disease in typical adults (Helfand & Force, 2004). In the general population subclinical hypothyroidism is considered a risk factor for progression to overt hypothyroidism, Hashimoto's disease, hyperlipidemia, osteoporosis, and mood disturbance; and subclinical hyperthyroidism increases risk for progression to overt hyperthyroidism, thyroid nodules, Grave's disease, atrial fibrillation, osteoporosis, and mood/anxiety disorders. The relationship between thyroid disease and other medical conditions is beginning to be explored in children and adults with DS, with a recent study suggesting a role for both hypothyroidism and oxidative stress in association with osteoporosis (Villani et al., 2016).

Although evaluation methods to screen for thyroid disease are generally available and well established in clinical practice there is a lack of consensus about the frequency and interval of thyroid screening in asymptomatic adults with DS. The true incidence of symptomatic thyroid disease and recommendations for screening has been discussed, with debate focusing on the "normal" reference range for laboratory values (Prasher et al., 2011; Prasher & Haque, 2005).

Identification of individuals at high-risk for thyroid disease includes any individual ever treated with thyroxine, the presence of thyroid auto-antibodies, those with a positive family history of autoimmune thyroid disease or advancing age. The apparent association between autoimmune thyroid disease and other medical comorbidities especially autoimmune conditions deserves further investigation (Aversa et al., 2016; Soderbergh et al., 2006).

Fortunately, hormone replacement therapy makes the treatment of hypothyroidism fairly straightforward and cost-effective for adults with DS; whereas hyperthyroidism often presents a different set of clinical challenges. There is a lack of consensus about the role of thyroidectomy in the treatment of Grave's disease, due to concerns of risk with anesthesia and surgical outcomes in people with DS (Aversa et al., 2015; Goday-Arno et al., 2009).

3.9.2 | Cervical spine

It appears that addressing questions around degenerative disease of the cervical spine is a more urgent priority than screening for AAI per se, although both conditions can co-exist in adults with DS. Cervical spondylosis and cervical spondyolytic myelopathy (CSM) is not seen in childhood, thus clinical suspicion is required throughout adulthood. Because degenerative changes present earlier in adults with DS compared to the general population there needs to be some consensus about screening all adults with DS versus those at high-risk.

The incidence of cervical spondylosis defined as degeneration of vertebral facet joints and intervertebral discs is unknown, but CSM is believed to be the most common spinal cord disorder in typical adults >55 years of age (Young, 2000). Although not demonstrated in adults with DS specifically, typical adults presenting with gait impairment, sensory changes, and neck pain or stiffness are at high risk for disease progression, leading to functionally impairing paraparesis (St. Clair & Bell, 2007; Wang, Hwan, & Hee, 2010).

Evaluation using plain radiographs is generally available and informative regarding sagittal alignment and cervical instability in flexion-extension (Wang et al., 2010). Magnetic resonance imaging (MRI) is required for definitive diagnosis because of its accuracy differentiating neural, osseous, and soft tissue with high resolution and the degree of spinal canal stenosis and associated myelomalacia. If contraindication to MRI exists, computed tomography (CT) may be useful for determining the extent of cervical spondylosis. Although proper imaging can make the diagnosis reasonably straightforward,

treatment often requires surgical decompression-stabilization when severe myelopathy or radiculopathy is present.

Any recommendation to proceed with surgery in symptomatic individuals requires thoughtful consideration, as symptom stabilization rather than complete symptom resolution may be the goal; especially in elderly adults with moderate-severe dementia who are unable to participate in rehabilitation. Surgical outcomes in DS have not been reported as they have for posterior arthrodesis to treat cervical instability (Doyle, Lauerman, Wood, & Krause, 1996).

Putative pathogenic mechanisms include inflammation, collagen sub-types ratio, the integrity of the vascular supply and possibly alteration in bone turnover, none of which have been explored in DS (Nouri, Tetreault, Singh, Karadimas, & Fehlings, 2015; Tetreault et al., 2015).

3.9.3 | Hearing impairment

The prevalence of hearing impairment in adults with DS is >70% and increases dramatically with aging (Lavis, 1997; Meuwese-Jongejeugd et al., 2006). In the general population hearing loss is thought to occur in 25–40% of adults and the prevalence rises to 40–66% in those >75 years, and >80% in those 85 yr and older (Reuben, Walsh, Moore, Damesyn, & Greendale, 1998; Yueh, Shapiro, MacLean, & Shekelle, 2003). In the general population hearing loss is also considered a risk factor for depression, social isolation, poor self-esteem and functional decline (Gates et al., 1996). These same factors deserve further consideration in adults with DS.

Although several screening and evaluation methods are available in clinical practice there is a lack of consensus about the best method or frequency of screening. Current approaches to screening are typically individualized. Routine screening for all adults >40 years which is being incorporated into primary care practice (Patterson & Renaud, 2012) may be especially pertinent to adults with DS who are non-verbal or unable to self-report. The costs, benefits and frequency of repeat screening for all adults with DS versus those at high-risk requires some consideration.

There is a growing recognition about the role of subtle inner ear malformation and temporal bone dysplasia in people with DS discernible by radiologic imaging (Intrapiromkul, Aygun, Tunkel, Carone, & Yousem, 2012; Saliba et al., 2014). The role of risk factors such as childhood history of otitis media or cholesteatoma are also not well investigated (Bacciu et al., 2005). While the evaluation of hearing impairment can be relatively straightforward, newer treatments using amplification or cochlear implants requires further study in adults with DS (Hans, England, Prowse, Young, & Sheehan, 2010; Phelan, Pal, Henderson, Green, & Bruce, 2016; Sheehan & Hans, 2006).

3.9.4 | Overweight-obesity

The consistently high prevalence of overweight-obesity across all studies, and the finding that overweight-obesity is often present by adolescence in people with DS demands greater attention from clinical researchers. Etiology appears to be multifactorial including social, lifestyle, and family variables in addition to an apparent physiologic predisposition (de Winter et al., 2012b).

Recent efforts have confirmed the validity of using body adiposity index (BAI) and dual energy X-ray absorptiometry (DXA) as an alternative to calculated BMI to study obesity in DS (Bandini, Fleming, Scampini, Gleason, & Must, 2013; Nickerson et al., 2015). Obesity itself or its underlying causes appear to contribute to both reduced quality of life (QOL) and high medical complexity especially in the presence of sleep apnea, hepatobiliary disease, musculoskeletal degeneration, cardiopulmonary disease, metabolic disturbance, eating disorders, mood disorders, and reduced physical activity. Some of these relationships are beginning to be explored in youth and adults with DS but their potential interactions require a better understanding (de Winter et al., 2012a; Foerste, Sabin, Reid, & Reddihough, 2016; Galli, Cimolin, Rigoldi, Condoluci, & Albertini, 2015; Ordonez et al., 2012; Ordonez, Rosety, & Rosety-Rodriguez, 2006; Real de Asua, Parra, Costa, Moldenhauer, & Suarez, 2014a, 2014b; Tenenbaum et al., 2011; Wee et al., 2014).

The USPSTF currently recommends that calculated BMI is an acceptable screening modality in the general population, and that waist circumference may be an acceptable alternative in some sub-populations (Moyer, 2012). USPSTF also recommends that typical adults with BMI >30 be referred to an intensive multicomponent behavioral intervention. Adequate evidence indicates that multicomponent behavioral interventions can be effective and that potential benefit outweighs risks. However, evidence for any impact on long-term health outcomes is limited (Moyer, 2012).

Clinical trials focused on weight reduction, long-term management and prevention of obesity in adolescents and adults with DS are needed in conjunction with exploration of predisposing physiologic factors (Bertapelli, Pitetti, Agiovlasitis, & Guerra-Junior, 2016; Fleming et al., 2008).

3.9.5 | Congenital heart

The high prevalence of CHD during infancy and generally good surgical outcomes has in part contributed to the quality of published evidence available on this condition (Fudge et al., 2010; Jacobs et al., 2010). In clinical practice the need for regular follow-up of repaired congenital heart disease (CHD) throughout adulthood is well accepted. Those with previously repaired atrioventricular septal defect (AVSD) appear to have the greatest likelihood of serious long-term complications involving left ventricular outflow obstruction and/or Eisenmenger syndrome, that may require repeat surgical intervention (Martinez-Quintana et al., 2010). In some settings adults with DS alive today may never have had an echocardiogram, and should be screened as the incidence of undiagnosed CHD and valve regurgitation are both high (Baraona et al., 2013). It is perhaps less well appreciated that infants born without CHD can also develop valvular disease as adults (Goldhaber, Brown, & Sutton, 1987; Goldhaber et al., 1986; Pueschel & Werner, 1994). The question of routine cardiac screening for adults without any history of CHD requires clarification.

3.9.6 | Sleep apnea

Both the prevalence and severity of obstructive sleep apnea appears to be higher in the adults with DS ascertained from clinical samples, compared to adults from the general population suspected of sleep disturbance (Jennum & Riha, 2009).

The American Academy of Sleep Medicine (AASM) Adult OSA Task Force provides guidance about high risk individuals in the general population, specific questions and symptoms to consider at the time of evaluation as well as indications for the use of portable monitors (Epstein et al., 2009) Identification of individuals with DS at high-risk for OSA based upon identified symptoms (respiratory pauses, daytime fatigue), risk factors (upper airway anatomy, obesity), or the impact of other co-morbidities (cardiac, mental health) has only recently started to receive attention (Brooks et al., 2015; Fernandez & Edgin, 2013; Konstantinopoulou et al., 2016; Lal, White, Joseph, van Bakergem, & LaRosa, 2015).

The diagnosis and successful treatment of OSA in every person with DS/ID is neither straightforward nor easily achieved. The use of alternative diagnostic methodologies for individuals who cannot tolerate laboratory based PSG is being studied (Maris et al., 2016). In the AASM Task Force article both standard and alternative approaches to therapy are addressed, and supported by the use of clinical decision-making algorithms (Epstein et al., 2009). Practice parameters for surgical modification of the upper airway for OSA in adults has also been addressed by the AASM (Aurora et al., 2010). Evidence is critically reviewed and graded, recommendations made, and commentary regarding values and trade-offs well-articulated.

The pathophysiology of OSA is complex and risk-factors probably differ in children compared to adults with DS. Thus, in adults with DS the previous identification or absence of OSA on PSG during childhood, and role of prior (childhood) surgical interventions (adeno-tonsillectomy, lingual tonsillectomy or midline glossectomy) as putative "protective factors" is probably not justified (Donnelly, Shott, LaRose, Chini, & Amin, 2004; Propst et al., 2016). Newer treatment approaches that address glossoptosis have arrived (Diercks et al., 2016) and are currently undergoing clinical trials in adolescents and young adults with DS (Hartnick, 2017).

A USPSTF report recently reviewed the published evidence on screening, treatment and health outcomes associated with OSA in typical adults (Jonas et al., 2017). The report addresses a series of critical questions including, benefits and harms of screening, diagnostic accuracy and reliability of portable monitors, and potential benefits of various treatments such as continuous positive airway pressure, airway surgery, mandibular advancement, and weight loss. The impact of OSA on several health outcomes such as cardiovascular mortality, stroke, cognitive decline, and dementia were also examined. These same outcomes also deserve further exploration in adults with DS.

Any recommendation to proceed with positive airway pressure (PAP) or airway surgery in symptomatic individuals with DS requires thoughtful consideration for elderly adults with moderate-severe dementia who may be unable to tolerate or benefit from available treatment options.

Mainstream research questions focused on the general population need to be conducted in adults with DS (Lal, Strange, & Bachman, 2012; Macey, Woo, Kumar, Cross, & Harper, 2010; Tsai, 2010; Vgontzas, Bixler, & Chrousos, 2005). For persons with DS the potential costs and benefits of screening all adults versus just those at high-risk require consideration; as do clinical trials examining costs and benefits/harms of both PAP and surgical treatments. The impact of chronic, untreated disease on cognition, mental health, obesity, quality of life (QOL) and mortality also requires further study. The high prevalence and severity of OSA, and decreased resiliency to both the cognitive and mental health consequences requires that we persevere in our efforts to treat these conditions (Capone et al., 2013).

3.9.7 | Osteopenia-osteoporosis

In the DS population, a high prevalence of osteopenia-osteoporosis (>50%) is observed across all studies reviewed, and manifests at an earlier age compared to typical adults. It is unclear if total prevalence of this condition is increased in DS, but it is expected that age-matched prevalence would be higher in DS compared to typical adults. In the general population (50–65%) of women >50 yr, and (30–52%) of men >50 yr have osteopenia-osteoporosis. Interestingly, both males and females with DS may be equally affected. It remains unclear if there is a corresponding increase in bone fracture in DS adults with osteopenia-osteoporosis, some studies suggest this is the case (Schrager et al., 2007).

Dual energy X-ray absorptiometry (DXA), the most widely used and accepted method of screening, is generally available and has been well standardized in typical adults. It is a quick, non-invasive method that uses minimal radiation and does not require modification. The USPSTF recommends that all women >65 yr, or those at high risk for fracture be screened using DXA (Berg, 2003). A review of recommendations from other professional and healthcare organizations has also been conducted (Lim, Hoeksema, Sherin, & Committee, 2009) and recommends that all adults >50 yr be screened for risk-factors, and that DXA screening be implemented in women >65 yr and men >70 yr. Younger post-menopausal women <65 yr undergo screening only when risk factors are present. Thus, the designation of DS individuals as being at high-risk for osteopenia-osteoporosis requires further consideration in clinical practice as DXA screening prior to 45–50 yr of age may be justified in both men and women.

Risk factors such as immobility, physical inactivity, and low sunlight exposure are potentially modifiable risk factors which are not always easily achieved in adults with DS (Hawli, Nasrallah, & El-Hajj Fuleihan, 2009; Matute-Llorente, Gonzalez-Aguero, Gomez-Cabello, Vicente-Rodriguez, & Casajus, 2013). Low calcium and vitamin D intake lend itself to dietary modification (Zubillaga et al., 2006) as does increasing physical activity (Gonzalez-Aguero et al., 2012; Reza, Rasool, Mansour, & Abdollah, 2013) with some degree of success in adolescents with DS having been demonstrated.

The etiology of osteopenia-osteoporosis is likely multifactorial including dietary and environmental factors, but diminished bone formation and low turnover is probably a key factor (McKelvey et al.,

2013). Thus medications which inhibit bone resorption may not be an effective treatment. Research studies addressing bone formation and turnover, hypogonadism, and other endocrine disorders such as low thyroid or parathyroid hormone, oxidative stress, and effects on bone mass are indicated (Fowler et al., 2012; Villani et al., 2016; Zubillaga et al., 2006).

4 | DISCUSSION

4.1 | Limitations of the study

Limitations of this study include the restriction of our review only to that literature written in English and available through the NLM PubMed. Second, the number of studies available for review was limited and the quality of those studies was generally poor to fair, especially for those studies relying on data collected retrospectively from chart reviews, or when using convenience samples without adequate controls. Many studies were performed in a medical or residential setting because that is where one finds large numbers of adult individuals with DS. Thus, any resulting ascertainment bias may tend to oversample symptomatic individuals with severe disease. Perhaps this ascertainment bias reflects a common experience among adult primary care providers who are expected to manage patients with DS and complex symptomatology. It is these providers who will benefit most from having clinical guidance documents to assist in patient care and management. Third, a single reviewer extracted the data from each article and summarized the findings before it was re-reviewed by a panel of expert practitioners experienced in caring for adults with DS. Inter-rater reliability was not assessed. Despite these limitations, the study represents a coordinated effort by leading medical experts to critically review and synthesize the existing and emerging knowledge to best inform health screening and evaluation practices for adults with DS.

4.2 | The adult population in perspective

The number of persons with DS living in the United States (2008–2010) is estimated to be between 200,000 and 250,000 (de Graaf et al., 2017; Presson et al., 2013); and the number of adults (>18 yr) with DS living in the United States approaches or exceeds 125,000 individuals.

As longevity continues to increase it is also expected that greater numbers of adults with DS will live to be of advanced-age (>45 yr) (Bittles & Glasson, 2004). This presents ongoing challenges to the primary care physicians expected to manage an array of congenital, chronic and age-related conditions (Bittles et al., 2007). Of the co-morbid health conditions typically mentioned, visual and hearing impairment, thyroid disease, obesity, sleep apnea, cardio-pulmonary function, cervical and lumbar spondylosis, seizure disorder, and dementia are likely to remain the major considerations (Esbensen, 2010; Glasson et al., 2014). In this regard, guidance around end-of-life and palliative care also remains an area of need (McCallion et al., 2017).

4.3 | Strategic planning

For planning purposes and informed by this review we estimate that the number of adults (>18 yr) with DS currently living in the United States with a specific co-occurring health condition can be determined by the following: estimated disease prevalence in the DS population (rounded up to the nearest 5%) × 125,000 estimated individuals (>18 yr) living in the United States = number of individuals with DS affected by the condition.

Thus, for hearing loss (100%) = 125,000; for sleep apnea (85%) = 106,250 individuals; for overweight-obesity (70%) = 87,500; for cervical spondylosis (60%) = 75,000; for osteopenia-osteoporosis (50%) = 62,500; for previously repaired or uncorrected CHD (35%) = 43,750; for thyroid disease (30%) = 37,500.

Due to the unique biologic underpinnings of trisomy 21 some medical conditions may exhibit unique features of etiology-pathogenesis and natural history compared to individuals without this chromosomal condition (Zigman, 2013). In clinical practice, multiple medical co-morbidities is the rule not the exception, and this requires difficult decision-making and management considerations (Evenhuis, Schoufour, & Echteld, 2013; Schoufour, Evenhuis, & Echteld, 2014). Taken together, these factors suggest a modified approach to both diagnosis and treatment in elderly or medically frail adults with DS. In such situations, assessment of the specific risks and potential benefits of diagnostic evaluation and its intended therapeutic purpose needs to be discussed openly with decision-makers. Management alternatives for those of advanced-age or nearing end-of-life need to be made available to healthcare providers and family decision makers to use as they see fit in their specific circumstances.

4.4 | Toward guidelines

The single biggest challenge for guideline development is based upon their intended scope, breadth and depth. As DS is not a specific disease, but rather a unique human condition associated with a variety of developmental–anatomical differences, acquired (chronic) medical conditions, and precocious aging, such guidelines would potentially involve every major organ-system and life-stage experienced throughout adulthood. The best precedent for creating guidance documents has come from the efforts of the American Academy of Pediatrics (AAP, 2011). Although guidance beyond 21 yr is not within the scope of the AAP document, it never-the-less serves as an important educational tool about DS that would be of benefit to any physician. Much like an airline pilot flying without instrumentation, adult trained providers unfamiliar with DS or the AAP document remain in the unwelcome position of practicing medicine without any guidance whatsoever.

The intended audience for adult guidelines requires thorough consideration throughout the development process. Primary health care providers (physicians, nurses, nurse practitioners, and physician assistants) who will be providing direct care to adults are a primary target group (Qaseem, Snow, Owens, & Shekelle, 2010). The other stakeholder groups include caretakers (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 (IOM, 2011). Stakeholders should be included in the review process particularly in determining whether an assessment of benefits, harms and potential alternative options are fully addressed (Diaz Del Campo et al., 2011). Deployment of invested stakeholders will be critical to the prompt dissemination and successful adoption of health guidelines in both the public health and primary care settings (Luke, Wald, Carothers, Bach, & Harris, 2013).

4.5 | Realigning clinical research

Based simply on population prevalence in the United States DS is on the cusp of being considered a rare disease (frequency <200,000) (NIH, 2017). Further, it is likely that the prevalence rate for most co-occurring conditions is well within the range of rare disease designation. And so, it remains challenging to plan, organize, fund and enroll sufficient numbers of adult participants into existing data collection efforts and screening protocols, in part because of their numbers and geographical distribution.

It is not known what percent of the estimated 125,000 adults with DS living in the United States utilize services at an existing specialty clinic. Those who do almost certainly receive more comprehensive care compared to those who do not (Jensen et al., 2013; Skotko, Davidson, & Weintraub, 2013). Although the number of DS clinics serving the needs of adults are few, many are located at large, university-affiliated medical, research and training centers (AUCD, 2017; DSMIG-USA, 2017). Despite such advantages, clinical research on adults has not kept pace with the need for relevant information. What is required are better efforts to organize and support existing clinical DS programs to collect and share information on medical screening, diagnostic evaluation and treatment outcomes, as routinely performed at the point of care. Recent efforts to conduct multicenter data collection and sharing using clinician input data are successfully underway (Lavigne et al., 2015, 2017) and may provide the necessary mechanism for further progress if properly funded. Efforts to engage the larger community of families living with DS to participate in clinical research studies is also underway (Peprah et al., 2015). However, the availability of research funding commensurate with stated long-term goals has never materialized (NICHD, 2014).

Presently, the availability of dedicated research personnel and lack of infrastructure support each represent limiting factors in advancing a truly comprehensive data collection effort and person-centered research strategy. While the provision of high quality clinical care to persons with DS is challenging enough, it is yet another matter to capture this experience for the purpose of informing evidence-based care (Murillo, Reece, Snyderman, & Sung, 2006). With the necessary support and leadership it is well within the capacity of existing clinical programs to step up and address this urgent need (Carfi et al., 2015; McCabe, Hickey, & McCabe, 2011; Real de Asua et al., 2015).

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