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Thyroid dysfunction in patients with Down syndrome: Results from a multi-institutional registry study

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The goals of this undertaking were to assess the outcomes of thyroid screening tests and adherence to thyroid screening guidelines across five Down syndrome (DS) specialty clinics in various states. Data related to thyroid screening were collected for 663 individuals across five clinics specializing in the comprehensive care of individuals with DS for a period of 1 year. Of the 663 participants, 47.7% of participants had a TSH and free T4 ordered at their DS specialty clinic visit. Approximately 19.0% (60/316) had a new thyroid disorder diagnosis made. We conclude that a sizable proportion of the patients with DS are not up-to-date on current guidelines when they present to a DS specialty clinic, while adherence to thyroid screening guidelines helps facilitate early diagnoses. Hypothyroidism is prevalent in the population, consistent with reported literature. DS specialty clinics can help patients stay current on screening guidelines.

KEYWORDS
Down syndrome, patient database, registry, subclinical hypothyroidism, thyroid disease, trisomy 21

1 | INTRODUCTION

Down syndrome (DS) is the most common chromosomal condition (Canfield et al., 2006; Fergeson et al., 2009) with approximately 206,000 persons with DS living in the United States as of 2010 (De Graaf, Buckley, & Skotko, 2016). The association between DS and thyroid disease is well known (Claret et al., 2013; Cohen, 2006; Gibson et al., 2005; Grabe, Chacko, Regelmann, Costin, & Rapaport, 2012)

Abbreviations: AAP, American Academy of Pediatrics; BCH, Boston Children's Hospital; CD, Celiac disease; CHP, Children's Hospital of Pittsburgh; DUMC, Duke University Medical Center; DS, Down syndrome; DSMIG, Down Syndrome Medical Interest Group; fT4, Free thyroxine; GD, Grave's disease; HT, Hashimoto's thyroiditis; LCH, Levine Children's Hospital at Carolinas Medical Center; MGH, Massachusetts General Hospital; TSH, Thyroid stimulating hormone.

with prevalence rates reported as high as 28% (Prasher & Haque, 2005). Hypothyroidism is more common than hyperthyroidism in these patients (Pascanu et al., 2009), and subclinical hypothyroidism, characterized by a normal free T4 and elevated TSH, occurs in 13.0–36.5% (Pascanu et al., 2009; Prasher & Haque, 2005). Research among patients with DS has found a high occurrence of undiagnosed hypothyroidism (Prasher & Gomez, 2007) with clinical signs including impaired intellectual development (Prasher & Gomez, 2007), dry skin, weight gain, and constipation. Oftentimes, these symptoms overlap with common features of DS making hypothyroidism more difficult to diagnose (Cohen, 2006; Fergeson et al., 2009). Fortunately, once diagnosed, effective treatment for thyroid disease is available (Prasher & Gomez, 2007).

Dysregulation of the immune system in people with DS is thought to be the cause of an increased prevalence of various autoimmune conditions in this population (Aversa, Lombardo, et al., 2015). Autoimmune thyroid disorders also demonstrate increased prevalence rates in people with DS when compared to controls. For young children with DS, the prevalence estimates for Hashimoto's thyroiditis (HT) ranges from 13% to 34%, and for Grave's disease (GD) around 6.5% (Aversa, Lombardo, et al., 2015; Goday-Arno et al., 2009; Popova, Paterson, Brown, & Donaldson, 2008). This is significantly higher than prevalence rates for the general pediatric population, where the prevalence of HT is 1.2–1.3%, and GD is 1.07% (Aversa, Lombardo, et al., 2015; Cooper & Stroehla, 2003; Rallison, Dobyns, Keating, Rall, & Tyler, 1975; Tozzoli & Perini, 2007).

When compared to the general pediatric population, patients with DS often have an earlier presentation of HT and a more severe biochemical and clinical course of HT (Aversa, Salerno, et al., 2015; Aversa, Valenzise, et al., 2015). This is in contrast to GD, where studies have shown that that people with DS and GD often have a less severe clinical and biochemical course when compared to the general population (Aversa, Valenzise, et al., 2015; De Luca et al., 2010). Children with DS and HT were also shown to have a higher rate of conversion to GD over time (Aversa, Salerno, et al., 2015; Aversa, Valenzise, et al., 2015; De Luca et al., 2010). Some literature reports have also demonstrated that having DS even in the absence of a thyroid condition may be associated with higher baseline TSH levels, thought to be the result of an intrinsic TSH-setting disorder unique to people with DS (Aversa, Salerno, et al., 2015; Meyerovitch, Antebi, Greenberg-Dotan, Bar-Tal, & Hochberg, 2012).

Due to the complexity of diagnosing thyroid disorders among patients with DS, routine serological screening is recommended. The American Academy of Pediatrics (AAP) recommends screening for thyroid disease at birth, 6 months, and 12 months of age, then annually (Bull, 2011). Consistent and routine screening for thyroid dysfunction is also recommended for adults with DS (Esbensen, 2010), especially since the risk for hypothyroidism increases with age in individuals with DS (Bull, 2011). The purpose of this study was to assess the adherence of thyroid screening guidelines across five DS specialty clinics using data from the first multi-institutional, national database of individuals with DS.

2 | MATERIALS AND METHODS

2.1 | Participants

All data were collected as part of the National Down Syndrome Patient Database (Lavigne et al., 2015) (Patient Database) during its pilot year (July 1, 2012 to June 30, 2013). The Patient Database is a voluntary study open to all patients with DS who have been diagnosed by clinical examination and/or karyotyping and are enrolled as a patient in one the participating DS specialty clinics: Boston Children's Hospital (BCH), Children's Hospital of Pittsburgh (CHP), Duke University Medical Center (DUMC), Levine Children's Hospital at Carolinas Medical Center (LCH), Massachusetts General Hospital (MGH). Individuals with DS and their families were excluded only when, as a family unit, they were unable to complete the clinics' intake forms even with assistance or unable to provide needed information by interview.

Institutional Review Board approval was obtained from each participating hospital. Consent was obtained from participants or their designated legal guardian to participate in the Patient Database and to allow the review of their medical records.

2.2 | Data collection

The Patient Database is designed to collect observational data from routine clinical visits to DS specialty clinics; no additional tests or procedures performed outside of standard of care are collected. Our main objective for this study was to assess if the national DS guidelines, established by the AAP (Bull, 2011), are being followed in regard to thyroid testing by DS specialty clinics participating in the Patient Database. To examine our compliance, we used data from two questions that were asked as part of the Patient Database related to thyroid screening.

First, we asked if the patient had thyroxine stimulating hormone (TSH) and free thyroxine 4 (fT4) performed within the 12 months prior to their DS specialty clinic visit, as a reflection of their primary care. The answer to this question was either reported by the parent or caregiver, in which case we tried to verify with medical records, or extracted directly from the patient's medical record. If the patient had a TSH and fT4 within the previous 12 months, we asked for the results of those tests, when available.

Next, we asked if TSH and fT4 were ordered at the current DS specialty clinic visit, and, if so, how many new thyroid diagnoses were made as a result of those tests. Exact TSH reference ranges varied slightly from one institution to the other, but caution was taken to ensure pediatric reference ranges were used when reviewing results in a pediatric patient, whereas adult standards were used in the adult DS study population. These questions were answered by review of the patients' medical records.

2.3 | Data analysis

We used descriptive statistics to report demographic and clinical characteristics. After careful consideration about whether to include inferential statistics, such as significance testing or confidence

TABLE 1 Patient demographics for the National Down Syndrome Patient Database as of July 1, 2013, overall and by site

Characteristic	All sites	BCH	MGH	DUMC	CHP	LCH
All patients	663	258	108	9	215	73
Age						
<1 year	127 (19.5%)	50 (19.5%)	13 (12.0%)	1 (11.1%)	47 (23.2%)	16 (21.9%)
1 to <5 yrs	238 (36.6%)	125 (48.6%)	7 (6.5%)	3 (33.3%)	65 (32.0%)	38 (52.1%)
5 to <13 yrs	184 (28.3%)	66 (25.7%)	20 (18.5%)	4 (44.4%)	79 (38.9%)	15 (20.5%)
13 to <21 yrs	47 (7.2%)	16 (6.2%)	14 (13.0%)	1 (11.1%)	12 (5.9%)	4 (5.5%)
21+ yrs	54 (8.3%)	0 (0%)	54 (50.0%)	0 (0%)	0 (0%)	0 (0%)
Missing	13 (1.9%)[a]	1 (0.4%)[a]	0 (0%)[a]	0 (0%)[a]	12 (5.6%)[a]	0 (0%)[a]
Gender						
Female	308 (46.5%)	120 (46.5%)	57 (52.8%)	1 (11.1%)	97 (45.3%)	33 (45.2%)
Male	354 (53.5%)	138 (53.5%)	51 (47.2%)	8 (88.9%)	117 (54.7%)	40 (54.8%)
Missing	1 (0.2%)[a]	0 (0%)[a]	0 (0%)[a]	0 (0%)[a]	1 (0.5%)[a]	0 (0%)[a]
Race						
White	517 (84.1%)	190 (80.9)	86 (86.0%)	8 (88.9%)	189 (90.0%)	44 (72.1%)
Black/African American	37 (6.0%)	15 (6.4%)	3 (3.0%)	1 (11.1%)	9 (4.3%)	9 (14.8%)
Asian	5 (0.8%)	4 (1.7%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Am Indian/Alaska native	0 (0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hawaiian/Pac Islander	0 (0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Multiracial	25 (4.1%)	9 (3.8%)	3 (3.0%)	0 (0%)	8 (3.8%)	5 (8.2%)
Other race	16 (2.6%)	11 (4.7%)	4 (4.0%)	0 (0%)	0 (0%)	1 (1.6%)
Unknown/missing	15 (2.4%)	6 (2.6%)	4 (4.0%)	0 (0%)	3 (1.4%)	2 (3.3%)
Decline to participate	48 (7.6%)[a]	23 (8.9%)[a]	8 (7.4%)[a]	0 (0%)[a]	5 (2.3%)[a]	12 (16.4%)[a]
Ethnicity						
Hispanic/Latino	63 (10.2%)	33 (14.0%)	12 (12.0%)	2 (22.2%)	8 (3.9%)	8 (13.1%)
Not Hispanic/Latino	497 (75.7%)	178 (76.0%)	76 (76.0%)	7 (77.8%)	190 (91.8%)	46 (75.4%)
Unknown/missing	55 (8.9%)	24 (10.2%)	12 (12.0%)	0 (0%)	12 (5.7%)	7 (11.5%)
Decline to participate	48 (7.6%)[a]	23 (8.9%)[a]	8 (7.4%)[a]	0 (0%)[a]	5 (2.3%)[a]	12 (16.4%)[a]

Missing = Respondent agreed to complete the demographic survey, but left a response unanswered; Unknown = Respondent agreed to complete the demographic survey, but selected "unknown" as a response; Decline to participate = Respondent declined to complete the optional demographic survey. BCH, Boston Children's Hospital; MGH, Massachusetts General Hospital; DUMC, Duke University Medical Center; CHP, Children's Hospital of Pittsburgh; LCH, Levine Children's Hospital at Carolinas Healthcare System.

[a]Percentage of all patients.

intervals, we felt that the current registry sample could not (and should not) reasonably be construed as a random sample drawn from a population-base sample of people with DS. For this reason, we chose to report descriptive statistics in the form of frequencies and percentages.

3 | RESULTS

3.1 | Patient demographics

A total of 663 participants were enrolled ranging in age from 36 days to 70.8 years. Gender, race, and ethnicity demographics were also collected (Table 1). A small percentage of demographic information for race and ethnicity was unknown, either due to participants choosing to opt out of providing this optional information ($N = 48$, 7.6%) or because of a lack of opportunity to collect the demographic data form from parents or caregivers ($N = 15$, 2.4%, for race and $N = 55$, 8.9% for ethnicity). The latter will be referred to as "missing" in our presentation of results.

3.2 | Previous thyroid screening

Overall, TSH and fT4 were already ordered by another provider for 78.3% of participants in the 12 months prior to their DS specialty clinic visit (Table 2). Of the patients less than 1 year of age with data available, 91% (111/122) reported having a TSH and fT4 already done within the 12 months prior to their DS specialty clinic visit during other clinical visits. After 1 year of age, the percentage of individuals with DS who already had thyroid function testing within 12 months prior to their DS specialty clinic visit decreased slightly. Further information on previous thyroid screening in different age brackets can be found in Table 2.

TABLE 2 Demographics as compared with thyroid screening and diagnosis

Characteristics	TSH and fT4 already done prior to DS clinic, within past 12 months *N* (%)	Previous thyroid diagnosis *N* (%)	Of those with previous thyroid disease, *N* (%) on treatment	TSH and/or fT4 ordered at visit with DS clinic *N* (%)	Of those with either TSH and/or fT4 ordered, *N* (%) new diagnosis made
All patients	502/641(78.3%)[a]	137/619(22.1%)[b]	115/133 (86.5%)[c]	320/662 (48.3%)[d]	60/316 (19.0%)[e]
Age*					
<1 year	111/122 (91.0%)	9/119 (7.6%)	7/8 (87.5%)	60/127 (47.2%)	8/60 (13.3%)
1 to <5 yrs	185/234 (79.1%)	33/214 (15.4%)	26/31 (83.9%)	103/238 (43.3%)	14/99 (14.1%)
5 to <13 yrs	128/176 (72.7%)	51/177 (28.8%)	41/50 (82.0%)	91/184 (49.5%)	24/88 (27.3%)
13 to <21 yrs	34/47 (72.3%)	13/45 (28.9%)	11/13 (84.6%)	23/47 (48.9%)	4/22 (18.2%)
21+ yrs	36/50 (72.0%)	30/52 (57.7%)	29/30 (96.7%)	29/54 (53.7%)	9/28 (32.1%)
Gender*					
Female	228/300 (76.0%)	65/288 (22.6%)	54/62 (87.1%)	145/307 (47.2%)	27/141 (19.1%)
Male	273/340 (80.3%)	72/330 (21.8%)	61/71 (85.9%)	170/354 (48.0%)	33/165 (20.0%)
Race*					
White	391/501 (78.0%)	116/491 (23.6%)	99/112 (88.4%)	251/517 (48.5%)	45/243 (18.5%)
Black or African American	26/35 (74.3%)	3/31 (9.7%)	2/3 (66.7%)	19/36 (52.8%)	4/19 (21.1%)
Asian	5/5 (100.0%)	1/5 (20.0%)	1/1 (100.0%)	1/5 (20.0%)	1/1 (100.0%)
Am Indian/ Alaska Native	0/0	0/0	0/0	0/0	0/0
Hawaiian/Pac Islander	0/0	0/0	0/0	0/0	0/0
Other Race	11/16 (68.8%)	3/16 (18.8%)	2/3 (66.7%)	5/16 (31.2%)	2/5 (40.0%)
Unknown	1/1 (100.0%)	0/1 (0.0%)	0/0	0/1 (0.0%)	0/0
Missing	11/14 (78.6%)	2/12 (16.7%)	1/2 (50.0%)	7/14 (50.0%)	0/7 (0.0%)
Multiracial	16/22 (72.7%)	3/22 (13.6%)	3/3 (100.0%)	15/25 (60.0%)	5/14 (35.7%)
Ethnicity					
Spanish/ Hispanic/ Latino	47/62 (75.8%)	10/60 (16.7%)	9/10 (90.0%)	28/64 (43.8%)	3/26 (11.5%)
Not Spanish/ Hispanic/ Latino	377/483 (78.1%)	108/474 (22.8%)	93/104 (89.4%)	248/499 (49.7%)	48/241 (19.9%)
Unknown	9/12 (75.0%)	4/10 (40.0%)	1/4 (25.0%)	6/13 (46.2%)	1/6 (16.7%)
Missing	69/84 (82.1%)	15/75 (20.0%)	12/15 (80.0%)	34/86 (39.5%)	8/34 (23.5%)

*Sum of subgroups in columns may not add up to the number of "all patients" because of missing values.
[a]22/663 individuals had a missing value.
[b]44/663 individuals had a missing value.
[c]Although 137 individuals were reported as having a previous thyroid disorder diagnosis, for four of these individuals treatment or lack thereof was not confirmed during the DS clinic visit.
[d]1/663 individuals had a missing value.
[e]4/320 individuals had missing values for both TSH and fT4, which is why a value of 316 is reported here.

TABLE 3 Thyroid function and diagnoses before and at DS clinic

Thyroid function and diagnosis	Before visit to DS clinic	At visit to DS clinic
Abnormal TSH only	18/317 (5.7%)[a]	47/311 (15.1%)[a]
Abnormal fT4 only	8/274 (2.1%)[b]	7/280 (2.5%)[b]
Both TSH and fT4 abnormal	2/271 (0.7 %)[c]	6/311 (1.9%)[c]
Diagnoses made	137/619 (22.1%)[d]	60/316 (19.0%)[e,f]
Hypothyroidism	116/137 (84.7%)	6/22 (27.3%)
Hyperthyroidism	1/137 (0.7%)	0/22 (0.0%)
Subclinical hypothyroidism/hyperthyrotropinemia	20/137 (14.6%)	16/22 (72.7%)

[a]Denominator includes patients who had at least TSH ordered.
[b]Denominator includes patients who had at least fT4 ordered.
[c]Denominator includes patients who had both TSH and fT4 ordered.
[d]44/663 individuals had a missing value.
[e]A total of 320 patients had thyroid function testing ordered at their DS clinic visit, and 4/320 had missing values for both TSH and fT4.
[f]38/60 patients had missing values for a specific diagnoses, although 60 in total were confirmed to have evidence of thyroid hormone dysfunction by the provider.

3.3 | Thyroid diagnosis and treatment status prior to DS specialty clinic

Overall, 22.1% (137/619) of participants already had a thyroid diagnosis prior to attending their DS specialty clinic (Table 2). The most common diagnosis was hypothyroidism, followed by hyperthyrotropinemia and then hyperthyroidism (Table 3). Most participants (86.5%, 115/133) with a previous thyroid diagnosis are on treatment, with almost all (96.7%, 29/30) individuals 21 years of age or older on treatment.

3.4 | Thyroid screening ordered by specialty clinics

Almost half, 47.7% (316/662), of participants had a TSH and fT4 ordered at their DS specialty clinic visit (Tables 2 and 3). In some instances, due to clerical error, only fT4 values were reported, and this is represented by the data conveyed in our table for TSH and/or fT4 values. This number (316) excluded individuals who already carried a thyroid disorder diagnosis. Of those individuals who reported they had not had thyroid function testing in the 12 months prior to their DS specialty clinic visit, a TSH and/or fT4 were ordered on 77.7% (108/139) of them.

3.5 | New diagnoses made at DS specialty clinic

As a result of a TSH and fT4 being ordered at the participants' DS specialty clinic visit, 19.0% (60/316) had a new thyroid diagnosis made (Table 2). The majority of these participants were individuals between 5 and 12 years of age (27.3%, 24/88) and individuals greater than 21 years of age (32.1%, 9/28).

4 | DISCUSSION

Prior to their DS specialty clinic visits, not all patients with DS were up-to-date on thyroid screening. The AAP recommends testing with a TSH at 6 and 12 months of age (Bull, 2011); approximately, 9% of patients <1 year old seen in our DS specialty clinic had not yet had testing. After 1 year of age, a TSH is recommended annually. Approximately 25% of our patients above 1 year of age were not current on annual TSH guidelines. Patients who were up-to-date with testing most likely had the labs drawn at prior visits with their primary care physician or endocrinologist, especially if they already were being treated for thyroid disease.

Patient demographic information was collected according to U.S. Census categories (Table 1). Although the vast majority of patients identified as white, other races and ethnicities were also represented. Notably, race, ethnicity, and sex did not appear to affect whether or not the patient was up-to-date on screening.

As patients aged, more of their caregivers reported a diagnosis of thyroid disease, consistent with previous literature demonstrating the prevalence of thyroid disease increasing with age in individuals with DS (Karlsson, Gustafsson, Hendov, Ivarsson, & Annerén, 1998). In addition, the majority of participants who had a previous thyroid diagnosis were on treatment.

At the DS specialty clinics, approximately half of patients had thyroid function tests ordered. Reasons for not being up-to-date could include the caregivers preferred to wait and do the blood work at a DS specialty clinic, the PCP did not order TFTs because of oversight, and/or the patient did not show up for a PCP visit within the past year. Of the approximately 25% who were not already current on the guidelines, the DS specialty clinics ordered the thyroid function tests about 80% of the time. Possible reasons for thyroid tests not being ordered in these instances include patient or caregiver refusal or patients already planning on getting thyroid testing in a near future visit with their primary care physician or endocrinologist. Also, the DS specialty clinics might have not ordered the tests because other pressing medical issues were the focus of the visit or because of simple oversight.

In a previous retrospective study of one DS specialty clinic, during its inaugural year, 43.7% (45/103) of patients age 3 or older were not up-to-date with the annual thyroid screening recommendations (Skotko, Davidson, & Weintraub, 2013). In that study, 57.1% (60/105) of patients received thyroid testing as a result of their DS specialty clinic visit, a percentage similar to our findings. In another

study examining thyroid testing adherence in Nebraska and Oklahoma among children between the ages of 0.5–10.0 years (Fergeson et al., 2009), only 14% (11/80) and 13% (6/48) of children, respectively, were compliant with screening recommendations. These data were obtained from the children's primary care physicians. While the data used for this study represent over 600 individuals with DS of all ages in the United States, our data are not population-based. To date, though, no population-based registries for individuals with DS exist. The NIH has recently established a contact registry called DS-Connect® (Peprah et al., 2015), where health information is collected directly from individuals with DS and their families. However, the current registrants are not considered to be representative of the full population of people with DS. Our National Down Syndrome Patient Database is distinctive for including healthcare provider-entered data. Currently, our Patient Database represents people with DS from the Northeast and Southeast regions of the United States, serving diverse populations from rural areas of North Carolina and western Pennsylvania to distinctly urban populations in and around Boston. Our demographic distribution represents the best-available group in terms of diversity. Unfortunately, population-based data for race and ethnicity among individuals with DS in the areas served by our clinics are not available; as such, we cannot determine how representative our clinic samples are.

Since the initial year in which data were collected (July 1, 2012 to June 30, 2013), the Patient Database has continued to enroll individuals with DS and had 1,193 participants enrolled at the close of 2016. In the coming years, the National Down Syndrome Patient Database has plans to expand to include more of the ~58 DS specialty clinics currently located in 32 U.S. states.

Our study is also subject to selection bias. Patients with DS with more complex medical needs might be more apt to seek subspecialty care in addition to the routine care provided by their primary care physician. Therefore, the individuals enrolled in the Patient Database may not represent individuals with DS who are relatively healthier. Future research would benefit from larger population-based registries, which may allow similar results to be generalized to the entire DS population. Moreover, while a great deal of existing research and guidelines focus on thyroid disease prevalence, screening, and treatment plans in the younger patients with DS, data that pertain to thyroid function in adults with DS are lacking. In our present study, only a small selection of patients consisted of adults, originating from only one of the five DS specialty clinics.

Another limitation of our study is that we did not assess the portion of patients who were already being followed by an endocrinologist. Approximately 22% of our patients had a previously diagnosed thyroid disorder, while 48% had thyroid blood work ordered at the DS specialty clinic. This suggests that a large portion of patients with a pre-existing thyroid disorder had blood work done at a DS specialty clinic in conjunction with or in place of a visit to an endocrinologist or PCP. For many patients with DS, thyroid disease is treated entirely by the PCP or DS specialty clinic without additional evaluation from an endocrinologist. Free T4 values may also be abnormal in rare cases when individuals are on certain medications that may bind to thyroid-binding globulin, which was not assessed in this study. Finally, tracking the treatment response to thyroid disease was beyond the scope of this project.

5 | CONCLUSION

Most of the patients who had had thyroid dysfunction diagnoses prior to presentation to a DS specialty clinic had hypothyroidism instead of hyperthyroidism. Nearly one in every five of the patients seen in the DS specialty clinics were diagnosed with a new thyroid disorder. Our findings demonstrate that DS specialty clinics help ensure that individuals with DS stay current on healthcare guidelines. Collaboration between DS specialty clinics, PCPs, and endocrinologists can increase diagnoses and treatments in children and adults with DS.

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CONFLICTS OF INTEREST

We do not believe that any of the authors have conflicts of interest as defined in the Guide for Authors.

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