INVITED COMMENT

AMERICAN JOURNAL OF medical genetics PART A

National Down Syndrome Patient Database: Insights From the Development of a Multi-Center Registry Study

Jenifer Lavigne,[1] Christianne Sharr,[2] Al Ozonoff,[3,4] Lisa Albers Prock,[3,5] Nicole Baumer,[3,5] Campbell Brasington,[1] Sheila Cannon,[6] Blythe Crissman,[7] Emily Davidson,[3,5] Jose C. Florez,[2,3] Priya Kishnani,[7] Angela Lombardo,[5] Jordan Lyerly,[1] Jessica B. McCannon,[2,3] Mary Ellen McDonough,[2] Alison Schwartz,[2,3] Kathryn L. Berrier,[7] Susan Sparks,[1] Kara Stock-Guild,[5] Tomi L. Toler,[2] Kishore Vellody,[6] Lauren Voelz,[5] and Brian G. Skotko[2,3]*

[1]Department of Pediatrics, Clinical Genetics, Levine Children's Hospital at Carolinas Healthcare System, Charlotte, North Carolina

[2]Down Syndrome Program, Division of Genetics, Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts

[3]Harvard Medical School, Boston, Massachusetts

[4]Center for Patient Safety and Quality Research, Program for Patient Safety and Quality, Boston Children's Hospital, Boston, Massachusetts

[5]Down Syndrome Program, Division of Developmental Medicine, Department of Medicine, Boston Children's Hospital, Boston, Massachusetts

[6]Down Syndrome Center of Western Pennsylvania, Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

[7]Comprehensive Down Syndrome Program, Division of Medical Genetics, Duke University Medical Center, Durham, North Carolina

Manuscript Received: 22 June 2015; Manuscript Accepted: 15 July 2015

The Down Syndrome Study Group (DSSG) was founded in 2012 as a voluntary, collaborative effort with the goal of supporting evidenced-based health care guidelines for individuals with Down syndrome (DS). Since then, 5 DS specialty clinics have collected prospective, longitudinal data on medical conditions that co-occur with DS. Data were entered by clinical staff or trained designees into the National Down Syndrome Patient Database, which we created using REDCap software. In our pilot year, we enrolled 663 participants across the U.S., ages 36 days to 70 years, from multiple racial and ethnic backgrounds. Here we report: (i) the demographic distribution of participants enrolled, (ii) a detailed account of our database infrastructure, and

Jenifer Lavigne and Christianne Sharr are co-first authors.

Conflicts of interest: We do not believe that any of the authors have conflicts of interest as defined in the Guide for Authors, though we wanted to share the following about our connections to Down syndrome: Dr. Skotko serves in a non-paid capacity on the Board of Directors for the Band of Angels Foundation, a non-profit organization, and on the Medical and Scientific Advisory Board for the Massachusetts Down Syndrome Congress. He is a non-paid clinical adviser to the National Center for Prenatal and Postnatal Down Syndrome Diagnoses Resources. Dr. Skotko occasionally gets remunerated from Down syndrome non-profit organizations for speaking engagements about Down syndrome. He receives research support from Hoffmann-La Roche, Inc. He has a sister with Down syndrome. Dr. McCannon and Dr. Schwartz are co- investigators for research funded by Hoffmann-La Roche, Inc. Dr. Kishnani serves on the clinical advisory board for National Down Syndrome Society. She also serves on the board for DSConnect™, a contact registry for individuals with Down syndrome. She has received research support from Hoffmann-La Roche, Inc. Dr. Davidson and Dr. Baumer serve in a non-paid capacity on the Medical and Scientific Advisory Board for the Massachusetts Down Syndrome Congress.

Abbreviations: DS, Down syndrome; AAP, American Academy of Pediatrics; DSMIG, Down Syndrome Medical Interest Group; NICHD, Eunice Kennedy Shriver National Institutes of Child Health and Human Development; BCH, Boston Children's Hospital; CHP, Children's Hospital of Pittsburg; DUMC, Duke University Medical Center; LCH, Levine Children's Hospital at Carolinas Healthcare System; MGH, Massachusetts General Hospital.

*Correspondence to:
Brian G. Skotko, M.D., M.P.P., Down Syndrome Program, Division of Genetics, Department of Pediatrics, Massachusetts General Hospital, 185 Cambridge Street, Room 2222, Boston, MA 02114.
E-mail: bskotko@mgh.harvard.edu

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 6 August 2015
DOI 10.1002/ajmg.a.37267

(iii) lessons learned during our pilot year to assist future researchers with similar goals for other patient populations.

Key words: down syndrome; patient database; registry; trisomy 21

How to Cite this Article:
Lavigne J, Sharr C, Ozonoff A, Prock LA, Baumer N, Brasington C, Cannon S, Crissman B, Davidson E, Florez JC, Kishnani P, Lombardo A, Lyerly J, McCannon JB, McDonough ME, Schwartz A, Berrier KL, Sparks S, Stock-Guild K, Toler TL, Vellody K, Voelz L, Skotko BG. 2015. National down syndrome patient database: Insights from the development of a multi-center registry study.
Am J Med Genet Part A 167A:2520–2526.

INTRODUCTION

Although Down syndrome (DS) is common—approximately 250,000 persons in the U.S. have the condition [Presson et al., 2013]—evidence-based research for clinical care is scarce. DS healthcare guidelines have been available since 1970s for the pediatric population, but they have mostly been formed by expert consensus. Over the years, the guidelines have been revised and expanded [Cohen, 1999], most recently in 2011 by the American Academy of Pediatrics (AAP) [Bull, 2011]. For adults with DS, guidelines have been proposed and shared, but only by individual physicians [Cohen, 1999; Van-Cleve et al., 2006; Chicoine and McGuire, 2010].

Recent studies have shown that the majority of individuals with DS are not current with the AAP recommendations [Fergeson et al., 2009; Jensen et al., 2013; Skotko et al., 2013]. Their medical management has become increasingly complex [Cohen, 1999, 2006; Van-Cleve and Cohen, 2006; Bull, 2011], and even the most well intentioned primary care provider is often unable to adhere to the AAP recommendations due to constraints on time and resources within their practices [Skotko et al., 2013]. Approximately 58 DS specialty clinics in 32 U.S. states were created to fill this need, delivering comprehensive care and improving adherence to DS healthcare guidelines [Skotko et al., 2013].

Until now, this clinical framework had not been tapped to collect longitudinal data to better inform clinical decision-making. People with DS are also now living longer than ever before, with the average lifespan approaching 60 [Glasson et al., 2002]. What would evidence suggest be the standard of care for these adults? These are among the many questions that a network of DS specialty clinics is uniquely poised to answer.

In 2007, the National Center on Birth Defects and Developmental Disabilities at the Center for Disease Control and Prevention (CDC) sponsored a meeting together with the National Down Syndrome Society (NDSS) to develop priorities for public health research related to DS. Attendees of this meeting felt that "development of research databases and registries" was one of the priorities for future public health research [Rasmussen et al., 2008]. In 2014, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) updated its Research Plan on DS. A central tenet of the plan discussed the need for a national registry/database dedicated to DS [Eunice Kennedy Shriver National Institute of Child Health and Human Development, 2014].

In 2011, various advocacy groups, federal agencies, industry representatives, clinicians, and researchers again met at the NICHD to discuss the development of three research needs for DS: (i) a contact registry, (ii) a patient database, and (iii) a biobank [Oster-Granite et al., 2011]. Ideally, they would all be linked and stewarded by a consortium of key stakeholders from the DS community [Oster-Granite et al., 2011]. Since these meetings, the NICHD has prioritized the implementation of a contact registry, which became available online in September of 2013. This registry, called "DSConnect™" (downsyndrome.nih.gov/registry) was initiated to gather health information directly from people with DS and their families in order to improve understanding of DS and identify health gaps and challenges. DSConnect™ offers a secure location where people with DS and their families may enter health history and medical information. In the near future, researchers may also begin to use this contact registry to recruit patients with DS that fit their projects' eligibility criteria. DSConnect™ differs from our Patient Database in that our data are provider-entered, rather than patient- or caregiver-entered.

Our group sought to address the need for a patient database, with a goal of having healthcare professionals collect consistent and comprehensive data on their patients with DS. We have completed our first year of collaboration, and here we share our methodology, lessons learned, and shared goals for the future.

MATERIALS AND METHODS

Study Overview

The Down Syndrome Patient Database ("Patient Database") is a voluntary study designed to collect clinical and patient-reported data from routine visits to DS specialty clinics. No additional tests or procedures performed outside of standard of care were collected for this Patient Database; only observational data were collected. For our inaugural year, we sought to learn from our shared clinical expertise: when did we order thyroid function tests and celiac disease screens? How often did our medical work-up result in new diagnoses? The long-term objective of our Patient Database is to provide evidence-based recommendations for DS healthcare screening guidelines.

Database Development

Until now, no multicenter DS patient database existed to collect the clinical data needed for improving patient-centered outcomes. In response to the need for such a database, five large DS specialty clinics across the U.S. came together in 2012 to develop our Patient

Database: Boston Children's Hospital (BCH), Children's Hospital of Pittsburgh (CHP), Duke University Medical Center (DUMC), Levine Children's Hospital at Carolinas Healthcare System (LCH), and Massachusetts General Hospital (MGH). Relying on our shared expertise in caring for individuals with DS, we developed a list of the most pressing questions facing primary care physicians (PCPs) and specialists.

All of the DS specialty clinics in the United States with representatives in attendance during the 2011 symposium of the Down Syndrome Medical Interest Group (DSMIG) were invited to participate in this project. The project was also advertised via email listserv to all members of the DSMIG. Many clinics were interested and supportive of this work; however due to lack of resources and funding, few clinics were able to participate. The five clinics that joined had sufficient internal resources to support the study at their institutions. Fluctuation in staffing and available resources had an impact on enrollment at some clinics during this study period.

At first, monthly conference calls were held to brainstorm and develop the questions for the first year of data collection, develop the case report forms for data collection, and design and choose a database platform. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at each of our institutions [Harris et al., 2010]. REDCap is a secure, web-based application designed to support data capture for research studies, providing (i) an intuitive interface for validated data entry; (ii) audit trails for tracking data manipulation and export procedures; (iii) automated export procedures for seamless data downloads to common statistical packages; and (iv) procedures for importing data from external sources. All data collected for our Patient Database were entered into REDCap and maintained by each individual participating institution.

Study Management

Research personnel at individual institutions were responsible for obtaining and maintaining IRB approval, performing recruitment and enrollment procedures, collecting and entering patient data into their own REDCap database, and performing quality control checks of their data. Currently, there are five participating centers with IRB approval: BCH (IRB-P00000012), CHP (REN12100239/PRO11090231), DUMC (00034741), LCH (06-12-15E), and MGH (2012P000828). Each month, a conference call was held to allow members of the research team from each participating institution to discuss their progress, obstacles, and feedback. Agendas and Minutes for each conference call were maintained using a file sharing service accessible to research personnel at each participating institution.

Patient Eligibility and Enrollment

Our Patient Database is open to all patients who have a diagnosis of DS by clinical examination and/or karyotyping and are evaluated as a patient in one of the participating DS specialty clinics. Families not able to complete our clinics' intake forms even with assistance and unable to provide this information by interview were excluded (i.e., they were not offered consent). Our goal is to collect clinical data about individuals with DS of all ages. Some pediatric or adult clinics with institutionally set age limits are participating, and, in those cases, such centers collect data within their designated age range only.

Families of the potential subjects are provided with a consent and assent form. For patients with DS younger than 18 years old, their parents or legal guardian are asked if they feel that their son or daughter with DS has the cognitive capacities to provide assent, and, if so, then the person with DS was involved in the enrollment process. If the patient is older than 18 years of age and does not have a legal guardian, consent is sought from the patient, and, if possible and appropriate, from his or her parents/guardians. If the patient is older than 18 years of age and does have a legal guardian, then consent is obtained from that guardian. In these situations, the adult with Down syndrome is asked to provide assent, and, if any signs of dissent are appreciated by the research staff, then the patient would not be enrolled.

Recruitment procedures vary slightly between participating centers, according to each clinic's setting, available resources, and institutional policies. In general, prior to the scheduled clinic visit, the participant and his or her guardian are e-mailed or mailed an IRB-approved recruitment flyer or letter describing the purpose and scope of the study. If the participant or his or her guardian has any questions about the study, the contact information for the study coordinator is provided in the recruitment notice. Some large centers, usually those with high patient volume, notify eligible patients for the first time as they arrive to the clinic. During the clinic visit, a member of the research team obtains consent from the patient or, when needed because of age or intellectual capacity, their guardian.

Data Collection and Quality Control

All data entered into the Patient Database were collected during routine visits as part of standard care for patients with DS and, for the most part, were available in the patients' electronic medical records. All data were collected prospectively beginning at the time of consent. Upon enrollment and for subsequent follow-up clinic visits, a minimal set of data were collected for our inaugural year. During the pilot year of this study, we decided to collect data related to thyroid disease and celiac disease (Supplementary Figure S1). Part of these data included caregiver- or patient-reported symptoms. Each site asked the same questions, but these questions were embedded in the clinics' personalized intake forms. Each consenting patient and his/her caregiver was also asked to provide optional socio-demographic information. Individual sites had the option of collecting additional health and developmental information beyond that of the minimal dataset. To date, two sites have elected to collect additional data on cardiac conditions, sleep disorders, developmental regression, hearing and vision evaluations, and early intervention services (physical therapy, occupational therapy, and speech therapy). We anticipate adding clinical variables as the data collection continues.

Data entries are source verified whenever possible. For all laboratory data, the sites indicated whether or not the value was source verified. In order to ensure that the proper information

was collected during these annual visits, checklists tracking data collection were maintained and updated for all participants. To ensure strong data integrity, forms in REDCap contained field-specific validation (e.g., integer limits), alerting sites if entered data violated specified limits [Harris et al., 2010]. For quality assurance, 5% of all data entries were re-entered by a second coder and crosschecked by a third research member ("monitor") at each site. The monitor facilitated resolution of discrepancies and logged the reason for differing data via standardized codes, so that trends in data entry could be tracked. Longitudinal visits are tracked by research staff at each specialty clinic. Each participant's medical record is checked at least every 6 months and, usually, more frequently to update the Patient Database with information from return visits. Participating clinics generally recommend that patients return at least once annually; however, some families seek follow-up care more often. If a patient does not return to clinic within 2 years, they are re-contacted by clinical staff. Our Patient Database collects health data only stemming from discussions and medical decisions made within the context of our clinics.

Reporting Data From the Patient Database

We incorporated a data sharing agreement statement in our protocol, which allowed for publication of multicenter research results. REDCap easily allows for the sharing of de-identified data. Pooling de-identified data from all participating institutions enabled data to be analyzed with statistical power that no one clinic could achieve on their own within one year. Each participating clinic aimed to enroll as many patients as possible since various research questions required different statistical power and sample considerations.

RESULTS

Patient Demographics

After one year of data collection, 663 participants (354 males, 308 females, and 1 missing) were enrolled ranging in age from 0.1 to 70.8 years (Table I). The majority of participants were Caucasian (84.1%), followed by Black/African American (6.0%), Multiracial (4.1%), Other (2.6%), and Asian (0.8%). Most participants identified as Non Spanish/Hispanic/Latino (75.7%). A small

TABLE I. 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[a]	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 years	238 (36.6)	125 (48.6)	7 (6.5)	3 (33.3)	65 (32.0)	38 (52.1)
5 to <13 years	184 (28.3)	66 (25.7)	20 (18.5)	4 (44.4)	79 (38.9)	15 (20.5)
13 to <21 years	47 (7.2)	16 (6.2)	14 (13.0)	1 (11.1)	12 (5.9)	4 (5.5)
21+ years	54 (8.3)	0 (0)	54 (50.0)	0 (0)	0 (0)	0 (0)
Missing	13 (1.9)[b]	1 (0.4)[b]	0 (0)[b]	0 (0)[b]	12 (5.6)[b]	0 (0)[b]
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)[b]	0 (0)[b]	0 (0)[b]	0 (0)[b]	1 (0.5)[b]	0 (0)[b]
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)[b]	23 (8.9)[b]	8 (7.4)[b]	0 (0)[b]	5 (2.3)[b]	12 (16.4)[b]
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)[b]	23 (8.9)[b]	8 (7.4)[b]	0 (0)[b]	5 (2.3)[b]	12 (16.4)[b]

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.
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.
[a]Of the 663 participants, 84 (12.7%) returned to clinic for a second visit during the study period and 6 (0.9%) returned for a third visit.
[b]Percentage of all patients.

percentage of participants chose not to provide demographic information for race and ethnicity (7.6%). Another small percentage chose to respond to some but not all of the demographic variables. The data from our thyroid and celiac screening questions will be reported elsewhere. Of the 663 participants, 84 (12.7%) returned to clinic for a second visit during the study period and 6 (0.9%) returned for a third visit.

Lessons Learned

Study start-up. As we envisioned our Patient Database, we thought first about seeking IRB approval. We found multidisciplinary collaboration to be tremendously useful in conceptualizing the protocol. We designated one team member as the lead protocol writer. Feedback was gathered from participating centers, and we prepared an "On-boarding Toolkit," consisting of the protocol, sample consent form, and demographic questionnaire. This toolkit was distributed to new clinics interested in joining the project. New clinics then transferred relevant information from the toolkit into their local IRB submissions and added center-specific details. This approach facilitated faster IRB approval than we experienced in previous collaborations. Also, we noted that having these toolkit documents ready provided a clear, consistent look into the project for clinics determining whether participation was feasible for their local teams.

Data management. Our larger team met monthly to review questions that came up during data entry. During our pilot year, we considered topics such as consistent coding of partial dates (e.g., how to code when day or month are missing?) and date ranges (e.g., how to code when caregivers reported a medication started "2–3 years ago?"). We also used the teleconferences to fine-tune our quality control process. We thought about questions such as: should labs arranged by specialists outside our DS specialty clinics be recorded in our database? Should we cross-link unique participants seen at multiple centers? Maintaining a monthly meeting schedule allowed data issues to be resolved in a timely way.

In general, we had good success resolving data discrepancies, inconsistencies, and adjusting data fields by the next monthly teleconference, which we attribute to the team model of this research database. In sharing resources between participating centers, we were able to access someone with expertise related to particular data questions more quickly than we could using any one institution's resources. Along the way, we compiled a data management Standard Operating Procedure (SOP) with instructions pertaining to specific fields and the rationales behind our coding decisions. This document resides as a secure, password-protected, shared document so that data procedures are readily available to all team members as data are entered, and new team members can catch up on decisions made prior to their involvement.

Across the team we noted increasing facility with REDCap throughout our pilot year. As updates were made to the core software, team members identified new features that might be helpful to our project (e.g., the potential to add new fields, generate missing data reports, or specify a reason code at the time data are updated). We considered whether and how new features might benefit our project on our monthly calls.

Data collection. Forthcoming papers will detail our specific results about thyroid disease and celiac disease in our patients with DS (Supplementary Figure S1). Here, we wish to describe our lessons learned, in general, about data collection.

A large portion of our pilot year was dedicated to working out minor inconsistencies in data collection. For example, when we first compiled our collective data, we realized our well-intentioned plans to protect participant confidentiality prevented our central statistician from seeing age data for all participants. To solve this issue, we added an age field to the database that auto-calculates age from the DOB and date of visit fields for prospective data. For retrospective data, each center undertook calculations in Microsoft Excel and then utilized an import feature in REDCap to upload these data. Our experience adding this new age field was an exercise in utilizing our collective resources and savvy to learn about functionality available through REDCap, including some trial and error by data entry staff before we arrived at our final solution.

Data cleaning. As we prepared the data from our first year for publication, we came across expected instances where data were missing. We explored these missing data points together and, wherever possible, identified the missing values. In doing so, there was a significant time investment at each center and, in particular, for our central statistician who generated missing data reports. In some cases, we found data were not truly missing. Instead, data were not appearing when exported based on how REDCap permissions or data access groups (i.e., which users can edit or export data) were initially organized by software administrators at each center. Despite best efforts to standardize our database at study start—for example, we were careful to develop a consistent data dictionary and ensure our data would be scalable to a large number of participants—some lessons were learned only through the practice of compiling multicenter data.

Multidisciplinary collaboration. A common theme throughout our lessons learned was the benefit of multidisciplinary collaboration. This project is truly the product of teamwork. Despite competing interests of limited time, other research commitments, and the demands of clinical care, the participating centers remained committed to the importance of this Patient Database in providing evidence-based research for the clinical care of persons with DS. Our collaboration could not have formed without a bit of financial ingenuity, especially as we relied entirely on limited departmental funds at each of the participating centers to support our efforts. Key to our success was using REDCap, a database platform free to academic medical centers which houses our data, and a free, web-based organizational tool where we could store shared agenda items and meeting notes. Importantly, the REDCap database allows individual centers to collect data above and beyond our shared minimal dataset. This feature of the database encouraged several of the participating centers to sign on, as it allows for center-specific data to be collected for their own research projects. In our pilot year, when funding was unavailable, we also relied on donated time and effort from many team members.

DISCUSSION

Plans for Future

Moving forward, our hope is to continue to expand this Patient Database, with enrollment targeted in the thousands. Ideally, our

data would be linked with DSConnect™ and a national DS biobank using a Global Unique Identification (GUID), allowing a powerful synergy between caregiver-entered and provider-entered data. With this in mind, we have structured our IRB documents and project operations in a flexible way, such that a future amendment and re-consenting effort would allow our database to sync with other projects. Of course, these types of collaborations may take time and funding allocation; so, in the meantime, we have built the infrastructure to on-board as many clinics as possible in our Patient Database in its present state. In terms of funding for the immediate future, we have submitted a private grant application that would allow one coordinating center, Massachusetts General Hospital, to reimburse other centers per each new participant and return visit. Given the renewed interest in DS research in the last decade [Oster-Granite et al., 2011], some of our team's efforts at individual centers have been supported by philanthropy. We envision philanthropy will continue to play a major role in supporting our efforts, as is common with subspecialty clinics. We will continue to seek funding sources to support our thyroid and celiac projects, as well as projects on additional conditions that co-occur with DS.

Limitations

During the first few months of our pilot year, we were limited by an adjustment period as collaborating providers at participating centers determined how to document data on thyroid and celiac disease in ways that were maximally thorough and efficient for clinical care and research. Each center developed a template or trained providers on the information we sought to capture for this project. During this period, a handful of data points were marked missing when providers were not yet accustomed to documenting participant data. Another limitation for one of our multidisciplinary clinics was the availability of historical medical information at the time of the first visit, which was needed to answer questions such as, "Has Total IgA and TTG ever been tested?" Most clinics collect medical history on intake forms that the patient or family completes, either prior to the visit or at the time of the visit (data are collected from the intake forms after consent is obtained). In some cases, these forms remained incomplete in the context of a clinical visit with many competing priorities. In some cases, especially with our older adults with DS, historical information was unavailable due to lack of records or access to family members. This limitation is sometimes heightened in this population which has highly variable caregiver/guardianship arrangements.

Our demographic data (Table I) demonstrate that individuals from most racial groups were recruited and willing to participate in our Patient Database; however, non-white patients were underrepresented in our sample. One possible explanation is that, for some of our participating clinics, language presented a barrier to enrollment. One clinic's IRB, for example, requires two interpreters fluent in English and the language of the participant. One interpreter must be available at the time of the clinic visit to translate the English consent form, and the second interpreter reviews the consenting documents at a later time to ensure that the interpretation was conducted per IRB protocol. At this center, limited resources for such translators limited their enrollment of diverse populations. To minimize such limitations in the future, our team is seeking funding mechanisms to translate our research materials into several languages.

Process Changes Based on Pilot Year

Due to the positive feedback we received from participating centers about the "On-boarding Toolkit," we have decided to create a "Data Collection Toolkit." During our inaugural year, we learned that participating sites collect their data differently because of staffing or clinic flow. The "Data Collection Toolkit" will contain templates of those collection tools already being used at participating centers for collecting the minimal required dataset. Data collection templates targeted for the patient or caregiver will be included, as well as data collection templates for use by the research or clinical staff. The demographics survey, previously provided in the "On-boarding Toolkit," will also be included in the "Data Collection Toolkit." The "Data Collection Toolkit" will make a variety of data collection options available to participating centers allowing them to submit materials to their IRB quickly. We anticipate this will minimize duplication of work, maximize efficiency in beginning data collection, and help prospective clinics feel well supported. This may be especially helpful for participating institutions with limited time and resources. We will continue to add templates to the "Data Collection Toolkit" as participating institutions develop new templates or modify existing templates to meet their specific needs.

Moving forward, we would like to explore available features of REDCap that we are currently not using or under-utilizing. For example, REDCap has a feature that allows users to quickly check for forms containing missing data (non-required and required data fields). Users can also easily check for questions where "unknown" or "missing" was selected as an answer by generating a report. The report provides a list of participant IDs meeting the search criteria. Directly from the report, the user can click on a participant ID and jump to the exact form and field where data are missing or checked "unknown" or "missing." This feature would provide an extra measure to ensure data quality by allowing individual centers to quickly and easily check for missing data and potentially resolve any discrepancies or provide an answer where "unknown" or "missing" was previously selected. To date, our central statistician has generated missing data reports in Microsoft Excel and distributed them via e-mail. This updated approach would allow data cleaning to be managed directly in REDCap by each center.

Future Research

At present, our Patient Database provides an infrastructure for expanding knowledge about two pressing health conditions for people with DS: celiac disease and thyroid disease. There is much work to be done, however. A gap in clinical knowledge remains in the following conditions, and more:

- developmental milestones (crawling, walking, talking, etc.),
- atlantoaxial instability and cervical spine X-rays (especially in asymptomatic patients needing these for Special Olympics or other athletic activities),

- sleep studies in asymptomatic patients prior to age of 4,
- annual audiograms,
- screening ophthalmologic exams,
- annual hemoglobins,
- timing and types of seizures (e.g., infantile spasms),
- attention-deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), and autism dual diagnoses.

A long-term goal for this database would be to make it population-based, as well as expand the number of co-occuring conditions studied.

As a team of health care professionals dedicated to providing evidence-based care to individuals with DS, we are excited about the potential impact of this Patient Database, both in terms of educating the medical community and helping individuals with DS live full, meaningful lives, free from preventable constraints of underlying medical problems.

ACKNOWLEDGMENTS

We would like to thank Dr. Tracy McGregor and James Heller, M.A., M.S., for their initial consultation on our Patient Database. We are grateful to Anna's Angels Foundation, which provided support for the coordination of this study at Duke University Medical Center.

REFERENCES

Bull MJ. 2011. Health supervision for children with Down syndrome. Pediatrics 128:393–406.

Chicoine B, McGuire D. 2010. The guide to good health for teens & adults with Down syndrome. Bethesda, MD: Woodbine House. pp 362–369.

Cohen WI. 2006. Current dilemmas in Down syndrome clinical care: Celiac disease, thyroid disorders, and atlanto-axial instability. Am J Med Genet C Semin Med Genet 142C:141–148.

Cohen WI. 1999. Health care guidelines for individuals with Down syndrome. Down Syndrome Quarterly 4:1–16.

Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, DHHS. 2014. National Institutes of Healthm (NIH) Research Plan on Down Syndrome (NA). Washington, DC: U.S. Government Printing Office.

Fergeson MA, Mulvihill JJ, Schaefer GB, Dehaai KA, Piatt J, Combs K, Bright BC, Neas BR. 2009. Low adherence to national guidelines for thyroid screening in Down syndrome. Genet Med 11:548–551.

Glasson EJ, Sullivan SG, Hussain R, Petterson BA, Montgomery PD, Bittles AH. 2002. The changing survival profile of people with Down's syndrome: Implications for genetic counselling. Clin Genet 62:390–393.

Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. 2010. Research Electronic Data Capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42:377–381.

Jensen KM, Taylor LC, Davis MM. 2013. Primary care for adults with Down syndrome: Adherence to preventive healthcare recommendations. J Intellect Disabil Res 57:409–421.

Oster-Granite ML, Parisi MA, Abbeduto L, Berlin DS, Bodine C, Bynum D, Capone, G, Collier E, Hall D, Kaeser L, Kaufmann P, Krischer J, Livingston M, McCabe LL, Pace J, Pfenninger K, Rasmussen SA, Reeves RH, Rubinstein Y, Sherman S, Terry SF, Whitten MS, Williams S, McCabe ERB, Maddox YT. 2011. Down syndrome: National conference on patient registries, research databases, and biobanks. Mol Genet Metab 104:13–22.

Presson AP, Partyka G, Jensen KM, Devine OJ, Rasmussen SA, McCabe LL, McCabe ERB. 2013. Current estimate of down syndrome population prevalence in the United States. J Pediatr 163:1163–1168.

Rasmussen SA, Whitehead N, Collier SA, Frías, JL. 2008. Setting a public health research agenda for Down syndrome: Summary of a meeting sponsored by the Centers for Disease Control and Prevention and the National Down Syndrome Society. Am J Med Genet A 146A:2998–3010.

Skotko BG, Davidson EJ, Weintraub GS. 2013. Contributions of a specialty clinic for children and adolescents with Down syndrome. Am J Med Genet A 161A:430–437.

Van-Cleve SN, Cannon S, Cohen WI. 2006. Part II: Clinical practice guidelines for adolescents and young adults with Down syndrome: 12 to 21 Years. J Pediatr Heal Care 20:198–205.

Van-Cleve SN, Cohen WI. 2006. Part I: Clinical practice guidelines for children with Down syndrome from birth to 12 years. J Pediatr Heal Care 20:47–54.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.