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ORIGINAL ARTICLE

Creation of the Web-Based University of Chicago Monogenic Diabetes Registry: Using Technology to Facilitate Longitudinal Study of Rare Subtypes of Diabetes

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Abstract

Background:

Monogenic diabetes is a group of disorders caused by mutations in any one of a number of genes. Although a monogenic diagnosis—estimated to represent as much as 2% of all diabetes patients—can have a transformational impact on treatment, the majority of monogenic cases remain unidentified and little is known about their natural history. We thus created the first United States Monogenic Diabetes Registry (*http://www.kovlerdiabetescenter.org/registry/*) for individuals with either neonatal diabetes diagnosed before 1 year of age or with a phenotype suggestive of maturity-onset diabetes of the young.

Methods:

Inclusion criteria and consent documents are viewable on our Web site, which allows secure collection of contact information to facilitate telephone consent and enrollment. Relevant medical, family, and historical data are collected longitudinally from a variety of sources and stored in our Web-accessible secure database.

Results:

We have enrolled well over 700 subjects in the registry so far, with steady recruitment of those diagnosed under 1 year of age and increasing enrollment of those diagnosed later in life. Initially, participants were mostly self-referred but are increasingly being referred by their physicians. Comprehensive survey and medical records data are collected at enrollment, with ongoing collection of longitudinal data. Associated private Facebook and email discussion groups that we established have already fostered active participation.

Conclusions:

Our early success with the Monogenic Diabetes Registry demonstrates the effectiveness of low-cost Web-based tools, including surveys, the Research Electronic Data Capture database program, and discussion groups, for efficient enrollment and support of rare patients, and collection and maintenance of their data.

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Abbreviations: (HIPAA) Health Insurance Portability and Accountability Act, (iBi) Initiative in Biomedical Informatics, (IRB) institutional review board, (MODY) maturity-onset diabetes of the young, (REDCap) Research Electronic Data Capture, (SSL) secure sockets layer

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Introduction

The study of rare diseases can be greatly limited by the ability to recruit sufficient patients through a center at a single geographic location. For studies not primarily based on an investigational intervention, however, detailed information and even research samples may be collected even in the absence of direct face-to-face patient contact. In this regard, increasing familiarity, comfort, and accessibility to the Internet by people from all walks of life, including email, Web browsing, as well as increasing use of social networking sites, makes the prospect of recruiting and collecting valuable research information a much less daunting prospect than in the past.

Monogenic diabetes mellitus is a group of disorders that collectively may represent as much as 1–2% of all diabetes cases[1,2] and is caused by mutations in any one of a number of genes or by alteration of a single chromosomal locus.[3,4] The most common forms are characterized by the maturity-onset diabetes of the young (MODY) phenotype: autosomal dominantly inherited diabetes with onset at a young age (most often before 25 years of age), typically lacking features of type 1 (e.g., autoantibodies, severe diabetic ketoacidosis, and/or disease that is difficult to control and requires complete replacement doses of insulin) or type 2 (e.g., obesity and/or evidence of insulin resistance) diabetes.[5,6] Neonatal diabetes occurs in approximately 1 in 100,000 live births.[7,8] Although it is more rare, cases with a possible monogenic etiology are clearly identified by their very early age of onset of disease, especially when diabetes is diagnosed before 6 months of age. Other excessively rare syndromic forms are usually recessive and characterized by extra-pancreatic features.[9]

Although uncovering such a genetic diagnosis can have huge ramifications on treatment, understanding of possible associated features, and genetic counseling of family members, the majority of cases remain unidentified and there is limited information regarding the long-term treatment outcomes and natural history of these forms of diabetes.

As a result of wide publicity starting in 2006, with the care of one of the first patients in the United States found to have a *KCNJ11* mutation allowing for switching from insulin treatment to oral sulfonylurea therapy, many other patients and clinicians began contacting us to enroll in our genetic studies of diabetes.[10–14] We thus created the first U.S. Monogenic Diabetes Registry to facilitate recruitment of appropriate patients and to gather longitudinal information to better understand and treat these types of diabetes. In 2008, we began recruiting to the Neonatal Diabetes Registry anyone diagnosed with diabetes before 1 year of age and subsequently expanded to recruit those diagnosed with diabetes at any age, if suspected or known to have an underlying monogenic cause. Our overall goals are to estimate incidence and prevalence of these disorders, clarify genotype/phenotype relationships, better understand associated features and natural history of the various causes, establish treatment guidelines, as well as to raise awareness among clinicians and provide support for clinicians, families, and patients dealing with these disorders. In this article, we describe our experience so far with the use of readily available, low-cost Web-based tools to collect a wide range of longitudinal data on rare patients from diverse geographic locations.

Methods

Overview of Web Site and Recruitment

Our Web site interface (http://www.kovlerdiabetescenter.org/registry/) is part of the Kovler Diabetes Center at the University of Chicago, which is composed of integrated Web-based applications supported by a centralized MySQL database back end. The public pages allow for unrestricted viewing of our inclusion criteria and consent documents, with a secure registration form allowing for collection of contact information to facilitate subject telephone consent and enrollment (see schematic in **Figure 1**). The front-end engine that is currently utilized as the interface between approved registry staff users and the database back end is the Research Electronic Data Capture (REDCap) program, which provides an interface allowing for all data creation, retrieval, updates, and deletion. REDCap was created at Vanderbilt University to support data capture for research studies[15] and is now available at no cost to participating Consortium members supported by the National Institutes of Health Clinical and Translational Science Awards program, such as our Institute for Translational Medicine supporting the Initiative in Biomedical Informatics (iBi) at the University of Chicago that hosts our REDCap database and related Kovler Diabetes Center Web sites.

Physicians who learn about the registry are asked to encourage potential patient participants to access the Web site directly (or alternatively may provide our telephone

contact information to anyone without reliable Internet access). After being given the opportunity to review inclusion criteria and consent forms available for viewing or downloading on the Web site, the prospective research subject or parent/guardian may then enter his/her contact information, as well as that of his/her physician/diabetes provider, directly into the secure Web site form. Initially, this contact information was then sent by encrypted email to be decrypted on registry computers onto which the de-encryption key had been installed (open-source Gnu Privacy Guard encryption engine v1.2.1 using free software Windows Privacy Tools). The Web form is now being adapted to utilize a REDCap-provided application programming interface to allow subject-submitted information to be dumped directly into the MySQL centralized REDCap database back end as a temporary record. Upon consent, the record is converted to a permanent subject record or otherwise deleted if the prospective participant failed to meet inclusion criteria or decided not to enroll in our studies.

Consent

The institutional review board (IRB) of the University of Chicago has approved all studies, with approved registry consent forms freely available on our Web site to view, download, and print. Each Web site registrant is subsequently contacted by registry staff to arrange for telephone consent and review of inclusion criteria. Those without Internet access who contacted us directly may be provided with the consent forms through their physician or by mail. Those who agree to participate are then asked to sign the forms and mail them back to be signed by registry staff. All consent forms are then scanned and uploaded to the REDCap database, and a copy is mailed back to each participant. Given that the proposed research involves no greater than minimal risk to subjects, participation of children requires the written informed consent of one parent, with assent being requested from children aged 7 years or older. Because we propose to keep the collected data indefinitely, once any subject turns 18 years of age, reasonable effort is made to contact the subject to obtain informed written consent.

Data Collection and Surveys

Following consent, patient/parent participants are sent emails with a secure sockets layer (SSL)-encrypted link to surveys created through SurveyMonkey.com, where de-identified data may be stored on secure servers and downloaded with SSL encryption to registry computers for analysis. Because names and contact information were previously collected, the surveys do not ask for such protected health information. At any point, participants may elect to communicate directly with registry staff through email or by phone, and registry staff may also contact participants to clarify data elements and ensure completeness of data. For patients/families who prefer non-Internet interactions, surveys may be completed with registry staff by telephone. All surveys are now being adapted to utilize the REDCap Survey tool, which will soon allow for survey answers to be linked directly to existing databases.

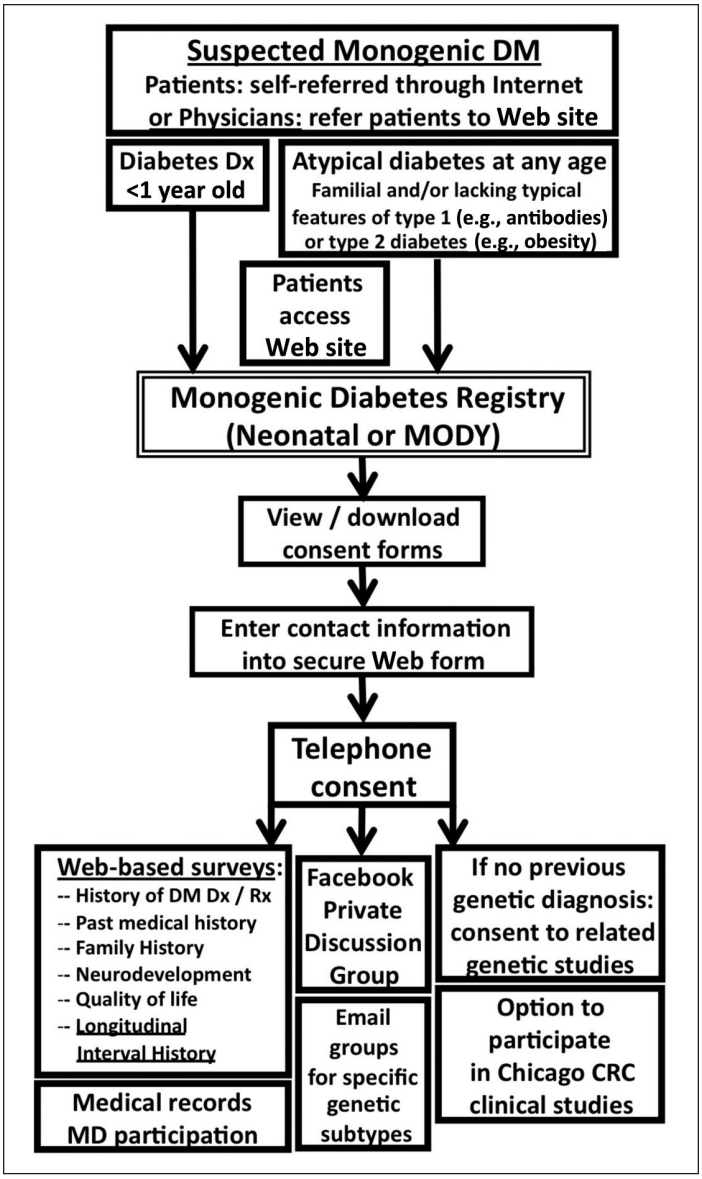

Figure 1. Overview of enrollment and data collection for the U.S. Monogenic Diabetes Registry at the University of Chicago Kovler Diabetes Center (*http://KovlerDiabetesCenter.org/Registry*). DM, diabetes mellitus; CRC, Clinical Research Center.

The initial survey collects a wide range of information (**Table 1**), while interval surveys collected at least annually

will allow for brief updates of relevant information. Original medical records are also collected whenever possible, with medical record release forms being available on the Web site and collected during the consent process for this purpose. Key data elements may be confirmed by initial diabetes diagnosis hospital records, and in addition, physicians may also be contacted, whether or not they referred the patient to the registry. Ongoing clinic records, laboratory or radiology results, local neurodevelopmental assessments, or other relevant information may be submitted by physicians, patients, or their families or requested directly in a manner compliant with The Health Insurance Portability and Accountability Act (HIPAA) of 1996. Quality-of-life information, adapted from validated measures, is also gathered.[16] An overview of the data elements collected is provided in **Table 1**.

Internet Discussion Groups

Participants are invited to join genetic-subtype-specific or general registry Web-based discussion groups, which are open only to consented participants and moderated by registry staff. In order to participate, parents/guardians or children who are 12–17 years of age must first have completed the consent process for the main study and are then asked to review and sign a separate discussion group consent form. Physicians/diabetes providers treating consented patient participants may also choose to consent to their own participation in the discussion groups by signing a separate consent form.

The groups are not guided by registry staff, but rather provide a forum for discussion of various aspects related to the subtypes of monogenic and/or neonatal diabetes for those with these rare conditions or those treating them. Moderators of the discussion groups attempt to provide clarification of what is known or unknown regarding the disorders and their treatment and provide editorial clarifications if any misleading or inaccurate information is posted. Participants are always strongly encouraged to discuss any possible modifications to their treatment regimen with their physician/provider before making any changes. Patient/parent participants are warned of the risk of loss of confidentiality, particularly if they choose to share identifying information. Physicians/diabetes providers are reminded to adhere to HIPAA guidelines. Participants are informed that the investigators may choose to publish findings related to the discussion groups, e.g., by quoting from the discussion. In such instances, every effort is made to protect the confidentiality of participants.

Table 1.
Overview of Data Elements Collected in the Monogenic Diabetes Registry

1. History of diabetes diagnosis (initial collection only, priority for verification by original medical record)
Date of birth/date of diagnosis/transient/permanent/ongoing Circumstances/symptoms/doctor/hospital at diagnosis Details of any autoantibody or C-peptide testing ever done Clinical/laboratory characteristics at diagnosis (hemoglobin A1c/glucose/pH/bicarbonate levels)
2. Other medical history (initial collection, with updates through interval survey)
Race/ethnicity/possible consanguinity Birth weight/length/gestational age Other possibly associated problems (with narrative detail): poor weight gain or growth concerns; developmental delay; speech problems; learning disorders or difficulties; hearing or visual problems; seizures or neurological problems; obesity, overweight, rapid, or abnormal weight gain; early or late puberty; concerns about heart function; high blood pressure; high cholesterol; kidney abnormalities; liver problems; neuropathies; autoimmune disease; anemia; abnormality of the pancreas; thyroid problems; macroglossia; umbilical hernia; recurrent infections; other medical problems (with description) Family history of diabetes/prediabetes/other medical problems
3. Comprehensive history of genetic testing
All commercial-based genetic testing reports collected Data from research testing also collected, including variants of uncertain significance Tracking of sample storage, quality, and results from collaborators
4. Current treatment (initial and repeat interval collection)
Current weight/height/hemoglobin A1c Hypoglycemia history, including frequency/severity/description Diabetic ketoacidosis history Details of current or previous insulin regimen and/or any other treatments, including sulfonylureas Current problems possibly related to sulfonylureas: diarrhea/upset stomach/vomiting; weight loss or poor weight gain; abnormal or rapid weight gain, overweight or obesity; yellowing of the teeth; any type of rash; lowering of white blood cell or other cell counts; elevation of liver enzymes; ischemic heart disease/angina/heart arrhythmia; kidney or electrolyte problems; other problems (with description)
5. Eleven questions on diabetes-specific quality of life (initial and interval survey)

In addition to a private Facebook discussion group for all participants in the Neonatal Diabetes Registry, participants may choose to join various subtype-specific email distribution lists hosted through the University of Chicago, e.g., subjects whose diabetes is treatable with glyburide instead of insulin, subjects with transient neonatal diabetes, or subjects with insulin gene mutations. The list mechanism ensures that all participants receive all emails but also protects the confidentiality of subjects

who may not wish to participate actively. Participants are reminded that their email address will be visible whenever they choose to email the group and that they should be careful to share only the information that they are comfortable discussing with others. Subjects may unsubscribe at any time.

Neurodevelopmental Assessment

An optional additional segment of the Neonatal Diabetes Registry involves screening assessment of neurodevelopment, behavior and sleep, through collection of age-appropriate validated survey instruments by study staff over the telephone, through mailings, or in person whenever possible.

REDCap Database

While our registry data were originally maintained using standard spreadsheet software, we subsequently transferred all data to the secure, Web-based REDCap application. The multiple forms in our REDCap database are tailored to our inter-related research studies, facilitating organized, validated data collection with audit trails. The online editor has allowed our forms to be completely customized to collect specific detailed data elements regarding diabetes diagnosis and medical history, family history, as well as interval medical history to be collected longitudinally using REDCap Survey. Consent to our multiple related studies is logged for each subject with uploading of all scanned consent forms as well as any medical records, and other forms allow for sample inventory and tracking as well as capture of detailed sequencing and related research testing information. REDCap also unifies records and enables all research staff to access identical data, and as a Web-based tool, REDCap is fully portable, allowing multiple users to access, add, and update records simultaneously. REDCap has built-in tools for data cleaning and evaluation that allow for immediate and repeated graphical representation and descriptive statistics on all data, including missing data. Furthermore, data can be quickly and repeatedly interrogated by building an unlimited number of reports on any combination of variables that remain available for online viewing or easy export to Microsoft Excel or any statistical software for more detailed analysis.

Supporting Hardware Architecture and Security

The Bioinformatics Research Development Facility and iBi of the Biological Sciences Division at the University of Chicago are fully compliant with HIPAA requirements and standards, including personnel compliance training. All servers are located in a locked, well-ventilated building in downtown Chicago, with monitored cooling and power. Physical security is maintained by an electronic alarm system with window and door contacts, motion detectors, and keycard access entry to the building, with all entry logged and monitored via video surveillance. Servers employ power-on and user passwords, virus protection, and battery backup systems. Authorized users have restricted access to files requiring sophisticated rotating passwords. Operating system and security patches are current. Servers are constantly monitored for break-in attempts or other illegal activity. Only gateway machines or bastion hosts are accessible outside the firewall. All other systems are behind the monitored firewall. The Oracle, DB2, MySQL, and other database servers are not directly accessible from the Internet. The iBi currently supports and maintains multiple instances of REDCap in Redhat Enterprise Linux 5 (RHEL 5) to ensure a secure deployment. All Web servers are secured behind a Web proxy that requires authentication to access any Web applications, including REDCap. Intrusion detection software and certified SSL encryption is available for Web transactions, such as the registration Web form of participant contact information. Backups to tape are maintained nightly, and full-backups are conducted monthly with periodic transfer to an offsite location for storage.

Collection of DNA Samples for Related Genetics Studies

Any eligible subject who does not have a known genetic diagnosis is also given the option of consenting to participate in our IRB-approved genetic studies. Although providing a blood sample is one option, it has been particularly efficient and convenient to collect saliva samples directly from participant probands and relevant family members (typically both parents, if available, and any other family members with diabetes). Oragene® DNA sample collection kits (*http://DNAGenotek.com*) have generally provided a high-quality DNA sample, including from infants (who use a modified kit with swabs).

Results

Neonatal Diabetes Subjects (Diagnosed under 1 Year of Age)

Enrollment of neonatal diabetes subjects (diagnosed under a year of age) began in 2006 and has been steady since our Web site was created in 2008 (**Table 2**). Initial enrollment included a large proportion of those who are currently much older but had a history of being diagnosed with diabetes before 1 year of age, whereas the proportion

of newly diagnosed neonatal cases has been steadily increasing. During our ongoing process of transitioning from SurveyMonkey to REDCap Survey, we have invited 135 of 172 neonatal probands to complete the survey, and 98 have done so to date (73% response rate). We only recently began systematic collection of data regarding how subjects found out about the registry but estimate that initially 90% found us independently of their physician/provider, either because of media coverage, patient groups such as the Juvenile Diabetes Research Foundation, or by Web-searching using terms such as "neonatal diabetes" while trying to learn more about their condition. Over time, the fraction of subjects being referred by their physicians has grown to approximately 50%, as we have become increasingly recognized as a major referral center for the study of monogenic diabetes in the United States.

Monogenic Diabetes Registry

We expanded the registry to also include those diagnosed with diabetes beyond infancy but with features suggestive of a monogenic diabetes diagnosis or already known to carry a genetic cause. Since being open for wider enrollment of this relatively more common group of patients, the registry now includes over 700 participants, and counting. The balanced gender distribution and range of ages and ethnicities of participants suggest that a wide variety of subjects are able to join and are interested in joining our registry (**Table 2**). Of note, subjects also come from disparate geographical locations, with most hailing from all over the United States. A DNA sample is available for 94% of all participants (and 95% of neonatal diabetes cases; **Table 2**), with the remainder having agreed to do so, but the sample has not yet been received. Data for some subjects was derived from what was submitted as part of their enrollment to our genetic studies before the registry was fully implemented to allow for survey data collection. Some data for family members of probands are incomplete, though we expect to gather complete information through longitudinal surveys. Of note, those in the registry diagnosed after 1 year of age represent a heterogeneous group with a variety of indications for inclusion, and as such, many do not fit all the classical indicators of MODY. For instance, many cases were included based on early age of diagnosis, usually with negative autoantibody results, but did not necessarily have a suggestive family history or a mild progression of disease.

Internet and Email Discussion Groups

The Neonatal Diabetes Registry private Facebook group currently includes almost 100 members, including several physicians and registry staff. This represents a participation rate of 46% among neonatal probands or parent representatives who have been offered the chance to join the group to date. Participants have intermittently engaged in numerous discussion threads on a wide variety of topics centered on neonatal diabetes. In addition to active discussion on the group, some with common interests have elected to "friend" each other to facilitate interaction outside the scope of the group. We have also provided a structure for email discussion groups for those interested in more frequent direct interaction. While we are currently considering a number of groups for specific genetic subtypes of neonatal diabetes, so far our most active email group has been among subjects or parents of children with neonatal diabetes due to mutations in the adenosine-triphosphate-sensitive potassium channel who can be treated with glyburide instead of insulin. Frequent in-depth discussion involving many individuals has included topics such as different methods of administration and doses of sulfonylurea medications, frequency of high and low blood sugars, recurrence risk of genetic mutations in families, plans of care for children in school, as well as themes regarding the struggles and successes of the 20–30% of patients who also exhibit a range of neurodevelopmental disability. This has provided an immediate direct impact on patients, parents, and physicians struggling to understand their rare disease. Such a sentiment has been expressed repeatedly by various stakeholders, represented

Table 2.
Enrollment to the University of Chicago Monogenic Diabetes Registry

	All participants	Neonatal probands (diagnosed with diabetes <1 year of age)
N	727	172
Subjects who provided DNA *N* (%)	682 (93.8%)	164 (95.3%)
Gender male/female (% male)	367/360 (50.5%)	102/70 (59.3%)
Current age (years) Mean (range; standard deviation) *N* >18 years (%)	22.7 (0.1–77.8; 18.5) 242 (33%)	12.6 (0.1–49.1; 9.9) 43 (25%)
Ethnicity (C/AA/L/A/O/NA)[a]	412/24/24/18/28/220	128/4/11/8/14/6

[a] C, Caucasian; AA, African American; L, Latino; A, Asian; O, other or mixed; NA, information not yet available.

in the following quotes from participating parents: "It really is so nice to have people who get your situation finally!" and "This is an amazing group to be a part of!"

Discussion

Over a relatively short period of time, our Web-based registry has facilitated enrollment of a large number of rare patients with possible or known monogenic diabetes. Participants come from disparate geographic locations and appear to be well selected for inclusion in our studies. Our registry demonstrates the efficacy of using low-cost Internet tools not only for recruitment, but also for data collection and maintenance, linkage with related research information, as well as data analysis. We expect longitudinal data to be collected in the coming years to reveal great insight regarding the effects of treatment over time, natural history of disease progression, and details on possible associated features or complications. Importantly, our discussion groups have provided a meaningful forum for discussion and support among patients, family members, and even their treating clinicians who are trying to understand more about these rare diseases.

The low proportion of neonatal diabetes subjects (those diagnosed under 1 year of age) in the registry who are currently older than 18 years (**Table 2**; and only 10 probands who are currently older than 30 years of age) reinforces our suspicion that adult endocrinologists may be less likely than pediatric endocrinologists to appreciate the potential ramifications of an early diagnosis of diabetes. It could also suggest a lower prevalence of neonatal diabetes among those in older age categories, possibly due to increased mortality resulting from complications arising after more than 20 years of diabetes. The gender distribution of all participants is 50:50, as would be expected given that no prior study has suggested any gender discrepancy in any form of monogenic diabetes. Extremely rare exceptions are X-linked causes, particularly a form of neonatal diabetes caused by mutations in the *FOXP3* gene. Such causes are too rare, however, to explain the slight male predominance among the neonatal subjects in our registry. Whether this predominance represents insufficient sampling of the overall population, a survival advantage, or a previously undescribed mechanism for males being more likely to be diagnosed under 1 year of age should be clarified in the years to come with increasing enrollment to the registry.

Although participants in our registry already include those from a range of ethnicities (**Table 2**), the over-representation of Caucasians suggests that the registry is subject to recruitment bias to those more comfortable with Internet-based technology or could also reflect differences in access to health care and information or even a survival advantage. However, comfort with and access to the Internet is increasing even among those with lower educational attainment, socioeconomic status, and even geographic location.[17,18] Furthermore, our expanding network of participating clinicians will continue to help identify appropriate cases as well as facilitate their registration and inclusion, such as by providing access while such patients are present in their office. A possibility that the spontaneous mutation rate for monogenic diabetes genes is higher in Caucasians is rather unlikely, although little relevant data exists, and the registry should help clarify this possibility.

Another limitation is that currently all information, including Web sites, consents, and surveys, are available only in English, though we are currently developing our materials in Spanish and will consider doing so for other languages, as needed, and as more funding becomes available.

Conclusions

The University of Chicago Monogenic Diabetes Registry will continue to allow for the successful recruitment of a relatively large number of rare patients who will provide great insight into our understanding of these sub-types of diabetes. Data can be efficiently collected and maintained in a secure, confidential, HIPAA-compliant manner using low-cost readily available Internet-based tools. The registry will continue to serve the interests of many stakeholders who will benefit from its continued success: not only clinicians, patients, and families directly dealing with these rare disorders, but also geneticists and other researchers, health systems planners and epidemiologists, and government entities.

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