The context and approach for the California newborn screening short- and long-term follow-up data system: Preliminary findings

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Purpose: State newborn screening programs are designed to prevent morbidity and mortality from hereditary disorders through early detection and ongoing disease management. These programs have traditionally focused on short-term follow-up. However, capturing data on the long-term follow-up process is emerging as a new priority. Long-term follow-up data can be used to assess the accessibility, continuity, and quality of care provided to these children. The California Newborn Screening Program uses a Web-based data collection system for short- and long-term follow-up. This article provides a description of the follow-up data collection system in addition to preliminary findings to demonstrate the efficacy of the California data collection approach. **Methods:** A preliminary analysis of short-term follow-up data collected from July 7, 2005, through April 30, 2009, and a preliminary analysis of long-term follow-up data collected from July 1, 2007, through April 30, 2009. **Results:** A majority of children are able to access ongoing care through age 5 years. The majority also have positive health outcomes at each year of follow-up. **Conclusion:** California's short- and long-term data collection system can serve as a model for other states interested in implementing a comprehensive Newborn Screening Program follow-up data system. ***Genet Med* 2010:12(12):S242–S250.**

Key Words: *newborn screening, surveillance, metabolic disorders, follow-up*

The main goal of a successful state-run newborn screening (NBS) program has been the effective and timely delivery of high quality, population-based screening services.[1–5] Given this goal, NBS program evaluation has mostly focused on performance measures for the "short-term follow-up" (STFU) process. The STFU process begins at the time the blood specimen is collected. Once the test results are released, screen-positive cases are referred to a specialty follow-up center that determines the final case status of the newborn as either having a confirmed disorder or not having a confirmed disorder. For those confirmed to have a disorder, STFU ends when a treatment or intervention has been initiated. Some of the more commonly reported STFU performance measures are the percent of the population successfully screened; the sensitivity and specificity of the screening test; the time to initiation of follow-up care, the age of child at diagnosis and treatment initiation; and the percent of newborns asymptomatic at the time of diagnosis. More recently, there has been a recognition of the importance of long-term follow-up (LTFU) for children with disorders diagnosed through NBS. LTFU involves tracking the quantity and quality of services these children receive and monitoring their health outcomes over time.[6–9]

Several nationwide surveys conducted in the last 4 years have evaluated the percent of state NBS programs engaged in LTFU. In addition, these surveys assessed the programs' follow-up processes and evaluated program staff views on their roles and responsibilities related to follow-up. Results indicate that many NBS program staff has not seen their role as extending beyond the STFU period,[10] and as recently as 2006, only approximately 50% of programs were engaged in LTFU activities.[11,12] These findings are not surprising and reflect the historical focus on STFU in state NBS programs. However, this view is changing.

In the last 3 years, a new philosophy is emerging among State NBS programs, which recognizes that the effectiveness of NBS cannot be addressed without LTFU data.[8] The article by Wilcken et al.[13] demonstrates the utility of using LTFU data to evaluate the impact of NBS on health outcomes in a cohort of children who were followed up through age 6 years. Many states, with funding and guidance from the Centers for Disease Control and Prevention (CDC), Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDNC), and State Regional Genetics Networks,[14] are taking on the challenge of designing and implementing LTFU data systems. According to the CDC, the continued success of NBS will depend on long-term surveillance systems to enable ongoing evaluation and program improvement.[15] All three groups have initiated projects to define the components of a LTFU system, including defining a core set of questions that LTFU data should be able to answer and developing a minimum set of data elements that state NBS programs interested in LTFU should consider collecting.

The California Genetic Disease Screening Program (GDSP) recognized the value of NBS follow-up data collection and developed a system that integrates STFU and LTFU data into a comprehensive NBS data record. The STFU and LTFU components were designed from the public health perspective, and both components use a longitudinal, population-based surveillance tool to capture data. The STFU data collection system is encounter based and collects details about the patient's clinical encounters. The LTFU system asks clinicians to annually assess the health status of the child. This annual assessment includes the collection of valuable data on the availability, accessibility, continuity, and quality of care provided to children diagnosed with disorders, through the age of 5 years. This article provides a detailed description of the STFU and LTFU data collection systems. After this, we present preliminary findings to demonstrate the efficacy of the data collection approach being used in California.

Overview of the GDSP screening information system and follow-up process

In July 2005, the GDSP implemented a Web-based screening information system (SIS) that would provide the basis for nearly all of the business functionality of the statewide prenatal screening (PNS) and NBS programs that are administered by the GDSP. SIS allows GDSP staff to provide PNS and NBS screening services to

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approximately 475,000 pregnant women and approximately 550,000 newborns each year, respectively. SIS helps coordinate and track the delivery of screening test kits and patient education materials to >6,000 prenatal providers, >700 maternity hospitals, and >3,500 pediatric care providers throughout the state. Prenatal and NBS test results from eight state-contracted laboratories are electronically provided, and positive test results are followed up through a network of clinical care coordinators (CCCs) who ensure that all at-risk women and newborns are referred to 1 of the 104 prenatal and 60 newborn specialty follow-up centers throughout the state.

When a case is screen positive, a CCC contacts the patient's primary care physician and reviews the patient's demographic and screening interpretation factors (different for PNS and NBS screening). If a test is still assessed to be positive after this review, the CCC electronically refers the case to an appropriate follow-up center. Newborns with test results positive for one of the disorders detected by tandem mass spectrometry (MS/MS; including phenylketonuria [PKU]), galactosemia, and/or biotinidase deficiency are referred to 1 of the 15 metabolic follow-up centers. Screen-positive cystic fibrosis cases are referred to 1 of the 16 cystic fibrosis follow-up clinics. Screen-positive hemoglobinopathy cases and endocrine disorders are referred to a network of sickle cell centers and endocrine centers, respectively. Screen-positive cases are referred to a specialty care center based on their geographic location, determined by zip code, and based on the advice of the patient's primary care provider.

MATERIALS AND METHODS

The GDSP STFU system

The implementation of the centralized Web-based computer system (SIS) on July 7, 2005, coincided with the addition of MS/MS to the routine NBS screening panel in California. When SIS was initiated that summer, the data system consisted of a STFU component to track newborns that were referred to one of the state-contracted metabolic centers as a result of a positive MS/MS screening test. Before SIS was implemented, follow-up center staff received training on the STFU data entry screens. Data provided by metabolic centers is transmitted via a secure environment (SIS) that is Health Insurance Portability and Accountability Act compliant. In accordance with California law, public health agencies, such as the state NBS program, are allowed to collect data on individuals for the purposes of program evaluation and public health surveillance to monitor the quality and impact of program services. Other data security safeguards include user-specific permissions that control who has access to patient information. For example, specialty care follow-up centers can only view the screens that are pertinent to the work they need to do, and they can only view and enter data on the patients assigned to their center.

Each metabolic follow-up center is paid a flat fee in return for the collection and entry of follow-up data into SIS. Each center has an active contract with the state in which the details of this partnership are outlined. Families with screen-positive newborns receive diagnostic follow-up services at no additional charge beyond the cost of the screening test, which is currently $102.75 per newborn.

The STFU system begins with a case referral screen that is divided into three grids corresponding to: "New Cases" that are awaiting action, "Pending Cases" that are in the process of receiving a diagnostic workup, and a third section, where all "Resolved Cases" are listed. Follow-up staff documents the initiation of care by clicking on the patient name in the New Cases grid. This takes the provider to the metabolic service report (MSR). The MSR is the data screen that documents the STFU process. Providers are asked to indicate the type of services provided, the date of the encounter, the type of health care professionals involved in the encounter, the tests ordered at the encounter, new treatments initiated at the encounter, and the health status of the child at the date of the encounter.

After the first MSR is entered, the case moves down to the Pending Cases grid on the same computer screen. An unlimited number of MSRs can be entered during the STFU process. These MSRs document the follow-up process until the case is either resolved to have a disorder or resolved to not have the disorder. At that time, the case status changes from pending to resolved, and the patient name automatically moves to the lowest grid on the screen where resolved cases are listed. The MSR allows for close to real time data on the STFU process.

If a case is resolved as having a disorder, the provider is prompted to indicate the name of the specific disorder from a pull-down menu containing a list of all disorders included in California's NBS panel (currently 76 disorders in total). They can also indicate if a child was diagnosed with a disorder that was not on the screening panel or if the child's positive result was due to a maternal condition.

If the newborn status is indicated as "Resolved Disorder" on the MSR, when the form is saved, the case is automatically entered into the LTFU data system (described below). At that time, the original CCC receives an electronic notification that the newborn has been diagnosed with a disorder. The CCC then contacts the metabolic follow-up center to confirm this information. After this is complete, the case is electronically sent to a NBS Registry Monitor.

The NBS Registry Monitor reviews the case information again and has the option of indicating (in consultation with the metabolic center staff) if the diagnosis is certain, probable, or tentative. Depending on the disorder, the case information is then sent to the appropriate NBS registry. The NBS Registry Monitor is also required to indicate how the diagnosis was ascertained. Cases may have been diagnosed through the California NBS program, missed by the NBS test (a false negative), or originally screened and/or diagnosed in another state.

If a patient moves to another part of the state while the case is still in STFU, the center is required to indicate the new follow-up center that will take over the child's care. After this information is entered into SIS, this new center becomes the point of contact for future data about the follow-up process. Case note screens and text fields allow clinicians to provide specific details about each case when important information cannot be captured by the preexisting data elements.

The GDSP LTFU system

The LTFU data system was designed as an interval-based longitudinal surveillance tool to track all resolved diagnosed cases through age 5 years using an automated annual survey that is electronically sent to the designated metabolic follow-up center in SIS. The Metabolic Center Annual Patient Summary (MCAPS) is the data screen used to collect annual LTFU data on each child with a resolved disorder. MCAPS was seamlessly integrated into SIS, and the centers began to use the MCAPS system in the summer of 2007. When centers log into SIS, they can view a list of the children with disorders referred to their center that require the completion of an MCAPS. Once a year, after the child's birthday, the name of the child appears on the center's MCAPS list indicating that the MCAPS data report is due. This list is updated daily. When the MCAPS report is completed and saved, the child's name falls off of the list, but

it appears again the next year after the child's next birthday. In this way, each child should have up to five MCAPS reports by the time they reach the age of 6 years. These reports represent the status of the child at ages 1, 2, 3, 4, and 5 years.

The specific data elements included in the MCAPS reports are patient clinic status; the services provided by the metabolic center (during the previous year); the date of the last visit/interaction with the patient; the total number of patient visits to the metabolic center (during the previous year); the total number of hospitalizations and emergency room visits (during the previous year); and the length of stay of each hospitalization and reason for each hospitalization. The MCAPS includes a question ascertaining if the patient was symptomatic in the previous year. If symptomatic, the provider is requested to indicate the health problems and symptoms the child experienced. The MCAPS also instructs the provider to indicate any treatments, therapies, or interventions initiated or changed in the previous year. For each treatment category indicated, the provider is asked to indicate the date the treatment was initiated or changed and the level of adherence to the treatment regimen. The provider is asked for an assessment of the patient's development and function in five domains of development (speech/cognitive/physical/fine motor/gross motor). As another indicator of whether the child is deteriorating over time, the provider is asked if the child experienced a loss of skills that had been previously achieved. Finally, the provider is asked for a subjective assessment of the overall health status of the child, compared with a child of the same age without the disorder, using a global health assessment Likert scale: 1, critical; 2, poor; 3, fair; 4, good; 5, very good; and 6, excellent.

STFU and LTFU data collected through SIS is stored on a Microsoft SQL server data platform. Preliminary analyses on STFU and LTFU data have been conducted using Statistical Analysis Software.[16]

Capturing information on mortality

Deaths are captured in SIS throughout the follow-up process. Screen-positive cases are managed by CCCs who facilitate the process of referring a child to a metabolic center for diagnostic follow-up work. If a child dies before follow-up has been initiated by the metabolic center, the CCC closes the child's case in SIS indicating that the newborn died before follow-up. If the child dies during the STFU process, the center can indicate the child's death on the MSR, the data collection screen used to document the STFU process. They can check that the patient has died and provide the date and cause of death. If the child is resolved to have a disorder, they enter the LTFU system. During LTFU, the center can indicate the child's death on the MCAPS. The center can indicate whether the death was a complication of the metabolic disorder, the date of death, and the cause of death. As described above, deaths are captured in the system from the time a case screens positive through the age of 5 years.

RESULTS

Introduction

The STFU and LTFU data in this section are presented to demonstrate the feasibility and efficacy of the California data collection approach. Most of the LTFU data has been presented with all disorders aggregated (Tables 2 and 3). As we accumulate more data over time, more meaningful disorder-specific profiles (similar to the medium chain acyl-CoA dehydrogenase deficiency [MCADD] profile) will be available that represent the full range of clinical outcomes observed in children with metabolic disorders identified through NBS. Thus, at this point in time, these interim results should not be used to draw any conclusions. The results reflect the potential of this data collection approach. Furthermore, once our efforts to improve data quality are complete (see Data Limitations section), we will be able to conduct more meaningful analyses of the data that can be used to draw conclusions about the short- and long-term health of children with these metabolic disorders.

STFU data: Preliminary findings

Between July 7, 2005, and April 30, 2009, 2,105,119 newborns were screened in California and 4,580 (0.22%) were referred to 1 of the 15 metabolic clinics throughout the state as a result of a positive screening test result for disorders detected by MS/MS plus galactosemia, or biotinidase deficiency. Of these, 754 were resolved disorders (16%, or 1 in 6 referrals), and 3,334 (73%) were resolved to not have a disorder (Table 1). Sixty-two died before follow-up could be initiated by the metabolic center. A total of 14,282 MSRs, representing the individual clinical encounters of referred cases during the STFU process, were entered during this time period.

For all referred cases, the median number of days between the patient's date of birth and the date follow-up care was initiated was 8 days. The median time from birth through case resolution (as having a disorder or not having a disorder) was 29 days. The median number of days to resolve disorders was 23 days, whereas the median number of days taken to resolve those referrals who were found to not have a disorder was 30 days. The three disorders that took the least amount of time to resolve were citrullinemia—type I (median = 7 days, $n = 7$); methylmalonic acidemia: mut0 (median = 8.5 days, $n = 12$); and maple syruip urine disease (median = 10 days, $n = 14$). This is in contrast to carnitine transporter deficiency (median = 91 days, $n = 27$); methylmalonic acidemia: mut— (median = 65 days, $n = 18$); and short chain acyl-CoA dehydrogenase deficiency (median = 65 days, $n = 53$), which took a much longer

Table 1 Patient status for 4580 referrals to California metabolic follow-up centers because of positive NBS test result (July 7, 2005 to April 30, 2009)

Patient status	Count (%)
Lost to follow-up	31 (0.68)
Maternal condition	72 (1.57)
Newborn expired before follow-up	62 (1.35)
No response from parent	25 (0.55)
Other	30 (0.66)
Other nonscreened disorder	19 (0.41)
Parent refused	27 (0.59)
Pending	226 (4.93)
Resolved	
Disorder[a]	754 (16.46)
No identified disorder	3334 (72.80)
Total	4580

[a]Resolved disorders are screen-positive cases that metabolic specialists determined to have a metabolic disorder based on diagnostic testing.

time to resolve. In addition, at the time of case resolution, 77.8% of the confirmed disorders were asymptomatic and apparently healthy.

LTFU data: Preliminary findings

Between July 1, 2007, through April 30, 2009, there were a total of 676 MCAPS submitted representing 475 individual children (475/754 = 63%); 285 reports for the first year of life; 212 for the second year of life, 90 for the third year of life, 49 for the fourth year of life, and 40 for the fifth year of life. Of the MCAPS submitted, seven indicated that the child had died: five during the first year of life, one during the second year of life, and one during the third year of life. For six of these deaths, the cause of death was indicated as related to the metabolic disorder, whereas this information was unknown for the remaining one death. When the MCAPS system was initiated, metabolic centers began entering data on all children that they were providing services to, not just those beginning at age 1 year. Thus, the data presented for each year are cross-sectional and do not necessarily represent the same cohort of children. However, there is some overlap between cohorts because some children have annual patient summaries available for consecutive years. As more MCAPS are completed, there will be more cases that have consecutive year summaries, and it will be possible to conduct longitudinal analyses for these groups of individuals.

Description of long-term data by age of child

Among children with annual patient summaries, a majority were being actively followed up by their metabolic center at each year of life (Table 2). A small proportion of these children were lost to follow-up at each year. Among the group of children with annual patient summaries submitted for the second year of life, the proportion lost to follow-up was the highest for this year, but this was still only 5%. The data suggest that metabolic centers are effectively maintaining contact with these children to provide them with the ongoing care they require.

As presented in Table 3, during each year of life, a majority of annual patient summaries reported the child to be asymptomatic. However, at each year of follow-up, there were a fairly large proportion of children who were reported to have symptoms; 24% among Year 1 summaries and 26% among Year 2 summaries. Regarding development status for speech, cognition, motor skills, and physical growth, a majority of children were reported to be age appropriate, and a small percent of children had reported delays (~10–20% depending on age).

Hospitalizations and emergency room visits are collected as indicators of disorder-related complications and overall health status. Among annual patient summaries submitted at each year, a majority of children were reported to have no hospitalizations, and the hospitalization rate tended to decline with each year of life: 28% among Year 1 summaries; 11% among Year 3 summaries; and 2% among Year 5 summaries. Similarly with emergency room visits related to the metabolic disorder, most children (85–100%) had no reported visits, and for those who had any visits, the majority of cases experiences between one and two visits per year.

When we looked at the four disorders that had the highest number of completed MCAPS reports (MCADD, 3-methylcrotonyl-CoA carboxylase deficiency, PKU, and very long chain acyl-CoA dehydrogenase deficiency), fewer hospitalizations were reported in each of the first 3 years of life. For example, with MCADD, the percent of children who had no hospitalizations reported was 62% for the first year reports, 73% for the second year reports, and 100% for the third year reports. As more MCAPS data are entered into the system and a longitudinal analysis can be conducted, it will be interesting to determine if hospitalization rates are truly decreasing over time. A similar pattern of lower hospitalization rates for each subsequent year of life was observed for 3-methylcrotonyl-CoA carboxylase deficiency cases (no need for hospitalization was 78% in Year 1, 80% in Year 2, and 88% in Year 3) and PKU cases (95% to 100% in Years 2 and 3, respectively). Among these four disorders, PKU cases had the highest percent of children reported as asymptomatic in Year 1 (86%), and for the other three disorders, the percent ranged from 65% to 70%.

The annual patient summary also asks the provider to rate the overall health of the child compared with a child of the same age without the disorder. Among summaries, a majority of children were assessed to be in excellent, very good health, or good health: 75% at Year 1, 69% at Year 2, 71% at Year 3, 78% at Year 4, and 76% at Year 5. Again, the data indicate that there is a consistent percent of children who are not fairing as well: 15% were assessed to be in poor or critical health among Year 1 summaries, 20% among Year 2 summaries, 16% among Year 3 summaries, 18% among Year 4 summaries, and 17% among Year 5 summaries.

Clinicians are also asked if the child lost any skills that they had acquired in the previous year. Among second year summaries, 79% reported the child did not lose any skills that they had acquired in the previous year of life, 83% reported no loss of skills between the second and third years, 84% reported no loss of skill between the third and fourth years, and 80% reported no loss of skills between the fourth and fifth years. Thus, a majority of summaries reported children were not deteriorating in terms of skill acquisition.

Table 2 Follow-up status of children at each year of follow-up

	First year, *n* (%)	Second year, *n* (%)	Third year, *n* (%)	Fourth year, *n* (%)	Fifth year, *n* (%)
Active	241 (85)	173 (81)	76 (85)	41 (84)	32 (80)
Lost to follow-up	10 (3)	10 (5)	4 (4)	2 (4)	—
Moved to another state	3 (1)	10 (5)	2 (2)	2 (4)	2 (5)
Patient died	5 (2)	1	1 (1)	—	—
Parents refused	8 (3)	2 (1)	—	—	1 (2)
Transfer to another center	6 (2)	2 (1)	2 (2)	1 (2)	3 (8)
Treatment not necessary	12 (4)	14 (7)	5 (6)	3 (6)	2 (5)
Total at each year	285	212	90	49	39

Table 3 Indicators of patient health status at each year of follow-up

	First year, *n* (%)	Second year, *n* (%)	Third year, *n* (%)	Fourth year, *n* (%)	Fifth year, *n* (%)
Developmental delays (includes those with mild, moderate or severe delays)					
Speech/language	28 (10)	39 (18)	20 (22)	4 (8)	4 (10)
Physical growth	26 (9)	25 (12)	13 (14)	1 (2)	1 (2)
Mental/cognitive	26 (9)	26 (12)	14 (15)	4 (8)	2 (5)
Gross motor skills	34 (12)	27 (13)	9 (10)	None	1 (2)
Fine motor skills	27 (9)	25 (12)	9 (10)	1 (2)	None
Age appropriate development					
Speech/language	236 (83)	147 (69)	61 (68)	39 (80)	33 (82)
Physical growth	244 (86)	164 (77)	70 (78)	42 (86)	37 (92)
Mental/cognitive	239 (84)	157 (74)	68 (75)	38 (78)	36 (90)
Gross motor skills	235 (82)	161 (76)	73 (81)	43 (88)	37 (92)
Fine motor skills	233 (82)	161 (76)	69 (77)	42 (86)	38 (95)
Symptoms					
No symptoms	190 (67)	125 (59)	66 (73)	32 (65)	30 (74)
Symptoms	69 (24)	56 (26)	18 (20)	7 (14)	5 (13)
Unknown	26 (9)	31 (15)	6 (7)	10 (21)	5 (13)
Loss of skills from previous year					
No	NA	167 (79)	75 (83)	41 (84)	32 (80)
Yes	NA	3 (1)	2 (2)		
Unknown	NA	42 (20)	13 (15)	8 (16)	8 (20)
Hospitalizations					
None	207 (72)	172 (81)	80 (89)	49 (100)	39 (98)
1–2	65 (23)	31 (15)	7 (8)		
3–4	8 (3)	7 (3)	2 (2)		1 (2)
5–6	2 (1)	1 (0.5)	1 (1)		
7–8	1				
9–10					
>10	2 (1)				
Unknown		1 (0.5)			
Emergency room visits related to metabolic disorder					
None	234 (82)	174 (82)	76 (85)	49 (100)	40 (100)
1–2	43 (15)	31 (15)	11 (12)		
3–4	5 (2)	5 (2)	2 (2)		
5–6		1 (0.5)	1 (1)		
7–8	1				
9–10	2 (1)				
Unknown		1 (0.5)			

(*Continued*)

Table 3 *Continued*

	First year, *n* (%)	Second year, *n* (%)	Third year, *n* (%)	Fourth year, *n* (%)	Fifth year, *n* (%)
Provider assessment of overall health of child					
Critical	20 (7)	19 (9)	4 (4)	6 (12)	6 (15)
Poor	23 (8)	24 (11)	11 (12)	3 (6)	1 (2)
Fair	27 (10)	22 (10)	10 (11)	2 (4)	3 (7.5)
Good	61 (21)	43 (21)	14 (16)	3 (6)	3 (7.5)
Very good	88 (31)	53 (25)	28 (31)	12 (25)	11 (28)
Excellent	66 (23)	51 (24)	23 (26)	23 (47)	16 (40)
Total MCAPS	285	212	90	49	40

A case study: MCADD

So far, 86 MCAPS reports have been entered on 64 newborns diagnosed with MCADD: 47 with data from the child's first year of life, 33 from the second year of life, and 6 from the third year of life. A majority of MCADD children were actively followed up by their metabolic center at each reported year (Table 4). However, 2% were lost to follow-up among Year 1 summaries, 5% among Year 2 summaries, and 17% (only 1 of the 6 children) among Year 3 summaries.

Table 5 presents data on the health status of children with MCADD as reported on annual summaries at each year of follow-up. At each year of follow-up, these health indicators suggest that a majority of children with MCADD are not experiencing severe complications from the disorder. Similarly, a majority of these children were not reported to have had an emergency room visit related to MCADD during the past year. A majority of children with MCADD were assessed to be at an age appropriate level of development in the five domains assessed (speech, cognition, gross motor skills, fine motor skills, and physical growth). Among Year 1 summaries, 2% reported delays in physical growth. Among Year 2 summaries, 15% reported delays in speech and language, and 3% reported delays in cognition.

Table 4 Follow-up status of MCADD patients at each year of follow-up

	First year, *n* (%)	Second year, *n* (%)	Third year, *n* (%)
Active	41 (88)	27 (82)	5 (83)
Lost to follow-up	—	2 (6)	1 (17)
Moved to another state	2 (4)	4 (12)	—
Patient died	—	—	—
Parents refused	1 (2)	—	—
Transfer to another center	2 (4)	—	—
Treatment not deemed necessary	1 (2)	—	—
Total	47	33	6

A majority of first year summaries (70%) indicated that the child was asymptomatic. A majority of children were assessed to be in excellent, very good or good health on the first and second year summaries, 70% at Year 1 and 63% at Year 2. Among summaries for each follow-up year, there were a proportion of children who were assessed to be in poor or critical health, 22% at Year 1, 23% at Year 2, and 34% at Year 3.

The annual summary also asks the provider to indicate whether the child had at least one of the six types of services listed on the MCAPS during the year. The service types are genetic counseling, health education, laboratory tests, nutritional counseling, physical examination, and social services. Among children with Year 1 summaries, a majority had laboratory tests, nutritional counseling, physical examination, and genetic counseling (Table 6). Among second year and third year summaries, a much smaller proportion had genetic counseling.

As observed in Table 7, the most common treatment indicated on Year 1 and 2 summaries for children with MCADD was medications. Among Year 3 summaries, the most common treatment was medical foods, supplements, and special formulas; however, this is only based on five MCAPS reports.

DISCUSSION

STFU system

SIS made it possible for GDSP staff to design and implement a computer-based STFU data collection system for all referrals made to the state-contracted metabolic centers. The initial design of the STFU component was based on the original patient tracking system used in the 18-month MS/MS pilot project[1] that investigated the feasibility of MS/MS screening in California. The STFU system was initially designed only to assess the effectiveness and efficiency of the NBS follow-up for disorders detected by MS/MS, but it has now been extended to account for all metabolic disorders that are referred to the metabolic follow-up centers. The data collection approach was designed to answer the series of questions indicated in Table 8.

In addition to being able to answer these basic questions, STFU data describe the follow-up process for the resolved disorders group (true positives) and the group resolved to not have a disorder (false positives). Overall and group differences in health services utilization and program performance measures can be examined. There is also a potential for the encounter data to be used to estimate the total cost of follow-up

Table 5 Indicators of MCADD patient health status at each year of follow-up

	First year, *n* (%)	Second year, *n* (%)	Third year, *n* (%)
Age appropriate development			
Speech/language	46 (98)	25 (76)	4 (67)
Physical growth	45 (96)	29 (88)	5 (83)
Mental/cognitive	46 (98)	27 (82)	5 (83)
Gross motor skills	46 (98)	29 (88)	5 (83)
Fine motor skills	46 (98)	29 (88)	5 (83)
Symptoms			
No symptoms	33 (70)	16 (49)	5 (83)
Symptoms	11 (24)	10 (28)	—
Unknown	3 (6)	7 (19)	1 (17)
Loss of skills from previous year			
No	N/A	25 (76)	5 (83)
Yes	N/A	1 (3)	1 (17)
Unknown	N/A	7 (21)	—
Hospitalizations			
None	29 (62)	24 (73)	6 (100)
1–2	17 (36)	9 (27)	—
3–4	1 (2)	—	—
Emergency room visits related to metabolic disorder			
None	33 (70)	24 (73)	6 (100)
1–2	13 (28)	8 (24)	—
3–4	1 (2)	1 (3)	—
Provider assessment of overall health of child			
Critical	5 (11)	2 (6)	1 (17)
Poor	5 (11)	6 (19)	1 (17)
Fair	4 (8)	3 (9)	1 (17)
Good	10 (21)	8 (24)	—
Very good	15 (32)	4 (12)	2 (32)
Excellent	8 (17)	10 (30)	1 (17)
Total MCAPS	47	33	6

Table 6 Service utilization of MCADD patients at each year of follow-up (percent of children who used service at least once during the year)

	First year, *n* (%)	Second year, *n* (%)	Third year, *n* (%)
Genetic counseling	40 (85)	14 (42)	2 (33)
Health education	40 (74)	19 (57)	3 (50)
Laboratory tests	46 (96)	27 (82)	5 (83)
Nutritional advice	45 (91)	29 (88)	5 (83)
Physical examination	45 (91)	30 (91)	5 (83)
Social services	32 (74)	21 (64)	4 (67)

Table 7 Treatment type for MCADD patients at each year of follow-up (percent of children with each treatment implemented during the year)

	First year, *n* (%)	Second year, *n* (%)	Third year, *n* (%)
Medical foods/supplements/ special formulas	10 (30)	8 (32)	5 (83)
Medications/prescription drugs[a]	27 (82)	21 (84)	—
Enteral feeding	1 (3)	—	—
Vitamins	8 (24)	4 (16)	1 (17)
Total children with treatment information	33	25	6

[a]Includes carnitines.

Table 8 California's STFU system can answer the following questions

How old was the child when follow-up care was initiated and how long did it take for the case status to be resolved?
What was the frequency and type of services and tests provided during the diagnostic workup process and what type of providers provided the services?
Was the child symptomatic during the diagnostic process, and if yes, what types of symptoms were evident?
What type and how many clinical encounters occurred (i.e., count of routine follow-up visits, urgent office visits, emergency room visits, or new hospitalizations)?
How did the provider rate the overall health status of the child at each patient encounter, and if a death occurred while the newborn was still being evaluated, what was the age of the child and what was the cause of death?

services and to comparatively study any differences in follow-up care costs between true positive and false positive cases.

LTFU data system

The LTFU data system has been operational for less than 2 years, but in this short amount of time, we have accumulated meaningful population-based data that captures information on the continuity, availability, and quality of care provided to children who are now living with the vast array of rare disorders that are diagnosed through the NBS program. The LTFU data system also provides valuable information on the natural history of these disorders. One of the advantages of our data collection approach is that we collect cross-sectional data about groups of children with similar disorders at similar points in time. This will allow us to capture age-specific mortality and morbidity

Table 9 California's LTFU system can address the following questions

What percent of children diagnosed with disorders remain in care between the ages of 1 and 5 yr old?
What percent become lost to follow-up?
What percent of parents refuse treatment?
What percent died due to problems associated with the disorder?
What percent were determined not to need ongoing treatment?
What percent of children (combined or by specific type of disease) had age appropriate developmental status with respect to speech, physical development, mental/cognitive development, and gross motor and fine motor development?
What percent of children were severely delayed with respect to any of the developmental measures and what year of life did the delays become apparent?
What percent of patients experienced symptoms associated with their disorder and at what age did the symptoms become apparent?
In any given year, what percent of children experienced the loss of skills they had previously acquired?
What percent of children had no hospitalizations or emergency room visits in the previous year of life?
What disorders are associated with the greatest number of hospitalizations and emergency room visits due to disorder-related complications?
What disorders are associated with the highest utilization of metabolic center visits?
What percent of children are receiving a multidisciplinary team of services, including nutritional counseling, health education, and social services counseling?

data and age-specific health care service utilization data. Some of the questions that the California LTFU system can address are presented in Table 9.

Given the large and diverse nature of the California population, the LTFU data will allow us to study whether different race/ethnic populations have different health outcomes and service utilization patterns. For example, we can look at lost to follow-up rates, treatment adherence rates, or parent refusal-to-treat rates among different race/ethnic groups, by insurance status or by specific disease groups. As more data become available over time, the sample size for population subgroups will increase, and the range of specific questions that can be answered will expand.

Data quality limitations

California is currently a partner in a 4-state (California, Utah, Iowa, and New York) collaborative project funded by the CDC (CDC-RFA-DD08-810) to develop a pilot population-based registry for disorders identified through MS/MS screening. The project is supporting the development of state follow-up data collection systems that can compile information on health outcomes and health service utilization to longitudinally monitor newborns. In California, the CDC grant is supporting a systematic effort to improve the quality of the NBS STFU and LTFU data already being collected through the MSR and MCAPS systems described in this article.

This systematic effort has several components including (1) a baseline assessment of data quality at each of the 15 metabolic follow-up centers in California to identify the percent of missing and inconsistent data, (2) site visits to each of the centers to gain a better understanding of the limitations of the data provided from the perspective of the follow-up centers and to understand how variations in clinical practice impact the quality of the data, (3) the development and dissemination of a Guidelines for Data Entry Manual that will provide centers with standardized definitions for each data element and address problems in data entry for the MSR and MCAPS, and (4) a reassessment of the quality of center-specific data to determine the effectiveness of our intervention.

Based on the site visits conducted to date, we have discovered the following major data limitations. First, centers reported that cases cannot always be clearly defined as either having a confirmed disorder or not having a disorder. Rather, cases fall along a "continuum of certainty." In response, we plan to add a variable to allow the clinician to assess the level of certainty of a confirmed diagnosis and to identify what their diagnostic assessment is based on (DNA, biochemical findings, symptoms, etc). Second, the number of reported hospitalizations and emergency room visits is most likely an underestimate of the actual number because some centers are only able to access information on hospitalizations and emergency room visits at their own institution. Third, most centers report making a subjective assessment on the development status of the child because routine developmental assessments are not always performed, especially in the situation where the child appears to be developing normally. Fourth, the global health assessment variable was identified as being too subjective, and this data element will be removed. It will be replaced with a clearly defined variable asking whether the child's metabolic disorder is being effectively controlled and another variable documenting the number of incidents of metabolic decompensation in the previous year. Other questions that have been raised during these site visits include how to define the "initiation of treatment," how to define "significant clinical encounters," and how to define whether a child is "lost to follow-up." Ultimately, based on the final list of data elements developed through the CDC four-state collaborative project, the feedback provided from the metabolic center visits and the process of better defining data elements, the STFU (MSR) and LTFU (MCAPS) data entry screens will be updated.

Another important aspect of improving follow-up data will be to minimize the amount of missing data. For example, all the MCAPS reports described in this article represent 475 unique children. However, approximately 37% percent of the newborns resolved to have a disorder at the end of the STFU are missing in the requested first year MCAPS reports. Thus, the LTFU descriptive data presented in this article do not represent all known cases; it only reflects data on those cases with submitted information. In addition, the data provided in this article may not be a representative sample of all children with disorders diagnosed through NBS. Metabolic centers may not be completing annual summaries on children who have been more difficult to track and manage. This would include those lost to follow-up and also include children of families reluctant to seeking treatment and ongoing care. It may also disproportionately include children from disadvantaged socioeconomic and/or ethnic groups who may have more barriers to seeking and maintaining follow-up care (time constraints, transportation availability, and communication barriers). Thus, the data presented in this article may represent a group that is more likely to be in active follow-up and more likely to be in better health.

One limitation that impacts our ability to assess the overall effectiveness of NBS is the lack of an adequately sized comparison group to compare the natural history of the disorders identified through screening with the natural history of cases in the absence of screening. Short of an adequate comparison group, we will have to rely on reports from the literature to compare outcomes observed through our data collection system. For example, in the absence of NBS for MCADD, premature death or serious disability occurred in 20–25% of affected children,[17] and 33% of survivors were thought to have irreversible neurological damage.[18] The cross-sectional data for MCADD cases described in this article present a more positive profile. With time and with more cases reported, we expect our LTFU system to capture the full range of clinical presentations associated with MCADD cases detected through screening and all the other disorders that are being followed up.

Another interesting observation is that as NBS programs expand, more cases are diagnosed in any given period of time compared with the count of cases that were typically diagnosed as a result of clinical symptoms alone. For example, a 4-fold increase in MCADD detection has occurred as a result of expanded NBS in Massachusetts[19]; in Australia, there was a reported 5-fold increase in MCADD detection.[20] Similarly, the CDC estimated that the number of disorders that would have been identified in 2006 using the American College of Medical Genetics panel would have been 32% higher compared with the number of cases detected without expansion of the panel.[15] It has been speculated that this "excess in detection" may represent the identification of newborns with milder or benign forms of the disorder, which may be related to less virulent genetic mutations[21] that would not have been identified clinically before MS/MS screening. Unfortunately, we do not know the statewide prevalence of disorders detected by MS/MS that were identified clinically before the addition of MS/MS screening in 2005 nor do we know the clinical severity of those cases. However, SIS does capture genotype data, and as more case data become available, we may be able to examine the correlation between specific types of health outcomes and specific genetic mutations.

CONCLUSION

For many years, researchers have pointed out the need for adequate LTFU data,[9] but only in the past 3 years have these ideas been seriously considered.[6,22,23] As a result of this shift, LTFU data systems are evolving and are increasingly being incorporated into the "culture" of NBS.[11] Monetary resources and lack of staff have been identified as major barriers that hinder the development and implementation of LTFU data systems.[10,24] Furthermore, Hoff[11] speculated that if NBS program staff had additional training in epidemiology and biostatistics, they may be more likely to accept and engage in population-based surveillance activities.

As more state NBS programs move toward the establishment of LTFU data collection systems, they will have to address several issues that were highlighted in the recently released article produced by the LTFU data subcommittee of the ACHDNC.[8] If "the principal goal of LTFU is to assure the best possible outcome for individuals with disorders identified through NBS," then how do we connect the data collection process to actual improvements in patient care? For example, how do we use collected data on service delivery and treatment methods to define the optimal follow-up care plan for children with specific disorders? Ultimately, NBS follow-up data systems need to be able to evolve and expand as we continue to define the important questions that need to be addressed to better assess the effectiveness and efficacy of NBS.

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