Intervention and Outcomes in Duarte Galactosemia

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Intervention and Outcomes in Duarte Galactosemia: Project Protocol

Background and Goals: Duarte galactosemia (DG) is an autosomal recessive genetic condition characterized by partial loss of galactose-1-phosphate uridylyltransferase (GALT), which results in partially impaired metabolism of the sugar, galactose (Fridovich-Keil, Gambello et al. 2014). Galactose is abundant in milk and also found at lower levels in many other foods. DG affects close to 1/4000 births in the US. Many affected infants are detected by newborn screening (NBS) for galactosemia because of their diminished GALT activity and/or elevated galactose metabolite levels in blood (Pyhtila, Shaw et al. 2015). However, there is currently no consensus on long-term outcome prognosis for these infants; some studies suggest children with DG might be at increased risk for developmental difficulties later in childhood (Powell, Van Naarden Braun et al. 2009, Lynch, Potter et al. 2015), but no adequately powered study has been reported to document or contradict this hypothesis. There is also no consensus on whether children with DG might benefit from dietary restriction of galactose, at least in the first year of life, generally achieved by switching the baby from milk to soy formula. Because of the uncertainty, some healthcare providers recommend that infants with DG drink soy formula rather than milk in their first year of life; others do not (Fernhoff 2010, Fridovich-Keil, Gambello et al. 2014). The goals of this project are to assess whether children with Duarte galactosemia, ages 6-12 years old, experience developmental disorders relative to controls, and if so, whether dietary exposure to milk in infancy or early childhood is associated with developmental outcomes in this patient population.

To achieve these goals we will conduct a large multi-state case-control observational study. In Part 1 of this study we will recruit cases and gather demographic and diet history for these children using an online or telephone parent-response survey. In Part 2 of the study we will conduct direct, non-invasive developmental assessments on a subset of cases enrolled in Part 1. We will also recruit and enroll the siblings of cases to participate as controls in Part 2. The Specific Aims of this study are to:

1. Determine whether school-age children with DG are at increased risk for disorders in cognitive development, auditory processing, communication, socio-emotional development, and physical development and
2. Determine whether dietary restriction of galactose (milk) in infancy or early childhood is associated with developmental outcomes of school-age children with DG.

Recruiting and consenting study volunteers: We will recruit study volunteers diagnosed with DG in follow-up to newborn screening in collaborating states. Our team of collaborating states currently includes: AL, CA, GA, IA, IL, MI, MO, NC, NJ, OR, SC, TX, WA, and WI; however, we anticipate that through the course of this project additional states may be added, and some may withdraw. Once we have secured local IRB approval in a given state, if required, candidate study volunteers from that state will be recruited with the assistance of a liaison from the local NBS follow-up program. At minimum we will recruit using a hard copy invitation letter and "reasons to participate" summary sheet prepared by our research team but mailed by the NBS follow-up liaison. At the discretion of the NBS liaison, candidate study volunteers may also be contacted by telephone or by an electronic means (e.g. text). Also at the discretion of the NBS liaison candidate study volunteer names may be crosschecked against other databases available to them to obtain the most up-to-date address or other contact information.

Hard copy invitation letters will be addressed to the parents of infants born in that state who were diagnosed with DG in follow-up to NBS in the target years. Each envelope may also include a cover letter prepared by the collaborating state NBS program or follow-up metabolic center, at their discretion. Envelopes might also include a "Reasons to Participate" document that mentions an informational web site (duartegalactosemia.org) established to make information about DG, and about our study, more easily accessible to families and healthcare professionals.

Of note, the address labels for the recruitment envelopes will be prepared by the NBS follow-up collaborator who will also affix the labels to the pre-stuffed, pre-stamped envelopes and mail them. Each envelope may carry colorful stickers with the words "Duarte Galactosemia Study" and "Response Requested." Envelopes may also include a small item such as a "Reminder magnet." Finally, the envelopes will carry a return address for the NBS Follow-up office. This recruitment strategy will preserve the privacy of NBS records because we will only learn the identities of those candidate volunteers who choose to respond to the invitation letter. A round of reminder letters may be sent out to all non-responders 2-4 weeks after the

first letters were mailed. Additional reminder letters may be mailed at a later date.

The invitation letter received by each family will describe the study, explain that the 6-12-year-old child with DG in their family whose name is listed on the envelope may be eligible to participate as a "case," and explain that if there are other 6-12-year-old children in the household these children may also be eligible to participate, either as cases if they have DG, or as controls if they do not have DG. The letter will provide a telephone number and email address that the recipient can contact if they have questions or concerns, if they want to volunteer, or if they want to learn about specific exclusion criteria for the study. We will also provide the URL for a web site (e.g. ClinicalTrials.gov or duartegalactosemia.org) that will provide more information about the study.

Recruiting additional controls: To secure additional controls, as needed, for a given geographical area we may also send modified recruitment letters to the families of children with DG who are outside our enrollment age range (e.g. either <6 or >12), asking whether there are unaffected siblings in these families who are 6-12 years old who might be interested in participating in the study as controls.

Exclusion criteria: We will exclude participants with chronic illness or another condition unrelated to DG that is known to cause developmental problems; we will not exclude children with behavioral issues that might be related to DG. We will exclude candidate participants if either the parent or child is not conversant in English, because this could negatively affect the child's scores resulting from the direct child testing and parent response surveys, which will be conducted in English. We will also exclude children for whom the current parent/guardian was not the primary caregiver when the child was an infant because they may not know historical details of the child's diet.

The consent process: Families who express interest in participating in the study (by email or telephone) will be asked if they prefer to participate online or over the telephone. Those who choose to participate online will be asked to provide an email address that we can use to send them a clickable link to an online consent form and survey (administered through REDCap, the Research Electronic Data Capture system, http://www.project-redcap.org/). Those who choose to participate over the telephone will be asked to schedule a time when a member of our research team can call them back to administer the consent and survey over the phone.

Families choosing to participate in the study who complete the survey, either online or over the phone, within 2 weeks of receiving their invitation or reminder letter will be compensated for their time and effort with a $50 gift card.

The Part 1 Parent or guardian response survey: The Part 1 survey to be completed by a parent/guardian will include questions about child and family demographics and socioeconomic circumstances, early childhood educational experiences or interventions (if any), child general health, child response to sensory stimuli, and current and historical child diet (especially with regard to galactose exposures). The survey will also ask the respondent if we may re-contact them in the future. Details about the survey are provided in the "Procedures" section below. At the end of the survey the respondent will see a short debriefing document.

In total, we may receive up to 10,000 completed surveys for Part 1 of this study. We expect that respondents will be distributed geographically among the collaborating states, and that, as infants, the cases will reflect the full spectrum of dietary galactose exposures. From a pilot study, we also expect that the vast majority of respondents will give permission to be re-contacted. Finally, for Part 1 of this study we have requested a waiver of written consent (consent will be online or verbal) because survey respondents will participate either online or by telephone, and a waiver of child assent because the online or telephone logistics of this part of the study will make meaningful assent impractical.

Part 2 of this study will involve direct assessments of child developmental outcomes of both cases and controls. These direct assessments will be conducted in Direct Testing Blocks (explained below) to be distributed geographically across participating states and conducted at different times throughout the 3 years of the funded project.

From among the survey respondents in Part 1 we will recruit at least 144 cases to participate in Part 2 of

the study. We may also recruit parents from among the Part 1 respondents to participate in focus groups or other related research studies. Of course, we will only attempt to re-contact Part 1 survey respondents who have given explicit permission to be re-contacted.

From the Part 1 survey responses we will know the ages and genders of candidate controls from these families (children ages 6-12 who do not have DG). We will recruit at least 144 controls from these families to participate in Part 2 of the study. The parent/guardian of each of these controls will be asked to complete a shortened version of the Part 1 survey for their child.

To determine the locations of specific Part 2 direct assessment blocks we will sort survey respondent families into geographic areas defined by a 2-hour driving radius from a hub. We will classify each area in terms of the numbers of candidate DG and unaffected sibling volunteers and will also note the diet histories of the cases and the genders and other relevant parameters. *Geographic areas will be selected as potential sites for direct testing blocks that include >24 eligible children (cases + controls).*

We will re-contact the families of candidate cases and controls who live within a 2-hour drive of an anticipated direct assessment site using their contact information provided on the Part 1 survey. In some cases we may also invite families who live more than a 2-hour drive away from a testing site. For these families we may offer to reimburse limited hotel expenses in addition to mileage charges. We will explain the direct assessment process and invite child and parent participation. Those who express interest will be re-contacted again to work out the scheduling details. Although we will send copies of consent and assent forms for review to all anticipated Part 2 participants ahead of their scheduled participation, actual consent and assent for the direct assessment blocks will be administered in person by the Project Manager at the blocks. Families who participate in a direct assessment block (described below) will be compensated for their time and effort with a $200 gift card (per child participating) and will also be reimbursed for allowable travel expenses.

Assigning identification (ID) codes: ID codes that are devoid of protected health information (PHI) and that also do not distinguish case versus control status of the participant will be assigned to volunteers in chronological order, as follows: EDGS0001 (for Emory DG Study #1), EDGS0002, and so forth. To the extent reasonable we will use these codes in place of names or other PHI in records and communication between researchers. Each volunteer will also be assigned a Family Code (e.g. F001, F002) to designate linkage between relatives (siblings) in the study; relatives will have unique EDGS codes but will share the same Family Code. Accounting for family relationships is required for appropriate statistical analyses. Like EDGS codes, Family Codes will be assigned in chronological order and will be devoid of any PHI.

Procedures: In Part 1 of the study we will gather information from the parent/guardian of each participating case using a parent-response survey that gathers demographic and socioeconomic status information about the household and early childhood education and/or interventions, diet and general health information about the child. The online consent + survey for Part 1 should take no more than 20 minutes to complete. Parents will be asked to complete a shortened version of this survey for their children serving as controls in Part 2.

In Part 2 of the study we will gather information using a combination of parent-response surveys and direct child assessments, all non-invasive and all conducted or administered by trained professionals (details explained below). One parent-response survey will be administered online or by telephone prior to the actual direct testing appointment. The full schedule of assessments for any one child will take no more than 3½ to 4 hours, including breaks.

The only biological samples to be collected as part of this study are saliva samples (about 1 teaspoon full) to be collected from child participants during the direct assessment blocks using “spit kits.” This process is simple and completely non-invasive – the volunteer literally spits into a small container. We will use this saliva to isolate DNA for *GALT* genotyping. By doing *GALT* genotyping on these volunteers we will confirm case versus control status and also identify the specific *GALT* mutations present in each case. This analysis will also reveal which sibling controls are carriers. The consent form signed on behalf of each child volunteer will provide a space where the parent or guardian can indicate whether or not they wish to be informed of their child’s *GALT* genotype after participation.

Direct assessment blocks: We will conduct direct assessments of child outcome in each block using validated, standardized instruments administered by trained professionals. We will also collect child height,

weight, and head circumference, and biological parental heights, if available. The following developmental outcomes will be assessed: cognitive skills (especially memory, executive function, and auditory processing), communication processes (speech and language), physical development (including motor skills, coordination, and occurrence of tremors), and social-emotional development. The instruments we will use to quantify each of the outcome parameters are described below and listed in **Table 1**.

Each of the direct assessment blocks will be conducted at a local facility that provides office accommodations suitable for testing. A team of 5 professionals will conduct each block, including the Project Manager and 4 testers (2 doctoral level child psychologists and 2 speech/movement specialists). Although a Recruiter will have communicated directly with each family well in advance of their appointment to arrange scheduling details, the Project Manager will also contact them 1-2 weeks before their appointment to introduce herself and provide the family a collection of files including: a brief description of their test day schedule, copies of the consent and assent forms for review, and detailed driving instructions and information about parking at the testing facility. The Project Manager will explain that the family is encouraged to look over the consent and assent forms before their appointment and contact her if they have any questions or concerns. She will also provide the parent/guardian a link to an online parent-response survey about Child Educational Experiences and Medical History that the parent/guardian is to complete prior to their child's testing appointment. The Project Manager will also send each family a reminder email (or phone call) one day before their scheduled appointment, just to confirm.

On the day of their scheduled appointment the Project Manager will greet each family when they arrive at the testing location. The Project Manager will explain the anticipated testing schedule to each family, address any questions or concerns they may have, and administer consent and assent for all participants. From these interactions, the Project Manager will know which children have DG, but the testers will be kept blinded to each child's diagnostic status.

The schedule of assessments for each child will be carefully arranged with breaks between any long sessions. The full schedule of assessments for any one child will take about 3½ to 4 hours, including breaks. Of note, while some of the assessments involve sitting in a chair at a table, others involve hopping, jumping, tossing beanbags, drawing spirals, and so forth, presented in an almost game-like format. In our pilot study (Lynch, Potter et al. 2015), every child completed every assessment without apparent fatigue, and some even asked to keep going after the formal assessments were completed because they were "having fun."

While a child is being assessed, the parent/caregiver will be in an adjacent room completing ratings of child emotional and behavioral outcomes, child social skills, and their own (caregiver) stress levels. Because they will be asked to reveal information about themselves in addition to their enrolled child, these parents will also be consented volunteers. At the end of the testing schedule, the Project Manager will meet again with the parent and child to conduct a short oral interview and to hear from each child, in his/her own words, what they liked best and least about participating in the study. The Project Manager will also give the family a short debriefing document and offer to discuss it if there are any questions. While the parent is speaking with the Project Manager the child will be given the opportunity to select their "prize" from a "treasure chest" of age-appropriate small toys. Finally, the Project Manager will thank the family again, give them their gift card(s), help them complete any needed paperwork to ensure appropriate travel compensation, and see them safely out.

Before they leave, each family will also receive a 2 page hard copy Anonymous Feedback Survey with a pre-addressed, pre-stamped return envelope so we can learn what about the study is working well for study volunteers and what, if anything, we need to consider changing. For some direct testing blocks we may also invite parents/guardians to participate in a telephone focus group to tell us about their family's experiences participating in the study.

How will we assess child cognition? We will use a set of well-established standardized tests that focus on 3 areas of cognition: memory, executive function, and auditory processing.

- Memory: We will use a comprehensive memory battery. The Children's Memory Scale (Cohen 1997) provides indices of visual and verbal memory processes, immediate and delayed memory, working memory, and attention/concentration. We also will use two subtests, Spatial Span and Digit Span, from

the Wechsler Intelligence Scale for Children IV-Integrated (WISC-IV-Integrated) to focus on spatial and auditory working memory (Kaplan, Fein et al. 2004).

- Executive Function: Children in this study will be asked to complete subtests from the NEPSY-II (Korkman, Kirk et al. 2007), a respected test of neuropsychological development that is appropriate for our age range. We will include the Word Generation subtest to measure executive functioning in the verbal domain and Route-Finding, a measure of planning ability in the visual-spatial domain. We will use the *Behavior Rating Inventory of Executive Function* (BRIEF) (Gioia, Isquith et al. 2000) to assess parental perception of the child's planning, organizing, inhibiting, working memory, and emotional control.
- Auditory Processing: The Auditory Brainstem Evoked Response (ABER) measures the initial response of the auditory pathway to sounds by quantifying the cranial nerve 8 conduction and brain wave latency and amplitude (Kable, Coles et al. 2009). For this test, three electrodes are attached to the child with removable adhesive, one on the forehead and one on each earlobe, to assess response to stimulation. Responses to a clicking sound are recorded by a computerized software system. This task is usually conducted in a dimly lit room to decrease distraction. Like all other direct assessments to be administered, the ABER is a non-invasive and completely painless test.
- Intelligence: We will use the Wechsler Abbreviated Scale of Intelligence-II (WASI-II) to measure verbal, performance, and full-scale IQ (Wechsler 2011).

How will we assess child communication? We will screen child hearing using a pure-tone audiometer. We will conduct a motor speech exam consisting of a brief physical exam of the face and mouth, speech sample, and a word repetition task. We will assess speech sound production with the *Diagnostic Evaluation of Articulation and Phonology* (DEAP) (Dodd, Zhu et al. 2002) and the *Goldman-Fristoe Test of Articulation-3* (GFTA-3) (Goldman, Fristoe 2015) systematic measures of articulation that measure consistency and accuracy of speech sound production in words. We will assess receptive and expressive language using the Listening Comprehension and Oral Expression subtests of the *Oral and Written Language Scales, Second Edition* (OWLS-II) (Carrow-Woolfolk 2011).

How will we assess child social-emotional development? We will ask parents to complete the Child Behavior Checklist (CBCL) (Achenbach and Rescorla 2001) which provides summary scores on Internalizing, Externalizing, and Total problems as well as scores on symptom scales including depression, social problems, and aggressive behavior. To assess internalizing problems more directly, we will also ask each child to complete survey measures of depression and anxiety using the short forms of the Children's Depression Inventory-2 (Kovacs, 2010) the Revised Children's Manifest Anxiety Scale: Second Edition (RCMAS-2) (Reynolds and Richmond 2008), a self-report measure yielding a Total Anxiety score. Each measure should take about 5 minutes to complete.

Parents will be asked to complete the Social Skills Improvement System Rating Scales (SSIS) (Gresham and Elliott 2008). The SSIS provides standard scores on Social Skills and Problem Behavior, as well as scores on specific social skills (e.g., cooperation, assertion) and problem areas (e.g., hyperactivity, autism spectrum behaviors).

How will we assess child physical development? We will assess motor skills involving manual dexterity, static and dynamic balance, and catching and releasing a ball with the *Movement Assessment Battery for Children*--2nd Edition (MABC-2). The MABC-2 is the test most frequently used to diagnose developmental coordination disorder. Children scoring below the 5th percentile on the MABC-2 are considered to have a significant motor coordination disorder (Zwicker, Missiuna et al. 2012).

We will assess the possibility of tremors using *The Essential Tremor Rating Assessment Scale* (TETRAS) (Elble, Comella et al. 2012) that will be videotaped and scored by a tester with advanced training in kinesiology. In addition, Dr. Claudia Testa, a member of the Tremor Research Group that developed the TETRAS and a long-time colleague of the PI, will independently score 10% of the videos for reliability calculation. One of the TETRAS tasks involves drawing Archimedes spirals. In the proposed

study, the spiral will be drawn on a piece of paper placed on a Wacom Intuos5 electronic tablet, which records pen movements and pressure. Upper extremity steadiness and pen pressure recorded on the Wacom tablet will be quantified using NeuroGlyphics software (Haubenberger, Kalowitz et al. 2011). Analysis of spiral drawing with NeuroGlyphics software correlates with visual ratings ($P < 0.0001$), but is more sensitive for small effects and has better inter-rater reliability. Tongue strength, which is decreased in classic galactosemia and can contribute to speech disorders, will be assessed using the Iowa Oral Performance Instrument (IOPI) with the standard tongue bulb (IOPI Northwest 2005) (Potter, Nievergelt et al. 2013), and hand strength will be assessed with a standard pediatric dynamometer (van den Beld, van der Sanden et al. 2006).

How will we assess parenting/caregiver stress? We will evaluate caregiver stress using the short form of the *Parenting Stress Index, 3rd Edition* (Abidin 1995). The short form includes parental distress, parent-child dysfunctional interactions, and difficult child subscales.

Data capture, organization, storage, and analysis: As data are collected, information will be entered into the Research Electronic Data Capture application (REDCap, http://project-redcap.org/), an internationally recognized HIPAA-compliant online system available at Emory. REDCap will allow us to establish fields for all anticipated data items and enter these data in electronic form as they become available for each study volunteer. Any corresponding hard copy records will be maintained in locked file cabinets at Emory University with access limited to IRB-approved members of our study team. Using REDCap will allow us to store and maintain our data safely and will also allow us to export selected data fields into spreadsheets for subsequent analysis using the desired statistical software. Any electronic data not maintained in REDCap will be stored on HIPAA-compliant servers at Emory.

Table of Measures for Evaluation Session and Time Estimates for Child and Parent

Variable	Measure	Minutes Child	Minutes Parent
Cognitive Skills			
Memory	Children's Memory Scale (Cohen 1997)	30	
Working Memory	Wechsler Intelligence Scale for Children IV-Integrated (WISC-IV-Integrated): Spatial Span and Digit Span (Kaplan, Fein et al. 2004)	10	
Executive Function	Behavior Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith et al. 2000)		15-20
	NEPSY – Word Generation and Route Finding Tasks (Korkman, Kirk et al. 1998)	20	
Intelligence	Wechsler Abbreviated Scales of Intelligence (WASI) (Vocabulary and Matrix Reasoning subtests) (Wechsler 1999)	15	
Language			
Auditory Processing	Auditory Brainstem Response measure Pure tone assessment	10 5	
Articulation and Motor Speech	*Diagnostic Evaluation of Articulation and Phonology* (DEAP) (Dodd, Zhu et al. 2002), brief head and neck physical exam, word repetition task and speech sample (Murray, McCabe et al. 2015)	10	
Receptive and Expressive Language	OWLS-II -- LC/OE and RC/WE Oral and Written Language Skills, 2nd Edition (Carrow-Woolfolk 2011) Listening Comprehension (LC) (receptive) and Oral Expression (OE) (expressive) subtests only	~25	
Physical Development			

Balance, coordination, manual dexterity	Movement Assessment Battery for Children-2 (Movement ABC-2) (Henderson, Sugden et al. 2007)	~20	
Strength	Iowa Oral Performance Test (www.IOPImedical.com); some measures will be completed with handheld dynamometer	5	
Tremor	Essential Tremor Rating Assessment Scale (TETRAS)	15	
Social Skills, Behavior Problems, and Socio-emotional Development			
Social skills	Social Skills Improvement System Rating Scales (Gresham and Elliott 2008) Maternal Report. Subscales: Communication, Responsibility, Cooperation, Assertion, Empathy, Self-Control, Engagement. This measure also includes scales to measure Competing Problem Behavior and Academic Competence.		25
Behavior Problems	Child Behavior Checklist 6-18 (Achenbach and Rescorla 2001). Maternal Report. Provides scores on three broad dimensions of problem behavior: Internalizing, Externalizing and Total Problems.		15
Internalizing Problems	Children's Depression Inventory-2 (Kovacs, 2010) (Short Form) Revised Children's Manifest Anxiety Scale, Second Edition (RCMAS-2) (Reynolds and Richmond 2008) (Short Form)	5 5	
Participation in Special Education or Other Intervention Experiences	Questionnaire developed by project staff based on experiences of children with classic galactosemia with questions on specific problems experienced, when identified, placement or intervention, other problems.		15
Potential covariates/ confounding variables	Child prenatal or postnatal exposures to cigarettes or alcohol assessed through parent interview in Part 2. Family socioeconomic status assessed through parent response survey in Part 1. Assessment of parenting/caregiver stress in Part 2 using the short form of the *Parenting Stress Index, 4th Edition* (Abidin 1995)		10 10

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