



## What was the goal of this study?

The principal goal of this study was to provide a foundation of knowledge to help families, healthcare providers, and public health officials make evidence-based decisions about Duarte galactosemia (DG). To meet this goal, we designed our study to answer two questions:

- 1: Do children with DG experience more developmental problems than children without DG? and
- 2: Do children with DG who drank milk as infants experience more developmental problems than children with DG who drank low-galactose formula as infants?

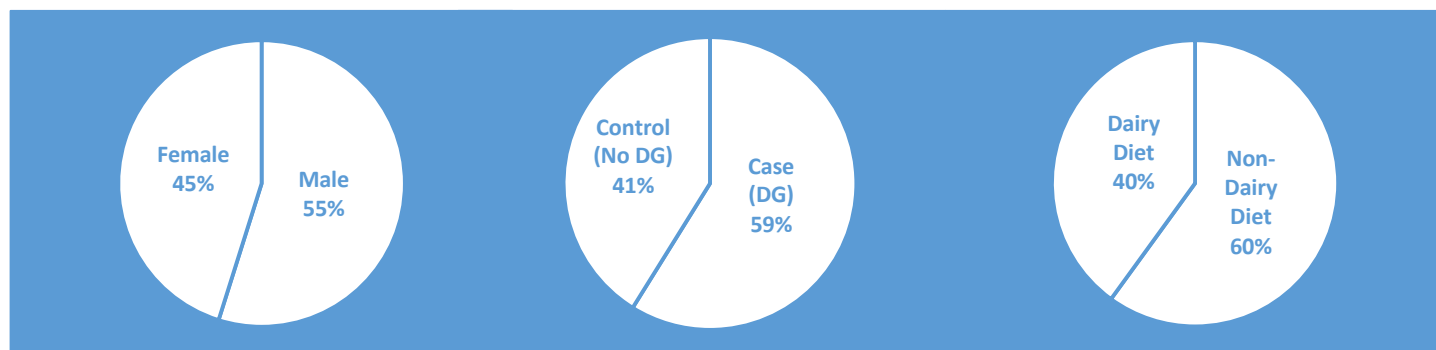
## What did we do?

**Recruitment:** With the help of local newborn screening programs and metabolic clinics we recruited hundreds of families, each including at least one child with DG, from the states indicated on the map. Cases for the study were children, 6-12 years old, who had DG; unaffected siblings served as controls.



**Online Survey (Part 1):** Families who chose to enroll in the study were asked to complete an online survey for each eligible child. This survey asked about family demographics, child health, child diet including exposure to milk in infancy, and other information. We received completed Part 1 surveys for a total of 566 children from 365 families.

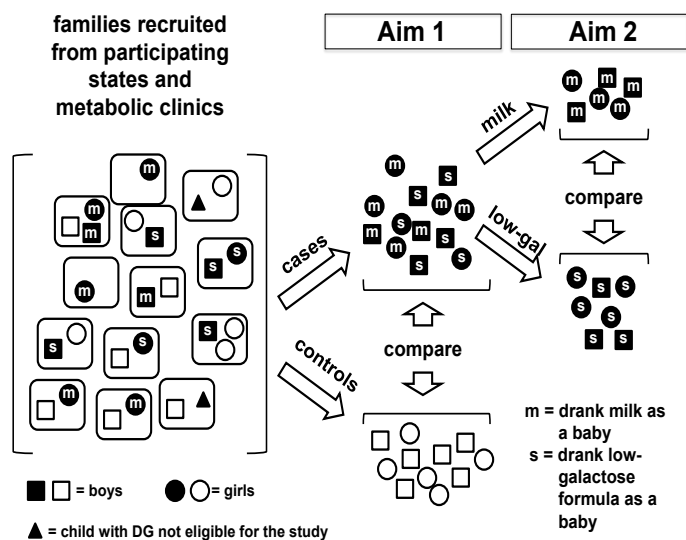
**Direct Testing (Part 2):** Next, we selected testing sites in central locations relative to survey respondents and invited nearby families with eligible children to participate in Part 2 of the study. Participation in Part 2 involved visiting a local site for direct assessments of child outcomes representing five general domains of development: cognitive, socio/emotional, speech and hearing (including auditory processing), physical, and motor. Parent/guardians also completed additional questionnaires, and each child donated a sample of saliva for *GALT* gene sequencing to confirm case/control status. A total of 350 children from 13 different states completed Part 2 of the study; 206 of these children had DG (cases) and 144 did not (controls). The average age of participating children was about 9 years old; 192 of the children were boys and 158 were girls. Of the children with DG, about 40% had consumed milk as babies and about 60% had consumed low-galactose formula.



Characteristics of the 350 children who completed both Parts 1 and 2 of our study.



**Data analysis:** Finally, we assembled and analyzed all of the information collected for the 350 children who completed both Parts 1 and 2 of the study. Specifically, to address our first study question (**Aim 1**), we compared developmental outcome scores for children with DG to scores of non-DG controls to see if there was any meaningful difference. To address our second study question (**Aim 2**), we compared scores for children with DG who drank milk as babies to scores for children with DG who drank low-galactose formula as babies. More details about our study including methods and results can be found in the resources listed at the end of this document.



## What did we find?

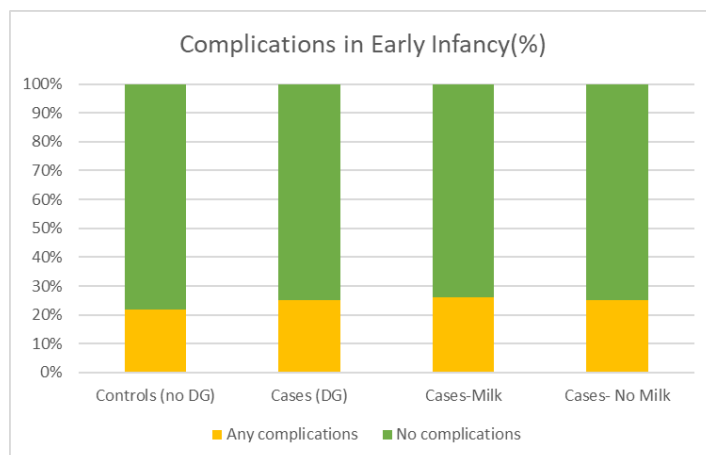
Our data analyses showed no statistically significant differences in any of the developmental outcomes tested between children with DG and children without DG (Aim 1). Our analyses also showed no significant difference in developmental outcomes tested between children with DG who drank milk as babies and children with DG who drank low-galactose formula as babies (Aim 2). Some of our findings are illustrated and explained below.

**Conclusion:** Our results suggest that children with DG are *not* at increased risk for developmental problems, and also suggest that drinking milk in the first year of life does not put a baby with DG at increased risk for developmental problems later in childhood.

## Parent-Reported Results: Some Highlights

This section shows some of the results from parent surveys completed as part of this study. In total, we received Part 1 survey results for 566 children, and Part 2 survey results for 350 of those 566.

**Complications in Early Infancy:** In the Part 2 survey we asked questions relating to pregnancy and health concerns in the neonatal period. For young infants, the rate of complications of any kind reported was about 1 in 4; **this rate was the same for babies with and without DG.** We also found that reports of complications for babies with DG were the same regardless of whether the baby drank a milk-restricted diet or drank breast milk and/or dairy formula. Further, when the types of complications were broken down into categories, again we saw no differences between groups.



# INTERVENTION AND OUTCOMES IN DUARTE GALACTOSEMIA (DG): STUDY SUMMARY AND RESULTS

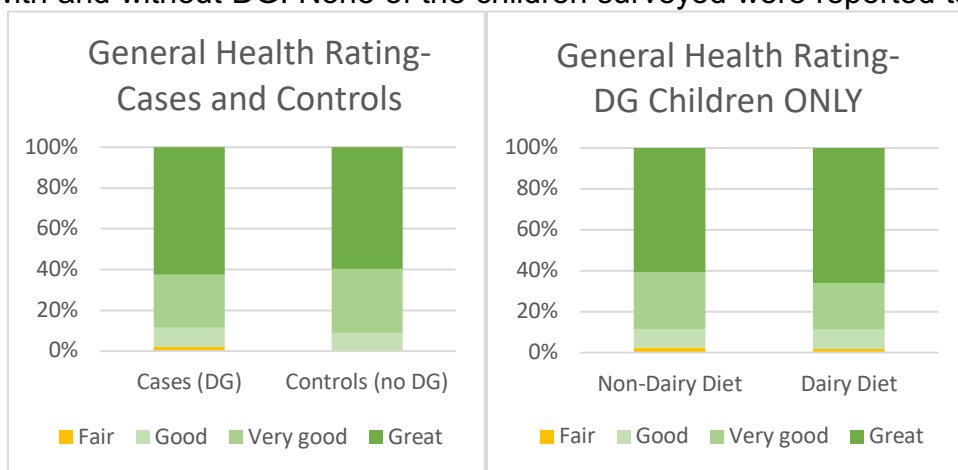


Of note, the most common neonatal complication reported in our study was jaundice, which impacts more than half of all babies born in the US ([www.cdc.gov](http://www.cdc.gov)). About 18% of both cases and controls in our study reported neonatal jaundice -- so less than the population average. Other neonatal issues, including failure to thrive, slow weight gain, and reflux/digestive issues were reported for about 1% to 3% of all children in our study; these percentages also did not differ between cases and controls.

**Conclusion:** These responses suggest that children with DG are not at increased risk of complications in early infancy, and that milk exposure does not cause health problems for the vast majority of infants with DG. Therefore, if an infant with DG does experience neonatal complications, other possible causes, including other causes of milk sensitivity, should be explored.

**Sensory Issues:** In addition to health and development questions, we also asked about possible sensory issues that the child might have. Specifically, we asked whether each participating child showed heightened sensitivity to sights, sounds, smell/taste, or touch. While we did notice a small trend of more parent-reported sensitivities for cases than controls, the difference was small, and among children with DG, parents reported more sensitivities for children drinking low-galactose formula than for children drinking milk. The difference was therefore in the opposite direction of what would be expected if milk exposure caused heightened sensory issues for children with DG.

**Overall Health:** We also asked parent/guardians to rate their child's general health, and found no difference in ratings for children with and without DG. None of the children surveyed were reported to be in "poor" health, and only about 1.5% of children were reported to be in "fair" health. The vast majority were reported to be in "good," "very good," or "great" health (see figure). When we compared children with DG who drank milk as babies (Dairy Diet) to children with DG who drank a dairy-restricted diet as babies (Non-Dairy Diet), we found that their health ratings were almost exactly the same, with no meaningful differences.

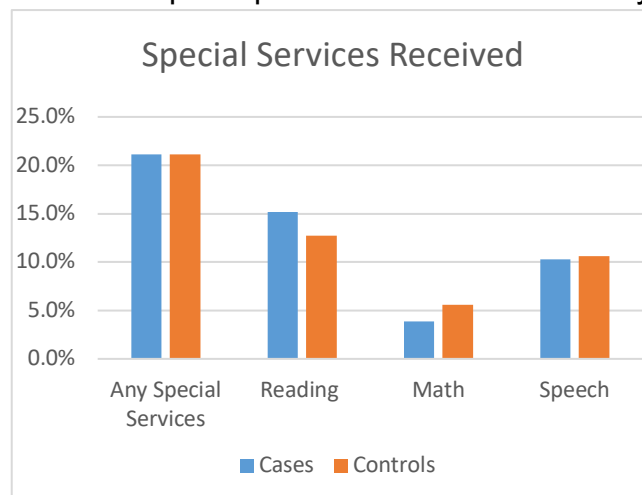


**Conclusion:** We found no long-term impact of DG on parent/guardian-reported overall child health, and consuming milk in infancy did not appear to either harm or benefit the general health of the child, which was also consistent with the findings of our direct testing.

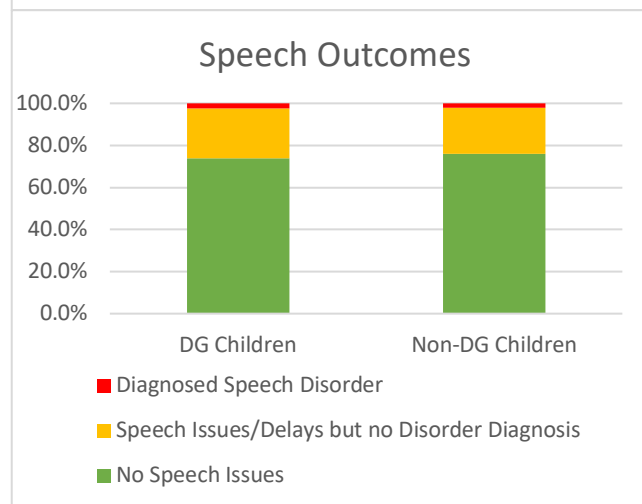
**Receipt of Early Interventions:** We asked about any early interventions received prior to age 3 for developmental indications, including problems with cognitive, physical, communication, social/emotional development, or adaptive functioning. **Children with DG in our study did not report early developmental problems at higher rates than their non-DG siblings.** We also asked about special services or interventions received between ages 3-5, including the specific reason/diagnosis. In all, fewer than 5% of the children in our study had received any kind of intervention when 3-5 years old, and again, receipt of these services did not differ between children with DG and their unaffected siblings, or among children with DG as a function of milk-exposure in infancy. In total, 26 out of 566 children were reported to have received special services, most for a speech/language indication.



**Receipt of Interventions After Age 6:** For the 350 children who participated in Part 2 of our study, parent/guardians completed a survey that asked about any special services or interventions received by their child after age 6. Based on the results of these surveys, **children with DG did not receive services at higher rates than their non-DG siblings.** In total, about 21%, or close to 1 in 5, of both cases and controls received some kind of special services after age 6. The most common areas where children received special services were reading, math, and speech/language. Specifically, 10% of children with DG and 11% of non-DG children in our study received some kind of intervention or services for speech and/or language, consistent with the national average of about 10%.



**Developmental Diagnoses:** In the Part 2 survey, we also asked whether each child had been formally diagnosed with any developmental, attention/behavioral, or other issues (e.g. ADD/ADHD, Bipolar, Intellectual Disability, etc.). For the overwhelming majority of children in the study, parent/guardians reported no diagnoses. A very small percentage of children in the study (1.5% of cases and 2.8% of controls) had been diagnosed with an Attention disorder (ADD or ADHD). The overall rate of all developmental disorders diagnosed was exactly the same for both cases and controls (6.3%).



**Parent-Reported Social Skills and Behavior:** During Part 2, parent/guardians filled out several surveys about their child's development, including surveys about social skills, emotional issues, attention and focus, and planning behaviors, among others. Overall, the results demonstrated that the vast majority of both cases and controls were doing very well in all of these areas, with most children scoring above average for their age. From these surveys, **we also did not find any difference in the rate of problem behaviors or other issues reported for cases and controls**, which was consistent with the findings of our direct measures of cognitive and socio/emotional development.

**Conclusions:** In summary, we did not find any significant differences between DG cases and controls, or between cases who received dietary intervention and those who did not, in the rates of reported developmental issues or special services received at any time period (ages 0-2 years, 3-5 years, or 6+ years) or in any area of development reported. These parent/guardian-reported findings suggest that children with DG are not at increased risk for developmental problems, and support the findings of our direct testing and analysis.

## Results from Direct Testing: Some Highlights

This section shows some of the results derived from direct assessment of the 350 children who completed both Parts 1 and 2 of this study. In sum, our team assessed each of these children for 73

# INTERVENTION AND OUTCOMES IN DUARTE GALACTOSEMIA (DG): STUDY SUMMARY AND RESULTS

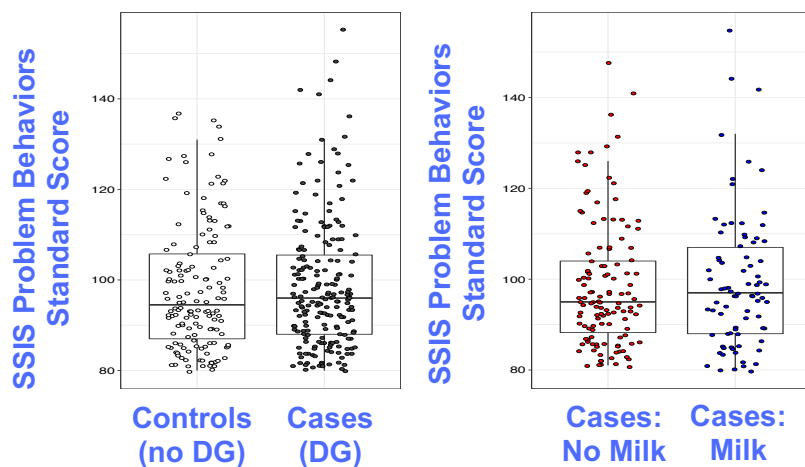


outcome measures representing 5 general domains of development: cognitive, socio/emotional, speech and hearing (including auditory processing), physical, and motor.

To illustrate these results, we show representative “box and whisker” plots of individual outcomes from each of the 5 developmental areas we assessed.

**How to read a Box and Whisker Plot:** Each dot on a box and whisker plot represents one child, so by looking at the pattern of dots for a given group you can see how clustered or scattered the individual scores are. The box in each plot shows the middle 50% of child scores for that outcome (from the 25th percentile to the 75th percentile). The line across the middle of each box shows the average score for that outcome in the population.

## Social/ Emotional Development:

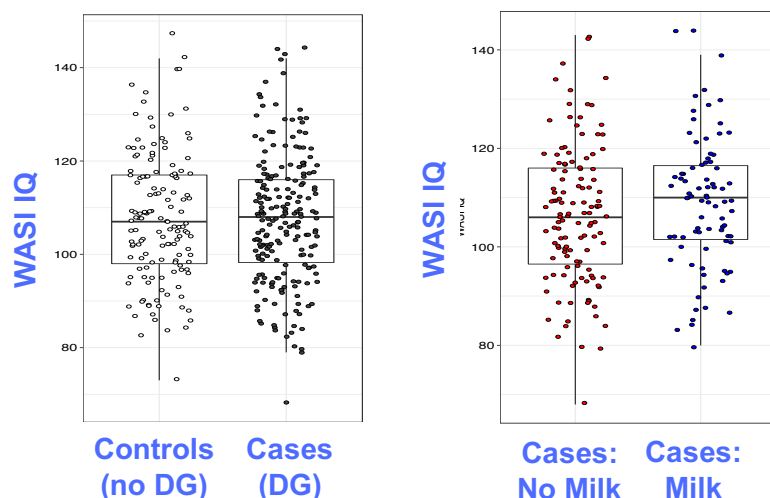


### SSIS Problem Behaviors Standard

**Score:** The Social Skills Improvement System (SSIS) is a survey that was completed by parent/guardians for their participating children. This survey assesses various social skills and is scored based on age-appropriate norms.

The Problem Behaviors Standard Score is one of the scores obtained from this survey; the average score for this measure is 100. Most children (both cases and controls) scored below 100, which means that parents reported that their children in the study had lower than average numbers of “problem behaviors”.

## Cognitive Development:

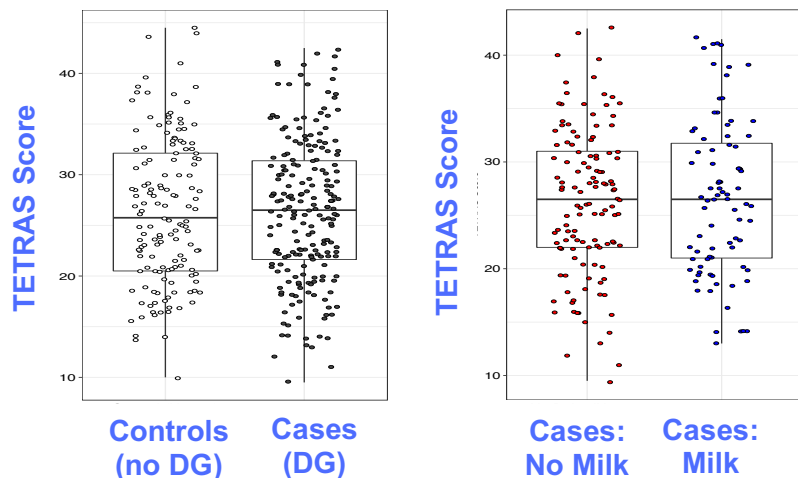


### WASI Full Scale IQ Score:

The Full Scale IQ is a score derived from administration of selected subtests from the Wechsler Intelligence Scales (WASI). This score is designed to provide a measure of an individual's overall level of general cognitive and intellectual functioning, with an IQ of 100 being the average score. In our study, the average IQ score for both DG children and their siblings was approximately 107, and most children fell within the normal IQ range of 90-110.

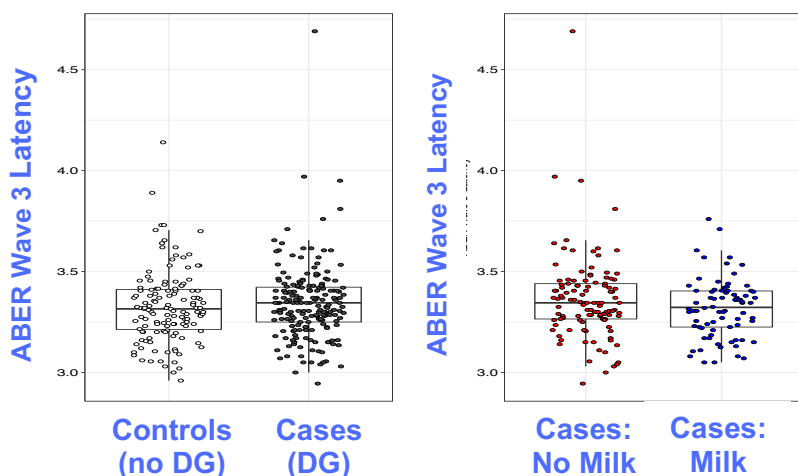


## Motor Development:



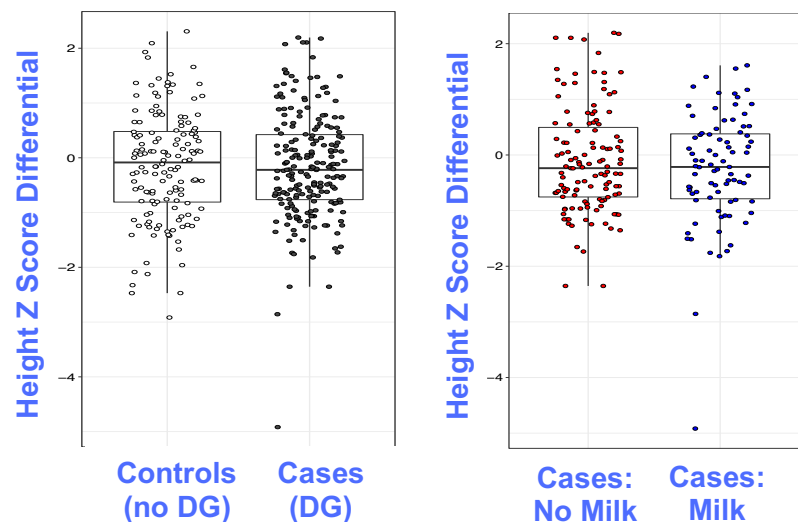
**TETRAS Score:** The TETRAS (Essential Tremor Rating Assessment Scale) is a rating scale used to assess and measure Essential Tremor, which is a neurological disorder that causes involuntary muscle contractions leading to shaky movements in one or more parts of the body, most commonly in the hands. We did not see any difference in the distribution of TETRAS scores, indicating no pattern of movement disorder in DG children or their siblings.

## Speech and Hearing:



**ABER Wave 3 Latency:** The ABER (Auditory-Brainstem Evoked Response) is a device that measures auditory processing (how the brain responds to sounds). The measure shown here is one of several waves that were observed; if DG children did have delayed auditory processing, then we would expect their average score to be higher. However, based on all the ABER measures collected, we saw no indication of a problem with auditory processing.

## Physical Development:



**Height Z Score Differential:** By using the height, age, and gender of the child, we were able to calculate a score for each child's expected height based on the adult heights of both parents. A score above zero means the child is taller than expected, and a score below zero means the child is shorter than expected. Looking at these charts, we can see that while there were some children who were much taller or much shorter than expected, most children in both the case and control groups scored close to zero, their expected height.



## Want to read more about Duarte galactosemia?

Here are links to some of the resources you can find online if you want to read more about Duarte galactosemia. Please note that most of these resources are updated with new information as it becomes available:

### **Resources intended for families:**

- A summary of our research findings and other current information and resources about Duarte galactosemia can be found at [www.duartegalactosemia.org](http://www.duartegalactosemia.org)
- A Wikipedia article about Duarte galactosemia, written by our team, can be found at [https://en.wikipedia.org/wiki/Duarte\\_galactosemia](https://en.wikipedia.org/wiki/Duarte_galactosemia)
- Information about Duarte galactosemia, and also other forms of galactosemia, can be found at the web site of the Galactosemia Foundation: <http://www.galactosemia.org/>

### **Resources intended for healthcare and biomedical professionals:**

- You can find a published paper describing our study (Carlock et al DOI: 10.1542/peds.2018-2516), including the full data analysis for all outcomes and a short video abstract, available open access in the journal *Pediatrics*, at: <http://pediatrics.aappublications.org/content/143/1/e20182516>
- You can find a companion article (DOI: 10.1542/peds.2018-3292), written by Dr. Shawn McCandless, that puts our paper into context at: <http://pediatrics.aappublications.org/content/143/1/e20183292>
- Please find a GeneReviews article about Duarte galactosemia at: <https://www.ncbi.nlm.nih.gov/books/NBK258640/>
- More information is also available at: <https://clinicaltrials.gov/ct2/show/NCT02519504>

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