

# Translating principles of precision medicine into speech-language pathology: Clinical trial of a proactive speech and language intervention for infants with classic galactosemia

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## Summary

Precision medicine is an emerging approach to managing disease by taking into consideration an individual's genetic and environmental profile toward two avenues to improved outcomes: prevention and personalized treatments. This framework is largely geared to conditions conventionally falling into the field of medical genetics. Here, we show that the same avenues to improving outcomes can be applied to conditions in the field of behavior genomics, specifically disorders of spoken language. Babble Boot Camp (BBC) is the first comprehensive and personalized program designed to proactively mitigate speech and language disorders in infants at predictable risk by fostering precursor and early communication skills via parent training. The intervention begins at child age 2 to 5 months and ends at age 24 months, with follow-up testing at 30, 42, and 54 months. To date, 44 children with a newborn diagnosis of classic galactosemia (CG) have participated in the clinical trial of BBC. CG is an inborn error of metabolism of genetic etiology that predisposes up to 85% of children to severe speech and language disorders. Of 13 children with CG who completed the intervention and all or part of the follow-up testing, only one had disordered speech and none had disordered language skills. For the treated children who completed more than one assessment, typical speech and language skills were maintained over time. This shows that knowledge of genetic risk at birth can be leveraged toward proactive and personalized management of a disorder that manifests behaviorally.

## Introduction

The realization that neither the “average patient” nor the “one-size-fits-all treatment” exists has led to efforts to design and deliver interventions that are tailored to the specific needs of a given patient. The term “precision medicine,” also referred to as “personalized medicine,” describes an emerging approach to diagnosis and treatment that is customized to individual patients. Knowledge of a patient's individual risk, for instance based on genetic profile, can be used to guide intervention decisions such as selecting the most effective drug or taking proactive measures. As the term implies, precision medicine was developed for medical conditions and is most often implemented in the management of diseases like cancer, cardiovascular disease, and rheumatoid disease.<sup>1</sup>

This data-driven, individualized approach is used far less commonly in the behaviorally expressed disorders, such as learning disabilities, disorders of spoken and written language, and disorders of social interactions. One likely reason is the fact that individual genetic risks for these disorders are less well characterized.<sup>2</sup> A more comprehensive understanding of genetic risk factors could facilitate early identification and motivate the development of proactive and personalized interventions. Classic galactosemia (CG), described in more detail below, is an example of a

condition of genetic origin that is associated with a known high risk for severe speech and language difficulties.

## Speech-language pathology as a potential field for genomics translations

One group of professionally trained service providers with the potential for impactful genomics translations are speech-language pathologists (SLPs). SLPs specialize in assessing and treating disorders of spoken and written communication. As outlined below, these disorders are common, burdensome, and costly. The fact that they have genetic components in many cases motivates investigating the feasibility of implementing principles of precision medicine in the field of speech-language pathology.

Disorders of spoken and written language in childhood take different forms. Speech sound disorders (SSDs) interfere with a child's ability to produce speech sounds accurately, which can make it difficult for others to understand what the child intends to say. Common examples are substituting [w] for/r/, substituting sounds produced in the front of the mouth ([t, d, n]) for those made in the back of the mouth ([k, g, ŋ/]), and leaving off consonants at the ends of words or as part of a consonant cluster. Approximately 4% of young school-aged children in the US have SSD.<sup>3</sup> One of the most severe forms of SSD is childhood apraxia of speech (CAS), estimated to occur

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in 0.1%–0.2% of children in the United States.<sup>4</sup> CAS interferes with transducing the intention to speak into precisely timed articulatory movements, a process referred to as motor planning. CAS is characterized by small consonant inventories, inconsistent speech errors, and speech that is highly unintelligible.<sup>5–7</sup> Fine and gross motor disorganization is often seen in children with CAS.<sup>8,9</sup> Developmental language disorder (DLD) can have expressive and receptive components, as it is characterized by difficulty combining words into sentences, difficulty comprehending what others say, and/or having a small vocabulary. In the US, approximately 7%–8% of young school-aged children have DLD.<sup>10</sup> As outlined below, difficulties with motor planning, similar to those exhibited by children with CAS, and expressive language delays are common challenges for individuals with CG.<sup>11–13</sup> Dyslexia interferes with learning to read and spell words despite access to instruction. It is diagnosed in 3%–7% of children in the US.<sup>14</sup> All three of these disorders can occur in primary form, in combination with each other, and/or as part of a syndrome such as autism spectrum disorder, Rett syndrome, trisomy 21, and developmental coordination disorder.

Children with disorders of spoken or written language pay a heavy toll. SSDs are associated with the frustration of not being understood,<sup>15</sup> negative perceptions and bullying by peers,<sup>16–19</sup> educational disadvantages,<sup>20–25</sup> and, if left untreated or undertreated, social and work-related difficulties in adulthood.<sup>26–28</sup> Treatment is lengthy and costly.<sup>29–31</sup> Similarly, children with DLD are at risk for educational and social disadvantages<sup>32</sup> and increased health costs.<sup>33</sup> Despite long and intense treatment, dyslexia can persist into adulthood.<sup>34,35</sup> This has limiting and negative effects on an individual's choice of occupation, leading to lowered employment achievement levels.<sup>36</sup>

Whether in their primary or syndromic forms, disorders of spoken and written language can be influenced by genetic changes. These changes are less well understood in the primary forms of SSD, DLD, and dyslexia, compared with the syndromic forms. As outlined in recent reviews and studies,<sup>37–41</sup> the etiology is heterogeneous, and non-syndromic candidate genes include *FOXP2* (MIM: 605317), *DCDC2* (MIM: 605755), *ROBO1* (MIM: 602430), *BCL11A* (MIM: 606557), and many more. It is thought that, to cause characteristic traits of SSD, DLD, and/or dyslexia, variants must occur in genes that are expressed in the early developing brain.<sup>42</sup> A new body of literature describes the role of the cerebellum in activities involving spoken and written language.<sup>43,44</sup> We and others hypothesize that disruptions in genes expressed in the early developing cerebellum cause difficulty with those aspects of spoken and written language that are highly dependent on cerebellar functions such as processing information sequentially, and that accompanying signs can include fine and gross motor discoordination due to more global cerebellar impairment.<sup>8,9,45–48</sup>

In conventional clinical management, therapy usually is implemented using behavioral techniques, where treatment goals are measurable behavioral outcomes. Therapy directly addresses the areas of need as observed with standardized testing, such as working on speech sound accuracy, vocabulary knowledge, or spelling skills. For each of these treatment areas, there may be many different treatment approaches. For instance, a child with SSD may receive treatment based on principles of motor learning, motor coordination, phonological awareness, and/or biofeedback. Generally, whether a given treatment approach can be considered effective is based on clinical trials designed to demonstrate average improvement, compared with untreated controls, a scenario prone to ignore individual variability within the treatment group.

Another important limitation of conventional clinical management is the fact that disorders of spoken and written language cannot be diagnosed and treated until children are old enough to exhibit signs and symptoms, typically not before age 2 or 3 years for spoken language disorders and not before 6 years for written language disorders, when children enter school and struggle with reading and spelling despite adequate instruction. Whether these disorders can be prevented is largely unknown, because their emergence cannot be reliably predicted in most cases.

A thorough understanding of genotype-phenotype associations could pave the way for novel approaches to clinical management, informed by the principles of precision medicine. A genetic risk determined at birth would make it possible to predict difficulties with speech and language long before the child is old enough to exhibit any signs or symptoms. This would allow for the development of preventative strategies. Knowledge of genotype-phenotype associations could also facilitate a more personalized approach to intervention, for instance focusing on cerebellar functions in children who carry disruptions in genes expressed in the early developing cerebellum. The relevance of this potential is beginning to be recognized by SLPs. In a recent survey, SLPs were aware of the emerging relevance of genetics in their field and indicated that additional training in genetics would be beneficial.<sup>49</sup>

To summarize, given the high prevalence levels of disorders of spoken and written language and the heavy burden they impose, a precision-based approach, if successful, could have a major transforming impact. The standard of care could shift from remediative and deficit-based approaches to personalized and proactive approaches.

### **Leveraging knowledge of genotype-phenotype association in CG toward preventing severe speech and language disorder**

Here, we describe a proof-of-concept study of a proactive and personalized speech and language intervention for infants with a newborn diagnosis of CG. Children with CG have a recessively inherited inborn error of metabolism characterized by defective conversion of galactose to

glucose due to a near absence of the enzyme galactose-1-phosphate uridyl transferase. This absence is caused by mutations in the *GALT* gene (OMIM: 606999). The most common genotype is homozygous Q188R, which is associated with the most severe health impairments.<sup>11</sup> CG is relatively rare, with annual incidence rates in the US ranging from 1/30,000 to 1/60,000,<sup>50</sup> whereas the incidence rate among individuals of Irish descent is higher, at 1/16,000.<sup>51</sup>

Despite early detection and strict adherence to lactose-free/galactose-restricted diets,<sup>52–54</sup> children with CG are at very high risk not only for fine and gross motor deficits and learning disabilities<sup>55–57</sup> but also for difficulty learning to produce speech sounds,<sup>13</sup> especially the CAS form of SSD,<sup>5,58–60</sup> and for difficulty with language.<sup>61–66</sup> It is estimated that 40%–85% of children born with CG will develop speech disorders,<sup>66–68</sup> compared with 4% of young school-aged children in the US.<sup>3</sup> CAS is diagnosed in 24%–63% of children with CG,<sup>5,58,66,69</sup> compared with 0.1%–0.2% of children generally.<sup>4</sup> The fact that the cerebellum has been implicated in CG<sup>70,71</sup> may explain the confluence of fine and gross motor delays and CAS. Disordered language is seen in 50%–78% of children with CG,<sup>65,66,68</sup> compared with 7%–10% of children generally.<sup>10</sup> Regarding language development, comprehension is affected less by CG than expression<sup>72,73</sup>; mainly, children with CG who have cognitive delays tend to also have delays in language comprehension.<sup>65</sup> Even at the earliest stages, there are some red flags for difficulties with speech and language: many children with CG do not meet cooing and babbling milestones,<sup>74–76</sup> and they are late in producing their first words. Their trajectory includes slow vocabulary growth, highly inaccurate speech sound productions, and difficulty producing sentences.<sup>61,65</sup> In many cases, struggles with verbal communication persist into adulthood, leading to diminished quality of life regarding social interactions.<sup>77</sup> Preventative measures are not available; assessments and deficit-based treatment are usually not initiated until ages 2–3 years.<sup>56,78</sup> Because CG is diagnosed via newborn screening, the known genotype-phenotype association can be uniquely leveraged to investigate the effectiveness of a novel proactive approach. The present work is a description and proof of concept of a novel approach to preventative treatment in a specific, at-risk population to demonstrate an end-to-end intervention model.

## Participants and methods

Babble Boot Camp (BBC) is a proactive intervention for infants with CG. It is currently undergoing a clinical trial funded by the National Institutes of Health (5 R01 HD098253). The intervention is approved by the Institutional Review Board at Arizona State University. Parents gave written permission for their infants to participate in the study, and they gave written consent for their

own participation. The clinical trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) under NCT03838016 and at Open Science Framework under <https://osf.io/sy3en/>.

Inclusionary criteria for participants with CG are a medical diagnosis of classic galactosemia at birth, confirmed with genotyping, and absence of any other sensory, chromosomal, or medical condition that could confound the results. The same criteria apply to the typical controls with the exception that presence of CG is excluded. Age of entry into the study is 2–6 months. The intervention ends when the children turn 24 months old. Note that the intervention is completed before children would typically qualify for conventional assessments and start treatment. Annual follow-up testing of speech, language, and motor skills is conducted at child ages 30, 42, and 54 months.

Families are randomized into two treatment groups. The Talk Time First group receives the speech and language intervention throughout the intervention phase, whereas the Motor Milestones First group begins with an intervention focusing on fine and gross motor skills, then switches to the speech and language intervention at age 15 months. These two intervention groups were designed to evaluate the effects of the earliest speech and language activities as well as the effects of the early motor intervention. Pediatric SLPs and occupational therapists implement the intervention via parent training using a “teach, model, coach, review” model.<sup>79</sup> The element of teaching includes explaining the rationale for a given intervention strategy and providing examples. The SLP models intervention strategies and coaches the parents by giving feedback on their implementation of the strategy. Finally, the SLP and the parents review the strategies together in their sessions and decide on next steps. Key principles of treatment include the following: the intervention and follow-up testing are conducted entirely in telehealth mode using Health Insurance Portability and Accountability Act (HIPAA)-compliant software. Parents meet regularly with their clinician to discuss the child’s current skill levels and decide together which skill will be targeted next. During the meeting, child progress is evaluated on the basis of two short home videos that parents provide prior to the meeting. All children proceed through therapy at their own pace, consistent with a highly personalized framework. The activities and routines are selected such that they are just beyond the child’s current skill level so that the child can master them with minimal and fading levels of parent support (“zone of proximal development”<sup>80</sup>).

This report focuses only on the speech and language intervention. Examples of treatment targets in the parent training include, in somewhat chronological order, increasing vocalization rates, stimulating babble frequency and complexity, building receptive and expressive vocabulary size, increasing sentence complexity, and increasing discourse skills. Implementation fidelity checks are conducted regarding the SLP’s training sessions with the parents by scoring the session recordings for the presence of

required components (teach, model, coach, review<sup>79</sup>). Parental implementation fidelity of the routines and activities is also checked using parent home videos for accurate implementation and also by tracking parents' compliance (attendance of the meetings, sending home videos).

As previously described,<sup>72,73</sup> progress is monitored closely throughout the intervention phase (<6 to 24 months) in multiple ways. Once monthly, parents create a day-long audio recording using the Language Environment Analysis (LENA) recording system (LENA Research Foundation, Boulder, CO). From these recordings, the three 5-min segments with highest child vocalization rates are exported and analyzed for measures of consonant and vowel complexity in babble (mean babbling level [MBL]<sup>81</sup>) and word productions (syllable structure level [SSL]<sup>82</sup>). Parents complete questionnaires about the child's motor, social-communicative, and problem solving skills using the Ages and Stages Questionnaires 3.<sup>83</sup> Receptive and expressive language skills are captured with the MacArthur-Bates Communicative Development Inventories 2 (MBCDI-2).<sup>84</sup> At each of the three follow-up assessments, standardized measures of speech production skills (Goldman-Fristoe Test of Articulation 3 [GFTA-3])<sup>85</sup> and language comprehension and formulation (Preschool Language Scales 5 [PLS-5])<sup>86</sup> are administered, and, at the last of these assessments, a measure of cognitive development, the Kaufman Brief Intelligence Test 2 (KBIT-2),<sup>87</sup> is added. Motor development is monitored during the intervention phase and at follow-up using the Developmental Assessment of Young Children 2 (DAYC-2)<sup>88</sup> and the Sensory Profile 2.<sup>89</sup>

To date, 44 children with CG and their parents are enrolled in BBC. All children with CG in the study are strictly adhering to a galactose-restricted diet. Over half of the children are homozygous for the Q188R variant in the *GALT* gene. A control group consisting of 29 infants with typical development participates in the close monitoring components and follow-up assessments. An additional control group of children with CG who are already too old for BBC consists of toddlers and preschoolers ages 2 to 4.5 years who only participate in the follow-up assessments. These assessments provide a basis of comparison for treatment effects in the Talk Time First and untreated control groups, whereas the Motor Milestones First group was started later and none of the children in that group were old enough for the follow-up assessments at the time of this writing. [Table 1](#) summarizes the current participant groups by racial and ethnic descriptors. Note that the high proportion of non-Hispanic whites among the participants with CG likely reflects the fact that CG is most prevalent among individuals of Irish descent.

In addition to these enrolled participants, anonymized data from 11 children (five boys, six girls) with CG, ages 2 to 7 years (mean = 2.5 years, SD = 1.5), all homozygous for the Q188R variant, from the National Centre for Inherited Metabolic Disorders, Children's Health Ireland at Temple Street, Dublin (Ireland), were included for purposes

of comparing the language status of the study participants at follow-up with additional children who received standard treatment according to current best practice. The Dublin-based study has been approved by the Ethics and Research Committee, Children's Health Ireland at Temple Street in Dublin, Ireland (21/14.041), and written informed consent has been obtained. The registry does not contain standardized speech and language test scores in all cases. Instead, language skills were annotated in a brief narrative. No speech data were available for these children. The specific developmental language information provided by the National Centre for Inherited Metabolic Disorders was mapped onto the PLS-5 using a consensus process by the BBC assessment team, confirming the prevalence estimate of expressive language disorder diagnoses. No deficits in receptive language were noted, consistent with previous observations that mainly expressive language is affected by CG.<sup>65,72,73</sup> Of the 11 children, five (45.4%) were flagged as having an expressive language delay. The proportion of children with language delays is in line with data reported elsewhere for older children regarding language delays.<sup>65,66,68</sup>

The following methods were used to assess early speech skills at baseline and at subsequent evaluations: We report on one measure collected during the intervention phase that allows comparisons among the treated children as part of this study, children with CG not yet receiving this intervention who receive standard care, and typical children. The MBL score reflects the level of babble sophistication in terms of consonant and vowel content. Three 5-min segments with the highest concentration of child vocalizations are extracted from the day-long LENA recording and child utterances are transcribed into the International Phonetic Alphabet. Transcriptions are scored according to the MBL criteria,<sup>81</sup> where scores range from 1 (most basic babble utterance; e.g., only one vowel or a consonant-vowel combination where the consonant is of the most rudimentary type, such as a glottal stop or glide) to 3 (most sophisticated; e.g., two or more different regular consonants plus at least one vowel). MBL levels are averaged for each child and month. We previously reported on MBL results in a smaller participant sample during ages 7 through 9 months.<sup>73</sup> For the purposes of this study, the average MBL score for ages 10 through 12 months was selected to allow comparisons among a larger sample of typical peers and children with CG who had, or had not yet, started the speech/language component of the BBC intervention.

Three post-intervention measures in this study are speech sound production accuracy as measured with the GFTA-3<sup>85</sup> and receptive and expressive language skills as measured with the Auditory Comprehension and Expressive Communication subtests of the PLS-5.<sup>86</sup> The GFTA-3 measures the accuracy of consonant productions in single words. Word productions are elicited with picture stimuli. All consonants of English are tested in all relevant word positions; e.g., /t/ in initial clusters ("brushing") and final

**Table 1. Participant group characteristics**

Participant group	CG earliest speech/ language intervention (<6 months to 24 months)	CG close monitoring only (<6 months to 24 months)	CG alternate motor intervention <6 months to 14 months, speech/ language intervention 15 months to 24 months)	Typical controls	CG untreated toddlers
# Children enrolled	24	1	22	29	6
White/non-Hispanic	23	1	16	14	6
White/Hispanic			2	3	
White/ethnicity not provided	1		2	3	
Black/non-Hispanic					
Black/Hispanic					
Asian/Non-Hispanic				2	
Asian Hispanic				1	
More than one race/non-Hispanic			2	3	
More than one race/Hispanic				1	
Race not provided, non-Hispanic				1	
Race not provided, Hispanic				1	
Completion status					
# Families completed treatment and/or close monitoring up to age 15 months	20	1	8	8	N/A
# Families completed treatment and/or close monitoring at 24 months	16	1	1	2	N/A
# Families completed follow-up testing at 30 months	13				3
# Families completed follow-up testing at 42 months	12	1			1
# Families completed follow-up testing at 54 months	5	1			

position (“door”). A raw error score is converted to a standard score using reference data for age and sex. The Auditory Comprehension subtest of the PLS-5 measures a child’s ability to understand words, concepts, word forms, grammatical structures, and inferences. The Expressive Communication subtest measures a child’s ability to name, describe, express quantity, produce appropriate prepositions and grammatical markers, and construct complete sentences. Standard scores are based on reference data by child age but not sex. We previously reported on these measures at a single time point.<sup>73</sup> In the meantime, these test scores were available for 13 treated and six untreated children with CG at one or more of the assessment age points.

## Results

### Babble complexity

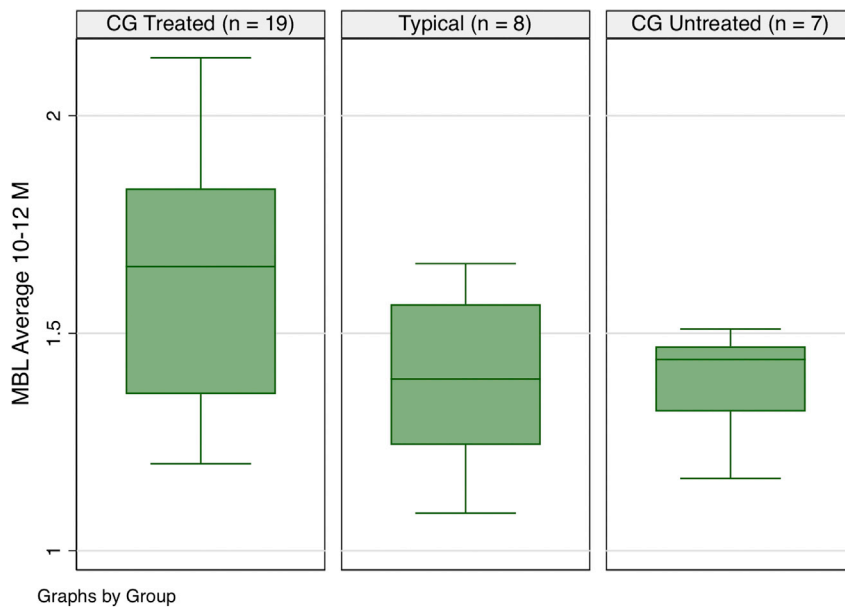
The MBL scores, where higher scores indicate better performance, averaged for ages 10 through 12 months, were 1.39 (SD = .21) for eight typical children, 1.39 (SD = .12) for seven children with CG who had not yet received the BBC intervention, and 1.62 (SD = .28) for 19 children

with CG who were receiving the intervention during this age bracket. Group differences were statistically significant overall ( $F = 3.59$ ,  $p = .0396$ ), with significant group differences between the treated and untreated group with CG ( $t = 2.02$ ,  $p = .0268$ ) and the treated group and typical controls ( $t = 2.00$ ,  $p = .0278$ ), but not the untreated group with CG and typical controls ( $t = .03$ ,  $p = .5119$ ). [Figure 1](#) shows boxplots of the MBL scores for the three groups.

### Speech and language assessments at post-intervention follow-up

Standardized testing of speech articulation skills using the GFTA-3 (population mean score = 100, SD = 15) ([Table 2](#)) showed that, at age 30 months, 12 of 13 treated children with CG (92%), all of whom had received the speech/language intervention since age <6 months, had skills within typical limits, with one child’s standard score of 70 falling below the conventional clinical cutoff standard score at 78 (–1.5 SD). One of three untreated enrolled controls with CG fell below that cutoff at that age. At age 42 months, 11 treated children with CG, all of whom had typical scores at 30 months, obtained typical scores again, whereas follow-up data for two treated children with CG were not yet available. Three untreated children with CG obtained





**Figure 1.** Mean babbling level scores for treated and untreated children with CG and typical controls at ages 10 through 12 months

a typical score and one untreated child with CG obtained a score far below typical limits. At age 54 months, four treated children with CG, all of whom had obtained typical scores at the two prior timepoints, obtained scores within typical levels again, whereas one untreated child with CG with a very low score at 42 months obtained an even lower score at age 54 months. One untreated child with CG obtained a typical score. Across all three test points, only one treated child obtained one low articulation score, whereas two of six untreated children obtained low articulation scores. Conservatively assuming a mean speech delay rate of 50% among the general population of children with CG,<sup>66-68</sup> finding only one of 13 children with a speech delay is statistically significant (chi square = 5.54,  $p = .019$ ).

Receptive language skills, as measured with the PLS-5 Auditory Comprehension subtest (population standard score = 100, SD = 15) (Table 2), showed that all children with CG regardless of treatment status obtained scores in the typical range at all available timepoints. Trends show a regression toward the mean between the first and subsequent assessments.

PLS-5 Expressive Communication scores (population standard score = 100, SD = 15) (Table 2) fell below typical limits for one untreated child with CG at both available timepoints (42 and 53 months) and another untreated child with CG at 54 months. Three untreated children with CG obtained typical scores at their only available time point (30 months). At all age points, all 13 treated children with CG scored in the typical range, although one score fell at the cutoff of 78. This is a statistically significant difference under the conservative assumption of 50% affectation rate in children with CG (chi square = 8.55,  $p = .003$ ).

In sum, one of 13 children treated with CG and three of six untreated controls with CG obtained a low articulation

and/or expressive language score. Table 2 details the results of post-treatment assessments, additionally with genotypes listed for each child. Note that, among the treated children, seven of 13 are homozygous for the Q188R variant, and the only low score, in this case for speech production, was obtained by one of them. Of the six untreated controls, three are homozygous for this variant, and two of these obtained low scores in speech and/or expressive language.

Finally, to investigate the predictive value of babble complexity on speech

and language skills later on, correlation coefficients were calculated between the MBL scores at 10 through 12 months and speech and language outcomes at 30 months. MBL and GFTA-3 scores approached statistical significance ( $r = .52$ ,  $p = .0678$ ). MBL was not significantly correlated with PLS-5 Expressive Communication or PLS-5 Auditory Comprehension subtest scores. GFTA-3 were correlated with PLS-5 Expressive Communication scores ( $r = .72$ ,  $p = .0052$ ) but not with PLS-5 Auditory Comprehension scores. The PLS-5 Expressive Communication subtest scores were correlated with the PLS-5 Auditory Comprehension subtest scores ( $r = .78$ ,  $p = .0016$ ). Figure 2 shows the scatterplot matrix of these measures.

## Discussion

Children with a newborn diagnosis of CG and their parents participated in BBC, a proactive clinical management program focused on precursor and early speech and language skills, during ages <6 to 24 months or, alternatively, during ages 15 to 24 months while completing an alternate motor intervention prior to age 15 months. At age 10 through 12 months, children with CG in the early speech and language intervention group showed more sophisticated babble skills, compared with the children with CG not yet treated with the BBC speech and language components, consistent with a beneficial effect of the intervention. The fact that the treated children even outpaced the typical controls suggests that the treatment provides a boost in babble skills. The fact that the untreated children with CG and typical controls did not differ in babble sophistication might indicate that babble sophistication is not primarily affected by CG. Similar results were previously reported for child ages 7 through 9 months<sup>73</sup>; the present results show that this trend continued at the next age interval at 10 through 12 months. It is possible

**Table 2. Standard scores from post-intervention assessments of speech sound production, receptive language, and expressive language, and, additionally, genotypes**

Group	ID	Genotype	GFTA-3			PLS-5 Aud Compr		PLS-5 Expr Comm			
			30 months	42 months	54 months	30 months	42 months	54 months	30 months	42 months	54 months
BBC	SLE_02	Q188R/Q188R	132	116	125	118	101	107	116	101	107
BBC	SLE_03	Q188R/Q188R	110	94	105	98	97	96	94	96	97
BBC	SLE_04	Q188R/Q344K	92	83	81	93	109	91	80	84	86
BBC	SLE_05	Q188R/Q344K	113	110	110	95	94	96	105	92	92
BBC	SLE_08	Q188R/Q188R	98	88		98	92		92	82	
BBC	SLE_09	Q188R/Q188R	96	114		95	94		94	90	
BBC	SLE_10	Q188R/Q188R	115	119		130	101		125	101	
BBC	SLE_11	Q188R/Q188R	101	112		101	101		105	101	
BBC	SLE_12	Q188R/Q188R	70 (BLN)			115			108		
BBC	SLE_13	Q188R/R258C	105	79		115	99		108	99	
BBC	SLE_14	Q188R/R328H	115	118		95	97		103	99	
BBC	SLE_15	Q188R/R148W	92	92		87	97		95	78	
BBC	SLE_16	L195P/H186Y	110			90			92		
Stand. care	CG_CTR1	Q188R/Q188R		47 (BLN)	40 (BLN)		92	87		66 (BLN)	60 (BLN)
Stand. care	CG_CTR2	Q188R/Y89D	92	95		104	101		111	92	
Stand. care	CG_CTR3	Q188R/H68P	85	96		107	97	90	97	90	
Stand. care	CG_CTR4	Q188R/L195P	76 (BLN)			84			95		
Stand. care	CG_CTR5	Q188R/Q188R			91			81			76 (BLN)
Stand. care	CG_CTR6	Q188R/Q188R		117			97			96	

BBC, Babble Boot Camp; Stand. care, standard care; GFTA-3, Goldman-Fristoe Test of Articulation 3; PLS-5, Preschool Language Scale 5; BLN, below normal levels; Aud Compr, Auditory Comprehension; Expr Comm, Expressive Communication. All standard scores based on population mean, 100, standard deviation, 15.

that the boost in babble skills provided precursor support for later speech skills, as the correlation between the MBL scores at age 10 through 12 months and the GFTA-3 scores at age 30 months approached significance. In typical children generally, a predictive association between early babble skills and later speech and language skills has been observed.<sup>81,90–92</sup> As more BBC data become available, the tentative benefit of babble treatment in children with CG will be disambiguated.

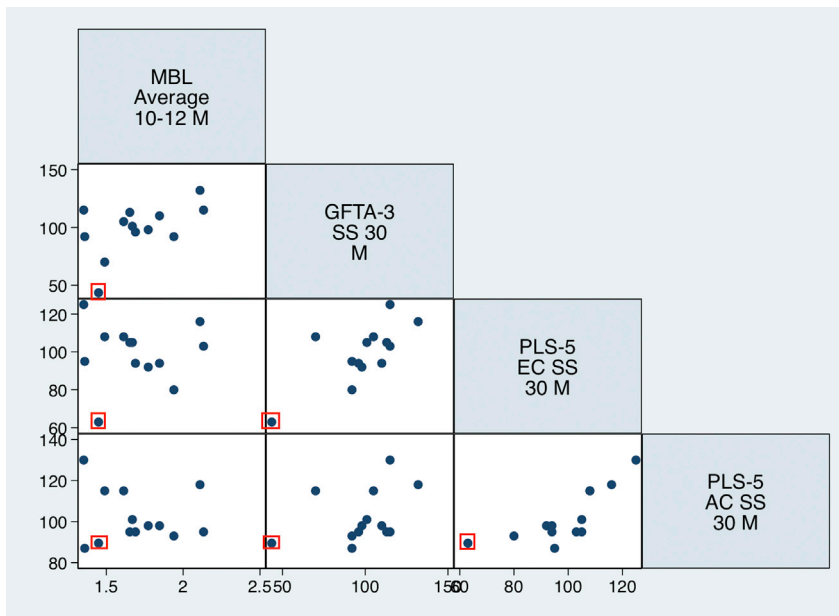
Follow-up testing showed that only one of 13 treated children with CG struggled with speech articulation as measured with the GFTA-3, compared with two of six untreated controls with CG. Given that 40%–85% of children with CG have SSDs in general,<sup>66–68</sup> this result is consistent with a beneficial treatment effect. For those treated children with CG who completed additional follow-up testing at ages 42 and/or 54 months, all results were within typical limits. This indicates that the typical speech skills observed at 30 months were maintained.

Consistent with previous observations<sup>65,72,73</sup> and the Irish comparison data, receptive language skills as measured with the Auditory Comprehension subtest of the PLS-5 were within typical levels for all children with CG, regardless of whether they had received the speech/

language intervention or not. Similar to the speech production outcomes, outcomes were maintained over multiple assessment timepoints. Language comprehension thus appears to be largely unaffected by CG.

In the area of expressive language, all 13 treated children with CG had typical scores at 30 months and only one had a marginal standard score of 78 at 42 months, whereas two of the six controls with CG obtained low scores. Again, given the expectation that 50%–78% of children with CG and 45% in the Irish comparison data have disordered language skills, these findings are consistent with beneficial effects on expressive language skills.

One control child with CG (code: CTR1) obtained low expressive language scores as measured with the Expressive Communication subtest of the PLS5, at both available timepoints (42 and 54 months). This was the same child who obtained low speech articulation scores at the same time points (Table 2). This child's profile fits that of the majority of children with CG who receive conventional treatment. In addition, he also produced some of the most rudimentary babble patterns at age 10 through 12 months (MBL = 1.45, cf. Figure 2). Conversely, one child treated with BBC (code: SLE\_02) obtained typical to high scores in the speech and language testing at follow-up. This child



**Figure 2. Scatterplot matrix of mean babbling scores at ages 10 through 12 months, Goldman-Fristoe Test of Articulation 3, and Preschool Language Scales 5 Expressive Communication and Auditory Comprehension subtests**

GFTA-3, Goldman-Fristoe Test of Articulation 3; PLS-5, Preschool Language Scale 5; BNL, below normal levels; Aud. Compr., auditory comprehension; Expr. Comm., expressive communication; box (□), child with CG who did not receive the intervention but provided continuous data from infancy (data at age 30 months are an estimate based on the mean from age 42 and 54 months).

also produced some of the most sophisticated babble patterns, as measured with the MBL at age 10 through 12 months (MBL = 2.1). It is possible that this child was among those children with CG who would not have developed severely disordered speech and language but whose communication skills received a boost through the intervention. Of note is the fact that both CTR1 and SLE\_02 are homozygous for the Q188R variant. Thus, the difference in communication skills between these two children may, at least in part, be a result of the BBC treatment.

We have shown how BBC is an example of translating principles of precision medicine into the world of speech-language pathology. Specifically, we leveraged knowledge of genotype-phenotype associations in CG toward both of the clinical strategies inherent in the precision medicine framework, prevention and personalized treatment. The newborn diagnosis of CG allowed us to select children with high predictable risk of severe speech and language disorders for a course of proactive intervention that focused on precursor and early communication skills. The principle of allowing all children to progress through the treatment at their own pace, addressing individual goals from week to week, is consistent with the personalized nature of treatment in the precision medicine framework.

Although encouraging, these findings are preliminary, as the clinical trial is still ongoing and the Talk Time First, Motor Milestones, and typical control groups will each continue to progress through all the various phases, with full data until age 54 months available for 25 children in each group over the next few years. The present data already suggest that, despite early newborn screening and immediate medical treatment, early speech and language intervention has a role to play in well-controlled children with CG, in addition to standard medical care. Future studies will yield more extensive findings, providing the basis for evaluating the BBC program as an evidence-based treatment option for in-

fants with a newborn diagnosis of CG, potentially replacing conventional deficit-based management approaches with proactive interventions as the new standard of care. Future studies will also evaluate the benefits of this management approach for other groups of infants at predictable risk for severely disordered speech and language. Identifying these other groups will be made possible by continued research efforts in the field of behavior genomics, where discovery of new genotype-phenotype associations in disorders of spoken and written language are an important focus.

## Data availability

Original data are available from the corresponding author at reasonable request.

## Web resources

OMIM.

<https://www.omim.org/>.

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## Declaration of interests

The authors declare no competing interests.



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