Prospective Longitudinal Studies of Infant Siblings of Children With Autism: Lessons Learned and Future Directions

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Objective: The objectives of this review are to highlight the impact of the first decade of high-risk (HR) infant sibling work in autism spectrum disorder (ASD) and to identify potential areas of translational focus for the next decade of research.

Method: A group of clinicians and researchers in ASD working both inside and outside of the HR design met on a regular basis to review the infant sibling research, and came to an agreement on areas that had changed clinical practice and areas that had the potential to change practice with further research. The group then outlined several methodological and translational challenges that must be addressed in the next decade of research if the field is to reach its potential.

Results: The review concluded that the HR design has yielded an understanding that ASD often, but not always, begins to emerge between 6 and 18 months, with early signs affecting social communication. Research using the HR design has also allowed a better understanding of the sibling recurrence risk (between 10% and 20%). Emerging areas of interest include the developmental trajectories of social communications skills in the early years, the expression of a milder phenotype in siblings not affected with ASD, and the possibility that early intervention with infant siblings may improve outcomes for those with ASD. Important challenges for the future include linking screening to intervention, collecting large sample sizes while ensuring cross-site reliability, and building in capacity for replication.

Conclusion: Although there are significant methodological and translational challenges for high-risk infant sibling research, the potential of this design to improve long-term outcomes of all children with ASD is substantial.

Key words: autism, longitudinal, sibling, development, opportunities

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Prospective longitudinal studies of infant siblings of children with autism spectrum disorder (ASD) have provided important insights into the emergence of the disorder. In this high-risk (HR) design, younger siblings of an older child with ASD are typically followed from the first year of postnatal life through to at least 36 months, the age at which ASD diagnosis is both highly reliable and stable.[1] Although the use of the HR design to study ASD is a relatively new approach, it has already led to major discoveries, including estimates of the recurrence risk for the disorder in first-degree relatives[2,3] and of trajectories of different phenotypes that constitute the disorder.

The first paper reporting results of the HR infant sibling design was published in 2012, with an increasing number of published reports through 2015. With the first decade of findings now published, a reflection on the early discoveries arising from the HR infant sibling design is presented herein, along with suggested directions for the next decade of research that emphasize translational potential. This review is meant to be a selective and high-level synthesis. It was written by both contributors and noncontributors to the HR-infant sibling literature so as to provide a balanced review of the research. More systematic reviews of findings are available elsewhere.[4-6] We begin by providing a historical background, then highlight 2 findings to illustrate the power of the HR infant sibling design to change clinical practice. Three areas are then highlighted in which emerging findings also have the potential to improve clinical practice with further research and replication. We conclude with 2 design limitations inherent in HR-infant sibling studies, along with a summary of key methodological and translational challenges that must be addressed if the HR infant sibling design is to meet its full potential in the coming decade.

HISTORICAL BACKGROUND

Studies of infant siblings of children with ASD were, in large part, motivated by 2 important findings. First, several decades of research had noted that ASD was a disorder that ran in families, and that siblings of probands with autism were at risk for developing the disorder themselves.[7] The HR design provided an opportunity to estimate the sibling risk more precisely and to explore the full range of variable expressivity of the risk genotype from a longitudinal perspective. Second, many studies had reported on the disconcerting time lag between parents' concern about the onset of the disorder (usually between 12 and 18 months)[8,9]

and the average age of diagnosis (usually between 4 and 6 years of age).[10] This time lag is associated with considerable parental distress during the search for a diagnosis.[11] ASD affects many children[10] and is associated with considerable social and economic cost.[12] There is widespread acknowledgment of the urgent need to increase knowledge about the earliest signs and symptoms of ASD to promote earlier detection, earlier intervention, and hopefully improved long-term outcomes. Recent evidence suggests that the beneficial effects of early intervention may diminish with age,[13-15] underscoring the importance of detection as early as possible. It was hoped that the HR design would provide new knowledge about early signs and symptoms of ASD to facilitate earlier diagnosis than is currently seen.

To increase knowledge about the emergence of ASD, researchers first used retrospective study designs in which data were obtained from home videotapes, medical records, and/or parent recall that focused on the early development of children already diagnosed with ASD. Studies of home videotapes of infants who later were diagnosed with ASD revealed that many of those infants displayed symptoms before or at age 12 months, including a failure to orient to name, reduced eye contact, pointing, and motor abnormalities.[16-19] Although retrospective studies generated important information about the early signs of ASD, limitations of this approach include recall bias that may affect parents' report of the onset and timing of symptom emergence. Parental recall may be influenced by many factors such as the number of previous children in the family, the time lag between the parent interview and the years being recollected, and general knowledge about child development. Furthermore, home videotapes prohibited the use of more experimental measures, such as neurophysiological and eye-tracking methods, to reveal more subtle patterns of atypical development, and could not describe patterns of developmental change (e.g., regressing, slowing, plateauing, accelerating). These limitations stimulated the implementation of longitudinal designs in which infants who were at genetic risk for ASD due to having an older sibling could be systematically followed. In the next section, an overview of some of the key findings to emerge from this HR infant sibling design that have informed clinical practice is provided.

HR INFANT SIBLING DESIGN REVEALS NEW FINDINGS THAT INFORM CLINICAL PRACTICE

Defining the Early Behavioral Markers of ASD

Some of the key initial questions that the HR infant sibling design addressed focused on the earliest age at which ASD can be reliably detected and the types of behavioral markers that may reliably differentiate siblings who eventually develop ASD from those who do not. Theoretical considerations and retrospective reports initially suggested that some of the core behavioral symptoms observed in infants with ASD, such as limited eye contact or lack of social smiling, would be present in the first year of life and would therefore enable identification of affected children earlier than previously possible. However, evidence from the infant sibling studies suggests that, on a group level, frank behavioral symptoms in the social-communication domain do not become pronounced until 12 months of age or even later.[17,18,20] Therefore, the presence of typical dyadic social-communicative behaviors such as good eye contact and socially directed smiling and vocalizations before age 12 months does not necessarily rule out the possibility of developing symptoms of ASD later on. Moreover, although it is plausible that HR siblings who are later diagnosed with ASD exhibit delays in, and atypical patterns of, social-communicative skills in the first year of life,[20,21] the deficits may be subtle and difficult to detect using existing observational methods.[22]

Two large multisite studies have focused on examining stability of early ASD diagnosis in infant siblings.[23,24] Ozonoff *et al.* examined the stability of clinical best estimate (CBE) diagnosis of ASD assigned at 18 and 24 months.[23] The study suggested that a diagnosis of ASD in an infant sibling at 18 or 24 months was extremely stable, but that many siblings who received a diagnosis at 36 months were not picked up earlier. This level of stability of the CBE diagnosis was comparable to that reported in clinic-referred samples.[25-27] In another large, multisite study, Chawarska *et al.*[24] focused more specifically on identification of behavioral signatures of ASD at 18 months. The researchers applied a decision tree learning algorithm to an array of behaviors recorded at 18 months. This analysis suggested that at 18 months, a large proportion of infant siblings who go on to develop ASD cannot be reliably identified. Among those who were identified correctly by the data mining approach, there were 3 subgroups of infants with ASD, each characterized by a different pattern of change in symptom severity over time. One of the groups was characterized by marked symptoms by 18 months that were maintained through 3 years. In the second group, relatively mild symptoms intensified by the age of 3 years, and in the third group, moderate level of symptoms was maintained from 18 to 36 months. Siblings with ASD who were missed at 18 months by expert clinicians or by the data mining algorithm showed not only lower levels of autism symptom severity but also significantly higher levels of verbal and nonverbal skills than children who were identified positively at 18 months.[24,28] Taken together, these studies suggested that around 40% of siblings with eventual ASD become symptomatic by 18 months, and in these children, stability of a diagnosis based on a comprehensive assessment is very high (93%). Based on these findings, toddlers who present with frank symptoms of ASD at 18 months should be referred for treatment, whereas the remaining siblings should be monitored. These findings also highlight the variability in the developmental trajectories of the affected children with familial risk factors and reinforce the need for monitoring development of all high-risk siblings over multiple time points in the first 3 years of life. This has important implications for screening protocols that target a single time point, and may

explain the low sensitivity of many of the current tools.[29,30] It also emphasizes the fact that clinicians monitoring infant siblings must be sensitive to the emergence of different risk markers at different time points if they wish to identify ASD as early as possible.

One of the key factors complicating diagnostic considerations in very young children with ASD is the marked phenotypic heterogeneity of syndrome expression. To address this question, Chawarska *et al.*[24] used the classification and regression trees algorithm to 30 Autism Diagnostic Observation Schedule–Generic items administered at 18 months. The study identified 2 combinations of features as particularly predictive of ASD: (1) poor eye contact combined with a paucity of communicative gestures and limited use of giving objects to share; and (2) intact eye contact paired with emerging repetitive behaviors and limited use of giving objects to others for requesting or sharing. High-risk siblings who exhibited either of the 2 combinations were 3 times more likely to be diagnosed with ASD than those who did not. Interestingly, affected children who exhibited the first combination had greater developmental delays compared to those who exhibited the second combination. The latter finding has important implications for the design of developmentally sensitive screening instruments for ASD, as it suggests that even within narrowly defined developmental epochs, a somewhat different combination of clinical features might be predictive of ASD outcome. Although all HR siblings should be monitored periodically throughout the first 3 years of life, the presence of either of these combinations of characteristics at 18 months should trigger consideration of a comprehensive diagnostic assessment. These findings also suggest that cognitive skills may modify the age of onset of the emergence of ASD; greater cognitive impairment is associated with earlier age of onset. Considering the highly variable timetable of symptom onset and complexity of early developmental trajectories in infants diagnosed with ASD, follow-up of these cohorts into school age will allow further elucidation of their range of outcomes, interactions between social vulnerability, and emerging comorbid disorders such as ADHD and anxiety.[31]

Another key finding to emerge from longitudinal studies of HR infant siblings is that it may be more beneficial to assess an infant's developmental trajectory instead of assessing different cross-sectional markers at different time points. For example, a slower growth in initiating joint attention (repeated at 8, 10, 12, 15, and 18 months) distinguished HR siblings with an ASD diagnosis from those without a diagnosis despite overall growth in this observational measure of referential communication.[32] Likewise, HR siblings with ASD outcomes are reported to have consistently higher levels of repetitive behaviors between 12 and 24 months than HR siblings without ASD at outcome.[33] This goes against the common clinical lore that repetitive behaviors emerge later than social-communication atypicalities and again has implications for the kinds of phenotypes that should be targeted in screening and surveillance.

These findings, as well as other studies,[34] indicate that models of symptom onset might be better captured by a multidimensional rather than a categorical approach, as it is likely that the departure from typical trajectories in specific domains may follow different patterns, take place during different developmental periods, and may be driven by different processes (e.g., decline in eye contact versus emergence of repetitive behaviors). While this framework awaits empirical verification and generalization to infants with ASD who do not have a family history, these findings inform clinical practice by sensitizing clinicians to the diversity of onset patterns across time and core areas of impairment.

Recurrence Risk Estimates for the Development of ASD in HR Siblings

Based on traditional studies of nuclear families, the sibling recurrence risk of ASD in siblings of older ASD probands was estimated at anywhere between 3% and 10%, depending on whether account was taken of the effect of "stoppage rules" on family size.[35] In the absence of sampling bias or differential attrition (see next paragraph), the HR design appears ideally suited to understanding true sibling recurrence risk (SRR) in first-degree relatives of individuals with ASD, information that is essential for genetic counseling. By prospectively following cohorts of later-born siblings, the SRR can be independently confirmed using standardized tools and corrected for stoppage. A seminal 2011 study[2] and expansion to 1,241 HR siblings in 2015[3] indicated a 19.5% recurrence rate with some variability in estimates across 15 different study sites.[2] Recurrence was the highest (~27%) in males and in children who had more than 1 older sibling with a diagnosis (~32%). Sex of the older sibling did not predict ASD in the sibling. These findings generated much interest and encouraged clinicians to closely monitor HR siblings for early signs and symptoms of ASD, even in the absence of signs before 12 months of age.

We now have high-quality data on sibling recurrence risk in community-based samples from recent, methodologically rigorous studies, as well. In a large epidemiologically based sample, the recurrence in full siblings was reported to be closer to 7% to 10%.[36-38] The reason for the disparity in recurrence risk estimates between the community-based and high-risk samples may be the use of a retrospective design in community-based studies and potential inflation of sibling recurrence risk in HR studies. Parents who volunteer to participate in infant sibling studies may do so because of concerns about their child's development, and may over-report symptoms in the infant sibling because they are sensitized to the presentation of ASD through their older child. In addition, families of HR siblings with no developmental concerns may drop out of these HR studies at a greater rate than families of children with concerns. Nevertheless, SRR even in the range of 10% to 20% supports the need for vigorous surveillance of infant siblings of children with ASD as a matter of "best practice." Importantly, however, information about SRR from either large community or HR studies should not be used in isolation for genetic

counseling. The recurrence risk for an individual family will depend on the nature of the genetic and/or environmental factors that led to the first child developing ASD, as well as family history and the sex of the child. Given the remarkable genetic heterogeneity in ASD, the SRR is expected to vary widely across families. The use of family history, supplemented by DNA microarray testing and exome or whole genome sequencing, has the potential to greatly help inform genetic counseling for HR families by specifying, for example, whether the putative causal genetic variant in the older child with ASD is de novo or inherited.[39,40]

EMERGING AREAS OF INTEREST STEMMING FROM HR INFANT STUDIES

The following 3 sections outline emerging areas of interest that also have the potential to transform clinical practice if the findings can be replicated using larger sample sizes.

Neurobehavioral, Neurophysiological, and Neuroanatomical Studies in the First Year of Life

A central strength of the high-risk sibling design is the potential acquisition of longitudinal neurobehavioral, physiological, and neuroanatomical data to chart the developmental dynamics of ASD in the first 12 months.[6] Jones and Klin,[41] for example, measured visual fixation to the eyes and body of a socially engaging woman among 25 typically developing low-risk and 10 high-risk boys later diagnosed with ASD. Compared to low-risk infants, infants later diagnosed with ASD exhibited increasing fixation of the model's body and decreasing fixation of her eyes between 2 and 6 months. Monthly changes in fixation levels (rather than absolute levels at a given month) resulted in maximum discrimination of these groups, suggesting that developmental change in the "salience" of a social stimulus provides a promising avenue for investigation of early trajectories predicting outcome. Another early atypical pattern of visual attention associated with later ASD diagnosis is the ability to flexibly disengage attention. Elsabbagh *et al.*[42] found that, between 7 and 14 months, infant siblings who were diagnosed with ASD at 36 months failed to show the increases in the speed and flexibility of disengagement of attention from ongoing stimuli observed in controls.[43] Based on 2 different free-viewing eye-tracking tasks, Chawarska *et al.*[44] and Shic *et al.*[45] reported that compared to high-risk siblings without ASD and compared to low-risk controls, 6-month-old siblings who later develop ASD exhibit atypical regulation of attention to complex social scenes and lesser attention to faces. A key finding was that the attentional patterns observed during the prodromal stages of the disorder in high-risk siblings were similar to those observed in clinic-referred samples of young children with ASD.[46-49]

Neuroanatomical and neurophysiological studies have also yielded new insights into early differences in brain anatomy and function of infant siblings. Based on a large, multisite, prospective study of infant siblings, Wolff *et al.*[50] reported that infants who exhibited signs of ASD at 24 months showed decreased growth in fractional anisotropy, an index of the directedness of cortical fibers. The importance of a longitudinal approach to development was underscored by the changing pattern of brain structure findings. HR infants with ASD outcomes showed higher levels of fractional anisotropy at 6 months, similar levels at 12 months, and lower levels at 24 months compared to infants without ASD outcomes. A number of studies using electrophysiological measures to study early brain activity in HR infants reveal early differences in neural sensitivity to social stimuli and atypical patterns of functional connectivity. Elsabbagh *et al.*[51] found that event-related brain potential responses to visual stimuli involving dynamic eye gaze shifts were sensitive indicators of later development of ASD. In another study, 14-month-old HR infants who later developed ASD showed a pattern of electroencephalogram (EEG) hyperconnectivity.[52]

Despite the suitability of longitudinal modeling to the HR sibling design, repeated measurements of key neurobehavioral markers are not always a focus of HR research in ASD, nor are such measurements consistently analyzed in a fashion that documents dynamics in the trajectories of these mechanisms. Multilevel, growth curve, and other similar approaches that document changes with age in characteristics linked to ASD outcome can help the field to determine whether the development of such neurobehavioral markers is delayed or chronically depressed in children progressing toward an ASD diagnosis. Research with these types of designs is necessary before such markers can be considered for possible translation into clinically relevant measures that are testable for use in screening over time.

Despite their various limitations, the studies begin to converge on several "signals" manifesting during the prodromal stages of the disorder. These signals include neurobehavioral and neurophysiological indices of attentional processing as well as atypical brain development in infancy. It is up to the new generation of studies on high-risk siblings to capitalize on the findings from early infant siblings, to build tasks capable of more effective separation of the affected and unaffected individuals, and to correlate these findings with emerging behavioral markers of ASD. Importantly, such studies have great potential to inform about which areas of vulnerability are primary in ASD and which are highly consequential for identification of novel treatment targets.

Characterization of HR Infant Siblings not Diagnosed With ASD

To date, several HR infant sibling studies have provided important new evidence on the developmental challenges seen in siblings who do not go on to develop ASD by 36 months. For example, Landa *et al.*[34] described a subgroup of siblings exhibiting language and/or social delays who did not meet criteria for ASD at age 3. Messinger *et al.* and the Baby Siblings Research Consortium (BSRC)[53] identified 2 subgroups of siblings without ASD facing challenges: 1 group with relatively high (but still subthreshold) levels of

autistic symptoms but without any accompanying language or cognitive delays, and another group with the reverse profile, that is, low levels of autistic symptoms but notable language and cognitive delays. Another study of 719 infants at risk suggested that almost 25% of high-risk siblings had atypical outcomes at the age of 3 years.[24] Several studies have suggested that this group begins to show atypical behavioral features besides ASD as early as at 12 months.[21,54,55] For instance, Georgiades *et al.*[54] reported that roughly 20% of siblings with elevated autistic-like traits at 12 months showed increased social-communication impairment, cognitive deficits, and internalizing problems by age 3 years but did not meet criteria for ASD.

These studies suggest that there is substantial variability in terms of both type and severity of other developmental challenges seen in a proportion of HR siblings without ASD. If these other developmental challenges prove stable, there is a strong argument that studies are needed that test the effectiveness of monitoring and potentially supporting these children during early childhood. These findings also emphasize the remarkable variability of expression associated with ASD in these families.[34,56,57] The true boundary between the phenotypes associated with ASD and those that fall outside the ASD category has yet to be clearly defined. A closer investigation of the individual and family factors that are associated with each sibling's position on the broader autism phenotype–ASD boundary is needed. This may enhance our efforts to identify the potential mechanisms involved in determining the developmental pathways and outcomes of all infant siblings of probands with ASD.

Interventions for Infants at Risk for ASD

An important question is whether early intervention, even before a diagnosis is given, could optimize outcomes for those infant siblings at risk for ASD or other developmental challenges. Research addressing this issue is currently underway, most often using a caregiver-implemented intervention model.[58-60] Results of these uncontrolled studies were promising enough to justify randomized control trials currently underway, 1 of which has now been published. Green *et al.* conducted a 2-site, 2-arm, assessor-blinded, randomized controlled trial that used a video-based feedback program to promote infant communication in high-risk siblings 7–10 months of age.[60] The primary outcome was a change in infant attentiveness to parent. Secondary analyses indicated that the intervention was associated with reduced autism-risk behaviors and improved parent-rated infant adaptive function. Interestingly, there was an unexpected finding of either no effect or a slightly negative effect on early language measures.[59] More clinical trials with larger sample sizes and longer follow-up are needed to help determine when exactly interventions should be initiated. Finally, potential moderators and mediators of treatment response need to be identified to maximize treatment effect. Inclusion of such variables will also necessitate larger sample sizes, which carry their own risk in terms of reliability of diagnosis (see Discussion).

LIMITATIONS OF THE HR INFANT SIBLING DESIGN IN ASD

Despite the clear advantages of focusing on prospective assessments of the development of siblings of children with ASD, 2 important limitations were recognized early on. The first is the extent to which findings derived from the siblings who developed ASD are generalizable to individuals with ASD sampled from the general population of families seeking clinical services. Most individuals with ASD do not have older siblings with the disorder. This family risk factor, or the experience of living in a family with a child with ASD, might have influenced sampling of families or the measurement of the early presentation of the sibling in some unknown way.

The second limitation (common to many longitudinal studies) is the extent to which intense monitoring and evaluation of the development of the sibling (often with large batteries of assessment tools and questionnaires every 6 months from birth to age 3 years) might influence the natural history of the "high risk" status. For example, infants exposed to repeated assessments may learn from these novel experiences, parents may learn new ways to interact with their children by observing the assessments conducted by a trained professional, or the very early detection of delays may result in enrollment in very early intervention, all of which could influence the child's developmental trajectory. Therefore, findings from the infant siblings design need to be considered in the context of other designs that also address early emergence of ASD symptoms in both population-based longitudinal cohorts, and those that define risk status in other ways (such as low birthweight or certain single gene disorders).

ISSUES INVOLVED IN TRANSLATING FINDINGS FROM THE HR DESIGN INTO PRACTICE

One of the main goals of the infant sibling research program is to provide data that can be used to find the lowest age at which children might receive a diagnosis of ASD and enter into early intervention programs. Developing screening tools is an important first step in such an effort. However, this is not a simple task. Translation of findings from infant sibling research into clinically useful screening tools requires a thoughtful stepwise process. The "first generation" of early screening tools for ASD used parent questionnaires[61,62] and direct observation tools[63] and were based on findings from studies that compared children with ASD to typically developing children and children with non-ASD developmental delays. In general, the sensitivity (the proportion of "true" cases of ASD identified by the tool) at 12 to 24 months of age was too low,[64,65] has necessitated updates to screeners,[66] and may reflect the fact that the markers are based on findings from infants who are diagnosed somewhat later.[67] A new generation of screening tools may be needed that captures developmental trajectories or operates within narrowly defined developmental periods and that is calibrated to what ASD

might look like within very specific developmental epochs.[61,67]

Studies that facilitate the translation of data derived from HR infant sibling research must grapple with methods that minimize both time and training to administer the screening tool to maximize feasibility but still capture the developmental changes in trajectories of skills that may be most discriminatory. These studies must not only develop new screening tools that incorporate findings from the HR studies but also identify the settings and group(s) of children with ASD to be screened (i.e., only infant siblings or the general population) and then conduct appropriate predictive validity studies to ensure that misclassification is minimized.

When assessing screening tools for clinical use, it is necessary to shift from estimating the strength of an association (through calculation of effect sizes and odds ratios) to estimating positive predictive value (PPV, true identified cases divided by all identified cases) and negative predictive value (NPV, true noncases divided by the number of nonidentified cases). Several studies have reported impressive associations between predictor variables taken at 12 to 18 months of age and later diagnosis at 36 months of age.[18,68,69] Yet we are aware of only a few HR infant sibling studies that have reported PPVs as opposed to effect sizes or risk ratios.[70-72]

If PPV becomes an important metric to assess the translational impact of an early screening tool, then the issue of generalizability of findings from the infant siblings sample to the general population of children with ASD becomes paramount. Sensitivity and specificity of a screening panel may be generalized between families in which there is already a child with ASD versus those without a sibling with ASD, as long as the clinical features of the ASD presentation are similar. On the other hand, PPV is profoundly influenced by the prevalence of the outcome (in this case, the diagnosis of ASD at 3 years of age). When prevalence of ASD goes down, as it will when generalizing from HR to LR families in the general population (i.e., from 20% to roughly 1%), the PPV also goes down, given the same specificity and sensitivity (the magnitude of the reduction is a function of specificity). The end result is that one can make no assumptions about the effectiveness of a screening panel (the PPV) across these 2 types of families.

Another very important consideration is that in public health policy, screening tools are seen as programs and are evaluated not only with respect to accuracy (sensitivity and specificity, PPV, NPV) but also as to whether they lead to better health outcomes compared to outcomes in individuals who are not screened or who screen negative.[73] Understood this way, randomized control trials (RCTs) with accompanying cost-effectiveness studies now play a significant role in the evaluation of screening tools used in public health. This can be accomplished by seeing whether individuals who are screened access services sooner than those who are not screened, or whether the intervention provided to individuals screened and identified earlier lead to better outcomes compared to outcomes in individuals not screened or not given the intervention. Similar to the concept of "number needed to treat,"[74] the "number needed to screen"[75] refers to the number of HR children who need to be screened to prevent 1 late ASD diagnosis or 1 poor outcome (e.g., lack of response to intervention). With this context in mind, the United States Preventative Services Task Force (USPSTF) recently issued a recommendation citing a need for evidence supporting the effectiveness of universal screening in affecting long-term outcomes.[76] The USPSTF cited the lack of randomized clinical trials as a challenge but nevertheless stressed the importance of such research. In fact, we are not aware of any screening tools in child and adolescent mental health or development that have been evaluated in this way, but it is now standard for screening for adult health (i.e., breast and prostate cancer, cardiovascular disease).[77] The need for RCTs evaluating the impact of screening on outcomes in ASD has generated considerable debate given the emerging evidence of the benefits of early intervention that may be implemented after as well as before a formal diagnosis.[60,78] What is not clear is whether early and multiple screening does in fact allow earlier access to treatment, whether this mediates better functional long-term outcomes for children with ASD, and whether the cost of screening in the "real world" is worth the benefit.

LOOKING TO THE FUTURE: THE NEED FOR LARGER SAMPLES AND HIGH-QUALITY DATA

Conducting studies at multiple sites has been an important and innovative aspect of much of the research using the HR infant sibling design. Individual study teams based at several sites are often nested within a larger collaboration that is based on a data-sharing agreement. These 2 approaches (multisite study teams and larger collaborations between teams based on agreements) differ with respect to the required use of common measures and the importance of similar training in the use of instruments. In the latter type of collaboration, support for standardization of judgments and methods has often occurred informally rather than formally. The expectation was that the diagnosis of ASD at age 3 years, which was the outcome classification gold standard, could be reliably ascertained across sites using standardized instruments and best-estimate clinical diagnoses. Although this may be true, concern has been expressed about the use of the subclassifications of ASD in other contexts (i.e., the Simons Simplex Collection, a 12-site genetics consortium).[79,80] Obtaining cross-site reliability on clinical "caseness" is different from more exploratory studies aimed at describing developmental trajectories inside and outside ASD (and within individuals genetically at risk). To maximize translational potential, the next generation of HR studies will require large sample sizes. In addition, if infant sibling researchers combine data from many sites, then efforts must be made to ensure that variables to be studied are collected in a reliable fashion and that summary values, such as clinical diagnosis, are either validated across sites or avoided completely through the use of dimensional measures. Even with these safeguards, it must be emphasized that findings across sites need to be replicated (often by

obtaining a "validation" or a "replication" sample). This will provide confidence that small sample size is not a "fatal flaw" in the high-risk design, as it is probably the most important contributor to the lack of reproducibility in psychological research.[81]

The HR infant sibling research design has been an extremely innovative and fruitful advance in ASD studies, providing many informative results and findings. We now have a much better idea of the emergence of early social-communication impairments in children 18 to 24 months of age, and a better understanding of the sibling recurrence risk in families with a child with ASD. There is real hope that these findings may eventually lead to better outcomes due to the possible efficacy of interventions delivered to those deemed to be at risk.

Building on this solid foundation is now the priority for the field. Where should we go? What should we study? Where should funding agencies put their scarce resources? Obtaining a better understanding of basic mechanisms, investigating developmental trajectories before 12 months, considering dimensions within broader phenotypes, and pushing outward into the links between screening and interventions are clear choices facing investigators and funding bodies. Clearly all of these research agendas need to be pursued, and combining study designs using large sample sizes may be a fruitful way to ensure that the HR design lives up to its full potential. Complementing the HR infant sibling design with other types of high-risk samples at very young ages (i.e., prematurity, Fragile X), testing screening instruments derived from HR studies, and linking those to interventions in the context of large sample sizes are exciting possible directions for the future. Designing studies that build in replication and cross-site reliability will be important for immediate translation into clinical practice. Furthermore, a greater focus on the potential for clinical translation at the start of a new decade of research may be a fruitful way to ensure that all children and families that live with ASD benefit from the full extent of these research efforts. &

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REFERENCES

1. Woolfenden S, Sarkozy V, Ridley G, Williams K. A systematic review of the diagnostic stability of autism spectrum disorder. Res Autism Spectr Disord. 2012;6:345-354.
2. Ozonoff S, Young GS, Carter A, *et al*. Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. Pediatrics. 2011; 128:e488-e495.
3. Messinger D, Young GS, Webb SJ, *et al*. Early sex differences are not autism-spcific: a Baby Siblings Research Consortium (BSRC) Study. Mol Autism. 2015;6:32.
4. Yirmiya N, Charman T. The prodrome of autism: early behavioral and biological signs, regression, peri-and post-natal development and genetics. J Child Psychol Psychiatry. 2010;51:432-458.
5. Chawarska K, Macari S, Volkmar F, Kim SH, Shic F. ASD in infants and toddlers. In: Volkmar FR, Paul R, Rogers SJ, Pelphrey KA, eds. Handbook of Autism and Pervasive Developmental Disorders. Hoboken, NJ: Wiley; 2014.
6. Jones EJ, Gliga T, Bedford R, Charman T, Johnson MH. Developmental pathways to autism: a review of prospective studies of infants at risk. Neurosci Biobehav Rev. 2014;39:1-33.
7. Smalley SL, Asarnow RF, Spence MA. Autism and genetics. A decade of research. Arch Gen Psychiatry. 1988;45:953-961.
8. Zwaigenbaum L, Bryson S, Garon N. Early identification of autism spectrum disorders. Behav Brain Res. 2013;251:133-146.
9. Young RL, Brewer N, Pattison C. Parental identification of early behavioural abnormalities in children with autistic disorder. Autism. 2003;7: 125-143.
10. Autism, Developmental Disabilities Monitoring Network Surveillance Year Principal I, Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. MMWR Surveill Summ. 2012;61:1-19.
11. Zuckerman KE, Lindly OJ, Sinche BK. Parental concerns, provider response, and timeliness of autism spectrum disorder diagnosis. J Pediatr. 2015;166:1431-1439.e1.
12. Buescher AV, Cidav Z, Knapp M, Mandell DS. Costs of autism spectrum disorders in the United Kingdom and the United States. JAMA Pediatr. 2014;168:721-728.
13. MacDonald R, Parry-Cruwys D, Dupere S, Ahearn W. Assessing progress and outcome of early intensive behavioral intervention for toddlers with autism. Res Dev Disabil. 2014;35:3632-3644.
14. Wong C, Odom SL, Hume K, *et al*. Evidence-based practices for children, youth and young adults with autism spectrum disorder. Chapel Hill, NC:

University of North Carolina: Frank Porter Graham Child Development Institute; 2014.
15. Weitlauf AS, McPheeters ML, Peters B, *et al*. Therapies for Children With Autism Spectrum Disorder: Behavioral Interventions Update. Rockville, MD: US Department of Health and Human Services; 2014.
16. Zwaigenbaum L, Bryson S, Rogers T, Roberts W, Brian J, Szatmari P. Behavioral manifestations of autism in the first year of life. Int J Devel Neurosci. 2005;23:143-152.
17. Landa RJ, Gross AL, Stuart EA, Faherty A. Developmental trajectories in children with and without autism spectrum disorders: the first 3 years. Child Dev. 2013;84:429-442.
18. Paul R, Fuerst Y, Ramsay G, Chawarska K, Klin A. Out of the mouths of babes: vocal production in infant siblings of children with ASD. J Child Psychol Psychiatry. 2011;52:588-598.
19. Werner E, Dawson G, Osterling J, Dinno N. Brief report: Recognition of autism spectrum disorder before one year of age: a retrospective study based on home videotapes. J Autism Dev Disord. 2000;30:157-162.
20. Ozonoff S, Iosif A, Baguio F, *et al*. A prospective study of the emergence of early behavioral signs of autism. J Am Acad Child Adolesc Psychiatry. 2010;49:258-268.
21. Macari SL, Campbell D, Gengoux GW, Saulnier CA, Klin AJ, Chawarska K. Predicting developmental status from 12 to 24 months in infants at risk for autism spectrum disorder: a preliminary report. J Autism Dev Disord. 2012;42:2636-2647.
22. Lambert-Brown BL, McDonald NM, Mattson WI, *et al*. Positive emotional engagement and autism risk. Devel Psychol. 2015;51:848-855.
23. Ozonoff S, Young GS, Landa RJ, *et al*. Diagnostic stability in young children at risk for autism spectrum disorder: a Baby Siblings Research Consortium Study. J Child Psychol Psychiatry. 2015;56:988-998.
24. Chawarska K, Shic F, Macari S, *et al*. 18-Month predictors of later outcomes in younger siblings of children with autism spectrum disorder: a Baby Siblings Research Consortium Study. J Am Acad Child Adolesc Psychiatry. 2014;53:1317-1327, e1311.
25. Guthrie W, Swineford LB, Nottke C, Wetherby AM. Early diagnosis of autism spectrum disorder: stability and change in clinical diagnosis and symptom presentation. J Child Psychol Psychiatry. 2013;54:582-590.
26. Chawarska K, Klin A, Paul R, Macari S, Volkmar F. A prospective study of toddlers with ASD: short-term diagnostic and cognitive outcomes. J Child Psychol Psychiatry. 2009;50:1235-1245.
27. Kim SH, Macari S, Koller J, Chawarska K. Examining the phenotypic heterogeneity of early autism spectrum disorder: subtypes and short-term outcomes. J Child Psychol Psychiatry. 2015 Aug 12. [Epub ahead of print] http://dx.doi.org/10.1111/jcpp.12448.
28. Ozonoff S, Young GS, Landa RJ, *et al*. Diagnostic stability in young children at risk for autism spectrum disorder: A Baby Siblings Research Consortium Study. J Child Psychol Psychiatry. 2015;56:988-998.
29. Charman T, Baird G, Simonoff E, *et al*. Testing two screening instruments for autism spectrum disorder in UK community child health services. Dev Med Child Neurol. 2015 Aug 25. http://dx.doi.org/10.1111/dmcn.12874.
30. Stenberg N, Bresnahan M, Gunnes N, *et al*. Identifying children with autism spectrum disorder at 18 months in a general population sample. Paediatr Perinat Epidemiol. 2014;28:255-262.
31. Miller M, Iosif AM, Young GS, *et al*. School-age outcomes of infants at risk for autism spectrum disorder [ePub ahead of print]. Autism Res. 2015 Oct 9. http://dx.doi.org10.1002/aur.1572.
32. Ibanez LV, Grantz CJ, Messinger DS. The Development of Referential Communication and Autism Symptomatology in High-Risk Infants. Infancy. 2013;18. http://dx.doi.org/10.1111/j.1532-7078.2012.00142.x.
33. Wolff JJ, Botteron KN, Dager SR, *et al*. Longitudinal patterns of repetitive behavior in toddlers with autism. J Child Psychol Psychiatry. 2014;55:945-953.
34. Landa RJ, Holman KC, Garrett-Mayer E. Social and communication development in toddlers with early and later diagnosis of autism spectrum disorders. Arch Gen Psychiatry. 2007;64:853-864.
35. Jones MB, Szatmari P. A risk-factor model of epistatic interaction, focusing on autism. Am J Med Genet. 2002;114:558-565.
36. Gronborg TK, Schendel DE, Parner ET. Recurrence of autism spectrum disorders in full- and half-siblings and trends over time: a population-based cohort study. JAMA Pediatr. 2013;167:947-953.
37. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. JAMA. 2014;311:1770-1777.
38. Risch N, Hoffmann TJ, Anderson M, Croen LA, Grether JK, Windham GC. Familial recurrence of autism spectrum disorder: evaluating genetic and environmental contributions. Am J Psychiatry. 2014;171:1206-1213.
39. Heil KM, Schaaf CP. The genetics of autism spectrum disorders—a guide for clinicians. Curr Psychiatry Rep. 2013;15:334.
40. Brandler WM, Sebat J. From de novo mutations to personalized therapeutic interventions in autism. Annu Rev Med. 2015;66:487-507.
41. Jones W, Klin A. Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. Nature. 2013;504:427-431.
42. Elsabbagh M, Fernandes J, Jane Webb S, *et al*. Disengagement of visual attention in infancy is associated with emerging autism in toddlerhood. Biol Psychiatry. 2013;74:189-194.
43. Fischer J, Koldewyn K, Jiang YV, Kanwisher N. Unimpaired attentional disengagement and social orienting in children with autism. Clin Psychol Sci. 2014;2:214-223.
44. Chawarska K, Macari S, Shic F. Decreased spontaneous attention to social scenes in 6-month-old infants later diagnosed with autism spectrum disorders. Biol Psychiatry. 2013;74:195-203.
45. Shic F, Macari S, Chawarska K. Speech disturbs face scanning in 6-month-old infants who develop autism spectrum disorder. Biol Psychiatry. 2014;75:231-237.
46. Campbell DJ, Shic F, Macari S, Chawarska K. Gaze response to dyadic bids at 2 years related to outcomes at 3 years in autism spectrum disorders: a subtyping analysis. J Autism Devel Disord. 2014;44:431-442.
47. Nakano T, Tanaka K, Endo Y, *et al*. Atypical gaze patterns in children and adults with autism spectrum disorders dissociated from developmental changes in gaze behaviour. Proc Biol Sci. 2010;277:2935-2943.
48. Falck-Ytter T, von Hofsten C. How special is social looking in ASD: a review. Prog Brain Res. 2011;189:209-222.
49. Jones W, Carr K, Klin A. Absence of preferential looking to the eyes of approaching adults predicts level of social disability in 2-year-old toddlers with autism spectrum disorder. Arch Gen Psychiatry. 2008;65:946-954.
50. Wolff JJ, Gu H, Gerig G, *et al*. Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. Am J Psychiatry. 2012;169:589-600.
51. Elsabbagh M, Mercure E, Hudry K, *et al*. Infant neural sensitivity to dynamic eye gaze is associated with later emerging autism. Curr Biol. 2012;22:338-342.
52. Orekhova EV, Elsabbagh M, Jones EJ, *et al*. EEG hyper-connectivity in high-risk infants is associated with later autism. J Neurodev Disord. 2014;6:40.
53. Messinger D, Young GS, Ozonoff S, *et al*. Beyond autism: a Baby Siblings Research Consortium Study of high-risk children at three years of age. J Am Acad Child Adolesc Psychiatry. 2013;52:300-308, e301.
54. Georgiades S, Szatmari P, Zwaigenbaum L, *et al*. A prospective study of autistic-like traits in unaffected siblings of probands with autism spectrum disorder. JAMA psychiatry. 2013;70:42-48.
55. Clifford SM, Hudry K, Elsabbagh M, Charman T, Johnson MH, Team B. Temperament in the first 2 years of life in infants at high-risk for autism spectrum disorders. J Autism Dev Disord. 2013;43:673-686.
56. Macari S, Campbell D, Gengoux G, Saulnier C, Klin A, Chawarska K. Predicting developmental status from 12 to 24 months in infants at risk for autism spectrum disorder: a preliminary report. J Autism Dev Disord. 2012;42:2636-2647.
57. Georgiades S, Szatmari P, Boyle M, *et al*. Investigating phenotypic heterogeneity in children with autism spectrum disorder: a factor mixture modeling approach. J Child Psychol Psychiatry. 2013;54:206-215.
58. Bradshaw J, Steiner AM, Gengoux G, Koegel LK. Feasibility and effectiveness of very early intervention for infants at-risk for autism spectrum disorder: a systematic review. J Autism Dev Disord. 2015;45:778-794.
59. Green J, Wan MW, Guiraud J, *et al*. Intervention for infants at risk of developing autism: a case series. J Autism Dev Disord. 2013;43:2502-2514.
60. Green J, Charman T, Pickles A, *et al*. Parent-mediated intervention versus no intervention for infants at high risk of autism: a parallel, single-blind, randomised trial. Lancet Psychiatry. 2015;2:133-140.
61. Rowberry J, Macari S, Chen G, *et al*. Screening for autism spectrum disorders in 12-month-old high-risk siblings by parental report. J Autism Dev Disord. 2015;45:221-229.
62. Robins D, Fein D, Barton M, Green J. The Modified Checklist for Autism in Toddlers: an initial study investigating the early detection of autism and pervasive developmental disorders. J Autism Dev Disord.. 2001;31:131-144.
63. Stone WL, Coonrod EE, Turner LM, Pozdol SL. Psychometric properties of the STAT for early autism screening. J Autism Dev Disord. 2004;34:691-701.
64. Pandey J, Verbalis A, Robins DL, *et al*. Screening for autism in older and younger toddlers with the Modified Checklist for Autism in Toddlers. Autism. 2008;12:513-535.

65. Robins DL, Casagrande K, Barton M, Chen CM, Dumont-Mathieu T, Fein D. Validation of the modified checklist for autism in toddlers, revised with follow-up (M-CHAT-R/F). Pediatrics. 2014;133:37-45.
66. Robins DL, Dumont-Mathieu TM. Early screening for autism spectrum disorders: Update on the Modified Checklist for Autism in Toddlers and other measures. J Dev Behav Pediatr. 2006;27:S111-S119.
67. Turner-Brown LM, Baranek GT, Reznick JS, Watson LR, Crais ER. The First Year Inventory: a longitudinal follow-up of 12-month-old to 3-year-old children. Autism. 2013;17:527-540.
68. Johnson MH, Gliga T, Jones E, Charman T. Annual Research Review: Infant development, autism, and ADHD—early pathways to emerging disorders. J Child Psychol Psychiatry. 2015;56:228-247.
69. Gliga T, Jones EJ, Bedford R, Charman T, Johnson MH. From early markers to neuro-developmental mechanisms of autism. Devel Rev. 2014; 34:189-207.
70. Samango-Sprouse CA, Stapleton EJ, Aliabadi F, *et al*. Identification of infants at risk for autism spectrum disorder and developmental language delay prior to 12 months. Autism. 2015;19:327-337.
71. Stone WL, McMahon CR, Henderson LM. Use of the Screening Tool for Autism in Two-Year-Olds (STAT) for children under 24 months: an exploratory study. Autism. 2008;12:557-573.
72. Baird G, Charman T, Baron-Cohen S, *et al*. A screening instrument for autism at 18 months of age: a 6-year follow-up study. J Am Acad Child Adolesc Psychiatry. 2000;39:694-702.
73. Raffle AJG, Gray JEM. Screening: Evidence and Practice. Oxford: Oxford University Press; 2007.
74. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med. 1988;318: 1728-1733.
75. Rembold CM. Number needed to screen: development of a statistic for disease screening. BMJ. 1998;317:307-312.
76. US Preventive Services Task Force. Draft Recommendation Statement: Autism Spectrum Disorder in Young Children: Screening. 2015. Available at: http://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement15/autism-spectrum-disorder-in-young-children-screening. Accessed November 20, 2015.
77. Sharma D, Newman TG, Aronow WS. Lung cancer screening: history, current perspectives, and future directions. Arch Med Sci. 2015;11:1033-1043.
78. Coury DL. Babies, bathwater, and screening for autism spectrum disorder: comments on the USPSTF recommendations for autism spectrum disorder screening. J Dev Behav Pediatr. 2015;36:661-663.
79. Fischbach GD, Lord C. The Simons Simplex Collection: a resource for identification of autism genetic risk factors. Neuron. 2010;68:192-195.
80. Lord C, Petkova E, Hus V, *et al*. A multisite study of the clinical diagnosis of different autism spectrum disorders. Arch Gen Psychiatry. 2012;69:306-313.
81. Button KS, Ioannidis JPA, Mokrysz C, *et al*. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14:365-376.