PERSPECTIVE

Cognition and behavior in neurofibromatosis type 1: report and perspective from the Cognition and Behavior in NF1 (CABIN) Task Force

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Individuals with neurofibromatosis type 1 (NF1) are prone to the evolution of neurodevelopmental symptomatology including motor delays, learning disabilities, autism, and attention deficits. Caused by heterozygous germline mutations in the *NF1* gene, this monogenic condition offers unique opportunities to study the genetic etiologies for neurodevelopmental disorders and the mechanisms that underlie their formation. Although numerous small animal models have been generated to elucidate the causes of these alterations, there is little consensus on how to align preclinical observations with clinical outcomes, harmonize findings across species, and consolidate these insights to chart a cohesive path forward. Capitalizing on expertise from clinicians; human, animal, and cellular model research scientists; and bioinformatics researchers, the first Cognition and Behavior in NF1 (CABIN) meeting was convened at the Banbury Center of Cold Spring Harbor Laboratory in October 2024. This Perspective summarizes the state of our understanding and a proposed plan for future investigation and exploration to improve the quality of life of those with NF1.

[*Keywords*: attention deficit; autism; clinical translation; cognition; informatics; NF1; preclinical modeling]
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Article published online ahead of print. Article and publication date are online at http://www.genesdev.org/cgi/doi/10.1101/gad.352629.125. Freely available online through the *Genes & Development* Open Access option.

Individuals with the neurofibromatosis type 1 (NF1) neurogenetic syndrome are at increased risk for the development of benign and malignant tumors, resulting in its frequent classification as a cancer predisposition syndrome. However, a substantial number of affected children exhibit cognitive and behavioral problems that impact on their scholastic performance, social relationships, and future employment opportunities (Hyman et al. 2005). Studies consistently show that NF1 is associated with a 0.6–0.8 standard deviation reduction in IQ, with verbal and nonverbal intellectual skills equally affected (Payne et al. 2019; Ottenhoff et al. 2020). Against this background, as many as 80% of children with NF1 experience deficits across specific domains, including executive function (Payne et al. 2012, 2021; Hou et al. 2020), attention (Isenberg et al. 2013), visuoperception (Maier et al. 2024), and language skills (Thompson et al. 2010; Haebich et al. 2023). These cognitive difficulties often underlie the increased rates of co-occurring neurodevelopmental conditions associated with NF1, such as learning difficulties (Barquero et al. 2015; Arnold et al. 2021), attention deficit hyperactivity disorder (ADHD) (Payne et al. 2012; Hou et al. 2024), autism (Garg et al. 2013; Morris et al. 2016; Chisholm et al. 2022), and auditory processing difficulties (Rance et al. 2021).

The preponderance of these neurobehavioral abnormalities suggests delays and disruptions in normal brain

development, perhaps resulting from primary or secondary effects of germline *NF1* gene mutations on neurons in the fetal or postnatal central nervous system. Understandably, the focus of much of the research in the NF1 field has centered on tumors, which has led to knowledge gaps relevant to future basic science investigations, preclinical modeling, drug discovery, and clinical translation to improved patient care for individuals with these neurocognitive challenges. To galvanize change in the field, Cold Spring Harbor Laboratory and Penny's Flight Foundation hosted a focused cross-disciplinary conference at the Banbury Center on October 21–23, 2024. To our knowledge, this meeting was the first conference of its kind, bringing together experts in NF1 cognition and behavior (Table 1) spanning clinical care, preclinical small animal modeling, drug discovery, and informatics (Fig. 1), and incorporating individuals from the NF1 community, including family members and representatives from NF advocacy organizations. The meeting was structured to include (1) brief formal presentations from members of each of the four working groups, (2) working group breakout sessions, and (3) entire group discussions. On day 3 of the conference, each working group presented an initial summary to the entire collective, which was then refined through group discussion and consensus. In this way, the Cognition and Behavior in NF1 (CABIN) collective identified key unmet needs and future opportunities for progress in the field and charted a course forward, leveraging the strengths of the four working groups and incorporating guidance and prioritization from stakeholders. This perspective was written by the two coleaders of each working group and the three main conference co-organizers (Kaleb H. Yohay, David H. Gutmann, and Linda Van Aelst).

Table 1. *Cold Spring Harbor Laboratory Banbury CABIN participants*

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Clinical Working Group—tools and challenges in assessing NF1 neurodevelopmental phenotypes

Although our understanding and description of the NF1 neurodevelopmental phenotype have been expanding over time, neurodevelopmental disabilities in children with NF1 remain underdiagnosed. This is in part due to the limited involvement of neurodevelopmental and behavioral specialists in the care of children with NF1; the unique phenotypic presentation of NF1-related neurodevelopmental disability compared with idiopathic counterparts (Garg et al. 2015; Morris et al. 2016; Chisholm et al. 2022); the complex evolution of cognition, behavior, and development in the context of progressive neurological pathology; and the frequent diagnostic overshadowing by severe, life-altering, medical comorbidities. Additionally, screening tools administered at the point of care to identify children at risk for developmental and/or behavioral differences are uncommonly and inconsistently used across NF clinical centers due to time, cost, expense, limited clinician experience, and lack of consensus guidelines. Advancing our understanding of the cognitive and behavioral effects of NF1 is critical to the early detection of children at the highest risk for NF1-related neurodevelopmental disabilities; however, it presents several significant challenges.

The first challenge lies in identifying the factors that drive the marked variability in the cognitive and behavioral effects of NF1. This heterogeneity likely arises from a complex interplay of genetic, molecular, and environmental influences, compounded by the inherent variability in *NF1* gene expression and function across individuals with NF1 (Anastasaki et al. 2015). A second challenge is to synthesize the existing knowledge of the NF1 neurocognitive phenotype to define its unique characteristics and describe what "it" is. A combination of systematic reviews, meta-analyses, and data from large, prospectively collected cohorts would help move the field beyond the single-domain approaches that have dominated to date. By integrating cognitive, behavioral, and psychosocial domains, a multidimensional framework should be created that more accurately reflects the specific neurocognitive profile driven by *NF1* variants rather than relying on Diagnostic and Statistical Manual of Mental Disorders (DSM) categories, which are consensus-based, human-defined, symptom clusters that often co-occur in the general population but are not etiologically grounded.

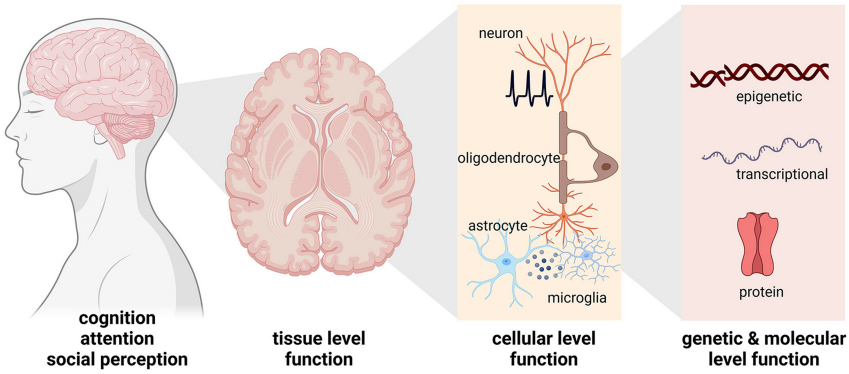

Figure 1. Multilevel interrogation of cognition, attention, and social perception in NF1 requires experts from various disciplines using numerous complementary approaches.

Several existing tools could be adapted to better characterize the NF1 neurodevelopmental phenotype. For example, a checklist similar to the TAND Checklist for Tuberous Sclerosis Complex (de Vries et al. 2015)), could be developed to systematically assess cognitive, behavioral, and psychosocial challenges in individuals with NF1. Given the well-documented deficits in executive function and attention, along with challenges in language, visuoperceptual skills, and social cognition, future neuropsychological assessments should prioritize domain-specific measures that capture the breadth of cognitive differences in NF1 rather than relying solely on full-scale IQ scores. In particular, real-world executive dysfunction is a hallmark of NF1, yet traditional laboratory-based tasks may fail to capture the full extent of these difficulties (Payne et al. 2011). As such, the Behavior Rating Inventory of Executive Function (BRIEF) provides a more ecologically valid assessment by measuring how executive function deficits manifest in daily life, complementing performance-based measures. Similarly, although cognitive assessments shed light on core deficits, evaluating adaptive behavior is equally critical, as individuals with NF1 often demonstrate a disconnect between cognitive abilities and everyday functioning (Eby et al. 2019). Tools like the Vineland Adaptive Behavior Scales can provide insights into communication, socialization, and daily living skills, helping to contextualize cognitive profiles within a broader functional framework. Taken together, efforts focused on creating a standardized neurodevelopmental inventory for NF1 (NF1-NDI) would enable a more comprehensive understanding of the NF1 neurocognitive phenotype, agnostic of the DSM classification. Such an approach has the potential to enhance the screening, diagnosis, and monitoring of key neurodevelopmental challenges for children with NF1, enabling clinicians and researchers to track intervention responses while empowering families and clinicians to provide holistic, individualized management for these often-impairing difficulties.

A final challenge for the field is identifying which children within the first 1000 days of life are most likely to benefit from early treatment, particularly as next-generation models identify promising therapies (Anastasaki et al. 2022b; Payne 2025). Early intervention during this critical developmental window has the potential to prevent or mitigate neurocognitive and behavioral manifestations associated with NF1. Achieving this, however, depends on the identification of reliable markers or predictors to effectively stratify risk and tailor treatments. Although preliminary work in small cohorts indicates that this is possible (Lorenzo et al. 2015; Slevin et al. 2024), future efforts must focus on developing cognitive and behavioral developmental charts through collaborative longitudinal cohorts and multidisciplinary approaches spanning neuropsychology, developmental neuroscience, and genomics. Incorporating machine learning and wearable technologies to uncover patterns in variability and phenotype expression holds the potential to create an invaluable resource, enabling precision medicine approaches that optimize developmental trajectories from the earliest stages. However, to effectively capitalize on the efficiency of machine learning methodologies and generate clinically relevant and accurate models, there will need to be concerted efforts within the NF clinical and scientific communities to adopt and adhere to a standardized lexicon (i.e., NF1 terminology and medical coding)—a universal NF1 language.

Preclinical Models Working Group—avatars to study NF1 neurodevelopmental phenotypes

Multiple preclinical animal and humanized avatars have been developed to model NF1 cognitive and behavioral phenotypes, including *Drosophila*, mice, rats, zebrafish, pigs, and human induced pluripotent stem cell (hiPSC)-derived models (Table 2; Diggs-Andrews and Gutmann 2013; Wegscheid et al. 2018; Atsoniou et al. 2024; Botero and Tomchik 2024).

Drosophila with genomic deletions of the *Nf1* fly ortholog have been used to model cognitive phenotypes with abnormalities reported in body size, learning and memory (Guo et al. 2000; Buchanan and Davis 2010; Georganta et al. 2021), circadian rhythms (Williams et al. 2001; Bai et al. 2018), sleep (Bai and Sehgal 2015; Durkin et al. 2023), grooming (King et al. 2016, 2020; Suarez et al. 2024), locomotion (van der Voet et al. 2016; Suarez et al. 2024), social behavior (Moscato et al. 2020), tactile sensitivity (Dyson et al. 2022), and metabolism (Tong et al. 2007; Botero et al. 2021; Botero and Tomchik 2024; Sofela et al. 2024). Although some of the *Drosophila* phenotypes (e.g., learning and sleep disruptions) are reminiscent of the

Table 2. *Summary of the key features of current NF1 preclinical models*

Species	Mutation	Key behavioral/cognitive deficits	Strengths	Limitations
Drosophila	*Nf1*-null	Deficits in learning, memory, circadian rhythms, sleep, locomotion, social behavior, and tactile sensitivity	• Conserved genetic sequence • Conserved intracellular signaling • Fast and inexpensive generation • Completely mapped connectome • Amenable to large-scale genetic screening	• Requirement for biallelic *Nf1* mutation to elicit phenotype • Neuronal circuits vary greatly from the human brain
Zebrafish	*nf1*$^{a/b}$-null	Deficits in visual and auditory habituation, motor learning, and memory	• Amenable to large-scale screening • Robust measurable visual, auditory, and motor behaviors	• Requirement for concomitant homozygous *nf1*^{a} and *nf1*^{b} mutations to elicit deficits • Genome duplication confounds genetic translatability • Not all observed behaviors align with clinical cohorts
Mice	*Nf1* heterozygous (multiple germline mutations)	Deficits in spatial learning, long-term potentiation, social learning, sensory and novelty responses, object recognition, auditory cortex connectivity, attention, early communicative vocalization, sleep, and motor learning	• Mammalian model • Multiple genetically engineered germline *Nf1* mutant strains available • Heterozygous *Nf1* mutation-driven deficits • Neuronal circuit structural and molecular similarity to the human brain • Ability to engineer precision strains with patient-derived *Nf1* mutations	• Not all behaviors align with clinical cohorts • Not all mouse strains exhibit clinically relevant deficits • Treatments successful in restoring behavioral deficits in mice have failed in patient clinical trials
Minipigs	*NF1* heterozygous	Deficits in spatial learning, motor function, and glial and neuronal function	• Large mammalian model • Sufficiency of *NF1* heterozygosity to elicit clinically relevant NF1 pathophysiology • Amenable to complex behavior surveys	• Expensive generation and maintenance
Human iPSC-derived neurons and organoids	*NF1* heterozygous (multiple mutations)	Deficits in neurofibromin expression, dopaminergic signaling, neuronal survival, differentiation, and maturation	• Human cells amenable to genetic editing • Patient-derived cells harboring NF1 patient-derived *NF1* mutations, including large genomic deletions • Platform for personalized targeting	• Lack of complexity conferred by a whole organism

human NF1 condition, their strongest value in disease modeling is arguably their utility as phenotypic platforms to dissect both cell-autonomous and circuit-level effects of *Nf1* loss (The et al. 1997; Williams et al. 2001; Walker et al. 2006). Given their largely conserved genetics and intracellular signaling, fast generation turnover time (10–14 days), and completely elucidated connectome (Dorkenwald et al. 2024), *Drosophila* are easily amenable to genetic screens (St Johnston 2002). For example, anaplastic lymphoma kinase (ALK) was identified in a *Drosophila Nf1* modifier screen (Gouzi et al. 2011) and represents a promising target for cognitive symptoms in mammals (such as the learning deficits) (Weiss et al. 2017; Weiss and Raber 2023). However, *Drosophila*

models carry caveats, including the requirement for biallelic *Nf1* mutation and significant divergence in brain connectivity.

Similar to *Drosophila*, zebrafish are also highly amenable to genetic and therapeutic screening, especially during their embryonic and larval stages (first 7 days postfertilization). Additionally, both larval and adult zebrafish exhibit robust, predictable, and measurable behaviors in response to stress stimuli, allowing for behavioral endpoint assessments on a large scale (Nelson and Granato 2022). As vertebrates, *Nf1*-null zebrafish exhibit visual (Randlett et al. 2019) and auditory habituation (Shin et al. 2012) defects, as well as motor learning and memory abnormalities (Wolman et al. 2014). However, genetic studies may be complicated by the fact that zebrafish have a duplicated genome.

Although the use of zebrafish models is on the rise, a large number of neurobehavioral studies have been performed using mouse models of NF1. Using these *Nf1* mutant mice, deficits in GABA-mediated hippocampal-based spatial memory and long-term potentiation (Silva et al. 1997; Costa et al. 2002), social learning (Molosh et al. 2014; Petrella et al. 2016), sensory responsivity and novelty responses (Robinson et al. 2019), object recognition (Krenik et al. 2022), and auditory cortex connectivity (Shofty et al. 2019) have been reported. Additional models using conditional *Nf1* inactivation have similarly revealed deficits in spatial memory (Diggs-Andrews et al. 2013), comparable with mice with *Nf1* loss in dopaminergic neurons (Anastasaki et al. 2015), as well as defects in dopamine-regulated attention (Brown et al. 2010), early communicative (ultrasonic) vocalization (Muddathir et al. 1987), and sleep fragmentation (Anastasaki et al. 2019). Moreover, oligodendrocyte precursor-specific *Nf1* mutation causes motor learning defects (Pan et al. 2024).

The major strengths of rodent models include their amenability to neuronal circuit analysis in a mammalian nervous system with structural similarity to humans and their ability to delineate molecular mechanisms governing cognitive dysfunction. With the relatively recent appreciation that neurofibromin has Ras-independent functions and all germline *NF1* gene mutations are not functionally equivalent, precision mouse models are being engineered harboring NF1 patient-derived *NF1* gene mutations (Li et al. 2016; Toonen et al. 2016; Anastasaki et al. 2022a, 2024), which could emerge as instrumental next-generation tools for dissecting the basis for NF1 clinical and behavioral heterogeneity. However, it should be appreciated that not all cognitive and behavioral deficits detected in *Nf1* mutant mouse strains align with those encountered in people with NF1. To this end, treatments such as lamotrigine and lovastatin, which demonstrated positive preclinical benefits, have unfortunately only demonstrated limited efficacy in clinical trials (Payne et al. 2016; Stivaros et al. 2018; Ullrich et al. 2020; Jung et al. 2023; Ottenhoff et al. 2025). To improve translatability of future murine studies, efforts should be made to prioritize the assessment of cognitive and behavioral outcomes that directly mirror those evaluated in clinical trials (Payne et al. 2019).

In addition to rodents, some groups have developed swine models of NF1. *NF1* mutant minipigs exhibit behavioral alterations, including impaired spatial learning (Isakson et al. 2018), and alterations in motor function (Swier et al. 2024). The study of minipig cognitive phenotypes is still in the early stages; however, alterations in glial and neuronal function, including imbalances in inhibitory GABAergic signaling, have been reported (Swier et al. 2024). Although expensive to maintain, *NF1* mutant minipigs spontaneously develop aspects of NF1 without further engineering and allow for an analysis of complex behaviors more akin to people with NF1.

Finally, several groups have invested in hiPSC engineering to study the impact of germline *NF1* mutations on human brain development to complement studies performed in small animal models of NF1. Particularly relevant to neurodevelopment, hiPSCs can also be induced to generate three-dimensional brain organoids, which spontaneously assemble into organized "minibrain" structures. In the context of NF1, hiPSC-derived neurons in either 2D or 3D organoid cultures harboring different patient *NF1* mutations exhibit differential levels of both neurofibromin protein and dopamine irrespective of RAS activity (Anastasaki et al. 2015), reinforcing murine model observations of dopaminergic deregulation-mediated learning deficits (Diggs-Andrews et al. 2013). Moreover, hiPSCs can be generated from patients with specific types of *NF1* mutations, such as those with large genomic 17q chromosome deletions who exhibit increased developmental and cognitive delays relative to the general NF1 population. Studies using these patient-derived hiPSCs revealed a gene (cytokine receptor-like factor-3 [*CRLF3*]) within the *NF1* genomic locus that regulates neuronal survival, differentiation, and maturation (Wegscheid et al. 2021). The use of hiPSCs harboring NF1 patient-derived *NF1* germline mutations offers the promise of more personalized strategies to treat NF1-associated neurobehavioral abnormalities.

Taken together, the combinatorial deployment of multiple preclinical models that are individually best suited to address distinct aspects of NF1 clinical behavior are key to identifying optimal treatment strategies for children with NF1.

Therapeutic Intervention Working Group—approaches to identifying treatments for NF1 neurodevelopmental phenotypes

The effective management of NF1 neurobehavioral challenges requires a comprehensive approach that includes pharmacological treatments, behavioral interventions, and educational support. Current approaches to pharmacological treatments for neurobehavioral issues in NF1 have focused on addressing symptoms of cognitive performance, ADHD, anxiety, and mood disorders. Although several classes of drugs have shown promise in clinical studies, there are currently no medications specifically approved for NF1-associated cognitive or behavioral challenges.

In the general population, first line treatment for ADHD is stimulant medication, such as amphetamines and methylphenidate (Cortese et al. 2018). Consistent with preclinical studies in *Nf1* mutant mice (Brown et al. 2011; Diggs-Andrews et al. 2013), numerous studies have shown that methylphenidate improves attention, impulsivity, and hyperactivity in children (Lion-François et al. 2014; Pride et al. 2018). Similarly, N-acetyl cysteine (NAC), an antioxidant glutamate-modulating compound, has been shown to improve motor function and learning in *Nf1* mutant mice (Mayes et al. 2013), prompting its evaluation for ADHD/impulsive symptoms, executive function, and working memory in children with NF1. For individuals who do not respond well to stimulants or experience undesirable side effects, nonstimulant ADHD medications such as the α2a adrenergic agonist guanfacine may be an effective alternative (Lukkes et al. 2020).

Other pharmacological treatment approaches have been guided by insights from basic science discoveries. The best-established function of neurofibromin is to regulate RAS/MEK signaling. Because statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, leading to impaired RAS post-translational modification, membrane localization, and subsequently RAS/MAPK pathway activation, they were initially evaluated in *Nf1* mutant mice prior to testing in children with NF1 (Li et al. 2005). Although safe, there is no current evidence demonstrating that either lovastatin or simvastatin exert a beneficial effect on cognitive function or behavioral problems in children with NF1 (van der Vaart et al. 2013; Payne et al. 2016; Agouridis et al. 2023). Although MEK inhibitors have been evaluated for their impact on the neuropsychological profile of individuals with NF1 (Walsh et al. 2021; Lalancette et al. 2024), these have been small-scale incidental studies occurring during trials of MEK inhibitors for NF1-associated tumors and were not primarily designed to evaluate cognitive outcome.

Another approach involves targeting GABAergic dysregulation, which underlies working memory impairments seen in people and mice with NF1 (Costa et al. 2002; Cui et al. 2008; Shilyansky et al. 2010; Violante et al. 2013) using transcranial noninvasive brain stimulation (Garg et al. 2022). Whereas anodal transcranial direct current stimulation (atDCS) can reduce GABA in the stimulated cortex in NF1 subjects, it does not improve task performance. Additionally, *Nf1* mutation in mouse hippocampal interneurons alters hyperpolarization-activated cyclic nucleotide-gated channel 1 (HCN1)-induced hyperpolarization (Omrani et al. 2015), which can be reversed by lamotrigine, an antiseizure and mood-stabilizing drug safely used in children for decades. Although lamotrigine effectively rescues electrophysiological and hippocampal-based cognitive deficits in *Nf1* mice, it did not result in cognitive improvements in adolescents with NF1 (Ottenhoff et al. 2025). As other functions of neurofibromin in neurons become revealed through experimentation, additional targeted therapies might emerge. In this regard, reduced sleep in *Nf1* mutant flies has been linked to metabolic deficiency, mitochondrial defects, and reduced nicotinamide adenine dinucleotide (NAD) (Sofela et al. 2024). NAD is often used as a dietary supplement and could be readily assessed for NF1-related sleep deficits. We recognize that variability in phenotypes and treatment responses in individuals with NF1 (Wang et al. 2021) and regulatory challenges to use new therapeutics in the clinic (Medlinskiene et al. 2021) are potential barriers to clinical translation.

Beyond medicinal strategies, nonpharmacological approaches are a cornerstone of managing neurobehavioral issues in NF1. First, cognitive behavioral therapy (CBT) is an evidence-based therapeutic approach that helps individuals manage pain, anxiety, depression, social difficulties, and sleep deficits by teaching coping strategies, problem-solving skills, and cognitive restructuring. As one example, the iCanCope-NF application has been assessed for various outcomes including pain and pain-related activity limitations, sleep functioning, and emotional functioning (depression and anxiety) with some success (Buono et al. 2022, 2023). Second, educational support and academic accommodations are frequently provided in school. These may include extended test times, preferential seating, or modifications to assignments to address cognitive delays or learning disabilities. Special education services, speech therapy, and occupational therapy additionally provide targeted support to enhance academic and social development (Chambers et al. 2018). Several independent trials have demonstrated reading improvements (Barquero et al. 2015; Arnold et al. 2016) and ameliorated short-term memory, attention, and executive functioning (Hardy et al. 2021) with training/intervention in children with NF1. Third, social skills training can help individuals with NF1 develop appropriate social behaviors, interpret social cues, and build meaningful relationships. Social skills programs often involve role-playing, modeling, and guided interactions to enhance interpersonal communication and reduce social anxiety. A recent study using a telehealth intervention (the Program for the Education and Enrichment of Relational Skills [PEERS]) showed initial feasibility for children with NF1 (Glad et al. 2024). Similarly, resiliency training using stress and symptom management programs tailored for those with NF1 improve coping abilities and may help successful navigation of psychosocial challenges associated with NF1 (Lester et al. 2020; Presciutti et al. 2023). Last, education and support for families are crucial in managing the neurobehavioral challenges of NF1. Parents benefit from learning about the nature of the disorder, available resources, and effective strategies for supporting their child's development. Family therapy, as well as Internet support groups, are also beneficial for improving communication and reducing stress associated with managing behavioral issues at home (Martin et al. 2018).

Although there has been much progress in the field, we still have a limited understanding of the critical developmental periods in which interventions might be most effective for NF1. As such, future studies are needed to address this knowledge gap. Furthermore, developing new biomarkers to assess positive outcomes following treatment, even in the absence of significant behavioral

or cognitive improvements, would be valuable to evaluate novel therapeutic interventions. Before moving forward with large-scale, costly clinical trials, small-scale experimental clinical trials should be considered to assess how these interventions affect the brains of people with NF1. Finally, the latest developments in clinical trial methodologies (Baud 2024) should be considered for inclusion as part of these future intervention studies.

Informatics Working Group—multimodal tools to examine complex neurodevelopmental phenotypes

The emergence of artificial intelligence (AI), smartphone, and wearable techniques in the informatics and data science communities has shown great promise, particularly for complex and rare diseases like NF1. These advancements enable innovative utilization of existing data sets and facilitate the collection of intensive longitudinal data, providing insights unattainable through traditional methods.

AI-based risk prediction models can be developed using existing, large-scale data sets, enabling systematic tracking of NF1 disease surveillance and management. These models hold the potential to function as real-time clinical decision support tools at the point of care. Real-world clinical databases, like electronic health records (EHRs), provide large and diverse health care data to develop AI models for individuals with NF1, compared with research databases that have fewer participants and collect limited data elements. The EHR is a comprehensive and longitudinal collection of clinically significant data regarding individual patient health including laboratory results, vital signs, comorbidities, medications, imaging, and clinical assessments. EHR data consist of both structured tables (e.g., demographics and laboratory results) and unstructured data (e.g., clinical and imaging notes). Although structured data are useful for developing AI models, critical information relevant to treatment and management of a clinical condition often resides in relatively inaccessible unstructured clinical notes within the EHR. For this reason, algorithms using natural language processing (NLP) and large language models (LLMs) need to be developed that can use structured and unstructured clinical data extracted from the EHR and extract clinical important information such as family history of NF1, allergies, symptoms, and other comorbidities, as well as any psychometric data such as cognitive and behavioral test scores. In addition, imaging data from the EHR can also provide useful information, as previously reported for optic pathway glioma (OPG) identification and progression (Pisapia et al. 2020).

Supervised learning or machine learning (ML) models can also be used to develop early-warning predictive models for diagnosing various NF1 clinical features, enabling timely and accurate intervention strategies. The few studies published to date that have applied a ML strategy to develop predictive models for clinical features associated with NF1 (Sbidian et al. 2010; Morris et al. 2021) demonstrate that this approach can be used to create and verify predictive phenotype models useful for risk stratification and disease management in NF1. The ML models most widely used for similar clinical prediction problems include random forest (Breiman 2001), support vector classifier (Cortes and Vapnik 1995), logistic regression, and gradient boost classifier (Friedman 2001), all of which achieve good predictive performance in studies using EHR data (Lingren et al. 2016; Zhang et al. 2019; Zhao et al. 2019). In addition to ML models, deep learning (DL) models are also useful for identifying temporal patterns in the EHR, as DL models encode longitudinal concepts such as event trends, episodes, cycles, and abnormalities (Wang et al. 2013). Temporal neural network models have been used to predict clinical intervention time and mortality in the intensive care unit setting (Catling and Wolff 2020), as well as specific medical conditions and medication uses (Choi et al. 2016; Jagannatha and Yu 2016), which could be applied for specific questions in children and adults with NF1.

In addition to supervised learning approaches, unsupervised learning methods such as clustering can group individuals with similar characteristics (e.g., genetic markers, clinical symptoms, or other relevant features). By identifying and examining the characteristics of these subgroups, risk factors and endophenotypes identified in preclinical studies can be validated using real-world clinical data obtained from clinical registries (Tabata et al. 2020; Bergqvist et al. 2022). In an analogous manner, EHRs can be used to conduct similar studies on large and diverse data sets and provide more generalizable subphenotypes of NF1 (Baksh et al. 2023).

Smartphones and wearable devices provide opportunities to collect rich intensive longitudinal data critical for individualized interventions. Neurobehavioral function (e.g., cognitive, socioemotional, and behavioral) can fluctuate across time and context. For example, processing speed, executive function, and memory performance may decline when individuals are tired or in distracting environments (Bielak et al. 2019; Weizenbaum et al. 2020), whereas adolescent ADHD symptoms peak in the afternoon on school days, but not on non-school days (Pedersen et al. 2020). Understanding when and under what conditions neurobehavioral function worsens or improves in the daily lives of individuals with NF1 is an essential step for developing personalized interventions to improve their neurobehavioral function. In sharp contrast to traditional neuropsychological assessments that typically ask about experiences over prior weeks or months, the use of smartphone-based ecological momentary assessment (EMA) collects real-time neurobehavioral function data in daily life settings, reduces recall bias, increases accessibility for participants in diverse regions, and provides information on intraindividual variability and contextual predictors. As such, smartphone-based EMA neurobehavioral measures have shown reliability and validity in various populations, including individuals with mild cognitive impairments (Brouillette et al. 2013; Moore et al. 2017; Sliwinski et al. 2018; Bartels et al. 2020). Moreover, wearable devices like smartwatches and biosensors can collect continuous data on factors influencing neurobehavioral function, such as physical activity, sleep, heart rate

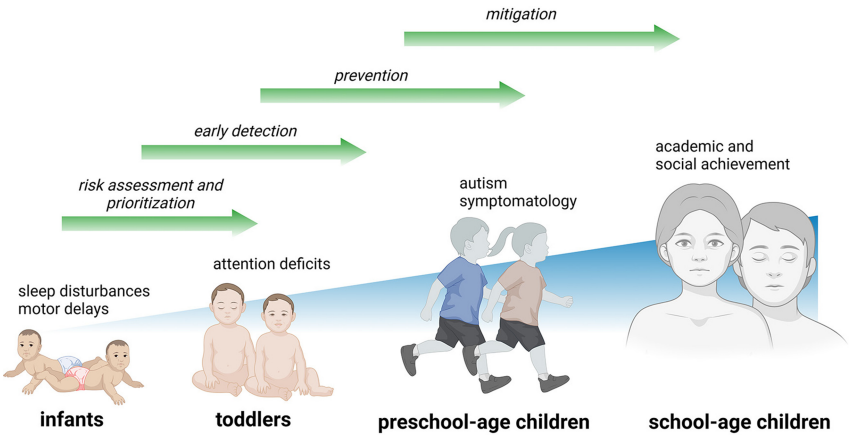

Figure 2. Information gathered from a longitudinal natural history study of cognitive and behavioral delays in children with NF1 would facilitate the identification of potential time intervals for risk assessment, early detection, prevention, and treatment (mitigation).

variability, and environmental exposure, which are passively collected over extended periods (Diaz et al. 2016; Reid et al. 2017; Godino et al. 2020).

Integrating wearable devices and EMA with multilevel modeling (MLM) (Kranzler et al. 2018; Pedersen et al. 2020; Chen et al. 2024) or personalized machine learning models (Shah et al. 2021) offers valuable opportunities to predict neurobehavioral problems within the context of an individual's unique physiological, psychosocial, lifestyle, and environmental factors. These personalized prediction models for neurobehavioral function could serve as a foundation for developing tailored, "just in time" adaptive interventions (JITAIs) leveraging smartphone and wearable technologies. Furthermore, innovative multiscale modeling and analysis (MMA) entail identifying higher-order motifs comprising measurable data points that span multiple scales and data types, such as clinical (structured, text, and imaging) and biomolecular phenotypes and behavioral and environmental factors alongside computable knowledge resources (publications and ontologies). Use of MMA techniques that combine clinical and biomolecular-scale patient features with correlative biomedical knowledge resources will enable the identification of actionable prognostic marker complexes that can be used to improve disease staging and management in NF1. Such MMA techniques have become increasingly prevalent when investigating complex disease phenotypes (Blois 1988; Payne et al. 2009, 2010; Tsafnat and Coiera 2009). These techniques provide a comprehensive framework for improving NF1 disease management and understanding rare disease phenotypes.

Perspectives and future directions

Drawing from the diverse expertise of the CABIN team members, we outlined several key directions for further investigation. First, there is a great need to define what the relevant NF1-specific neurobehavioral phenotypes are in patients and which should be modeled in small animal disease avatars. To this end, existing assessment tools should be adapted to better characterize the NF1 neurodevelopmental phenotype. This will require developing a common nomenclature and lexicon and a standardized battery of tests for the practitioner. Additionally, a longitudinal natural history study will be necessary to identify periods for early detection and mitigation (Fig. 2). Second, preclinical and clinical behavioral testing paradigms should be developed that harmonize between humans and other species used in laboratory-based investigations. Additionally, cross-species phenotypes should be tabulated and compared. This would allow for the use of the most relevant preclinical model to assess therapies that target that specific human cognitive or behavioral deficit. Third, as the neurobehavioral subphenotypes become better categorized, targeted therapies designed to ameliorate that specific endophenotype can be identified and refined. This would necessitate prioritizing and repurposing drugs according to the phase of symptom evolution, as well as the identification of biomarkers of disease activity for implementation in future clinical trials. Fourth, we recommend full integration of informatics into all phases of research. Its capacity to transform

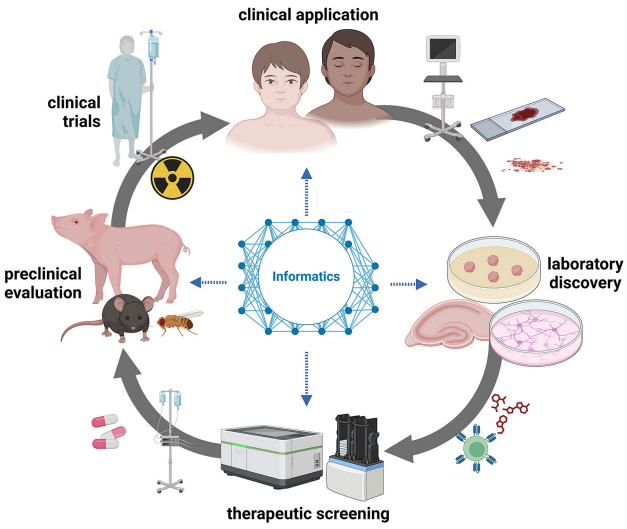

Figure 3. Proposed CABIN iterative approach to understanding and translating discoveries from the laboratory to clinical care, involving expertise from specialists in clinical science, laboratory research, drug discovery, informatics, and preclinical evaluation.

population-based research, provide real-time assessments, and integrate data at multiple scales makes it an integral and obligate component. In this manner, one could envision an iterative cycle of discovery, preclinical evaluation, and clinical translation (Fig. 3). Fifth, the coalignment of preclinical and clinical trials, coupled with the use of optimized clinical trial designs, increases the likelihood that promising interventions will be discovered for NF1-associated cognitive and behavioral abnormalities. Last, the energy and passion of the participants have already resulted in the establishment of new research efforts, which will be the subject of the planned CABIN meeting to be held at the Banbury Center in October 2025.

Competing interest statement

K.H.Y. serves as a member of the Scientific Board for Infixion Bioscience, Inc.; serves as Chair for the programmatic Review Committee of the Department of Defense Congressionally Directed Medical Research Programs Neurofibromatosis Research Program; and has served as a consultant for Alexion. The other authors declare no competing interests.

Acknowledgments

We thank program officers from the Gilbert Family Foundation (Kalyan Vinnakota, PhD), Department of Defense (Theresa Williams, PhD), and National Institutes of Neurological Disorders and Stroke (Jill Morris, PhD) for their participation. We also appreciate the efforts of Dr. Mekka Garcia, who provided scribe services for the meeting, as well as the patient advocates and parents who attended the meeting and provided insightful feedback. We also thank Penny's Flight Foundation (Kate and Chad Doerge) and The Banbury Center (Rebecca Leshan, PhD) for their support of this initial meeting.

Author contributions: All authors contributed to the writing of the initial drafts of the manuscript, and D.H.G., K.H.Y., and L.V.A. did the final editing.

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Genes Dev. published online March 24, 2025
Access the most recent version at doi:10.1101/gad.352629.125