



Postnatal Neurodevelopmental Disorders: Meeting at the Synapse?

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in linkage and association analyses, will have to be collected prospectively to avoid biases associated with amnesic information, use of proxy informants, and physiological changes that are a consequence of, rather than a cause of, the disease process. Family-based designs will be particularly attractive because they more effectively control for differences in the genetic background among affected and unaffected persons and for measured nongenetic risk factors (50, 51). Such an effort will require collaborations between clinicians, epidemiologists, and geneticists to develop and standardize the collection of phenotypes and to design new statistical approaches that can model complex multifactorial and polygenic causologies (52, 53). This will be useful not only for the adult-onset neuropsychiatric disorders discussed here but also for most other common, complex disorders.

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VIEWPOINT

Postnatal Neurodevelopmental Disorders: Meeting at the Synapse?

Huda Y. Zoghbi

We often think of neurodevelopmental disorders as beginning before birth, and many certainly do. A handful, however, strike many months after birth, following a period of apparently normal growth and development. Autism and Rett syndrome are two such disorders, and here I consider some of their similarities at the phenotypic and pathogenic levels. I propose that both disorders result from disruption of postnatal or experience-dependent synaptic plasticity.

Falling silent. After a child is born, parents watch with anticipation the normal developmental program that ensues. The baby smiles and follows faces at 6 weeks, acquires sufficient motor control to sit and transfer toys by

6 months, and typically walks and says a couple of words by 12 to 15 months. Language and thought continue to develop as children begin to understand make-believe play, to use verbs to describe a mental state, and to imitate complex actions.

Ashley delighted her parents as she progressed through early developmental milestones. She learned to crawl, babble, walk, and sing nursery rhymes, all at the expected ages. At 18 months, however, her progress ceased.

No more songs or words, only a vacant stare. Ashley's ability—or inclination—to use her hands was overwhelmed by incessant hand-wringing; tremors, rocking, and loss of balance robbed her of normal motor control; apnea and hyperventilation indicated autonomic control was going haywire, too. Her head growth slowed, and her social interactions became almost nonexistent.

Alex, born to a different family at a different time, has a similar story. He was a healthy boy who smiled and followed faces by 6 weeks, made eye contact, and enjoyed interactive games. At 10 months of age he showed an unusually intense interest in wheels, but he continued to interact socially and was saying several words and walking by 13 months. Some time between 15 and 18 months, however, Alex, like Ashley, fell si-

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Table 1. Postnatal neurodevelopmental phenotypes associated with mutations in genes for MECP2 and NLGN-3 and -4, and 15q duplications.

Gene	Females	Males
MECP2	Rett syndrome including more severe congenital form or milder preserved speech variant Angelman syndrome phenotype Autism Mental retardation Mild learning disability	Fatal encephalopathy Rett if 47, XXY, or somatic mosaicism Mental retardation, tremors, and seizures Mental retardation, spasticity, and psychosis
NLGN-3	Asymptomatic	Autism or Asperger
NLGN-4	Asymptomatic	Autism or Asperger
Duplications of 15q11–q13 (especially maternally inherited)		Autistic spectrum disorder or autism plus one or more of the following: Mental retardation, hypotonia, seizures, short stature, and abnormal epicanthal folds

lent. He stopped trying to communicate through gestures or words. He lost interest in social interactions and became utterly absorbed with lines on a tile or wheels on a toy. He seemed less sensitive to pain but hypersensitive to heat. He flapped his hands constantly and picked at his skin.

Similar histories, different diagnoses: Ashley has Rett syndrome and Alex is autistic. Both disorders become manifest after a period of apparently normal development. Both disrupt social and language development and are accompanied by unusual stereotypies. Despite the intellectual regression that marks the majority of Rett patients and ~30% of autistic patients (1, 2), neither disease is neurodegenerative in nature. Many children can improve somewhat as they get older. Although neither Ashley nor Alex have any language skills, they do have better eye contact now and seem to recognize family and friends at their respective ages of 23 and 11 years. The onset of both disorders after neurogenesis, neuronal migration, and maturation have occurred suggests that these disorders might affect synaptic maturation, connectivity, or stabilization.

Rett Syndrome: One Gene, Many Phenotypes

Rett syndrome was first described by the Austrian pediatrician Andreas Rett (3), but skeptical clinicians doubted its identity as a distinct syndrome until 1983, when Hagberg and colleagues reported on 35 patients with an undeniably unique postnatal developmental disorder (4). One difficulty in diagnosis was (and is) that clinical and laboratory tests are nonspecific. The electroencephalogram (EEG) is typically normal the first 2 to 3 years of life (5, 6), after which the background activity gradually slows, and repetitive high-amplitude spike and wave discharges appear in 60 to 70% of these patients. Imaging studies reveal changes in blood flow reminiscent of patterns seen in young infants, suggesting some arrest in development (7, 8). Pathological studies show other changes, also nonspecific. Neurons are abnormally small and densely packed, and have markedly shortened

and simplified dendritic arbors, although migration seems to be normal (9–11). A degenerative process is unlikely, because brains of Rett syndrome children weigh about 30% less than normal at any given age (12, 13).

Mutations in the X-linked methyl-CpG-binding protein 2 (*MECP2*) gene cause the majority of Rett syndrome cases (1, 14). Both mutation type and, in females, patterns of X chromosome inactivation (XCI) create a surprisingly wide range of phenotypes. Females with favorably skewed XCI can be asymptomatic or have mild learning disability, autism, or mild, later-onset versions of Rett (15–20). In males, the range is even wider: mutations that would cause classic Rett in females produce severe neonatal encephalopathy, motor abnormalities, respiratory dysfunction, and death by the second year. Mutations that cause little or no phenotype in female carriers cause male children to develop X-linked mental retardation with seizures, tremors, spasticity, macrocephaly, or bipolar disease (21–25). One boy with a receptive language disorder developed childhood-onset schizophrenia (26). This phenotypic diversity

(Table 1) raises questions about the differential effects of the mutations, regional or neuronal vulnerability to MeCP2 dysfunction, effects of genetic modifiers, and the nature of MeCP2's role in the brain.

MeCP2 was first identified as a member of the methyl-CpG-binding domain (MBD) protein family (27) and has been thought to serve as a methylation-dependent repressor (28, 29). MeCP2 dysfunction could thus disrupt the normal developmental program of gene silencing, but how this might result in a predominantly neurological phenotype has been a pressing question. It is interesting that MeCP2 is more abundant in brain tissue than most peripheral tissues (30, 31), is expressed in neurons but not in glia, and is localized to cell nuclei (30–32). Even more interesting, MeCP2 levels increase in cortical neurons throughout development (31–34) (Fig. 1). In addition to providing one possible explanation to the postnatal onset of symptoms, this expression pattern suggests that MeCP2 might help maintain or modulate neuronal maturity and plasticity.

Evidence from animal models and hu-

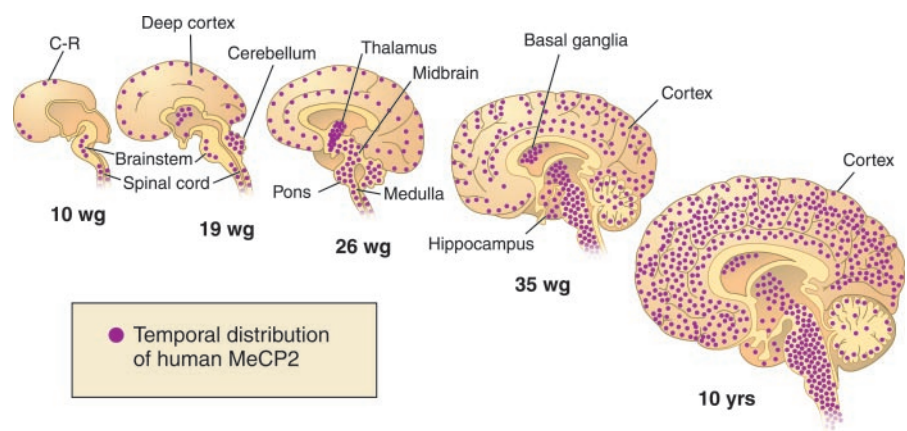


Fig. 1. Spatial and temporal distribution of MeCP2 during human development. MeCP2 is abundant in mature neurons and has an expression pattern that correlates with the ontogeny of the CNS—spinal cord first, cerebral cortex last. Cajal-Retzius (C-R) neurons are the first cortical neurons to mature and express MeCP2, followed by midbrain, thalamus, cerebellum, and deep cortical neurons. Expression in basal ganglia, hypothalamus, hippocampus, and superficial cortical layers appears later, and the number of MeCP2-positive neurons in the cerebral cortex continues to increase until 10 years of age. Wg, weeks of gestation.

mans supporting transcriptional alteration of neuronal genes is somewhat mixed. Human brain tissues show alterations in gene expression (35), but the role of these changes in pathogenesis is difficult to ascertain because of the confounding effects of chronic disease. Male *Mecp2*-null mice are small, hypoactive, clasp their hind limbs, have breathing abnormalities, and die by 3 months of age; female mice develop similar features but a bit later than males (36, 37). Conditional deletion of *Mecp2* in postmitotic neurons recapitulates these features, albeit more slowly (36). Yet transcriptional profiling of brain tissue from *Mecp2*-null mice has revealed no dramatic changes in gene expression (38). Elevated levels of acetylated histone H3, however, were found in brains of mice bearing a truncating mutation similar to one found in classic Rett patients (*Mecp2*³⁰⁸). These mice develop a progressive neurological phenotype reminiscent of Rett syndrome, and that supports the hypothesis that transcriptional misregulation could account for at least some aspects of the phenotype (39).

In *Xenopus*, absence of xMeCP2 function disrupts normal neuronal differentiation mediated by the Notch-Delta signaling pathway. Normally, xMeCP2 interacts with the SMRT (silencing mediator for retinoid and thyroid-hormone receptors) corepressor complex and silences *xHairy2a* by binding a methylated CpG site in its promoter. Expression of MeCP2 lacking a transcriptional repression domain causes an increase in the number of differentiated neurons due to abnormal regulation of *xHairy2a* expression (40). Whether similar specific neuronal targets will be identified in mice and human remains to be seen. Loss of MeCP2 in mammals does not alter neurogenesis, probably because the timing of its expression in the CNS is different from that of its *Xenopus* homolog, but it is conceivable that misregulation of *HES1* (the mammalian homolog of *Hairy2a*) contributes to neuronal dysfunction. The future of Rett research clearly depends on identifying MeCP2 targets in the CNS and understanding the cascade of events that follows their dysregulation.

Autism: Many Genes, One Family of Phenotypes

Like Rett syndrome, autism covers a range of phenotypes. Infantile autism, described in 1943 by Leo Kanner as an inability of affected children to develop social reciprocity (41), is the more severe form. Hans Asperger used the term "autistic psychopathy" to describe similar patients in 1944; Asperger syndrome patients typically do not have significant delay in language or cognitive development—indeed, they can function at quite a high level—but suffer social deficits and various stereotypies.

Unlike Rett children, autistic individuals tend to have larger head size than expected for a given age (42–44). Autistic brains are larger; the white matter is more prominent, although the cerebral cortex, hippocampus, and amygdala are smaller than normal (44, 45). It is interesting that, at birth, the brains of autistic children tend to be smaller than those of healthy infants, but between 6 and 14 months of age they undergo abnormally accelerated growth (46). Whether the increase in brain size is due to the formation of too many connections or poor elimination of inappropriate connections is not known. A study aimed at understanding the neuroanatomical basis of spatial working deficits in autism found decreased activation in the dorsolateral prefrontal cortex and posterior cingulate cortex with the use of functional magnetic resonance imaging (MRI) (47). Functional imaging studies during tasks that invoke mentalizing show that Asperger pa-

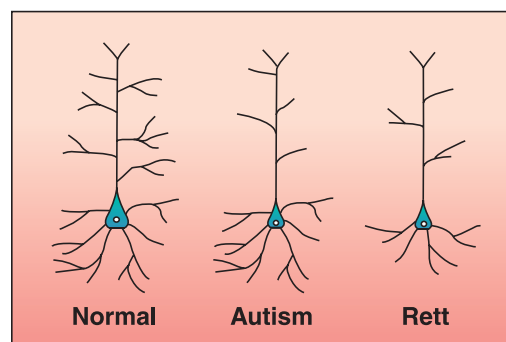


Fig. 2. Schematic representation of pyramidal neurons from control, autism, and Rett brains. In autism, the cell body is small and there is reduced dendritic branching. Similar changes occur in Rett, along with reduction in basilar dendritic branching. The reported changes are subtle and apply to a few neurons in selected brain regions in each disorder (50, 81).

tients have less activation in the critical medial prefrontal region, superior temporal sulcus, and peri-amygdaloid cortex (48). Neuropathological studies show fewer Purkinje cells than normal, small neuronal size, and increased packing density in several nuclei of the amygdala (49); small neurons with decreased dendritic branches have occasionally been observed in CA1 and CA4 (50).

Twin studies provide the most compelling evidence for a genetic origin of autism (51). The concordance rate in monozygotic (MZ) twins is 70 to 90% and for dizygotic (DZ) twins is 0 to 10% (52–55). The high concordance rate in MZ twins suggests either de novo sporadic mutations in a single gene for a particular autism locus or a multilocus model involving two or more interacting loci (56). Although these models are not mutually exclusive, the data thus far support the existence of several autism loci with mutations in

a single gene underlying the etiology for a specific locus.

A variety of chromosomal rearrangements have been reported in autistic children, with extra copies of 15q11–q13 being the most frequently reported (57–68). Nullisomy, disomy, trisomy, and tetrasomy of 15q11–q13 have all been associated with classic autism or other developmental disabilities, which suggests that dosage of one or more genes in 15q11–q13 is critical for neuronal function. Because many of the duplications causing an autism phenotype are of maternal origin, one cannot help but consider the *UBE3A* gene, mutated in Angelman syndrome, a prime candidate for mediating some of the phenotypic features. *ATP10C* is another gene that is maternally expressed in some tissues and may contribute to the phenotype (69).

Single gene mutations can also produce an autistic phenotype. A recent study identified *MECP2* mutations in 2 out of 68 females with an autistic disorder (20). These two females had mutations that typically cause classic Rett syndrome, so it is likely that modifier genes and/or regional-specific differences in XCI patterns are responsible for their autism phenotype. Mutations in neurologin-3 (*NLGN-3*) and *NLGN-4*, mapping to Xp22.3 and Xq13, respectively, can cause autism or Asperger syndrome (70). A screen of 140 male and 18 female siblings and twins identified a frameshifting mutation in *NLGN-4* and missense mutations in an evolutionarily conserved residue in *NLGN-3*. That both mutations were found in asymptomatic mothers could be explained by XCI, but it is possible that the missense mutation is a benign variant. The case of the truncating mutation in *NLGN-4* is more convincing, given that its de novo nature has been established. These data show that mutations in a single gene can indeed repro-

duce all the classic features of autism and, for some cases, provide a genetic mechanism for the high male-to-female (4:1) ratio in autism. They also provide neurobiologists with two excellent molecules with which to begin studying pathophysiologic mechanisms in autism. It is tempting to speculate that additional autism genes might be soon identified by following the pattern of Rett research, i.e., by focusing on cases with a strictly defined phenotype (e.g., classic autism with or without regression) to decrease the effects of genetic heterogeneity. As causative genes are found, they can be tested in patients with variant phenotypes.

Do Rett and Autism Meet at the Synapse?

For all the apparent differences, there are striking similarities between Rett syndrome and autism. Indeed, Rett has been classified

as a pervasive developmental autistic spectrum disorder in the ICD-10 (71). The timing of disease onset is similar; some neurons show reduced dendritic arborization (Fig. 2); and both disorders manifest abnormal social reciprocity, lack of communication, and stereotyped behaviors. Could there be mechanistic relationships between the two diseases? The continuous increase in abundance of MeCP2 in cortical neurons throughout childhood (31) (Fig. 1) points to the dynamic regulation of this protein, perhaps as neurons form new synaptic connections that might be experience-dependent. I suggest that both Rett and autism could be disorders of synaptic modulation or maintenance.

Recent data consistent with such a hypothesis came from a study of MeCP2 expression in olfactory receptor neurons (ORNs), which display postnatal neurogenesis (72). MeCP2 expression localizes to mature ORNs. After ablation of ORNs, which induces neurogenesis, MeCP2 expression gradually reaches prelesion levels unless the ORN targets are removed by bulbectomy. Without ORN targets, and thus without functional synaptogenesis, the levels of MeCP2 in the mature ORN are not completely restored (72). Thus, MeCP2 is expressed in mature neurons before synaptogenesis and might be critical for maintaining or modulating synapses. In human patients, the data are consistent with the idea that MeCP2 is not essential for initiating synaptogenesis—clearly, there are enough viable synapses that Rett patients can function at some level—yet the precipitous loss of learned skills (and even the loss of learning itself) hint that the ability of Rett patients to maintain or form new synapses is impaired.

In autism, mutations in two different neuroligins draw attention to the synapse. NLGN-3 and -4 belong to a larger family of postsynaptic cell adhesion molecules, some of which are known to interact with β -neurexin (73, 74). Neurexins are encoded by three large genes that each give rise to α and β

(short) isoforms, depending on the choice of promoter (75, 76). α -Neurexins are essential for calcium-triggered neurotransmitter release through their ability to cluster or activate calcium channels at presynaptic terminals near the synaptic vesicles and release machinery (77). They have no effect on synapse formation. In contrast, the smaller β -neurexins induce presynaptic differentiation in immature cerebellar granule neurons and hippocampal neurons through their interaction with neuroligin-1 (74). Neuroligin-1 stimulates presynaptic differentiation and synaptic vesicle recruitment by clustering β -neurexin; furthermore, overexpression of neuroligin-1 induces postsynaptic differenti-

that some of its targets will directly or indirectly regulate gene products involved in autism. These interactions might occur at the synapse or regulate synaptic functions.

In contemplating possible pathogenetic relationships between Rett syndrome and autism, the *UBE3A* gene (located on 15q11–13), which causes Angelman syndrome, emerges as a tantalizing, if highly speculative, link. Angelman syndrome resembles both autism and Rett syndrome: Affected children suffer developmental delay, movement disorder, tremulousness, hand-flapping, short attention span, slowed head growth, increased sensitivity to heat, stereotypic mouthing behaviors, and a fascination with water. Indeed, several patients with Angelman syndrome

meet the behavioral criteria for the diagnosis of autistic spectrum disorder, and *MECP2* mutations have caused some children to display an Angelman phenotype (78–80). Given the importance of DNA methylation in regulating neuronal expression of this gene, could it be that MeCP2 regulates *UBE3A* expression? As for autism, loss of function, duplications, and triplications of *UBE3A* have been associated with autistic features in patients with 15q11–q13 anomalies; could *UBE3A*, a ubiquitin ligase, be involved in the degradation of NLGN and/or one of its partners? We can now test whether some molecular pathways are shared by these three disorders (or groups of disorders), because specific molecules are in hand, and there are excellent mouse models for Rett

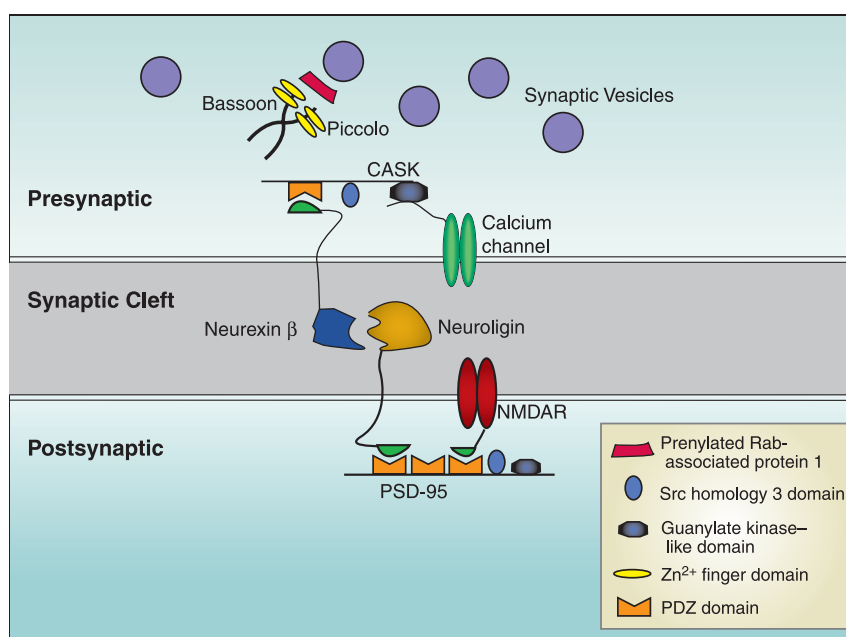


Fig. 3. A model depicting the role of neuroligins for clustering β -neurexin and inducing presynaptic differentiation. Neuroligin in the postsynaptic membrane recruits β -neurexin molecules in the presynaptic membrane and leads to their clustering. Clustered β -neurexin molecules recruit scaffolding and signaling molecules that, in turn, signal the recruitment of synaptic vesicles. Neuroligin might contribute to postsynaptic differentiation by interacting with scaffolding proteins such as PSD-95, which also interact with glutamate receptors. This model is based on data from a study of neuroligin-1 and β -neurexin (74). Whether NLGN-3 and NLGN-4, mutated in autism, have similar or related functions needs to be investigated.

ation based on the increase in PSD-95 and puncta positive for glutamate receptors GluR2/3 (Fig. 3). Focusing attention on the synapse provides molecular targets that deserve to be thoroughly investigated in autism (Fig. 3). Because of the extensive alternative splicing that occurs in this family of genes, some cases of autism might be due to tissue-specific splicing defects. Such abnormalities might be harder to detect by sequencing of coding regions and/or might result from dysfunction in RNA-binding proteins that mediate processing of such RNAs.

Although we have not yet identified neuronal MeCP2 targets in mammals, I suspect

and Angelman syndrome. Although there are other causes of autism (and possibly Rett) that remain to be discovered, knowing the genetic basis of some cases is sufficient to allow us to begin unraveling the complex and fascinating pathogenesis of these unusual and devastating disorders.

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REVIEW

Looking Backward to Move Forward: Early Detection of Neurodegenerative Disorders

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Early detection of neurodegenerative disorders would provide clues to the underlying pathobiology of these diseases and would enable more effective diagnosis and treatment of patients. Recent advances in molecular neuroscience have begun to provide the tools to detect diseases like Alzheimer's disease, Parkinson's disease, and others early in their course and potentially even before the development of clinical manifestations of disease. These genetic, imaging, clinical, and biochemical tools are being validated in a number of studies. Early detection of these slowly progressive diseases offers the promise of presymptomatic diagnosis and, ultimately, of disease-modifying medications for use early in disease and during the presymptomatic period.

In the past decade, an explosion of information in molecular neuroscience has markedly enhanced our understanding of and potential therapy for neurodegenerative disorders. These diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), motor neuron disease, Huntington's disease (HD), and other neurodegenerative dementias, generally begin late in life

and slowly but inexorably cause progressive neuronal degeneration and result in disability or death. Recent studies have demonstrated that these disorders are characterized by a presymptomatic phase, likely lasting years, during which neuronal degeneration is occurring but before clinical symptoms appear. This presents both a challenge—How do we identify individuals during this preclinical period—and an opportunity: Can preventive therapy be started during the preclinical period before disease symptoms appear? Therefore, a major goal of clinical research is to improve early detection of these diseases by developing tools to move diagnosis backward in the neurodegeneration temporal course (Fig. 1).

These tools would enable us to (i) identify at-risk groups both for disease onset and progression during the preclinical period; (ii) accelerate and enhance the accuracy of diagnosis in the early clinical phase to ensure appropriate treatment; and (iii) speed the development of drugs that might modify disease progression during the (earlier) preclinical and clinical periods and, ultimately, enable these therapies to be directed at individuals in the preclinical phase of illness to prevent or slow the onset of clinical manifestations of disease. Strategies might include therapies specific for the disease pathobiology, such as anti-amyloid medications for AD, or interventions that address nonspecific disease mechanisms, such as inflammation or oxidative stress. In the case of AD, a delay in onset by 5 years could translate into a 50% decrease in disease prevalence (1). A delay of 10 years would result in virtual disappearance of the disease.

These tools emerging from many new technologies for neurodegeneration and/or for clinical manifestations of disease. Biomarkers are broadly defined as characteristics that can be objectively measured and evaluated

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