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Special article

A BIOMARKER-BASED SOLUTION FOR THE LIMITED ACCESS TO EARLY DIAGNOSIS AND ASSESSMENT OF AUTISM

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Abstract

With the upsurge of community uptake in population-based early screening for autism, the main obstacle to increasing access to early treatment and intervention services is the extremely limited access to high quality diagnosis, specifically the shortage of expert clinicians. Diagnostic evaluation models deployed by academic centers of excellence, which typically require the investment of 6-10 hours by specialized multidisciplinary teams, is not a viable solution to the vast needs of communities, resulting in parents' "diagnostic odysseys" and delays, often of several years, for treatment, interventions and supports. Biomarker-based objective procedures for early diagnosis and assessment of autism are now available, clinically validated, and cleared for broad implementation by the US Food and Drug Administration (FDA). They are intended to increase access while maintaining high quality. Such solutions, however, will require change in entrenched models of diagnostic care, and aggressive prioritization of the needs of the community at large. If these innovations are successful, the number of children diagnosed in the first three years of life will double or triple. This will, in turn, require much greater investments in resources for treatment, including massive workforce training of providers capable of delivering community-viable caregiver-mediated interventions, and of early educators capable of serving autistic children in therapeutic inclusive preschool settings.

Key words: autism spectrum disorder, neurodevelopmental disabilities, early diagnosis, biomarker

Resumen

Una solución basada en biomarcadores para el acceso limitado al diagnóstico precoz y evaluación del autismo

Con el aumento de la aceptación comunitaria de la detección temprana del autismo basada en la población, el principal obstáculo para aumentar el acceso al tratamiento temprano y a los servicios de intervención es el acceso extremadamente limitado a un diagnóstico de alta calidad, específicamente la escasez de médicos expertos. Los modelos de evaluación diagnóstica implementados por centros académicos de excelencia, que normalmente requieren la inversión de 6 a 10 horas por parte de equipos multidisciplinarios especializados, no son una solución viable para las vastas necesidades de las comunidades, lo que resulta en "odiseas diagnósticas" y retrasos, a menudo de gran importancia, para los padres varios años, para tratamiento, intervenciones y apoyos. Los procedimientos objetivos basados en biomarcadores para el diagnóstico temprano y la evaluación del autismo ya están disponibles, clínicamente validados y aprobados para su amplia implementación por la Administración de Alimentos y Medicamentos de EE. UU. (FDA). Su objetivo es aumentar el acceso manteniendo una alta calidad. Sin embargo, tales soluciones requerirán cambios en los modelos arraigados de atención de diagnóstico y una priorización agresiva de las necesidades de la comunidad en general. Si estas innovaciones tienen éxito, el número de niños diagnosticados en los primeros tres años de vida se duplicará o triplicará.

Esto, a su vez, requerirá inversiones mucho mayores en recursos para el tratamiento, incluida la capacitación masiva de la fuerza laboral de proveedores capaces de brindar intervenciones comunitarias viables mediadas por cuidadores, y de educadores tempranos capaces de atender a niños autistas en entornos preescolares terapéuticos inclusivos.

Palabras clave: trastorno del espectro autista, neurodesarrollo, diagnóstico precoz.

A personal introduction to early identification, diagnosis and treatment of autism

In my 35-year career as a clinician and diagnostician, I have had the privilege of being trained and then worked with some luminaries in diagnostics and clinical care of autistic children such as Donald J. Cohen, Fred R. Volkmar, and Sara S. Sparrow. I have also had the opportunity to build programs of care, science and training in this clinical domain, including one of the largest centers of its kind in the US. I have also been proud of leading clinical and research teams that adhere to the most rigorous standards of diagnostics, which emphasize the expert use of reference standard diagnostic and developmental tools and the deployment of clinicians with many years of clinical training and experience in the field. Most of all, I have achieved some professional fulfillment for serving many families who reached out to us, and we could serve, in the two academic health centers of excellence to which I have been affiliated throughout my professional life. And yet, the public health challenge that this domain of clinical care presents at a societal level is overwhelming and universal. It traumatizes families with endless waits and leads to missed opportunities to optimize the outcomes of the majority of autistic children. Autism is a lifelong condition, which can be associated with severe disabilities and challenges to child and family, and to costly burdens to the healthcare, educational and supports systems. If we believe that the children we do not see and serve are as important as the children that we do see and serve, there is an urgent need to recognize that academic health centers of excellence sometimes operate as an insolated, content with their rigorous standards but virtually inaccessible and irrelevant to the needs of the community at large, wherein most of the over 95 000 children born every year in the US who will have autism are not identified and diagnosed in their first three years of life. In this way, these many thousands of children will fail to benefit from early treatment and interventions that may afford optimized lifetime outcomes. This fact is the impetus for the work described in this manuscript.

The public health crisis of early identification, diagnosis and treatment of autism

Autism spectrum disorder (hereafter autism) is a neurodevelopmental disability diagnosed behaviorally by the presence of early emerging and persistent deficits in social interaction and communication skills, and by the presence of restricted and repetitive patterns of behavior. Early identification and treatment are two of the most important factors promoting improved lifetime outcomes for children with autism[1]. Because up to 80% of parents recognize developmental concerns in their autistic children by age 2 years, the American Academy of Pediatrics recommends universal screening for autism at 18 and 24 months[2] during well-child visits. More recently, many health insurance payers have made screening for autism a requirement for coverage of the well-child visits at these ages. This, in turn, has led to a dramatic upsurge in the uptake of early screening for autism by primary care pediatricians[3]. Although the most widespread screening tool for autism may still miss more children than it identifies, (with a rate of up to 60% of false negatives)[4], for the large number of toddlers who screen positive, the main obstacle to accessing services has become the limited access to diagnosticians[5,6]. Most diagnostic programs have long waitlists[7], contributing to the fact that only one in every 5 autistic children in the US is diagnosed before the age of 3 years[8]. Delay in diagnosis delays opportunities to support children and families at early ages, when the brain is still most malleable, treatment can provide optimal benefits, and before maladaptive behaviors may become entrenched [9,10]. With a prevalence rate of 1 in 36, autism is the most common complex neurodevelopmental disorder[11]. Therefore, as a result of

this challenge, many thousands of families are deprived from early intervention services every year, including services that should be available to them via federally mandated programs created to support any child with developmental concerns such as autism.

Clinicians' challenges in early diagnosis of autism

Expert diagnosticians are trained to perform extensive observations of children using standardized tests, to elicit and review extensive information from parents and other sources, and then to reach a diagnostic assignment based on the totality of information available in a process that may take many hours and sessions. This laborious and costly model limits the number of children clinicians can diagnose, leading to waitlists, typically of many hundreds of families, and delays that may extend to months and years. Yet, most diagnosticians know that a very large percentage of these referrals have autism and, in some programs, the very referral to an autism clinic may carry an autism diagnostic predictive value of up to 80% to 90%. Therefore, maintaining these children in waitlists is unconscionable, and yet it is a burden experienced by most diagnosticians in the field. In addition, the diagnosis of toddlers can be very challenging, as symptoms are still emerging, developmental changes are occurring rapidly, and clinical tools are subjective, leading to the fact that in up to 30% of all cases, clinicians feel suboptimal confidence in their diagnosis[12]. These various challenges experienced by clinicians are exacerbated further by the knowledge that the families most likely to have limited access to their services are those from minority, low-income and rural communities[13], resulting in a system that is, overall, inequitable, unethical, and unacceptable.

Biomarker-based solutions to greater access to early diagnosis of autism

These public health and clinical challenges have accelerated research on biomarker-based solutions intended to make the diagnostic process more efficient and more accessible, while retaining high quality and the assurance of accuracy. One such solution, called EarliPoint, an eye-tracking based tool for early diagnosis and assessment of autism, was recently cleared by the FDA for broad clinical use. EarliPoint leverages an objective and quantitative biomarker –*social visual engagement*–or the way children look at and learn about their social environment, which directly reflects core features of emerging social disability[9]. Prior research indicated that dynamic quantification of social visual engagement has neurobiological and clinical face validity: individual variation in social visual engagement reflects individual genetic variation[14]; and autism-related differences[14,15] in social visual engagement are developmentally early emerging, and are predictive of later autism diagnosis[15].

Two recent simultaneously published reports provided clinical validation data for EarliPoint[16,17]. Pooled results across feasibility and pivotal studies involving over 1600 toddlers (age 16-30 months) and two independent replications indicated strong diagnostic performance: accuracy of 84.0%, sensitivity (se) of 80.6%, specificity (sp) of 87.0%, positive predictive value (PPV) of 84.4%, and negative predictive value (NPV) of 83.7%. EarliPoint also yielded accurate proxies for indices of social disability, (capturing 74.5% of the variance of the *Autism Diagnostic Observation Schedule, 2nd edition*), and for indices of verbal and nonverbal ability (capturing 79.5% and 69.0%, respectively, of the variance of the verbal and nonverbal age equivalent scores of the *Mullen Early Scales of Learning*). EarliPoint is intended to provide evidence-based clinical information to the diagnostician, in the form of a quantitative diagnostic classifier (of autism vs. not-autism) and quantitative indices of severity, all of which should inform clinical decision-making regarding modality and intensity of treatment and interventions.

Context of use of EarliPoint in early diagnosis and assessment of autism

EarliPoint was not intended to replace clinicians. Autism is a consequential diagnosis, and it is critically important that families have an opportunity to discuss the implications of autism with clinicians, and to avail themselves of supports to translate the results of an evaluation into a plan for treatment and access to the services and supports they need. EarliPoint was designed to provide a clinician with science-

based, objective and quantitative information on a toddler's diagnostic and developmental status. The procedure takes on average 12 minutes, as a toddler watches in a tablet the video scenes of other children interacting while eye-tracking data are collected at a rate of 120 times per second. Upon completion of the procedure, data are uploaded to a secure server and are processed through a data quality and analysis pipeline. Some 15 minutes later, a clinical report is issued to a clinician portal, containing a diagnostic classifier of autism or not-autism, including the predictive probability of the classifier: a positive predictive value if the diagnosis is autism, or a negative predictive value if the diagnosis is of not-autism. The clinical report also includes the three indices of severity: levels of social disability or autism, and age equivalent levels of verbal and nonverbal ability.

EarliPoint was intended to make the diagnostic process more efficient and less costly, and, in this way augment capacity of, and increase access to, diagnostic services. Because the tool was tested against expert clinicians conducting rigorous evaluations, while using standardized testing, the goal of EarliPoint is also to make high-quality diagnosis more accessible to families by broadening the pool of clinicians who can offer diagnostic services, from the limited number of highly experienced clinicians to a larger number of less specialized clinicians who can nevertheless support families' access to the services they need now. In our experience, EarliPoint can reduce the number of hours required for diagnostic evaluations by almost a third, and in this way, free clinicians to spend more time with families while also allowing them to augment the volume of their services, reduce waitlists and avoid economic losses, which could jeopardize the sustainability of their program.

The successful adoption of EarliPoint requires adjustments of patient flow and procedures to maximize its clinical utility. To optimize the clinical utility of the tool, these adjustments need to be made in a given context of use or clinic. One current model is to complete some procedures prior to an in-person visit to the clinic. Specifically, trained clinical staff can perform a diagnostic interview with parents via telehealth, and a trained technician can complete the EarliPoint protocol at the point of easiest access to the family, in a clinical setting or at home. The diagnostician then reviews the clinical information available –EarliPoint's results, the diagnostic interview, and a review of a child's electronic health record – in preparation for the in-person evaluation. During the in-person evaluation, if the totality of information is clearly consistent with a diagnosis of autism, the clinician can proceed to explore the needs for any behavioral management supports (e.g., how to address a child's problem behavior) or additional referrals (e.g., for genetic testing), and move forward with a parent conference in which the focus is on supports the child and family need, and on how to pursue those in their community. If the totality of information is either not entirely consistent with autism, or is consistent with a non-autistic developmental delay, the clinician may choose to conduct additional but abbreviated behavioral observations to disambiguate the diagnosis and, typically, to identify the form of non-autistic developmental delay a child may have (e.g., a language, a cognitive, or a global developmental delay).

A key consideration in the context of use, or where EarliPoint is being deployed, is the quantitative predictive values associated with the diagnosis it returns. Fundamentally, a diagnostic test is evaluated by its ability to classify patients correctly. While the performance of any diagnostic test derives from statistical measures obtained in clinical trials, some of these measures are more important to clinicians than others. Sensitivity (se) and specificity (sp) refer to the intrinsic ability of a test, independent of population context (i.e., independent of where it is used), to correctly identify those with the diagnosis (se) and those without the diagnosis (sp) when compared with the performance of a gold standard such as expert clinicians conducting an extensive evaluation. While informative to those interested in overall performance of the test, se and sp do not provide what a clinician needs when using the test to make a diagnosis in the case of an individual child. In such real-world implementation context, it is the Positive Predictive Value (PPV) and Negative Predictive value (NPV) that describe the proportion of patients with positive or negative test results who

are identified correctly. That is the reason why EarliPoint's results include a PPV statement (if the diagnosis is autism) and an NPV statement (if the diagnosis is not autism) with the precise probability that the results return for the individual child in the specific clinic where the evaluation is taking place. Of great importance, PPV and NPV are influenced strongly by the prevalence of the autism in the clinic where the test is being used (e.g., the proportion of children evaluated in the clinic who typically receive the diagnosis of autism)[18]. Equipped with this quantitative information --for example, that a child meets criteria for autism with 92% of probability—a clinician can decide whether this level of certainty is acceptable or whether additional information, or testing, are needed. Because these PPV and NPV considerations apply to any diagnostic test in medicine, and because some clinicians might not be aware of these statistical facts, or might not be used to data-driven clinical decision-making processes, EarliPoint has the potential of aiding clinicians who are less specialized or experienced in autism diagnostics to achieve higher levels of accuracy, approaching the rigor that defines gold standard diagnostic evaluations in autism.

Opportunities and challenges ahead

EarliPoint has the potential to meaningfully address the limited access to high-quality diagnosis and assessment of autism by replacing costly procedures and by providing clinicians with objective, quantitative and accurate clinical information. In this way, it will create efficiencies in clinical care, reduce costs, augment volume, and make high-quality diagnosis more available to families. However, there will be challenges to its adoption. For example, because clinicians have essentially been diagnosing autism in the same fashion, subjectively, via behavioral observations, since Leo Kanner first described autism in 1943, it is unlikely that expert clinicians will change their clinical procedures overnight by adopting biomarker-based tools. EarliPoint achieves quantitative results of clinical utility and issues a clinical report in about 25 minutes. This compares with several hours of testing and evaluation required by experienced diagnosticians. Therefore, we expect that in academic centers of excellence, confidence in EarliPoint's results is likely to first come from the use of EarliPoint in parallel to current diagnostic models, allowing clinicians to acquire their own sense of trust in the tool. This reluctance, however, is unlikely to be shared by clinicians who work in large, typically public programs of treatment and services, whose ability to serve families depends on diagnosis, and their access to expert diagnosticians is extremely limited.

The contrast of these two attitudes defines the main clinical policy discussion ahead of us: should we maintain our traditional models of autism diagnosis, despite of the fact that most families do not have access to it? Or, should we instead leverage science-based tools to increase objectivity, efficiency and accessibility to diagnosis, even if this is new? The answer to that question is likely to depend on where a given stakeholder stands in the ecosystem of autism diagnosis and care. If your perspective is that of a parent who knows that "earlier is better", but who also knows that access to diagnosis may take months, maybe years, if ever, the choice should be clear.

Beyond EarliPoint: in search of biomarkers to guide intervention in autism

While EarliPoint is the first diagnostic and assessment biomarker in autism cleared by the FDA, the field of biomarker research in autism has continued to grow exponentially in the past few years, with, however, limited success. In a recent review[19], evidence for 940 biomarkers was synthesized covering molecular biomarkers (including cytokines, growth factors, measures of oxidative stress, neurotransmitters and hormone), neurophysiology (such as EEG- and eye-tracking-based), and neuroimaging (such as functional MRI). The conclusion was that there is currently no response biomarker with sufficient evidence to inform autism clinical trials. In another wide-ranging systematic review[20], extending the focus from autism to neurodevelopmental disorders more generally, 780 studies covering biochemical, genetics, neuroimaging, neurophysiological and neuropsychological studies were assessed, and no evidence for a validated biomarker was identified that met the

authors' criteria of representing consistent findings in two or more studies from independent research groups, and sensitivity and specificity exceeding 80%. An additional concern in biomarker-based research, in autism and in other areas of medicine, and particularly about tools or procedures leveraging artificial intelligence (AI) analytic methods, is the methodological pitfall of "overfitting". This phenomenon refers to the possibility of achieving high accuracy results via machine learning, sometimes with sensitivities and specificities that approach perfect performance, but these results remain specific to a single cohort of participants, with no successful attempt to implement the algorithmic biomarker in an independent cohort of participants. Because of this danger, unless such AI-based biomarkers are successfully replicated in an independent cohort, their clinical utility remains unproven, and their potential remains suggestive but not definitive[21].

Beyond diagnosis

If only 1 in 5 autistic children is diagnosed with autism before the age of 3 years in the US, the advent of efficient and accessible biomarker-based diagnostic tools is likely to double and triple the number of children diagnosed early in their lives. This will shift the bottleneck to the treatment and support system, which is already grossly inadequate to provide services to all those who need it now. However, it would be cynical to propose that the status quo should not be improved because the current system will not have capacity to address increasing needs. There is already accumulating evidence that community-viable modalities of early treatment such as caregiver-mediated interventions and inclusive therapeutic pre-school settings, can deliver effective results if services are delivered early in a child's life. And yet, while the evidence for effectiveness already exists, there is a chronic shortage of providers, few incentives for these providers to pursue and stay in these careers, and mandates to cover the costs are underfunded. It will take societal fortitude to invest in such a new system of early brain health. While challenges are expected, the community of families impacted by autism deserve no less.

Conflict of Interest Disclosure: Dr. Klin is inventor of technologies that were used in research described in this manuscript. These technologies are licensed to EarliTec Diagnostics. EarliTec Diagnostics is a company that develops medical technologies for early diagnosis of autism and gives revenue to support treatment of children with autism. Dr. Klin is an equity holder in EarliTec Diagnostics.

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