Translating the Biology of Adversity and Resilience Into New Measures for Pediatric Practice

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abstract

As the science of adversity and resilience advances, and public awareness of the health consequences of stress grows, primary care providers are being increasingly asked to address the effects of adverse experiences on child wellbeing. Given limited tools for assessing these effects early in life, the authors explore how enhanced capacity to measure stress activation directly in young children could transform the role and scope of pediatric practice. When employed within a trusted relationship between caregivers and clinicians, selective use of biological measures of stress responses would help address the documented limitations of rating scales of adverse childhood experiences as a primary indicator of individual risk and strengthen the ability to focus on variation in intervention needs, assess their effectiveness, and guide ongoing management. The authors provide an overview of the potential benefits and risks of such expanded measurement capacity, as well as an introduction to candidate indicators that might be employed in an office setting. The ultimate value of such measures for both pediatricians and parents will require vigilant attention to the ethical responsibilities of assuring their correct interpretation and minimizing the harm of inappropriate labeling, especially for children and families experiencing the hardships and threats of racism, poverty, and other structural inequities. Whereas much work remains to be done to advance measurement development and ensure its equitable use, the potential of validated markers of stress activation and resilience to strengthen the impact of primary health care on the lives of young children facing significant adversity demands increased attention.

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In 2016, the American Academy of Pediatrics (AAP) Committee on Pediatric Research identified 7 major achievements in the past 40 years that have reduced morbidity and mortality and increased the quality of life for children worldwide.[1] These advances included life-saving immunizations, curing acute lymphocytic leukemia, and saving premature infants by treatment with surfactant. In 2017, the Committee predicted that the next 7 "great pediatric research advancements" would include: (1) interventions focused on early life origins of adult health and disease; (2) effective prevention of impairments in individual and population health based on increasing knowledge of the interactive influences of biology and the physical and social environment; and (3) implementation and dissemination research that translates scientific advances into more effective policies and practices in the face of poor infrastructure, poverty, and limited government capacity.[2] These diverse advances (both achieved and envisioned) share 2 fundamental requirements for breakthrough impacts: (1) a deeper understanding of the underlying pathophysiology of the targeted health challenge; and (2) the availability of robust metrics to initiate specific interventions as early as possible and assess their effectiveness in guiding ongoing management.

In 2012, the AAP published a technical report and policy statement that called on pediatricians to play a leadership role in addressing the impact of toxic stress on young children.[3,4] Over the ensuing decade, other policy statements and clinical reports called for greater pediatric attention to the adverse impacts of poverty,[5] racism,[6] perinatal depression,[7] and intimate partner violence,[8] among other threats to child wellbeing. In 2021, the first AAP policy statement[9] and clinical report[10] on trauma-informed care, complemented by an updated policy statement on toxic stress,[11] all referenced the biology of adversity and resilience as foundational for clinical practice and public advocacy.

Although this science base is continuing to advance dramatically in the laboratory, the absence of relevant measures that can be implemented in an office setting is limiting progress in clinical practice. In 2021, the updated policy statement on toxic stress and relational health noted this concern by pointing to "an urgent need for a battery of biological, behavioral, and contextual markers that might better stratify both the risks and predicted responsiveness to interventions at the individual level."[11] In a parallel fashion, the 2021 clinical report on trauma-informed care noted that "clinic-friendly, noninvasive biomarkers could also be used to identify patient-specific response to both stressors and therapeutic interventions."[10] The fundamental distinction between toxic stress (prolonged, excessive stress activation) and tolerable stress (relatively shorter duration of increased activation) underscores the need for objective measures to guide clinical assessment and ongoing pediatric management.[12,13]

Despite these 2 calls for enhanced measurement capacity, multiple AAP policy statements and reports focused on the health effects of significant adversity over the past decade (as noted above) have said little about the limited ability of pediatric practices to measure biological indicators of stress activation and resilience directly in young children. This lack of attention to measurement constraints raises important questions about the current and future role of primary health care in the early childhood ecosystem (ie, the full range of policies and services focused on children from birth to age 5 and their families). For example, most current approaches to pediatric screening and assessment of intervention effects for young children facing adversity rely on parent reports and behavioral observations that are easily incorporated into nonmedical settings. No other delivery system has the expertise or trusted reputation to employ and interpret biologically based measures in young children. Moreover, if pediatricians do not embrace this responsibility, profit-seeking entrepreneurs and "minute clinics" will undoubtedly move into this space without including the enduring, personalized relationships that define the essence of pediatric primary care.[14]

Finally, and arguably most urgent, the absence of individualized measures of variation in sensitivity to adversity has become an increasingly important concern in the face of growing use of rating scales of adverse childhood experiences (ACEs) (eg, ACE scores) across the early childhood field. Although ACE scores provide important data on population-level risk that can inform policymaking, multiple studies have found these scores to be no better than chance at predicting individual-level outcomes.[15,16] The increasing use of such scores in pediatric primary care, without additional information to assess individual differences in response to adversity, presents serious concerns that demand attention.

The authors of this article aim to stimulate discussion across the

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pediatric community (including researchers, clinicians, and leaders of training programs) about new research findings on the biological consequences of adversity, increasing calls for trauma-informed care, and the limited capacity of primary care clinicians to measure stress activation and resilience in young children. The authors have been working on this issue under the auspices of the JPB Research Network on Toxic Stress since 2015 and are developing a candidate battery of measures that is currently being validated but is not yet ready for implementation in practice. Learning from this process has highlighted the need to close the gaps among what scientists are discovering, how medical schools and residency programs are incorporating that knowledge into their curricula, how clinical practice might be strengthened by AAP-sponsored workshops, and how a broad diversity of parents must be "at the table" as we contemplate the ethical responsibility of maximizing benefits and minimizing risks of measuring stress effects directly in young children. Stated simply, although specific biological measures are not yet ready for routine use, there is an urgent need for widespread education and proactive discussion about the opportunities and challenges they present.

EMPOWERING PRIMARY CARE PROVIDERS AND PARENTS WITH CUTTING EDGE SCIENCE AND NEW MEASURES

The science is clear that the foundations of learning, behavior, and a lifetime of physical and mental health are shaped by the interactive influences of genes and environments over the continuum of developmental timing.[17] Responsive relationships, health-promoting experiences, and sufficient material resources to meet basic needs all strengthen the foundations of healthy development. Excessive adversity, which may arise from many sources and affect children across the socioeconomic spectrum, can disrupt developing biological systems with lifelong consequences. The cumulative hardships of intergenerational poverty, systemic racism, and other societal-level burdens faced by many families with young children underscore the complex challenges facing policymakers, clinicians, and other service providers attempting to prevent harm and build resilience in the earliest years of life. In this context, moving beyond current best practices to achieve larger impacts in promoting health and preventing disease is most likely to succeed when efforts are informed by the best available knowledge (drawing on both science and lived experiences) and guided by rigorous measurement.

Over the past 2 decades, the dominant framework for science-based policies and services in the early childhood period has focused on: (1) the impact of early experiences on the developing brain, (2) the disruptive effects of toxic stress on the foundations of early learning, and (3) the importance of responsive relationships as a source of resilience and an active ingredient of effective interventions.[18] Whereas these core concepts remain sound today, advances in the biology of development underscore 3 additional concepts that together provide a more robust roadmap for the future of science-informed, pediatric practice.

(1) Connecting the Brain to the Rest of the Body

That early experiences affect lifelong health as much as they affect school readiness is not a new idea, but massive evidence of the interactive impacts of early adversity on multiple biological systems (eg, neural, immune, metabolic) now demands substantive integration of the health and education sectors in the early childhood period.[17,19,20] The health care system offers the most sustainable and scientifically-grounded infrastructure for identifying needs and accessing indicated interventions as early as possible because primary health care reaches almost all children shortly after birth and is supported by a relatively stable (albeit insufficient) funding base. To achieve this goal, pediatric practice and complementary, community-based programs must be aligned within an integrated system of services and not be viewed simply as adjacent sectors to be connected. Stated simply, enhanced interagency coordination should be viewed as a strategy not a solution.

(2) Understanding Heterogeneity in Sensitivity to Context.

Science confirms what almost all caregivers know: individual children, even within the same family, respond differently to both adverse conditions and supportive relationships.[21] Given this core concept, generalizations about social determinants of health can be misleading, harmful, and/or wasteful. The biological embedding of early experiences and exposures (for better or for worse) is influenced by highly complex interactions among multiple variables, mediated by epigenetic regulation of gene expression.[17] This complexity is being elucidated through continuing research and new scientific insights and tools are creating new opportunities for increasing the impacts of evidence-based programs. Among these opportunities is the potential to advance beyond measuring generic effectiveness and to design new strategies for discerning

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what works for some children and not others, and how context influences those differences.

(3) Focusing on Sensitive Periods in Development Across Biological Systems

Although the notion that "earlier is better" has driven early childhood policies for more than half a century, growing knowledge about sensitive periods in immune system development and metabolic regulation, as well as in brain circuitry and function, demands greater focus on the prenatal period and first 2 to 3 years after birth.[22,23] The effects of chemical exposures and under or overnutrition during these periods on the development of multiple organ systems (eg, brain, heart, and lung) can be particularly severe.[24,25] At a behavioral level, significant neglect early in life can disrupt, often irreversibly, the development of attention and self-regulatory skills.[26] It is also important to underscore that sensitive periods in the development of multiple biological systems present windows of opportunity for positive as well as negative effects.[27]

Drawing on this rapidly growing knowledge base, pediatricians are uniquely positioned to play an important role as the most trusted source of cutting-edge science to promote the healthy development of young children within community-based systems of services. With this vital role in mind, mutually rewarding experiences for both providers and recipients of primary health care across a broad spectrum of circumstances ultimately depend upon the quality of their relationships, the trust on which those relationships are built, and the knowledge and assessment skills that can be brought to bear to respond to parents' questions. Health care providers are valued for their ability to monitor growth and development, as well as address a broad range of concerns about child health and behavior. The game changing potential of biological indicators of excessive stress to strengthen early identification of risk, targeted referrals to appropriate services, and measurement of intervention effects is an idea whose time has come. Although documented evidence supporting that potential is in its infancy, the projected benefits underscore the compelling need for investment in both developing measures and evaluating their impacts on the following elements of pediatric practice in the early childhood period.

Health Care Providers are Often Called Upon to Address the Needs of Children Who Have Been Exposed to Significant Adversity

Although anticipatory guidance for a wide range of issues is a core component of primary health care,[28] routine integration of trauma-informed approaches is constrained by limited training in this area and unclear guidelines for best practices.[29] The availability of validated measures of stress and resilience would strengthen the capacity to provide a personalized response to caregiver concerns rather than relying on generic reassurance, automatic referral for services, or a nonspecific "wait and see" response.

Individualized Data on the Effects of Hardship or Trauma on Young Children Would Increase Clinicians' Capacity to Provide Credible Reassurance for Families of Children Showing Evidence of Resilience

This could be facilitated by documenting the absence of physiologic disruptions in the face of significant adversity or during recovery from trauma.

Primary Care Practice Could be Strengthened by Enhanced Ability to Make Referrals to Well-Matched Interventions, When Indicated, Based on Identified Effects of Excessive Stress Activation

Extensive evidence in adults has documented that elevated levels of inflammation are associated with diminished responsiveness to both pharmacologic and behavioral treatments for depression.[30,31] Although comparable data on children are limited, a recent study of parent-child psychotherapy for early life trauma (whose efficacy has been documented in multiple experimental studies) found that high pretreatment levels of specific maternal proinflammatory biological indicators predicted poor response to treatment in both mothers and their children.[32]

The Capacity to Measure Stress Activation and Resilience Directly in Young Children Would Assist Primary Care Clinicians in Deciding Which Services are Working Well for Some and Not for Others

Validated biological indicators of potential toxic stress (eg, neuroendocrine, immune, and/or metabolic assays)[33] and behavioral measures of resilience (eg, executive function, self-regulation),[34] complemented by caregiver reports, would strengthen the ability to provide ongoing pediatric care for children and families experiencing significant adversity. For example, a systematic review of 17 studies, 4 of which focused on ages birth to 6 years, found evidence that cortisol activity could be altered by psychosocial interventions.[35] Although data on inflammatory markers in young children are more limited, a randomized study of a psychosocial intervention focused

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on improving parenting, strengthening family relationships, and building competencies for 11-year-old youth living in a low-income rural area documented highly significant reductions in 6 proinflammatory cytokines measured at age 19.[36]

Documented Reductions in Excessive Stress Activation Would Strengthen the Case for Health Care Funding of Effective Interventions

Data on early childhood services that demonstrate beneficial effects on biological indicators of risk for later stress-related diseases (which incur enormous health care costs) would be particularly powerful. One state-level policy initiative has sought evidence for biomarkers to identify children at high risk of later health problems and has funded projects to build a database to inform future investments in the early childhood period.[37,38]

ENHANCED CAPACITY TO MEASURE THE IMPACTS OF ADVERSITY AS A PREREQUISITE FOR MAKING SCIENCE ACTIONABLE IN PRACTICE

The obstacles to reducing disparities in healthy development in the context of pediatric primary care begin with the limited capacity of individualized services to significantly affect macro-level adversities (eg, economic insecurity, systemic racism, housing instability, community violence), which impose enormous burdens on the daily lives of many families. One promising strategy for breakthrough thinking in this area is to revisit the role of measuring social determinants of health to inform the delivery of personal health care. On the positive side, these kinds of data (which are based on epidemiologic studies linking exposures to outcomes) have driven multiple advances in public health policies and broader awareness of environmental influences on child health and development. On the other hand, it is essential that we do not equate correlation at a population level with the ability to predict the future of any individual child or identify specific intervention needs. Compelling support for this distinction can be found in a growing number of related, cohort studies involving large data sets (noted earlier) that have documented the well-established influence of adverse childhood experiences on health outcomes at a population level but relatively poor capacity for predicting specific outcomes in individual children.[15,16]

This challenge leads us to consider other areas of clinical medicine (eg, cardiovascular disease, some forms of cancer) where predictive measures at the level of the individual have led to dramatic breakthroughs in prevention and treatment. Few would argue, for example, that exposure to a high fat diet alone adequately predicts risk for cardio-metabolic disease without considering other individualized risk factors, such as family history and protective influences like balanced nutrition and physical activity. Whereas the concept of precision medicine is capturing increased attention in biomedical research, the predictive algorithms of the American Heart Association have long been the focus of successful prevention. Relevant predictive factors include multiple measures at the level of the individual, including blood lipids, blood pressure and, more recently, platelet activating factors and proinflammatory signaling.[39,40] Current evidence for linking biological indicators of stress activation in early childhood to specific intervention recommendations or health outcomes is clearly far from matching the rich knowledge base that has been built over decades of basic research and clinical application for promoting cardiovascular health in adults. The need to build that knowledge base to address the early life origins of a host of stress-related diseases is also clear and a strong commitment to that goal is imperative.

Given pediatricians' high level of education and relatively advanced understanding of brain development and stress physiology, the limited utilization of that knowledge in guiding the content of day-to-day primary care practice is difficult to understand. This is particularly striking given the long history of advances in neonatal intensive care which have moved far beyond increasing survival by leveraging stress biology and novel measures to modify the intensive care experience (eg, increased attention to parent-infant bonding, decreased sensory overload)[41,42] to improve outcomes in both development and health.[43] This striking contrast raises an intriguing question for medical education and pediatric training programs: why have advances in science been embraced more readily in hospital-based, tertiary care compared with community-based, primary care practice?

In the sections that follow, we present an overview of promising indicators of stress activation that could be used in an office setting. These candidate measures have been drawn from existing knowledge of adaptations to a chronic stress response, which is in its relative infancy compared with metrics applied to specific diseases. Our aim is to strengthen the capacity of primary care clinicians to generate personalized indices of relative risk in young children and to assess intervention effects to facilitate ongoing care. The empirical assessment of each candidate measure (or cluster of measures) is designed to determine its predictive validity at the level of the individual

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as well as its potential for scalability in routine primary care practice.

Finally, it is important to note that the potential value of these candidate measures is not only for assessing risk but also for documenting physiologic resilience and evaluating short-term treatment effects. This can be viewed as similar to how measures of lipids or blood pressure are used to assess treatment effects on the risk for cardiovascular problems in adults. Increased capacity to quantify and mitigate the adverse effects of excessive stress activation will help generate a comparably effective clinical science of health promotion and disease prevention for pediatric primary care.

POTENTIAL DOMAINS OF MEASUREMENT

Indicators of stress activation in children can be assessed at several levels of resolution (eg, molecular, cellular, systemic, and behavioral). As the stress response involves multiple biological systems and their interactive adaptations, a compilation of measures in the form of a composite battery or algorithm is likely to be more informative than any single measure. Supplemental Table 3 provides a detailed overview (with extensive references) of a wide range of potential domains of assessment based on decades of research. Drawing on current translational and clinical science, Table 1 presents a curated list of promising candidates for primary care practice that fall within 3 categories: ready for consideration, need for further feasibility testing, and possible future candidates. The challenges of implementation and the rapid pace of new discoveries and innovative technologies make this a highly dynamic field of work.

CRITERIA FOR SELECTING SPECIFIC MEASURES

A battery that includes biological and behavioral indicators of stress and resilience, combined with contextual information about family and community, requires attention to multiple factors to assure that its component measures are responsive to the needs of both health care providers and families. These requirements include scientific rigor, practical considerations of implementation, assurance of appropriate interpretation, and relevance to the lived experiences of parents across a wide diversity of contexts. Table 2 presents an overview of those considerations.

A PROMISING CANDIDATE BATTERY UNDER DEVELOPMENT

The JPB Research Network on Toxic Stress, a project of the Center on the Developing Child at Harvard University, was launched in 2015 as a partnership among developmental scientists, pediatric clinicians, and parents and community leaders primarily from communities of color. The Network's goal is to build new measurement capacity that can empower health care providers, parents, and other caregivers to better understand, quantify, and mitigate the effects of significant adversity on the health and development of young children. A preliminary battery of minimally invasive biological and behavioral indicators of stress activation and resilience has been identified (categorized as "ready for consideration" in Table 1). Feasibility testing in pediatric primary care settings has demonstrated few challenges in sample collection, storage, or measurement, and broad acceptability by health care providers and parents. That said, the composition of this battery will continue to evolve as new research becomes available, and much validation work remains to be done to establish normative values and clinically meaningful cut points and predictive algorithms, as well as to evaluate its sensitivity, specificity, and efficacy for clinical decision-making, before it is ready for routine implementation.

CHALLENGES OF MEASURING STRESS AND RESILIENCE THAT DEMAND SPECIAL ATTENTION

The challenge of augmenting data from caregiver reports and behavioral observations during an office visit with direct measures of a child's internal, biological activation of stress response systems should not be underestimated. Several obstacles are particularly worthy of consideration before such measures can be considered ready for broad-based implementation.

RESISTANCE BASED ON CURRENT BURDENS OF RECOMMENDED SCREENING

Decades of survey data indicate highly uneven compliance with existing professional guidelines (eg, Bright Futures[28]) and mandated requirements for routine screening procedures in pediatric primary care.[44] When resistance occurs, it is often attributed to multiple factors, including (1) the time required for yet another screening demand on top of an already extensive load, (2) concerns expressed by clinicians about not knowing how to respond to positive findings based in part on inadequate education and training, (3) uneven availability or awareness of appropriate referral resources for young children whose difficulties lie beyond the capacities of the pediatric practice, and (4) complicated webs of access to services and payment systems. Although these barriers make routine screening for biological stress responses unlikely in the

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TABLE 1 Promising Candidate Measures for Primary Care Practice

Selected Examples	Domain of Measurement	Advantages	Challenges
Ready for Consideration			
Cortisol, cortisone, DHEA, progesterone, testosterone	Neuroendocrine function	Measurable in hair (provides data on levels over several prior months)	Establishment of normative and predictive values pending
Interleukins	Inflammation	Measurable in saliva	Values can be altered by common viral infections that are prevalent in childhood
Telomere length	Cellular aging	Measurable in buccal cells	Establishment of normative and predictive values pending
Endocannabinoids	Neuromodulation	Measurable in hair (provides data on levels over several prior months)	Establishment of normative and predictive values pending
Behavioral measures of executive function (eg, NIH toolbox[53]; Minnesota Executive Function Scale (MEFS)[54]; A Developmental NEuroPSYchological Assessment (NEPSYII)[55]; Cambridge Neuropsychological Test Automated Battery (CANTAB)[56]	Prefrontal function	Validated, short duration tasks in tablet format available for young children	Data processing and interpretation still not fully automated
Polygenic risk scores	Genomics	Improving levels of prediction of heritability and individual differences in biological processes; temporarily helpful during validation process to identify individual differences in responsivity to adversity	Bioinformatics processing needed; marker of susceptibility rather than response; not likely to be included in final battery for routine clinical application, pending further consideration of acceptability of genetic markers by parents and primary care providers.
Growth trajectories	Organ remodeling	Core measure in routine primary care	Can be challenging to classify accurately
Needs Further Feasibility Testing			
Fasting insulin, glucose, leptin	Metabolic regulation	Information about peripheral metabolism; normative values well established	Fluctuations with feeding/fasting
Electroencephalogram	Brain electrical activity	Portability has improved dramatically in recent years.	Still costly
Heart rate variability, systolic and diastolic blood pressure	Cardiovascular reactivity	Values readily available; no processing needed	Need electronic monitoring
F2-isoprostane	Oxidative stress	Measurable in urine	Difficulty collecting urine from young children
Possible Future Candidates			
Epigenetic clocks, polyepigenetic scores	Epigenetic processes	Dynamic measure that reflects the interaction between genetic background and environment	Currently cost prohibitive
Skin lipidomics	Oxidative stress	Easily collected	Currently cost prohibitive; collection needs validation in large samples
Gut/airway/skin microbiome genomic analysis	Gut/airway/skin microbiome	Easily collected	Bioinformatics processing needed; interpretation still elusive; collection needs validation in large samples
Heart rate variability, cortisol	Cardiovascular reactivity, neuroendocrine function	Easily collected via wearable transdermal sensors	Collection with transdermal sensors needs validation in large samples

Background data to support candidate measures provided in Supplemental Table 3.

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foreseeable future, selective screening when children have elevated ACE scores or parents have concerns about the effects of increased stress on their child's health or development could strengthen the ability of clinicians to provide science-informed guidance, prescribe well-matched services when indicated, and establish baseline data for evaluating short-term intervention effects.

IMPERATIVE OF ACCURATE INTERPRETATION OF BIOLOGICAL MEASURES IN CONJUNCTION WITH OTHER SOURCES OF INFORMATION

Beyond assuring their scientific validity and reliability, the ethical use of measures of stress activation and resilience, and the prevention of unintended or undetected, negative consequences, requires simultaneous attention to observations and questions raised by parents and other caregivers, as well as broad public understanding of the varied effects of early adversity on child health and development. Central to this shared understanding is the recognition that adverse experiences are often the result of societal-level influences that undermine the conditions under which families are raising children and are subject to limited individual control. Even more important, successful implementation also depends on the clear recognition by both clinicians and parents that excessive stress activation in a young child can be an indicator of relative risk, but it is not a diagnostic biomarker of a specific disease nor confirmed evidence of a cause of a future impairment. Rather, a panel of validated indicators of stress activation could serve as what an FDA-NIH Biomarker Working Group referred to as "susceptibility and risk biomarkers" (ie, measures reflecting the potential for developing a stress-related medical condition in children not currently affected).[45]

DISTRUST GROUNDED IN DEEPLY EMBEDDED RACISM IN THE HISTORY OF BIOLOGY AND MEDICINE

Centuries of racist health care practices, exploitative medical research involving people of color, and the use of biological language to advance concepts of white supremacy present extraordinary challenges that must be addressed and overcome before communities of color will trust the promised benefits of measuring biological effects of adversity on young children.[46,47] Longstanding problems related to clinician bias, unequal treatment, and reduced access to medical care based on race, ethnicity, social class, and immigration status have undermined trust in the health care system for many groups, and lessons learned from the coronavirus pandemic underscore the need to confront these deeply engrained inequities.[48,49] In the final analysis, the equitable and

TABLE 2 Criteria for Selecting Measures

Criteria	Domains of Measurement Fulfilling the Criteria
Assessment at multiple levels of resolution, including molecular, cellular, physiologic, systemic, behavioral, and social context	Measures of neuroendocrine function, neuromodulation, inflammation, oxidative stress, cellular aging, genomics, and executive function; focus on composite battery, not single measures
Designed from a developmental perspective, requiring the establishment of age and sex-appropriate normative values	Measures of cellular and systemic aging, growth, and executive function
Reliable information on both risk and protective factors in the family and community context	Essential for all measures
Imperative that measurement results are empowering for families and the caregiver-clinician relationship, with particular attention to understandable distrust by families of color based on deeply embedded history of racism in biological research and health care services	Essential for all measures and particularly challenging for genomic metrics
Promising evidence of ability to predict and/or document risk for health or developmental problems, positive response to supportive environments, and differential intervention effects	Measures of neuroendocrine function, neuromodulation, inflammation, oxidative stress, cellular aging, genomics, growth, and executive function
Attention to receiver-operating characteristic curves that can aid in measurement selection by graphically comparing sensitivity and rates of false positives, thereby maximizing the clinical utility of a given measure or measures	Essential for all measures especially when combined in a battery through a predictive algorithm
Relative value of composite batteries and the role of algorithms in the development of multiparametric measures (ie, machine learning approaches to combinations of measures)	Currently under investigation for cortisol, cortisone, DHEA, progesterone, testosterone, endocannabinoids, Interleukins (Il-1β, Il-6, Il-8, TNF-α), mtDNA content, telomere length, behavioral measures of executive function, and polygenic risk scores
Need for data collection to be logistically and financially acceptable within a diversity of community settings	Currently under investigation for cortisol, cortisone, DHEA, progesterone, testosterone, endocannabinoids, Interleukins (Il-1β, Il-6, Il-8, TNF-α), mtDNA content, telomere length, behavioral measures of executive function, and polygenic risk scores

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acceptable use of biological measures of stress and resilience in young children will require a credible, collaborative approach to their development, implementation, and continuing refinement by scientists, clinicians, parents, and community leaders. This effort must involve extensive representation of and partnerships with communities of color, as well as ethnic and religious minority groups, parents involved in the child welfare system, and other populations whose voices have had relatively limited impact on the design, delivery, and payment structures for child health care. Co-ownership of the measurement development process from the beginning can build trust, strengthen parent engagement, honor family strengths, avoid focusing primarily on deficits, prevent inappropriate labeling (including unwarranted implications of genetic determinism), and promote joint decision-making. The deep distrust that many marginalized groups feel about how scientific knowledge is generated and used must be addressed directly through continuous dialogue. Without shared leadership and sufficient funding to sustain authentic co-ownership of a reciprocal learning experience there will be no realistic pathway toward broad acceptance of biological measures of stress in pediatric primary care.

UNLOCKING THE GAME-CHANGING POTENTIAL OF NEW BIOLOGICAL AND BEHAVIORAL MEASURES IN THE EARLY CHILDHOOD PERIOD

The foundational importance of the science of stress and resilience for pediatric practice demands greater attention, and the capacity to measure biological indicators of adversity directly in young children, before overt manifestations are visible, is an essential prerequisite for translating that science into more effective health promotion and disease prevention. Whereas much work remains to be done in a fully inclusive and equitable fashion before new measures are ready for broad implementation, such metrics have the potential to advance the science of personalized pediatric practice as well as generate aggregate data for informing policies and services at a community level.

Currently mandated screening protocols rely largely on parent checklists of child skills and behaviors, demographic risk factors, and rating scales of adverse childhood experiences (eg, ACE scores), each of which adds important information but none of which sufficiently predicts individual trajectories associated with long-term outcomes. The opportunity to simultaneously consider parent reports (which provide important information about what caregivers think, observe, and choose to share) and individualized measures of stress responses directly in young children experiencing adversity would substantially facilitate the principle of proportionate universality, which apportions broadly available interventions according to varied levels of need.[50]

Documenting the disruptive effects of racism and intergenerational poverty on developing biological systems that are essential for lifelong health would also strengthen pediatric advocacy for more effective policies to address structural inequities that threaten child wellbeing above and beyond the provision of direct clinical services and family support.[51] Although the potential of biological measures of stress and resilience to address inequity by better aligning resources and needs has not yet been studied, evidence that social interventions can positively influence biological correlates of childhood adversity suggest that equity-focused initiatives can benefit from these types of measures in the future.[52]

At a time when many of the most pressing threats to child health and development require expertise and services that are beyond the domains of conventional pediatric practice, it is essential that primary health care for young children be viewed as an integral part of a larger, multisectoral, early childhood ecosystem. Among the many professional fields engaged in the design and construction of that ecosystem, including educators, social workers, child development specialists, mental health and behavioral health clinicians, childcare providers, other clinical specialists, and policy-makers, pediatricians are uniquely positioned to make the biology of adversity and resilience measurable.

Moreover, as pharmacies and walk-in, "minute clinics" are becoming increasingly successful in delivering immunizations, treating minor infections and injuries, conducting routine physical exams, and providing chronic disease follow-up, pediatrics must offer a competitive model for promoting the healthy development of children and supporting families. Beyond the need to address this existential challenge to primary care practice, new measures that draw on the scientific knowledge that dominates medical education and residency training would open promising pathways for greater professional satisfaction for pediatricians, add a powerful dimension to the clinician-parent relationship, and position pediatrics at the leading edge of a highly dynamic, science-informed, early childhood ecosystem.

Although measures of stress activation are not yet ready for "prime time" application in routine practice, the need for broad-based attention to the shortcomings of current measurement capacity in primary health care for young children is clear. The entire early

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childhood field has an important stake in unlocking this barrier to science-informed progress in confronting the origins of lifelong disparities in learning, behavior, and both physical and mental health. Pediatrics holds a key to open that lock.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
ACEs: adverse childhood experiences

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