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Proposed Endocrine Funding Priorities for the NICHD Strategic Plan: Expert Opinion from the Pediatric Endocrine Society

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Introduction:

In 2018, the NICHD requested public input for their strategic plan. The Pediatric Endocrine Society (PES) Research Affairs Committee (RAC) formed a subcommittee to develop recommendations related to pediatric endocrinology. The subcommittee solicited opinions from research subject matter experts representing diverse areas within pediatric endocrinology, RAC subcommittee members, PES membership. The results were shared with the NICHD, but we believe will also be of value to pediatricians and pediatric endocrinologists broadly, and so are summarized herein.

Methods:

Six thought leaders identified by PES leadership and RAC members provided detailed descriptions of priority areas/gaps for NICHD funding (Supplemental Materials S1). Further, an anonymous REDCapTM survey, approved by the RAC subcommittee and the PES Board of Directors, was emailed to all PES members (Supplemental Materials S2). No inducement was provided. The survey asked members to describe their top three priority research topics, and priority funding mechanism to support training. Information was collated and major themes identified and summarized by the RAC writing group.

Results:

Survey Response

The survey was emailed to 1388 PES members, and 188 (13.5%) completed. 62% of respondents were female; 85% were MDs, 6% MPH/MS, and 8% PhDs. Respondents varied

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in age (45% 26–45, 37% 46–65, and 18% >65 years old) and race (74% White, 14% Asian, 5% Black, 2% multiracial, 5% preferred not to say). Respondents were mostly from academic centers (82%) and had dedicated research effort (86%). 56 respondents had recently received NIH funding, 22 from NICHD.

Specific Topics (% of respondents in parentheses)

Pediatric obesity (40%) was noted as an important funding area given the risk for life-long morbidity, high societal cost/burden, and paucity of effective prevention and treatment strategies for obesity and its complications. Further research on the genetic/epigenetic and environmental triggers that influence appetite regulation and energy expenditure are needed. Little is known about the effects of inflammation on insulin, metabolism, and growth during adolescence. The critical windows of early development and puberty are unique time points where weight gain might influence inflammation, appetite, and insulin resistance.

Type 1 diabetes (T1D, 40%) was emphasized, with major potential research topics including identification and targeting of environmental and genetic causes, and socioeconomic/racial disparities in access to technology and treatment outcomes. Improved treatments, including automated insulin delivery, curative therapies such as beta-cell replacement/regeneration, and immunomodulation were highlighted. The high prevalence, burden of contemporary insulin regimens (making them unworkable for many families), risk of complications, and costs to patients, families, and society all make this research critical.

Type 2 diabetes (T2D, 38%) was emphasized as requiring further research, particularly due to the high costs associated with its increasing prevalence, complications, and morbidity/mortality. Large-scale studies, such as TODAY (1) and RISE (2), suggest that adolescents with T2D are a vulnerable population, with faster β -cell decline, poorer treatment response, and higher complication rate than adults. Thus, we need to better understand the pathogenesis, treatment, and prevention of youth-onset T2D and its complications, including NAFLD/NASH. Other gaps include difficulties with diagnosis, targeted treatments beyond metformin and insulin, and prevention strategies targeting *in utero* and early life development. How obesity development during the profound insulin-resistant state of puberty impacts ectopic fat deposition and beta-cell function remains unknown.

Many respondents identified transgender medicine (33%), given the increasing number of referrals and very limited evidence-base for treatment. Several topics need be addressed, including epidemiology, diagnostic tools, optimizing therapy, and effects of treatment on bone health, neurocognition, psychosocial outcomes, and fertility. In addition, studies are necessary to define the basis of gender identity and gender variance across a lifespan.

Citing the increased prevalence of childhood cancer survivors, endocrine disorders after cancer therapy (18%) was deemed an important field, with specific topics including evaluation of growth, puberty, and bone health in this vulnerable population. Other knowledge gaps include evidence-based screening guidelines in cancer survivors, established protocols for fertility preservation, and an understanding of how and when to replace deficient hormones, particularly growth hormone.

Endocrine disruptors (17%) affect many physiologic processes, including body weight, growth, puberty, and fertility. Studying the impact of environmental factors on the onset and timing of T1D and T2D is important. These are complex issues, where media focus can have a disproportionate influence given the limited available data. An investment in this area could provide widespread benefit and fill an important void.

Disorders of sex development (16%) were included as a priority. Reasons included the significant stress and burden these conditions place on patients and families, and the controversial nature of their treatment. Clinical decision-making is at risk of being dictated by advocacy groups in the absence of clear, long-term data. Thus, research is needed to better understand the genetic and biologic determinants of sex development and gender identity. Goals for this area include improving diagnosis (including prenatal), maintaining fertility, informing shared decision-making, and enhancing long-term medical/surgical outcomes to improve well-being, sexual function, and adult disease risk.

Many identified genetic syndromes/rare diseases (15%) as an important topic for funding. Advances in genetics and molecular medicine are facilitating diagnostic investigations, including uncovering more diagnoses of unclear significance. Genetic/molecular investigations could improve the care of rare disorders, such as hyperinsulinism and skeletal dysplasias, which cause significant morbidity and often have no identified mutation and few approved therapies. Given these knowledge gaps, a little effort could potentially yield large benefits. Additional specific areas of need include rare bone diseases, hypoglycemia, management of sex chromosome aneuploidies, and improved newborn screening.

Puberty (10%) is an important and understudied developmental stage associated with many hormonal, physiological, psychological, and neurological changes. While groundbreaking work on the developmental origins of adult disease has focused on fetal and early life, less is known about the impact of puberty. A better understanding of the regulation of pubertal timing and the effects of puberty on metabolism could reduce the psychological sequelae of precocious and delayed puberty and the rising prevalence of puberty-associated metabolic disorders, respectively. The NICHD could take the lead in funding research on the genetic, epigenetic, and neuroendocrine regulation of pubertal timing, and how metabolic, environmental, and socioeconomic factors may modulate these. Further work on the accretion of healthy and disordered bone in adolescents is critical to understanding and reducing osteoporosis in later years.

Related to this, sex steroid therapy for adolescents with hypogonadism and for transgender youth was noted as lacking a sufficient evidence-base. Few studies have collected data on how hormone replacement or cross-sex hormone therapy affects bone, brain, and cardiovascular tissues in adolescents, or their long-term health implications.

Short stature (10%), particularly the genotype/phenotype identification of idiopathic short stature (ISS) was prioritized as an opportunity to deepen our understanding of growth pathology and reduce healthcare expenditures. Improved genotypic characterization could help refine which forms of ISS are growth hormone (GH)-treatable targets. A collaborative NICHD-funded genotyping effort could provide useful mechanistic understanding of growth

pathologies, potentially eliminating the need for pharmacologic growth hormone secretion testing. This could yield tremendous healthcare savings on GH testing, brain MRIs, and targeted genetic testing, and lead to prospective trials of GH or other agents to better and more economically optimize height.

With respect to training support, respondents prioritized individual K-awards (35%), institutional K-awards (31%), T32s (23%), and finally individual training grants (11%). Members noted the importance of junior faculty awards during the critical fellowship-to-faculty transition. Individual K-awards were described as more democratic, allowing for support outside of major research centers, and possibly more successful, while K12s may reflect better research environments, and institutions may be better positioned to recognize promising candidates. Those supporting T32 awards spoke to the need to increase the number of pediatric endocrinologists in both clinical and research roles. However, data describing the efficacy of these mechanisms in fostering meaningful research is necessary to set training grant priorities.

Discussion:

The NICHD plays a critical role in supporting pediatric endocrine research. Across topic areas, pediatric endocrinologists prioritized investigations that would clarify the antenatal, early childhood, and pubertal antecedents of adult disease, and improve disease treatments to minimize later morbidity; these approaches dovetail with NICHD priorities established during previous strategic planning.

Our modest response rate was consistent with other physician surveys, for example (3,4). However, ~45% of PES members work in academic settings, so we heard from ~18% of our academic membership. In any case, it is clear that the highlighted priorities are of major importance to child health based on lives affected, unmet needs, and opportunities for impact. Given the focus of pediatric endocrinology on growth, puberty and weight gain, pediatric endocrine priorities are truly child health priorities and deeper research into these areas will improve the lives of children.

While diabetes/obesity research is supported by other NIH institutes, the child health and early life determinants aspects of these areas require more support. Rather than duplicating efforts, NICHD could collaborate with NIDDK on areas of particular relevance to the mission of NICHD, such as disparities in disease prevalence and outcomes, and psychosocial and developmental aspects relevant to these conditions.

Investments in research and the development of trainees in these identified priority areas are essential to improve the trajectory of pediatric health in this nation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure:

Priority areas identified by survey respondents. Respondents were allowed to select up to three areas, and so percentages do not add up to 100%.