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Pediatric Neurology Research in the Twenty-First Century: Status, Challenges, and Future Directions Post—COVID-19

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Abstract

Background: The year 2020 marked a fundamental shift in the pediatric neurology field. An impressive positive trajectory of advances in patient care and research faced sudden global disruptions by the coronavirus disease 2019 pandemic and by an international movement protesting racial, socioeconomic, and health disparities. The disruptions revealed obstacles and fragility within the pediatric neurology research mission. However, renewed commitment offers unique opportunities for the pediatric neurology research community to enhance and prioritize research directions for the coming decades.

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Methods: The Research Committee of the Child Neurology Society evaluated the challenges and opportunities facing the pediatric neurology research field, including reviewing published literature, synthesizing publically available data, and conducting a survey of pediatric neurologists.

Results: We identified three priority domains for the research mission: funding levels, active guidance, and reducing disparities. Funding levels: to increase funding to match the burden of pediatric neurological disease; to tailor funding mechanisms and strategies to support clinical trial efforts unique to pediatric neurology; and to support investigators across their career trajectory. Active guidance: to optimize infrastructure and strategies, to leverage novel therapeutics, enhance data collection, and improve inclusion of children in clinical trials. Reducing disparities: to reduce health disparities in children with neurological disease, to develop proactive measures to enhance workforce diversity and inclusion, and increase avenues to balance work-life obligations for investigators.

Conclusions: In this uniquely challenging epoch, the pediatric neurology research community has a timely and important mission to re-engage the public and government, advancing the health of children with neurological conditions.

Keywords

Pediatric; Research; Training; NIH; Disparities; Career; Funding; Neuroscience

Introduction

The field of pediatric neurology is undergoing a radical transformation. As a result of advances in molecular, genetic, electro-physiological, and radiological testing, the ability to diagnose neurological and neuromuscular disorders, investigate their pathophysiology, and establish novel therapeutic targets has increased dramatically. Therapeutic options are expanding rapidly, ranging from gene therapy, oligonucleotide, and small molecule therapies to neuromodulation.[1–3] In parallel, advances in electronic health records (EHRs) and patient-reported outcomes initiatives have created novel opportunities to collect, aggregate, and analyze valuable clinical data about the diagnostic process, symptom trajectory, treatment practices, health care utilization, and impact of pediatric neurological disorders on quality of life of patient and family. Driven by research advances in pediatric neurology, the ability to diagnose, treat, and even cure developmental brain and spinal cord disorders has increasingly become a reality. Specific examples range from gene therapy for spinal muscular atrophy, a previously fatal disease,[2,4] to the clinical application of rapid whole genome sequencing to diagnose critically ill infants in less than a week.[5]

At present, the research enterprise of pediatric neurology faces substantial challenges. The global coronavirus disease 2019 (COVID-19) pandemic has killed more than half a million individuals to date and disrupted or harmed the lives of billions. The killing of unarmed black men and women by police and the disproportionate toll of COVID-19 in economically disadvantaged or minority communities have led to renewed societal motivation to address racial and socioeconomic disparities. The burdens of racism and the pandemic present both challenges and opportunities for health care and biomedical research.[6] The historical norms

for the academic pediatric neurology researcher, including training, financial support, and structure, have been significantly disrupted.

In response to a Request for Information from the National Institutes of Health (NIH), National Institute of Neurological Disorders and Stroke (NINDS), and Strategic Planning Process (NOT-NS-19–079) in 2019, the Research Committee of the Child Neurology Society (CNS) systematically evaluated the current status of pediatric neurology research, identified barriers and challenges, and suggested future directions and efforts. Comments from the CNS and other groups were incorporated into the NINDS report released mid-2020.[7] The Research Committee carried out additional efforts with consideration to the impact of the COVID-19 pandemic and recognition of societal racial and socioeconomic biases. This task included conducting a survey of CNS membership focused on research challenges and opportunities including those produced by the COVID-19 pandemic. Recognizing the value of this information, the Research Committee has incorporated these data and recommendations into the current publication.

Current status

Research funding

Research advances in pediatric neurology are dependent on adequate financial support. The US NIH is the primary funding source in overall amount, oversight, and policy setting. NIH and, in particular, NINDS vitally support basic, translational, and clinical pediatric neurology research. There are other NIH agencies that provide funding to pediatric neurology-related research, for example, autism research is typically funded by the National Institute of Mental Health. NIH and its staff are a crucial and appreciated partner in research for pediatric neurology. Their mission is complicated by limitations in funding amounts and changing legislative regulations. NIH funding, and NIH regulatory and policy mandates, also require ongoing engagement with and response to the public and government policy makers.

The NIH total budget for fiscal 2015 was $30.4 billion, of which approximately 12%, $3.63 billion, was apportioned for all pediatric-related research. For neurological conditions, within the NINDS budget of $1.6 billion, only 5% is currently spent on pediatric neurology-related research, suggesting that pediatric neurology is relatively underfunded compared with disease burden.[8]

Although other research funding, including from foundations, industry, and philanthropy, has steadily increased over the past two decades, the aggregate funding from these sources is minor compared with the NIH funding. With the economic downturn in 2020 related to the COVID-19 pandemic, such funding sources may also decline, presenting further challenges to support research.

Research careers

The training of investigators and establishment of research careers provides the critical backbone required for advancing pediatric neurology research. Training of physician-scientists in pediatric neurology occurs through several avenues including MD, PhD, combined MD/PhD, MD/MPH, and combined MD/MSc training pathways. Advanced

degree programs are also available for clinicians, researchers, and specialists in a range of related medical fields (physical medicine and rehabilitation, neonatology, and so forth), and allied health care fields (research nurses, rehabilitation therapists, neuropsychologists, and others). In turn, a variety of training mechanisms including T32 NIH awards provide nonclinical PhD students with clinical training opportunities.

For physicians entering child neurology, terminal degree attainment is typically followed by residencies in pediatrics and child neurology, with postcollege training ranging from nine years to complete MD and pediatrics and child neurology residencies to 15 years for those pursuing combined MD/PhD training. Specialized postresidency fellowships, for example, in epilepsy or stroke also add further years, which results in a high debt burden, with 60% of trainees reporting more than $50,000 in student debt.[9] Related concerns around salary and compensation mechanisms,[10] as well as an increasingly time-consuming load of administrative and clerical tasks, are contributing to a deterioration in work-life balance, reduced career satisfaction,[11] and to burnout.[12]

The current and future needs for pediatric neurology, including clinical and research missions, require ongoing updated assessments. In recent years wait times for a nonurgent pediatric neurology appointments averaged four weeks, with 30% of sites reporting wait times greater than two months.[9] With advances in diagnosis and treatment for infants and children with neurological disorders, clinical care complexity increases, translating into increased clinical time commitments. A promising development is that the number of residency training slots available for child neurology has recently increased. In 2018 there were 168 spots and 166 US-trained allopathic applicants entered the Child Neurology Match (Charting Outcomes in the Matchd—US Allopathic Seniors, 2018). Twenty reported advanced degrees, including 11 with PhDs. However, whether the current and future pool of residents will be sufficient to meet the future increased clinical demands and retain the necessary energy and time to also pursue research is uncertain.

The current workforce in pediatric neurology has limited racial and ethnic diversity compared with the US population: less than 30% of the workforce and trainees are nonwhite, and only 2% are black and 6% Hispanic.[9] Interestingly, there is a shift in gender demographic in child neurologists: 37.5% of the current child neurology workforce is female, while 64% of trainees are female.[9] Thus there is a critical need to increase both racial and ethnic diversity as well as to increase support for the need of parents in the workforce (i.e., accommodations for pregnancy and child birth, access to child and elder care, and protection against gender bias). Active solutions will be needed to help with the recruiting of trainees and then workforce from disadvantaged or minority backgrounds, because of the barriers of the access to educational opportunities and the barriers of financial burden.

Communication and outreach

Currently, communication about advances in pediatric neurology research is chiefly limited to professional journals, scientific meeting presentations (both of which target specialized clinicians and researchers), or individual institution press releases. Recent examples of social media outreach include podcasts from journals including *Journal of Child Neurology* or

Developmental Medicine & Child Neurology, or from individual institutions including Child Neuro Chat—http://childneurochat.buzzsprout.com/. However, specific public outreach programs encouraging support for pediatric neurology research from either academic institutions or NIH have been limited. A wide audience could benefit from communication and translation of pediatric neurology research initiatives, opportunities, and findings; this includes education for patients and frontline caregivers about diseases, research opportunities and relevance of participation in research, access to evidence-based care practices, and finally findings of research discoveries and new health outcomes. There are limited data on how national and regional differences in caregiver, practitioner and patient disease-specific education, and outreach efforts contribute to disparities in health literacy, clinical research participation, or support for research.

National survey

To improve insight into the status of the pediatric neurology research community, the CNS Research Committee launched an e-mail survey titled "CNS Research Committee Survey: Have a Voice" to members of the CNS. The survey was open from May 15 to June 1, 2020. Participation in the survey was voluntary with implied consent. Participants completed a 28-item survey regarding their research activities, the potential impact of COVID-19 on their research, and their vision for prioritizing pediatric neurology research needs for the next five to 10 years. Respondents could include their name and e-mail or remain anonymous. The questions were set up to obtain both quantitative and qualitative responses with an emphasis on opportunities to elaborate using free text responses. Responses were deidentified for analyses. A working group (A.L.-W., G.d.V., J.L.B., R.J.F., R.M.G., and Z.M.G.) conducted a modified thematic analysis[13] of the free text responses to synthesize responses into themes based on their frequency, stated importance, and stated suggestions from the respondents. These qualitative data were supplemented with the quantitative survey responses for further analysis. The survey was conducted using SurveyMonkey (SVMK Inc, San Mateo, CA, USA). Excel (Microsoft, Redmond, WA, USA) was used to generate frequency distributions of all variables. There were 151 respondents (Table). Full results and analysis of the survey are being published independently.

Data from a separate survey (discussed in the Section Support pediatric neurologists across career and life domains) of junior pediatric neurology physician-scientists who were applicants to the Child Neurologist Career Development Program training grant were also included in the development of our recommendations.

Research domains: obstacles, opportunities, and suggestions

The CNS Research Committee reviewed published literature, the surveys results, and included expert opinion from committee members to identify key challenges and opportunities in pediatric neurology research. On the basis of the iterative discussions and development of consensus, we have will in the remainder of this article summarize the central components that will support advances in pediatric neurology research post—COVID-19. These include gaps, including areas of weakness, barrier, or need, and proposed

measures to address these gaps. In addition, we incorporated results from the survey of the membership of the CNS regarding major thematic questions.

The three central domains we identified are as follows:

1. Funding levels: A call to increase the overall funding levels for pediatric neurology research and to innovate specific funding mechanisms and strategies. This expert opinion was supported by most of the CNS survey respondents (74%) who believed that pediatric neurology research funding was inadequate; one survey respondent noted, “I feel like pediatric neurologists are almost invisible [to funding agencies].”
2. Active guidance of the research mission: A request for more active guidance for the pediatric neurology research mission was made. This mission included increased direction to enable potential researchers to optimize areas of research opportunities while avoiding potential pitfalls. The CNS survey respondents particularly emphasized the need for improved and sustainable research infrastructure, especially for multicenter collaborations. Another important point noted was the need to improve external outreach communication around the value of research in pediatric neurology.
3. Reducing disparities: To pursue proactive measures to reduce disparities in pediatric neurology research, including in composition of the workforce and accessibility of treatments. The CNS survey respondents also noted significant racial and ethnic disparities in the composition of the workforce and in thematic areas of research supported by funding agencies. Another observation from the survey was that although research in nonefirst world countries and regions has increased, the genomic backgrounds and specific health care needs of children with pediatric neurological disorders in those same countries were largely not considered. Respondents additionally reported substantial challenges in balancing career and family responsibilities, and inadequate mechanisms of institutional or funding agency support. The discordance between professional and familial responsibilities was noted to be a long-standing frustration, exemplified in the statement “it never has been that supportive. One has had to make a choice between family and research.”

Funding levels

Three major subthemes within research financial support were identified by expert opinion and supported by the findings of the research survey: (1) funding is insufficient relative to burden of pediatric neurological disease; (2) increased support of complex nonstandard clinical research efforts unique to pediatric neurology are needed; and (3) improved support of investigators across careers and across life domains would be beneficial.

Increase funding relative to disease burden

Current data suggest that pediatric neurological disease burden and prevalence are not matched by appropriate funding. A comprehensive review of the NIH portfolio to ascertain baseline levels and adequacy of support for pediatric neurology research across institutes

including the NINDS would be timely. A review of all US NIH grant-related funding shows that specific pediatric neurology research comprises only ~10% of all NIH-funded neurology research, for years 1985 to 2019 (Grantome, accessed 2020; keyword search for “pediatric neurology”) (Fig 1). Furthermore, the perception of insufficient funding and that research funding levels are expected to decline was common among CNS survey respondents (Fig 2).

Increase funding and support mechanisms for complex pediatric neurology studies

Long-term studies are necessary to determine natural history or developmental trajectories within pediatric neurological diseases. Many neurological diseases affecting children are rare, so their study requires multicenter enrollment networks and longer than typical enrollment periods to achieve adequate samples sizes. Funding mechanisms to provide support for age and disease-appropriate outcome measures, and sustained funding to permit well-powered studies of long-term outcomes for pediatric neurological diseases, are both needed. Importantly, new treatments for previously fatal diseases are creating “new” natural histories. Observational natural history data are becoming less relevant; contemporary post-intervention studies are needed for many diseases. The traditional five-year grant cycle is not conducive to this type of study. These funding needs reflect the challenge of adequate sampling of pediatric subgroups and generalizability across different genders, races, ethnicities, and age groups (e.g., infants, children, and adolescents). Better support for pooling of individualized patient data across multiple studies, for example, patient outcomes in nonexperimental treatment arms (e.g., placebo and standard therapy groups), could provide cost-efficient data collection and offset the challenges of enrolling sufficient patient numbers.

Improve funding mechanisms and organization

Efforts from private foundations and other sources of private research dollars often are separate from those coordinated with NIH priorities for research, which appears to be a missed opportunity despite occasional examples of success.[14] Private funding sources could partner with NIH-funded researchers to better leverage funds and expertise in advancing research in pediatric neurology, and advance a centralized coordination of funding priorities. Currently, multiple advocacy groups supporting the same disease may be working at cross-purposes and there is an unmet potential for advocacy groups to gain collective momentum in lobbying for translation of research findings into clinical practice. NIH and leaders in pediatric neurology research should consider partnership efforts to ensure disease-expert consultants can represent, interact, and help provide appropriate guidance for advocacy groups that may not have sufficient expertise. This effort could include the creation of disease-specific research advisory panels. Such efforts would support coordinated communication strategies relevant to those diseases externally and provide balanced input on the impact and significance of proposed research internally, ahead of external review. This input could inform the understanding of priorities and enhance fair proposal scoring by nonexpert reviewers. The NIH can serve as a critical ombudsman, for direction and incentives, to encourage synergy across advocacy groups to advance cohesive priority setting, to improve access to educational materials and rare treatments, and to build on the existing involvement of parents and patients in advocacy and research. Methods could

include expanding existing centralized web sites collating information about and contacts for the disease-specific groups and funded collaboration workshops for advocacy groups to work together, and train in effective lobbying.

There are opportunities to revise mechanisms and strategies to improve the efficiency of research funding, as well as to increase overall funding. Specific suggestions include (1) increase funding mechanisms, similar to the K24 mechanism, which provided support to the faculty mentor of junior faculty, but with broader inclusion criteria; (2) increased modular grant funding, from the current ~$250,000 to ~$300 to $350,000 per year. The modular budget of $250,000 was instituted in 1998, which in 2020 dollars is equivalent to $158,000 after correcting for inflation. Increasing the amount would improve grant review and administrative efficiency, and would provide more realistic funding to perform the research; (3) reduce administrative reporting requirements. For example, in the NIH the carryforward of 10% of funds could be streamlined to require less paperwork and to reduce the burden on both the investigator and the NIH.

There are also other government agencies such as the Centers for Disease Control, Patient-Centered Outcomes Research Institute, Agency for Healthcare Research and Quality, and so forth that engage in and support research efforts for children with neurological conditions. It will be important to further maximize engagement with these agencies to encourage continued and enhanced support for pediatric neurology-related research.

Support novel research directions

Efficient alternative study designs to traditional in-person assessments could emphasize convenience for families with young children including, where appropriate, validated telephone or telehealth interviews for parent- and patient-reported outcomes. Although desirable to families and fiscally efficient, flexibility by regulatory bodies is needed to accept such alternative nontraditional study design methods,[15] especially as many of these methods are undergoing validation research during the COVID-19 pandemic.

A challenge for studying many pediatric neurological diseases is the absence of validated animal models to understand pathophysiology and develop therapeutics. An expansion of support to develop and validate models for pediatric neurology conditions is needed.

The scope of pediatric neurology extends into other fields such as congenital heart disease, neonatology, mental health, oncology, and autoimmune disorders among others. The cross-disciplinary nature of medical and research topics and researcher backgrounds provides opportunities for the NINDS to enhance partnerships with other NIH institutes in developing cross-institute training programs and funding initiatives to promote more effective synergy across fields.

Improve strategies for pediatric clinical research and clinical trial readiness

Although the pediatric neurological disease burden in aggregate is significant, individual diseases are often rare, creating unique challenges necessitating multicenter collaboration. Enrollment-based funding support for clinical research studies, including clinical trials, is insufficient for the personnel and infrastructure, and shifts costs to hospitals or universities.

Centralized support of collection, transportation, analysis, and interpretation of genetic and genomic results is needed.

Despite intentions to include pediatric studies, disease-specific research networks such as StrokeNet and NeuroNEXT lack proportionate support of pediatric studies. For example, of 10 current studies in NeuroNEXT only two are related to pediatrics, and StrokeNet has only funded a single pediatric trial.

On the basis of the prior failed clinical trials, NINDS has appropriately placed increased importance on trial design in funding decisions over the last decade. However, the increasingly onerous requirements for advanced trial designs, often not feasible in pediatric neurology research, has presented barriers to investigators initiating clinical trials. NIH/NINDS and other peer-review funding agencies could consider taking a more proactive stance in flexible trial design, for example, by building and supporting phased stages of research leading to clinical trials and supporting meritorious efforts by partnering researchers with NIH-supported pediatric trial design specialists. This has started in some domains, for example, the Trial Innovation Network (https://trialinnovationnetwork.org/).

The NIH should continue to support and expand on granting mechanisms to develop both multicenter networks, crucial for rare pediatric neurological diseases, and trial preparedness targeted to pediatric patients, disorders, researchers, and institutions. Successful examples, although not exclusively pediatric, include the Rare Diseases Clinical Research Network (funding 23 disease groups), the Centers Without Walls funding mechanism, and the Comparative Effectiveness in Clinical Neurosciences (UG3/UH3). The design and implementation of rigorous trials in orphan, rare, and ultrarare diseases that are particularly prevalent in pediatric neurological conditions require creative solutions.[16,17] Trial readiness includes the need for rigorous natural history studies. The NIH should consider expanding funding allocated for clinical trial readiness for pediatric neurological conditions, including for multiyear longitudinal studies.

Support pediatric neurologists across career and life domains

Physician-scientist pediatric neurologists are affected by a longer career-training pathway, by a lack of integration between the PhD and MD training components, and by the absence of an organized pathway from residency to fellowship—both clinical and basic scienc—dthat optimizes the special skill set of physician-scientists. There is a perceived difficulty in obtaining sustained support for research.

A survey of junior pediatric neurology physician-scientists (consisting of unsuccessful applicants to the Child Neurologist Career Development Program training grant [CNCDPK12] from 2016 to 2018 [n = 23]), reported impediments to obtaining research funding included lack of time to write the proposal, lack of preliminary data, lack of publications, and lack of well-funded and published mentors (in order of most to least concerns) (Brenda E. Porter, unpublished data, 2019). This finding suggests that more widely available grant-writing workshops would be helpful and should be supported at programmatic levels.[18] Other problems, all self-identified, were a lack of preliminary data and publications, which are dependent on funding and protected time. Because child

neurology residency has little protected research time, this places a burden on departments for protecting the time, income, or further training (such as a master's degree) of newly hired junior faculty.

Also the physician-scientist pathway has personal financial challenges, including educational debt from training, a likelihood of lower salary compared with a clinical care only pathway, and a longer trajectory to arrive at faculty salary levels. These factors discourage junior faculty from pursuing research. There is also a lack of funding for physician-scientists after their fellowship. This is a problem because, for most pediatric neurology fellowships, there is substantial clinical burden, which makes it difficult to generate the preliminary data and publications required for successful grant funding, especially when competing against PhD scientists without clinical responsibilities. NIH funding mechanisms targeting funding options to support junior physician-scientists at this challenging juncture should be enhanced. Moreover, many academic medical centers lack the financial resources and research infrastructure to make the sustained commitments necessary to support junior physician-scientists to transition to scientific independence. The latter challenge may well be accentuated in the wake of the COVID-19 pandemic as academic medical centers face increased operating expenses and shortfalls in clinical revenue. Furthermore, embarking on a research career postresidency typically coincides with starting families, compounding time, and financial constraints. In the CNS survey, concerns regarding support of physician-scientists with families were common (Fig 3).

There is an increasing number of women in training and in early stage careers, and women will soon account for most pediatric neurologists. There is limited information on how this will affect the clinical and research workforce in child neurology. Recent data suggest that up to 50% of women and 27% of men employed in science, technology, engineering, and math (STEM) research leave full time STEM employment within one year of the birth of their first child[19]: 15% of new mothers and 3% of new fathers left the workforce permanently. Thus mechanisms to support and encourage early career faculty to remain in the pediatric neurology research workforce are essential. In particular, measures to increase the feasibility of returning to the workforce, with flexible work schedule considerations, and to a research career after a parenting-related gap are also needed.

Specific steps toward supporting and retaining pediatric neurology researchers should be taken at a variety of stages in the training and career pipeline. Flexible funding programs would permit investigators to start and maintain research programs at times when their overall effort must be reduced to accommodate family responsibilities, medical leave, or other life events. Examples of funding program changes that could facilitate these transitions include in the F32, increase the time to initiate application to two years after graduation, and increase support to the first four years (instead of current three years). This change would improve the ability of fellows to transition from training to first independent grant and potentially improve workforce supply. By incorporating reasonable parental and family leave periods and allowing extension of deadlines commensurate with the leave, grant funding mechanisms including the R25, K grants, other training grants, and standard R grants, would harness talent that is currently challenged by common life events.

Active guidance of the research mission

Continued NIH direction is needed to optimize the tremendous research opportunities while avoiding potential pitfalls, including setting fair and balanced rules on gene therapy use, data collection and infrastructure, privacy protections, and inclusion of children in clinical trials.

Data infrastructure

There is a critical need for building and supporting infrastructure for pediatric neurology research, ensuring that data are fully submitted with total transparency and are available without restrictions for qualified researchers. The data types and needs are diverse, encompassing point-of-care clinical presentation, risk factor and current treatment selection data, genetic and genomic results, and raw sequence data; brain imaging (structural and functional), pediatric neurophysiology data, such as electroencephalographs, intracranial pressure monitoring, and electromyograph; clinical trial results, such as for gene therapy or bone marrow transplants, which require years of continued monitoring; normative and abnormal radiological results; and finally, data from outside the United States. To address these needs, sustained and reliable longitudinal funding is needed for pediatric neuroscience database development, data collection, and maintenance. Furthermore, NIH should continue to fund and strengthen enforcement of requirements for large federally funded clinical research trials to submit collected anonymized individual level data to online repositories including neurophysiology recordings and imaging studies.

Together with ongoing support for building infrastructure to archive and share multimodal clinical research data, there is an opportunity to perform EHR standardization to advance pediatric neurology research (e.g., PCORnet, OMOP, and SNOMED).[20] Currently, EHRs have major gaps in support and vocabulary for neurological diseases, particularly for rare diseases in children.[21–23] Acting in concert with Medicaid and Medicare could encourage standardization of EHRs for pediatric neurological conditions facilitate research in comparative effectiveness, surveillance and epidemiology, and health services, and promote the use of common data elements (CDEs).

One opportunity to increase EHR standardization is the incorporation of CDEs, an initiative in which the NINDS has been a leader. CDEs are important for understanding disease natural history, for preparing clinical trials, and for conducting and analyzing results from clinical trials (https://healthdata.gov/dataset/nih-common-data-elements-repository). However, although some disease-specific forms exist for pediatric neurological diseases (https://www.ninds.nih.gov/Funding/Apply-Funding/Application-Support-Library/NINDS-Common-Data-Elements), there is a lack of wide acceptance and uptake of CDEs in pediatric neurology research. Efforts from all stakeholders should be made to modify CDEs to improve their interface for use in pediatric neurology clinical care and to support an increase in CDE focus on outcomes that are prioritized by researchers, clinicians, and families, but are efficiently attainable within the context of a busy clinical practice.

Privacy protections

There are inadequate federal guidelines or laws governing the storing, privacy, or access to genetic and genomic test results and raw sequence data by individuals or academicians.

This includes both academic institutions and commercial providers (e.g., 23andMe) and has eroded public and clinician perception of trust in genetic testing.[24] Currently, the only national law is with regards to nondiscrimination, the Genetic Information and Nondiscrimination Act of 2008, which protects the genetic privacy of the public, including research participants.[25] The Genetic Information and Nondiscrimination Act of 2008 makes it illegal for health insurers or employers to request or require genetic information or to use genetic information in a discriminatory fashion. There should be continued coordinated efforts by the NIH to work with Congress to help place laws in place that ensure patient privacy, but also to facilitate valuable research.

Regulations and guidance

Gene therapy and precise gene editing techniques are now feasible to correct genetic disease and to modify the human germline. There are many areas of debate that will require national guidance. Specifically, it is not clear what “best practices” should be, there is no infrastructure for sharing reagents, ethical questions exist, and there is limited established infrastructure to follow long-term multigenerational impacts of gene replacement and gene editing therapies.[26]

Enforceable, consistent rules are necessary to establish permissible and nonpermissible gene therapy and gene editing. Infrastructure—for sharing of gene therapy and gene editing technologies, for developed shared vectors, or other tools pre-approved for clinical use—would facilitate bringing new genetic targets to clinical trials. Studies of the financial and ethical considerations of gene therapies, gene editing, and other novel therapeutics should be prioritized.

Require and enforce rules regarding inclusion of children

Although NIH policy mandates inclusion of children in all NIH-supported human subjects research unless scientific or ethical reasons justify their exclusion (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html), this critically important policy is not fully enforced. NIH needs to increasingly work toward ensuring inclusion of children in NIH-supported human subjects research unless scientific or ethical reasons truly justify their exclusion. Programmatically, specific instructions in funding announcements (requests for applications) from the NIH could explicitly require inclusion of children into NIH-funded clinical research to allow more opportunities to understand how diseases affect children, including across the spectrum of different developmental stages. Efforts to accommodate for obstacles to pediatric inclusion are also needed. These include pediatric-proxy (parental) consent, a lack of age-appropriate pharmacokinetic data, challenges enrolling sufficient numbers of pediatric patients, and a necessity for longer-term outcome assessment, among others.

Communication and outreach

Public support for research in diseases affecting the developing nervous system is important for sustaining philanthropy and government funding. Because of the increasing recognition and diagnosis of specific disorders, fragmentation and redundancy within and across specific diseases are becoming more apparent.

Reliable information about research efforts, implications, and findings from research are important to prevent misinformation about medical conditions and treatments. There is an increasing thirst by the public for health-related knowledge, and in the absence of coordinated information from reliable sources, dissemination of non–evidence-based, inaccurate, or even wide misinformation can result. For example, vaccinations are considered as a cause of autism spectrum disorders by large segments of the public, despite clear scientific evidence to the contrary.

Public comments and legislation are necessary to establish regulations balancing privacy concerns with valid reassurances and encouragement to enable repositories safely housing clinical, imaging, and blood and tissue samples to accelerate research in pediatric neurological conditions.

The pediatric neurology research community, NIH, and other agencies could help provide funding to communicate: unmet needs for children and families affected by neurological disorders and why research is important; research engagement opportunities to patients/parents; and programs of brief, periodic evidence-based clinical practice updates for frontline practicing clinicians.

Educational resources and platforms for patients and their families are unevenly available across specific diseases and geographical areas. The willingness of children and their parents to enroll in research studies could be enhanced by videos and patient stories inspiring involvement of children in neurological research. Opportunities for enrollment in disease-specific studies could be advertised by and in partnership with appropriate advocacy groups.

Practitioners dealing with many rare disorders in our field are challenged to keep abreast of new findings and to translate evidence into practice. Evidence-based guidelines (EBGs) are unevenly available and inconsistently prepared. There is an opportunity for professional societies, including the American Academy of Neurology, American Academy of Pediatrics, and CNS, to coordinate and centralize EBGs. A good example of this is the American Academy of Pediatrics Red Book, for guidelines and information on pediatric infectious diseases. The pediatric neurology community could develop a “Blue Book,” with EBGs and with information on a wide range of pediatric neurological conditions and treatment. Another opportunity is for disease-specific expert groups to develop and disseminate periodic brief (10 minutes) updates, webinars or podcasts, including on new findings or recommendations, and rotating talks summarizing current knowledge regarding specific pediatric neurological disorders. This information would equip clinicians to better recognize and investigate rare conditions and implement evidence-based practices for common conditions.

NIH should consider efforts to support centralized language translation resources for research documents (e.g., consent), monthly webinars targeting MDs in private practice, and videos by and for patients and families incentivizing involvement in research. The NIH library does provide translation services, for example, and its infrastructure support could be expanded to be useful across the biomedical community (https://www.nihlibrary.nih.gov/services/translations). An interesting opportunity would be the application of novel

technologies to support translation efforts, for example, artificial intelligence and natural language processing software. Increasing language resources would increase enrollment opportunities and access of information to under-represented minorities in the country (and of course abroad). The NINDS should also continue to foster international research involvement—consortiums to advance understanding and treatment of neurological diseases affecting children given their rarity.

Reducing disparities

The pediatric neurology research community has an opportunity to lead on proactive measures to reduce disparities in pediatric neurology research, including the treatment affordability gap, increasing avenues to balance work-life trajectories for investigators, and to increase the diversity of the research work pool. The workforce for pediatric neurology research needs to adapt to the rapidly changing clinical landscape including the progress and availability of new therapeutic options, recognize the increasing subspecialization of pediatric neurologists, adapt to the increased proportion of women in the child neurology workforce, and address the lack of under-represented minority pediatric neurologists.

Disparities for patients: diagnosis, access, outcomes, and costs

It is now becoming apparent that major disparities affect children with neurological conditions. These disparities range from diagnosis,[27,28] to access,[29,30] outcomes,[31,32] and costs.[33] Compounding these disparities is that the costs of medicines and therapies, resulting from research in pediatric neurology and often supported by public funding, are escalating. The total spending on prescription drugs in 2017 was $333 billion, a 41% increase compared with a decade prior.[34] The most expensive “drug” is the gene therapy for a pediatric neurological condition, spinal muscular atrophy (onasemnogene abeparvovec-xioi), listed at $2.5 million per patient.[35]

The escalating affordability gap will continue to increase unless proactive measures are identified and implemented.[36] For medicines and therapies that are developed with support from the NIH, pricing regulations or a recompense mechanism is needed to address unequal accessibility to ensure that new therapies are an option for any child. Despite the investment of the public through the support of NIH, pediatric neurology researchers, and clinical trials, profits from sales are not regulated and do not account for the investment from the government and the taxpayers. The pediatric neurology research community should work actively to engage the public and governmental policy makers, to help guide changes in regulations and legislation.

Access

Most pediatric neurology practices across the country lack support or funding mechanisms to offer patients access to low-cost, high-quality genetic and molecular testing. Interpretation and sharing of research results is limited to academic centers, some testing companies, and some private initiatives. Unfortunately, insurance companies are also known barriers to appropriate genetic testing.[37] This barrier burden practitioners, limits access to diagnosis, treatment, and clinical trials, and exacerbates care inequalities and client dissatisfaction. A challenge for the NIH and researchers leading efforts is to take proactive steps for providing

access to research protocols for all children, regardless of geographical or socioeconomic barriers.[38,39]

Supporting workforce training

At this time there is a shortage of physicians, scientists, and physician-scientists in pediatric neurology research at all career stages, from trainees to mid-career and experienced investigators. Although the focus of this article is on the pediatric neurology workforce, it is important to consider, in particular, that research related to the normal and disease states of the developing nervous system is conducted by a wide range of professionals ranging from bench scientists to pediatric neurosurgeons. Current workforce in pediatric neurology is insufficient to provide clinical care for the number of children with neurological disorders; this shortage is further exacerbated by large regional disparities.[9] The workforce is further insufficient in quantity to conduct multicenter research studies needed for the many rare diseases in pediatric neurology. Current and future researchers will need expertise in biomedical informatics and in data science. Currently, the granular data necessary to evaluate the impact of clinical care loads on research effort are lacking. Furthermore, there are regional differences in the pediatric neurology research workforce that could affect types of research pursued and access for patients to research studies. For example, only 1% of pediatric neurologists report working in rural settings and 40% refer epilepsy patients with special needs to more than 60 miles away.[9]

Pediatric neurology includes a large and growing number of subspecialties that require additional training including clinical fellowships, to achieve sufficient expertise to either lead or participate in clinical research studies and trials. Although formal master's degree programs in clinical research have become more prevalent, there are no established postresidency or fellowship career-training pathways for clinical investigators, and a paucity of funding mechanisms to support training in clinical research methodology for early career faculty. There are few opportunities for training in data science and clinical informatics with an emphasis on the needs of physician-neuroscientists. This gap has led to a particular shortage of child neurologists trained to design and execute clinical trials, and presents a major barrier to translate advances in scientific knowledge to advances in clinical care. A greater emphasis on building partnerships with clinicians outside academic centers who could pose clinically relevant questions, opine on the feasibility of proposed treatments in clinical practice, and potentially enroll large number of patients from their clinics would be beneficial and should be incentivized.

There are important opportunities to improve the training and number of biomedical researchers in pediatric neurology. The challenges to the biomedical research effort from COVID-19 and from the systemic racial and socioeconomic biases suggest a need for joint efforts across the entire pediatric neurology community including the NIH. More programs to engage, attract, and develop research-oriented pediatric neurologists from all levels of training including high school, college, and medical school are needed. Financially, enhanced support for the Pediatric Subspecialty Loan Repayment Program, to offset increasing debt from a long duration of training, requires increased availability for loan repayment programs across research type, duration, and research effort.

Academic pediatric neurology faculty needs to accept and support family leave and lobby for their junior faculty. The NINDS should also be at the forefront for supporting and funding family medical leave as a means to attract and retain clinician-scientists. This could include a policy that permits funded investigators to work less than full time, as long as the investigator dedicates the requisite time to their funded research. There needs to be increased flexibility in the allowance of protected time for research training at all levels including masters and other research programs in clinical research methodology, as well as PhD programs.

For MD/PhD programs more flexibility in the timing and scope of funded support by the Medical Scientist Training Program should permit trainees to complete the PhD portion of their training after their residency and support tuition repayment for medical school for those who complete their PhD and pursue a career in research.

Funded career-training pathways should be designed and supported for MDs to obtain master's degrees in clinical research or public health before, during, or after their residencies, analogous to the Medical Scientist Training Programs. NINDS should partner with the National Library of Medicine to create training opportunities at the intersection of neurology, data science, and clinical informatics. Training in conducting clinical trials is loosely organized or not a component of many NIH K training programs, suggesting an opportunity for the NIH and NINDS to include this as an educational module as part of the K grant mechanisms.

Increased research training opportunities should be available for non-MD professionals (e.g., nurses, rehabilitation therapists, pharmacists, basic scientists, and psychologists) to participate in and lead research related to child neurology. Partnerships should be developed with industry and the National Center for Advancing Translational Sciences to provide hands-on disease-specific training of child neurologist, neonatologists, pediatricians, and nurse practitioners interested in developing a career in clinical research. There may be opportunities to enhance clinical research with increased development of cooperative teams with PhD and non-PhD partners.

Disparities in training and workforce

Less than 4% of current or in-training pediatric neurologists are from under-represented minority groups. Patient and caregiver education, and socioeconomic factors dramatically impact patient outcomes. Given national and regional differences in health care access and the delivery of neurological services, there are limited funding opportunities or proven methods to study and ultimately improve these discrepancies. Recruiting under-represented minority physicians and physician-scientists, including those from disadvantaged socioeconomic groups, has not been successful despite multiple efforts, suggesting that different approaches are needed.

The historically Caucasian male-dominated field of pediatric neurology, similar to other medical specialties, has struggled to identify and address implicit biases. More proactive and effective training regarding workplace culture would lead to decreased harassment, through programs such as the diversity mentorship program for clinical leaders being

developed by the American Academy of Neurology, or programs such as Crossroads (http://crossroadsantiracism.org/) or Anti-Racism Institute.

Pediatric neurology has an opportunity as a research community to lead efforts for diversity, equity, and inclusion. More straightforward examples would be increasing programs that develop talent in high schools and colleges, increased grant opportunities that specifically target under-represented groups early in high school to attract diverse researchers, and funding to support infrastructure in under-resourced states and colleges with large ethnic and socioeconomic diversity. Providing principal investigators with the resources to devote time and opportunity to mentor young inexperienced but motivated individuals from under-represented groups would increase the pipeline for a diverse workforce. However, for large-scale systemic change of the type that may be needed, the pediatric neurology research community can also play an important and proactive role.

Conclusions

Pediatric neurology is at a critical crossroads. The opportunities for rapid advances in research combined with the real ability to translate research into meaningful clinical treatments and even cures makes the coming era one of tremendous opportunity. However, major obstacles remain in the commitment to meaningful financial support of pediatric neurology research, which impacts training of new researchers and the protection of current researchers' time and all aspects of research productivity.

The COVID-19 pandemic and societal recognition of deep-seated racism are leading not only to disruptive but also to necessary changes in funding and infrastructure processes. These changes affect pediatric neurology research and provide an opportunity to renew partnerships and re-engage with the public and government. Although the related interruptions in bench research and clinical trials were noted with concern by the survey respondents, the changes have also caused some to re-evaluate their research priorities, and to place increased emphasis on the person-to-person interactions that drive ideas and science. As noted by a CNS survey respondent, "Zoom mentorship is just not the same!"

Pediatric neurology research is also not immune to the intrinsic racism that affects society. Racial and ethnic disparities in diagnosis and outcomes affect children with neurological conditions.[27,31,40–43] Recognition and a strong stance against racism is a necessary first step,[44] but meaningful solutions will require a thoughtful and well-implemented strategy, ranging from changes in training and advancement of under-represented minorities to how care is delivered.

There are many post–COVID-19 opportunities for increasing the long-term success trajectory in pediatric neurology research. The problems and recommendations identified in this article can be used to build on existing programs. Institutions can increase support and mechanisms for hiring and retaining of minority pediatric neurology researchers and for enhanced data collection and grant mechanisms to support long-term natural history studies. Another more ambitious option is to re-vision the pediatric neurology research mission, for example, guaranteed dedicated research support across decades for priority investigators

and arenas or development of pan-national research teams dedicated to specific disease processes. Whatever solutions are taken, the certainty is that change must occur.

For the pediatric neurology research community, including physician-scientists, academic societies, hospitals, universities, and funding agencies, our enterprise must be to overcome pandemic and racism challenges and to define a new path for the research mission of pediatric neurology in the twenty-first century to the benefit of children with neurological disorders.

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Summary table: key recommendations

1. Overall funding levels for research should be increased to appropriately match burden of pediatric neurological disease.
2. Grants and support mechanisms should be adjusted to support complex clinical trial efforts unique to pediatric neurology and to support investigators across careers and across life domains.
3. Rules and legislation are needed to support and guide gene therapy use, data collection and infrastructure, privacy protections, and inclusion of children in clinical trials.
4. The pediatric neurology research community should lead proactive measures to reduce disparities in pediatric neurology research, including the treatment affordability gap, increasing avenues to balance work-life trajectories for investigators, and to increase the diversity of the research work pool.

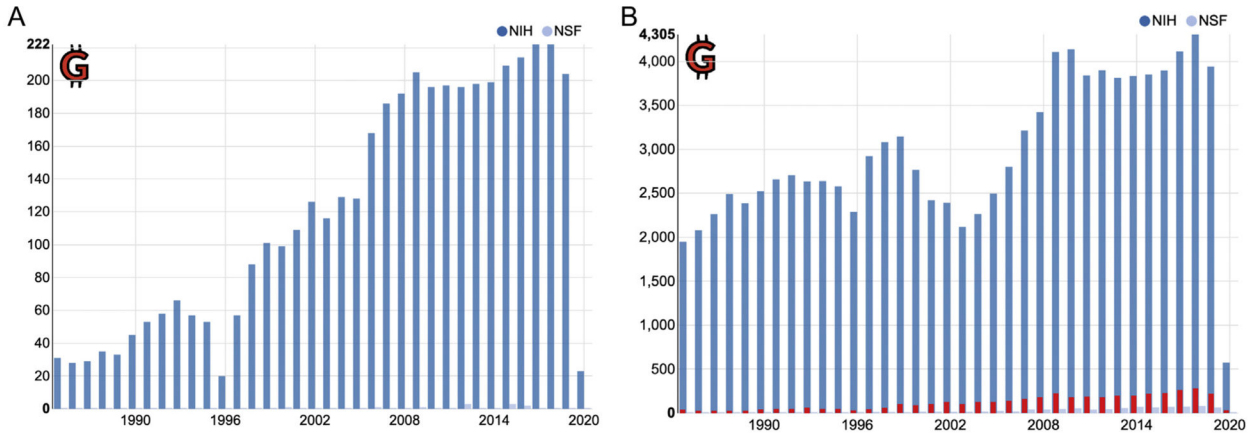

FIGURE 1.

Numbers of NIH or NSF grants for research related to pediatric neurology (A) or for all neurology (B). In (B), pediatric neurology grant numbers are represented in red on same scale as for all neurology. NIH, National Institutes of Health; NSF, National Science Foundation. The color version of this figure is available in the online edition.

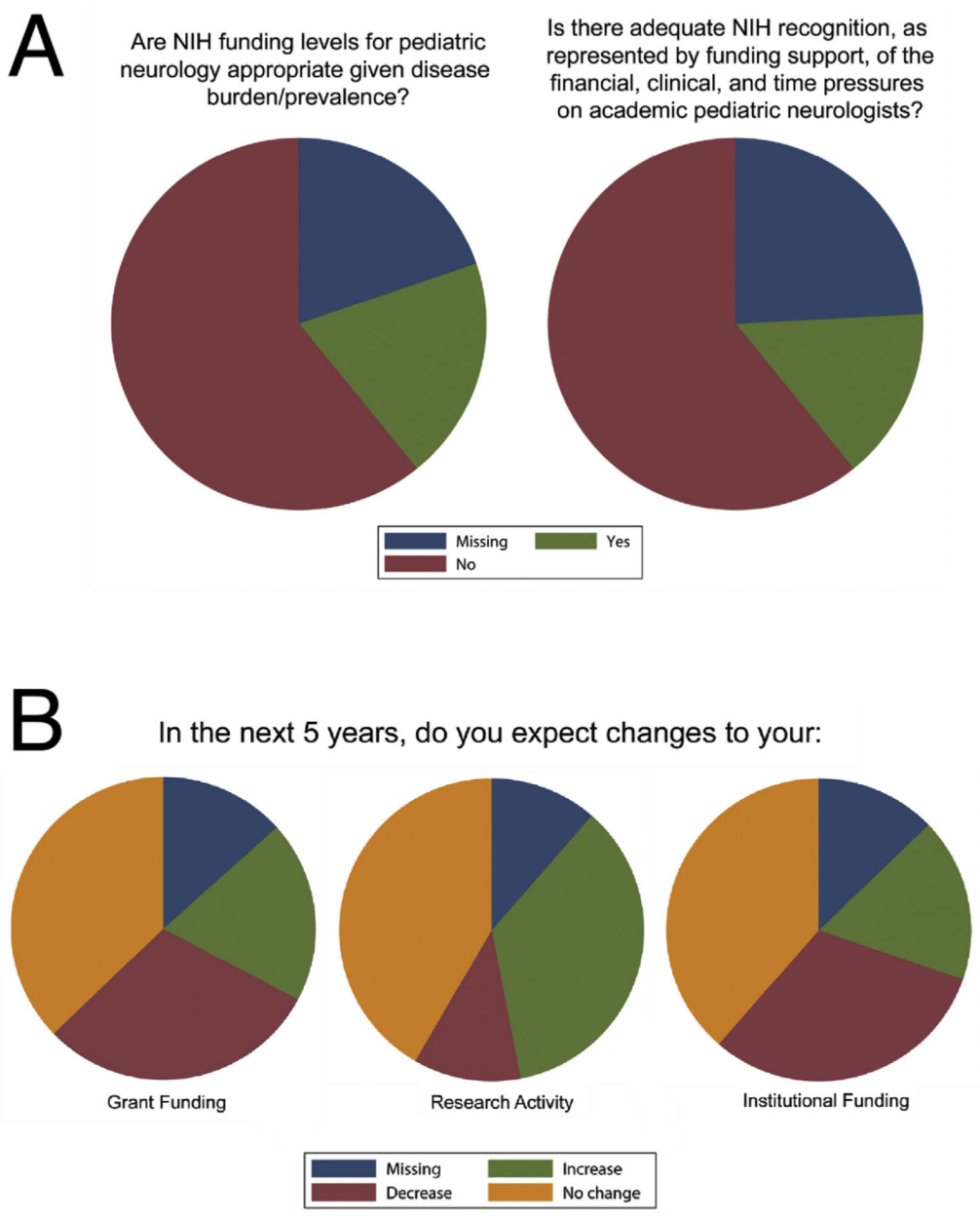

FIGURE 2.

CNS survey responses regarding (A) overall research funding support and (B) research funding support for next five years. CNS, Child Neurology Society. The color version of this figure is available in the online edition.

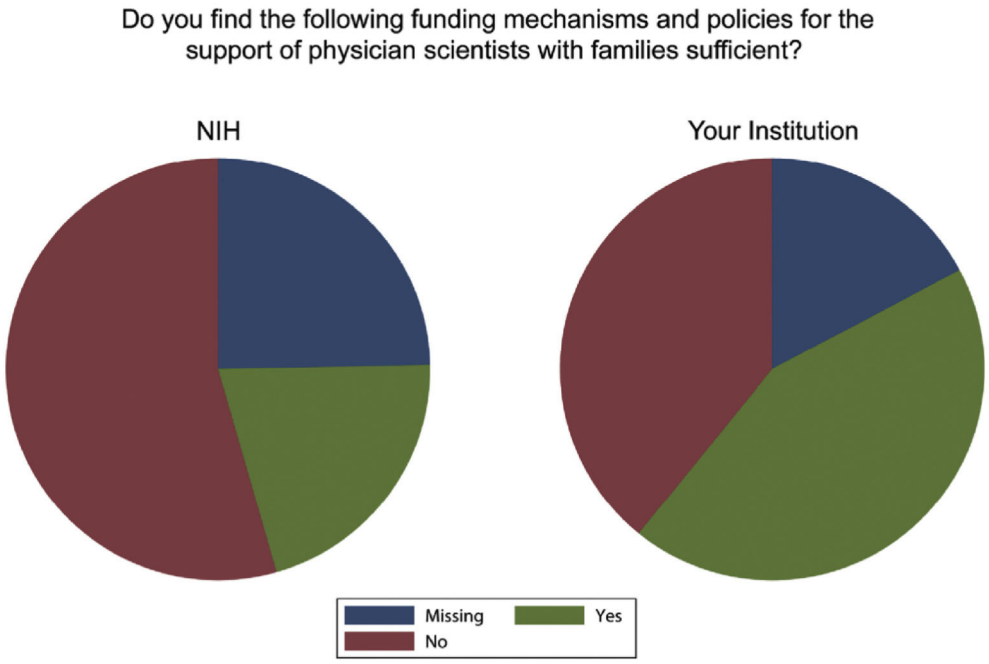

FIGURE 3.

Proportions of CNS survey respondents with concerns regarding policies and funding mechanisms for support of physician-scientists with families. CNS, Child Neurology Society. The color version of this figure is available in the online edition

TABLE

Demographics of Survey Respondents

Category	N (%)
Country	
USA	146 (97)
Canada	3 (2)
Other	2 (1)
US region	
Northeast	53 (35)
Southeast	12 (8)
Midwest	43 (28)
Southwest	11 (7)
West	27 (18)
Degree	
MD or DO	100 (66)
MD/PhD	34 (23)
MD/MS or MPH	17 (11)
Years since training	
<5	41 (27)
6–10	23 (15)
11–20	24 (16)
>20	63 (42)
Appointment	
Academic	131 (87)
Academic/private	4 (3)
Private practice	8 (5)
Retired	3 (2)
Resident/trainee	3 (2)
Public hospital, other nonprofit	2 (1)
Time spent in research	
<25%	56 (37)
25%–50%	32 (21)
50%–75%	31 (21)
>75%	32 (21)
% Time spent in clinical	
<25	52 (34)
25–50	45 (30)
50–75	28 (19)
>75	26 (17)