The Path Forward: Academic Neurology Responds to COVID-19

New daily routine
Supplants the one familiar
Brings different joys

Ken Dudzik, Baltimore, 2020

Over the past 3 months, for most of us engaged in academic neurology practice or neurology research, life has changed drastically. The coronavirus disease 2019 (COVID-19) crisis has disrupted lives on a global scale, and of course has led to 57,640 deaths through April 28, 2020.[1] The pandemic has forced innumerable changes in the delivery of health care, which have occurred on a very compressed time scale requiring significant improvisation and creativity. For academic neurologists these changes have included the redeployment, for some, into unfamiliar environments (eg, medical intensive care units [ICUs] treating patients with COVID-19 pneumonia). For others, the main change has been to learn how to maintain clinical services for urgent neurological disorders while maximizing safety for both patients and staff. Some of the biggest and perhaps most surprising changes have been in the collaborations among academia, industry, and government. Over 85 companies have entered vaccine research in the past 2 months, and more than 60 are involved in antivirals. Private entities, like the Gates and Rockefeller Foundations, have supplanted governments and international entities to become the major organizational forces orchestrating these changes.[2]

In-Person Academic Neurology

We can anticipate a major change to enter our care processes before neurology procedures, tests, or in-person visits are conducted: COVID-19 testing. This will require access to either molecular or serological techniques, and ultimately perhaps rapid diagnostic antigen testing. It remains unclear whether acute infection with severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is associated with specific neurological syndromes, including acute necrotizing encephalitis. The reported higher incidence of stroke may simply reflect the inflammatory milieu linked to the cytokine storm.[3] Three other centers, including Icahn School of Medicine, are also about to publish a paper on strokes in younger people with COVID-19. The work of the consortium, led by Dr. Sherry H.-Y. Chou at University of Pittsburgh, will be particularly informative in delineating the true incidence. The European Association of Neurologists also has a similar registry. Cases of Guillain–Barré syndrome (GBS) have already been reported, and it is quite likely when a vaccine is developed that we may encounter vaccine-related GBS, as was seen with swine flu in the 1976 epidemic. Health authorities reported an unusually high number of GBS cases, nearly 1,100—half of which occurred after immunization. In 2003, the Institute of Medicine concluded that there was a causal relationship and that one extra person out of 100,000 contracted GBS as a result of the vaccination. Until "herd immunity" develops in our communities, it is very likely that we will see cycles of resurgence of COVID-19, most likely emanating from vulnerable populations, particularly those incarcerated or jailed, and the elderly in assisted living facilities or skilled nursing homes.

Ambulatory Academic Neurology Practice

For the majority of neurology clinicians, neurological care for new or established patients is being delivered using telemedicine. We have rapidly learned to master the technical aspects of telemedicine. Neurologists often say that our discipline relies more on the physical examination than other specialties. Although true, we have developed new methods and tools to perform and quantify elements of neurological examinations during a televisit. Now, we conduct remote cognitive assessments, assess tremor, strength, dexterity, and walking ability, and even examine the retina using Smartphone photographs or nonmydriatic cameras. Prior to COVID-19, many institutions struggled with the logistical challenges of enacting telemedicine in such a complicated health care climate; the pandemic enabled the Centers for Medicare and Medicaid Services

(CMS) to relax rules over use of, and reimbursement for, telemedicine services for Medicare recipients—formerly only covered for patients in rural areas. The current CMS rules are not permanent, but are dependent on executive order and will require legislation to become permanent. Now that this trial-by-fire has settled into a routine, and many of the technical barriers have been overcome, the American Neurological Association (ANA) strongly supports that the federal government continues to relax the regulatory hurdles to providing telemedicine services to Medicare and Medicaid recipients. We also encourage the states to allow for the provision of televisits across state lines. For patients with chronic neurological disorders that affect mobility, for example, stroke, Parkinson's disease, or neuromuscular disorders, telemedicine represents an opportunity for in-home visits and prevents the necessity of burdensome, expensive, and, in the COVID-19 era, potentially unsafe travel to a distant clinic. Bloem, et al recently reviewed the state of teleneurology.[4] Even before COVID-19, research suggested, albeit inconsistent, evidence that teleneurology visits could improve access, reduce costs, and improve health outcomes, particularly for patients living in areas that are underserved by neurologists. Data from the CMS in 2017 projected significant neurologist shortages in certain states, such as Wyoming, North Dakota, South Carolina, South Dakota, and Oklahoma.[5]

Much has been written about the disproportionate impact of COVID-19 on people of color and the underserved populations. This certainly applies to access to telemedicine, which is, of course, dependent on access to high-speed internet and computers, smartphones, or tablets. In 2017, over 30% of Baltimore households reported having no access to broadband (Robert Deutsch Foundation, 2017). We need to ensure that ALL of our patients can receive the neurological care they need, whether in person or via telemedicine. Bridging the "digital divide" will require significant investment in broadband access both in rural and low-income urban areas.

An additional barrier to care exists for neurology patients with vision, hearing, or cognitive issues. The Health and Human Services (HHS) Office for Civil Rights has provided guidelines to temporarily permit the use of noncompliant Health Insurance Portability and Accountability Act (HIPAA) web and video conferencing platforms, such as FaceTime and Skype, however, more permanent low-cost platforms that maintain patient security and privacy need to be developed. Prior to COVID-19, physicians had to be licensed in the state where the patient is located at the time of the telemedicine visit. One challenge that still needs to be overcome is how to more effectively integrate learners—students, residents, and fellows—into telemedicine practice.

Following the pandemic, enacting either a national licensing practice or removing state-to-state practice barriers is needed. Enabling permanent changes at the federal and state level will allow neurologists to better care for an increasingly aging population, efficiently, conveniently, and safely, both during the COVID-19 crisis and afterward.

The next generation of teleneurology may actually be used through the use of kiosks placed in pharmacies or retail spaces. The CVS chain of stores has recently expanded its direct-to-consumer telehealth offerings of its MinuteClinic services to numerous states, in a partnership with Teladoc. Other platforms include devices equipped with blood pressure (BP) cuffs, high-resolution cameras, and even direct retinal photography. Academic neurology is actively engaged with designing and refining the capabilities of these platforms and has also played a major role in the development of digital devices to accelerate motor recovery after stroke and brain injury, such as the gamified neurorehabilitation system Mind Motion Go.[6] We have recently deployed 20 of these devices in our stroke unit and COVID units at the Johns Hopkins Hospital.

Clinical Research

In most academic centers, all non-COVID clinical research with a few exceptions, has been halted to prioritize the safety of research subjects and staff. Institutional review boards (IRBs) are either deferring protocol review or have pivoted to focusing on COVID-19 protocols. Steps to accelerate review have been put into place, including short-form proposals, and 24-hour reviews. In late March, the World Health Organization (WHO) proposed a master protocol for companies and institutions that aim to test therapeutics against COVID-19. In addition, the US Food and Drug Administration (FDA) launched the Coronavirus Treatment Acceleration Program (CTAP) on March 31, 2020. The CTAP is now able to review study protocols within 24 hours, can approve single-patient expanded access requests within 3 hours, and is analyzing the use of real-world data for illness patterns and treatment outcomes. There has been an explosion in therapeutic development directed at COVID-19. There are currently 72 agents directed at the SARS-CoV-2 in active trials, and another 211 development programs in the planning stages. Increasingly adaptive trial designs are being used, for example, in Gilead/NIAID remdesivir phase III trial for moderate COVID-19 (NCT04292730). The planned ongoing analyses in these adaptive trials have led to some confusion as there has

been some premature leakage of data from remdesivir trials.[7]

For non-COVID-19 clinical trials, contract research organizations (CROs), such as Parexel, have implemented procedures for remote monitoring visits, for example, exploring methods to access source documents remotely, using telemedicine for visits. The FDA is requiring that missed visits, patient discontinuations, and similar changes in protocol-specified procedures be tracked in case report forms and indexed to the COVID-19 pandemic.[8] Even before COVID-19, telemedicine had been demonstrated to be a feasible strategy for the remote recruitment, enrollment, treatment, and evaluation of patients with depression, pediatric migraine, Parkinson's disease, and multiple sclerosis. Safety monitoring can be integrated into telemedicine platforms in a relatively straightforward manner. Telemedicine holds promise to reduce access barriers to neurological clinical trials and developing outcome measures that can be assessed remotely. As one example, neurofibromatosis (NF) researchers are already using artificial intelligence (AI) and high-resolution digital dermoscopy to improve outcome measurements, for example, quantifying cutaneous neurofibromata.[9]

Boehringer Ingelheim is using Science 37's Network Oriented Research Assistant (NORA) platform to allow researchers to interact with patients throughout a clinical study via a video conferencing feature. NORA enables the direct capture of data with automatic integration to another electronic data capture system. Some of the same challenges for telemedicine also apply to its use for clinical research. There is still a lack of clarity about the need for in-state licensure for principal investigators (PIs), and study drug shipments may also be a significant hurdle from a regulatory standpoint.

The counterpoint to this is that some types of neurological research, for example, imaging and biomarkers studies for neurodegenerative disorders, simply cannot be conducted remotely.

Education and Training

Even before COVID-19, there had been a substantial move toward remote or asynchronous learning for medical students and postgraduate teaching through the use of technology developed primarily for undergraduate teaching in massive, open online courses. The pandemic has, of course, mandated an almost universal switch to remote learning. This year, the ANA will host its 145th annual meeting virtually, the first time that the organization has not held an in-person meeting since 1945. The challenge in virtual meetings is not in delivering the content, but in providing an interactive experience that can engage participants in discussion and questioning. Commercial platforms, such as Crowdcast or Webinar Ninja 5.0, have built-in functionality that help the audiences' engagement and interaction. In addition, they allow simulcasting to Facebook and YouTube. The continued need for education of medical students and residents has spawned a number of very creative approaches. As one of many examples, the Johns Hopkins University (JHU) Department of Medicine has completely redesigned its residency in response to the surge state of COVID-19. The highlights of the changes include creation of 100% geolocalized teams and patients, elimination of extended call shifts, increased supervision models, new ICU triage roles and additional ICU trainees (in new COVID ICUs). They also created new outpatient roles using telemedicine, and innovative "virtual" resident roles from home to support clinical care on our floors and ICUs (S. Desai, personal communication, April 27, 2020).

The (Altered) Financial Substrate of Academic Neurology

After the optimism of the previous sections, we need to face the reality that our parent universities and hospitals are facing a very altered financial landscape. Tuition revenues for undergraduates and international students will be substantially reduced, not just for the coming academic year, but very likely for the next several years. Reduced clinical fees and hospital revenues will impact our health systems and force hiring freezes, furloughs, and reduced benefits or salaries. As we shift into an era of progressively "opening up" areas of this country, we will need to provide greatly expanded testing, tracing, isolation, and treatment of SARS-Cov2. Our institutions and departments will need to bear some of the costs of this, which will need to factor in the cyclical resurgence of the virus, and new confirmed cases in our patients and our staff. Currently, for most of our departments, elective surgeries and procedures are prohibited for at least the next few weeks. There is concern that the anticipated "pent-up demand" for clinical services may be attenuated by the loss of employer-based health insurance for the 26 million Americans who have filed for unemployment, and by fear of entering hospital facilities that have high rates of COVID-19 positivity. It is apparent that COVID-19 is disproportionately affecting communities of color, and other underserved populations, including incarcerated individuals. Models of the return of surgical procedures as COVID-19 wanes suggest that even in the most optimistic scenario, surgical volumes will not reach baseline levels until January 2021.[10] Because surgical volumes drive clinical revenues for our institutions, this will impact even nonsurgical specialties. Levels of telemedicine activity are currently at or

approaching pre-COVID levels or outpatient activity for many institutions. In addition to the professional fees for these visits, facilities fees can also be charged by hospitals. As discussed above, the CMS will need to authorize the use of telemedicine on an ongoing basis, and this will require legislation.

Beyond these changes, the cross-subsidization of research from clinical dollars will shrink. For National Institutes of Health (NIH)-funded research, the closure of most research laboratories will impact our ability to continue to generate data and publications, and indirect costs are only paid out to our institutions when research costs—reagents, technicians' salaries, etc.—are incurred. Another area that has been substantially impacted is philanthropy. For some institutions, philanthropy represents a major contributor to departmental budgets, and we have seen this drastically decrease or be diverted to support of COVID-19 activities. Endowment payouts may also be affected by the fluctuations in the stock market and budget constraints.

The Promise of a "New" Academic Neurology

It is still unknown how quickly, and in which manner, the United States and other countries will be able to "open up" safely in the next few months. Bill Gates summarizes this well in an excellent review[2]:

> *"As we get into the summer, some locations that maintain behavior change will experience exponential decline. However, as behavior goes back to normal, some locations will stutter along with persistent clusters of infections and some will go back into exponential growth. The picture will be more complex than it is today, with a lot of heterogeneity."*

One positive byproduct of the pandemic for academia has been the strengthening of collaborations in clinical areas and in research. Increasingly, neurointensivists are working alongside their colleagues with pulmonary, anesthesiology, and surgery training, and these partnerships will hopefully endure post-COVID.

Shrinking clinical revenues and pressure on third-party payers from the loss of employer-based insured lives will force us to focus even more on value-based health care models. We will need to use new systems to track and quantify neurological outcomes more precisely in the management of both acute and chronic neurological disorders. These will need to be embedded into our telemedicine platforms so that the data are readily available. This will allow us to convince payers that neurologists can provide higher quality and lower cost care for many of these disorders.

Before COVID, neurology was deploying a number of gene-based therapies (eg, nusinersen [Spinraza] for spinal muscular atrophy [SMA], inotersen [Tegsedi] for hereditary transthyretin-mediated amyloidosis, and golodirsen [Vyondys 53] for Duchenne muscular dystrophy). Other antisense oligonucleotide-based therapies are in late-phase clinical trials for amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), and Huntington's disease (HD). Academic neurologists will need to develop COVID-safe processes that permit the continued safe administration of these transformative treatments. In addition, given their very high costs, we must ensure that the revenues from 340b Drug Pricing Program available in disproportionate share hospitals, and hospital-based specialty pharmacy benefits, accrue to our health systems.

We will also see proliferation of "virtual trials" and e-consenting. This will not necessarily be appropriate for some types of clinical research, especially that involving imaging or the collection of biospecimens. Ultimately, the hope is that virtual platforms may diversify clinical trials, and enable participation by any qualifying patient in clinical research regardless of where they live, what type of health insurance they have, and the quality of clinical care services available to them.

Alongside virtual trials and telemedicine, we will see the growth of "digital therapeutics," evidence-based therapeutic interventions driven by high quality software programs to prevent, manage, or treat neurological disorders. The FDA is reviewing for approval several smart phone or tablet-based digital therapeutics for chronic substance abuse (reSET from Pear Therapeutics Inc.) and attention deficit hyperactivity disorder (ENDEAVOR from Akili Inc.).

Academic neurology has a tremendous opportunity now to demonstrate "research resilience." The ANA has hosted several useful webinars on this topic led by junior members focused on how to pivot neurological research to focus on COVID-19, and how to restart non-COVID research. The NIH has partnered with academia to provide COVID supplements for research, to permit pre-award costs to be incurred from January 20, 2020, through the public health emergency period, and has relaxed reporting requirements and submission cycles for grant submissions.[11] Of particular note are allowing pre-award costs to be incurred from January 20, 2020, through the public health emergency period and prior to the date of a federal award for all applicants and recipients that have been affected by COVID-19. The NIH is also showing flexibility in the ability to submit financial and Research Progress Performance Reports (RPPR) later than the scheduled due date. In addition, the NIH is not requiring prior approval to re-budget funds, and,

importantly, is permitting payment of salaries and benefits during periods when no work is performed due to COVID-19. Finally, costs associated with grant-related travel or conference registration fees canceled due to COVID-19 may be charged to the NIH award.

Conclusion, and Choices for the Future

Academic neurology departments *have* responded quickly and creatively, and will surely need to regroup, but also have the choice to *remold themselves*, perhaps in somewhat different forms. Remaining issues facing those of us in academic neurology include:

1. Addressing the enhanced and urgent need to unravel the biology of SARS-CoV-2 as it relates to the nervous system;
2. Assessing organizational changes to support different modes of resident training and scope of faculty responsibilities;
3. Dealing with the financial and economic imperatives both for the short term, and over the next 2 to 5 years;
4. Addressing the enhanced need for streamlined neurology clinical research, some which may be conducted virtually;
5. Ensuring that the overall support for medical research increases, perhaps along with expansion of government-industry-academic medical center relationships, to overcome many historical barriers to their effective interactions.

AMCs have had to respond creatively and quickly to this pandemic. Fortunately, today we have tools, including both clinical capabilities and, perhaps equally important, data collection and communication platforms that have transformed how we have been able to respond to COVID-19. In many ways, however, the concepts of social distancing, wearing masks, and isolation mimics how our forebears responded to the 1918 influenza.

Academic neurology will need to rebuild and regroup in a very different environment, but, fortunately, we also have the tools and creativity to do so. We will continue to provide quality care and transformative research for the most complex of neurological disorders affecting our patients.

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References

1. Johns Hopkins Coronavirus tracker. Available at: https://coronavirus.jhu.edu/map.html. Accessed April 28, 2020.
2. Gates B. The First Modern Pandemic. Gates Notes The Blog of Bill Gates website. https://www.gatesnotes.com/Health/Pandemic-Innovation. Accessed April 23, 2020.
3. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;e201127. https://doi.org/10.1001/jamaneurol.2020.1127
4. Bloem BR, Dorsey ER, Okun MS. The coronavirus disease 2019 crisis as catalyst for telemedicine for chronic neurological disorders. JAMA Neurol 2020. https://doi.org/10.1001/jamaneurol.2020.1452
5. Rao A. Regional Shortage of Neurologists Revealed Across the U.S. Lecture Presented at Alzheimer's Association International Conference (AAIC). London, England, 2017.
6. Lohse KR, Hilderman CGE, Cheung KL, et al. Virtual reality therapy for adults post-stroke: a systematic review and meta-analysis exploring virtual environments and commercial games in therapy. PLoS One 2014;9:e93318.
7. Available at: https://www.bloomberg.com/news/articles/2020-04-23/gilead-plunges-after-report-that-chinese-trial-was-unsuccessful
8. Available at: https://www.fda.gov/media/136238/download
9. Bleicher B et al. Going digital with dermoscopy. Cutis 2018;102:102–105.
10. Jain A, Jain P, Aggarwal S. SARS-CoV-2 impact on elective orthopaedic surgery: Implications for post-pandemic recovery. J Bone Joint Surg Am 2015;1-5. https://dx.doi.org/10.2106/JBJS.20.00602. In Press.
11. Available at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-086.html

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