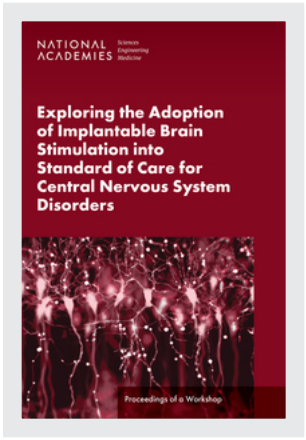

Exploring the Adoption of Implantable Brain Stimulation into Standard of Care for Central Nervous System Disorders: Proceedings of a Workshop (2024)

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Forum on Neuroscience and
Nervous System Disorders

Board on Health Sciences Policy

Health and Medicine Division

Proceedings of a Workshop

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[1] The planning committee's role was limited to planning the workshop, and the Proceedings of a Workshop was prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants; have not been endorsed or verified by the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine; and should not be construed as reflecting any group consensus.

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This Proceedings of a Workshop was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published proceedings as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the charge. The review comments and draft manuscript remain confidential to protect the integrity of the process.

We thank the following individuals for their review of this proceedings:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **ERIC LARSON,** University of Washington. He was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

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Acronyms and Abbreviations

AI	artificial intelligence
APP	advanced practice provider
CDRH	Center for Devices and Radiological Health
CMS	Centers for Medicare and Medicaid Services
DBS	deep brain stimulation
EEG	electroencephalogram
EHR	electronic health record
FDA	U.S. Food and Drug Administration
MDD	major depressive disorder
OCD	obsessive-compulsive disorder
RNS	responsive neurostimulation
TAP	Total Product Life Cycle Advisory Program
UPHS	University of Pennsylvania Health Systems

1

Introduction and Background[1]

With its ability to intervene directly in pathological neural circuits, implantable brain stimulation has had a profound impact on neuroscience research and, for several CNS disorders, clinical care. Implantable brain stimulation is a therapy that involves a surgery in which a device is implanted that sends electrical signals to designated brain areas such as deep brain stimulation (DBS)[2] or responsive neurostimulation.[3] In 1997 and 2002, the U.S. Food and Drug Administration (FDA) approved the use of implantable brain stimulation, specifically DBS, for the treatment of essential tremor and Parkinson's disease, respectively.[4] Since then, the number of publications in the implantable brain stimulation field has increased rapidly and the technology has become a viable treatment option for various central nervous system disorders in addition to Parkinson's disease, tremor,

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[2] For more information on deep brain stimulation, see https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/deep-brain-stimulation (accessed January 23, 2024).

[3] To learn more about responsive neurostimulation, see https://www.epilepsy.com/stories/what-responsive-neurostimulation (accessed January 23, 2024).

[4] For more information on the history of deep brain stimulation and regulatory approvals, see https://www.ninds.nih.gov/about-ninds/what-we-do/impact/ninds-contributions-approved-therapies/deep-brain-stimulation-dbs-treatment-parkinsons-disease-and-other-movement-disorders (accessed February 26, 2024).

dystonia, epilepsy, and obsessive-compulsive disorder (OCD) (Krauss et al., 2021; Lozano and Lipsman, 2013). Despite this growth, however, there remain unanswered questions about how implantable brain stimulation can be integrated into the standard of care across applicable CNS disorders.

To date, implantable brain stimulation has been most integrated into the standard of care for Parkinson's disease, as it is used regularly to relieve symptoms such as tremor, on-off fluctuations, and dyskinesia. It works by stimulating the basal ganglia, which can result in an altered basal ganglion neuron firing rate and pattern, increased calcium and neurotransmitter release, and increased blood flow and neurogenesis (Lee et al., 2004; Tawfik et al., 2010; Wichmann et al., 2011). However, it is unclear how these stimulation effects specifically influence Parkinson's disease symptoms (Okun, 2012).

Despite FDA approval via a humanitarian device exemption for the use of DBS in OCD and promising research in other psychiatric disorders, the use of implantable brain stimulation lags significantly behind other therapeutics. Barriers contributing to its application for psychiatric disorders include limitations in the current knowledge of the neural circuitry underlying these disorders, a lack of understanding of which physiologic changes from implantable brain stimulation are beneficial for which mental illnesses, and a need to identify which approaches are most appropriate for various subgroups of patients (Bilge et al., 2018; Holtzheimer and Mayberg, 2011). There is also a lack of coverage by private insurers for FDA-approved psychiatric indications that can restrict patient access to the therapy (Davis et al., 2021).

For Parkinson's disease, essential tremor, epilepsy, and psychiatric disorders, a number of challenges preclude the widespread adoption of implantable brain stimulation. One such challenge will be finding ways to making the technology scalable and sustainable. For example, the neurosurgery required to implant a brain stimulation device, coupled with the device's maintenance, are expensive and might not be reimbursable costs by insurers, especially for off-label therapies (Rossi et al., 2017; Vedam-Mai et al., 2021). If implantable brain stimulation is to be adopted into routine clinical care, addressing barriers such as reimbursement and accessibility may be important to ensure widespread patient adoption.

Both patient and physician engagement play an important role in advancing the use of implantable brain stimulation in clinical care. In a recent study, a survey conducted among patients with Parkinson's disease found that while patients had reliable knowledge of the procedure and potential side effects, there were still common misconceptions such as believing that implantable brain stimulation would alter the natural course of the disease (Chitnis et al., 2023). Unfortunately, patients who have heard of and are interested in implantable brain stimulation often report feeling

that they were denied treatment from their providers, perhaps because of clinicians' perception that these technologies are a "last resort" (Borovečki et al., 2023; Lökk, 2011). This perception and a lack of physician and patient education can have ethical implications on patient selection, expectations, and consent (Schermer, 2011).

Despite implantable brain stimulation's increased use in clinical care, there remain unaddressed barriers to fully adopting this technology into the standard of care for CNS disorders. To better understand the current state of clinical use of the technology as well as patient and physician education and economic considerations related to the technology, on October 31, 2023, the Forum on Neuroscience and Nervous System Disorders of the National Academies of Sciences, Engineering, and Medicine held a workshop, Exploring the Adoption of Implantable Brain Stimulation into Standard of Care for Central Nervous System Disorders.[5] Participants included clinicians and clinical researchers interested in the use of implantable brain stimulation to treat CNS disorders, several individuals who had differing experiences with implantable brain stimulation, representatives from federal regulatory and funding agencies, officers of advocacy organizations and health systems, and innovators and executives from companies that manufacture implantable devices for treating CNS disorders. Given that implantable brain stimulation is primarily used for movement disorders, a larger portion of the workshop and this proceedings focused on lessons learned from this disease space which may be useful to other CNS disorders moving forward.

WORKSHOP OBJECTIVES

Tim Denison, a professor of engineering science and clinical neurosciences at Oxford University and co-founder and chief scientific officer of Amber Therapeutics Ltd., described the workshop objectives in his introductory comments. The overall objective was to examine the current state of implantable brain stimulation in the treatment of CNS disorders, the current barriers to adopting this technology into standard of care, and opportunities for scalable utility in the future (see Box 1-1). More specifically, the workshop examined various barriers to the widespread adoption of implantable brain stimulation and what would be required to overcome these barriers. Denison identified four areas in which barriers may exist: (1) clinical necessity and including the lived experience throughout the design process to create solutions and treatments that will improve patient's lives

[5] To learn more about the workshop, see https://www.nationalacademies.org/event/40129_10-2023_exploring-the-adoption-of-implantable-brain-stimulation-into-standard-of-care-for-central-nervous-system-disorders-a-workshop (accessed November 26, 2023).

in a meaningful way, (2) regulatory pathways, (3) workflow viability that considers what clinicians need to adopt new technology, and (4) economic viability that examines what pathways and incentives are necessary to scale this technology.

ORGANIZATION OF THE PROCEEDINGS

This proceedings summarizes the presentations and discussions from the workshop (see Appendix B for the workshop agenda).

Chapter 2 reviews the current state of knowledge regarding the clinical use of implantable brain stimulation for several CNS disorders and discusses lessons learned from approved neuromodulation therapies, cochlear and retinal implants, responsive neurostimulation for epilepsy, and DBS for OCD. Particular attention was paid to the issue of "crossing the chasm," that is, moving a technology from pilot research and early adopters to mainstream clinical practice. Chapter 3 offers a firsthand look at the experiences of people with various disorders that implantable brain stimulation can address, with the goal of keeping patients at the center of efforts to expand the adoption of this technology.

The next three chapters examine numerous practical barriers to the acceptance of implantable brain stimulation as standard of care. Chapter 4 examines issues related to patient selection and engagement that may hinder increased adoption. Chapter 5 focuses on the roles that professional education and other factors play in leading clinicians to adopt new technologies or existing technologies for different roles. Chapter 6 explores how reimbursement and other economic considerations can speed up or slow down the adoption of a novel treatments.

Finally, Chapter 7 reviews the key points individual speakers made during the workshop and highlights potential next steps for moving the field forward. The references list includes all sources mentioned in Chapters 1–7, and the workshop agenda is provided in Appendix B.

BOX 1-1
Statement of Task

A planning committee of the National Academies of Sciences, Engineering, and Medicine will organize and conduct a 1-day public workshop that brings together experts and key partners from academia, industry, government, philanthropic foundations, and disease-focused nonprofit organizations to examine the role of implantable brain stimulation to treat central nervous system disorders. The workshop will explore barriers to adopting implantable brain stimulation into the standard of care across CNS disorders and potential strategies and collaborations to develop sustainable and scalable utility in the future.

Invited presentations and discussions may:

- Review the current state of knowledge regarding the clinical utilization of implantable brain stimulation across various CNS disorders and consider the future potential to improve quality of life for patients.
- Explore barriers and potential solutions to adopting implantable brain stimulation into standard of care, such as safety and efficacy, scalability, and regulatory support.
- Discuss the ethical and equity implications associated with reimbursement practices, accessibility, and technological distribution.
- Examine opportunities to enhance health professionals and patient education to ensure informed access to implantable brain stimulation.

The planning committee will develop the agenda for the workshop, select and invite speakers and discussants, and moderate the discussions. A proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

2

Crossing the Chasm: Lessons Learned Across Medical Technologies

HIGHLIGHTS

- The U.S. Food and Drug Administration has several programs intended to help innovative technologies through the regulatory process, including the Total Product Life Cycle Advisory Program, or TAP. (Pinto)
- Cochlear implants, often seen as a success story, have relatively low adoption compared with the number of people who could benefit from them due to several barriers, including regulatory issues, reimbursement challenges, and some resistance within the Deaf community. (Mann Woods)
- Responsive neurostimulation has faced challenges in adoption due to relative complexity of programming and high patient burden compared to devices with similar outcomes—emphasizing the advantages of collecting long term seizure data could be key to encouraging more widespread adoption. (Ganguly)
- Multiple barriers, including regulatory, referral, and reimbursement, have prevented deep brain stimulation from becoming widely adopted for the treatment of obsessive-compulsive disorder. (Greenberg)

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Helen Mayberg, the director of the Nash Family Center for Advanced Circuit Therapeutics at the Icahn School of Medicine at Mount Sinai, opened the workshop by saying, "We are actually not talking about science today," but rather about what is necessary to get implantable brain stimulation more widely adopted. "We're not where we want to be," she continued. "We need to figure [out] how to do better."

In treating patients with implantable brain stimulation, Mayberg said, five categories of questions must be answered:

1. Why is it needed? What are the specific symptoms and side effects?
2. What should happen? Should a circuit be activated or blocked? Should the stimulation be delivered continuously or intermittently? How will things change over time?
3. Where should the stimulation take place? Is there a critical node?
4. Who is the patient? Is the treatment one-size-fits-all, or do different patients require different targets?
5. How should the stimulation be implemented? What are the parameters? Should it be integrated with other treatments? What should rehab involve?

Once these questions have been answered, Mayberg said, the next step is to determine how to scale up the intervention in such a way that it has the biggest impact on the most people. This involves determining patient eligibility and the best way to implement the therapy on a large scale.

THE ADOPTION CURVE OF MEDICAL TECHNOLOGIES

Denison first provided some background, noting that in Europe alone brain diseases affect tens of millions of people a year and have a total cost of hundreds of millions of euros per year (DiLuca and Olesen, 2014). He then discussed where implantable brain technologies are in the process of moving from research into practice. To illustrate this process, he showed an adoption curve and indicated where different technologies fell on that curve.

Deep brain stimulation is still in the realm of pilot research, being carried out by early adopters and visionaries but not adopted in mainstream clinical practice in the way that cardiac pacemakers and cochlear implants have been. In this model of adoption, a chasm exists in the adoption curve between pilot research and mainstream clinical practice, for which a path is needed for uses proven to be safe and effective to cross that chasm to move from early demonstrations of the technology's effectiveness to widespread adoption, said Denison. The chasm, he explained, represents the transition from thinking about a technology as advanced care to standard care.

SETTING THE STAGE: A VISION FOR NEUROMODULATION TECHNOLOGY

Brian Litt, Perelman Professor of Neurology and director of the Center for Neuroengineering and Therapeutics at the University of Pennsylvania, set the stage for the workshop with a look at a possible future for implantable brain stimulation and a discussion of what it would take to get there.

Litt personalized that future by sharing what his neuromodulation clinic might look like in 2040. In that vision, a diverse collection of patients was being treated with brain stimulation: patients with new onset idiopathic Parkinson's disease, focal seizures, familial depression, congenital hearing loss, and blindness from macular degeneration. Today, he said, all of the devices used to treat these patients are therapies of last resort. "In 2040," he said, "I think they will be first- or second-line." Today, he continued, the therapies are targeted at a broad array of patients who may be poorly classified so that they work in some but not in others, while in this future scenario clinicians will be much better at individualizing and targeting therapies. Neuromodulation treatments are now carried out at specialty centers, but in 15 years they may have moved into the mainstream. And today the costs for such therapies are high, but in the future, those costs hopefully will be lower.

Litt identified six factors that may impact the adoption of neuromodulation technologies into the standard of care: effectiveness; acceptance by patients and clinicians; risk, morbidity, and measurable outcomes; complexity; regulatory issues; and total value.

Those who are interested in wider adoption of implantable brain stimulation can look to cardiac implants as a model, he said. The theory of heart pacing was first sketched out in 1889, but it was not until 1958 that the first wearable external pacemaker appeared, and 1960 for the first implantable pacemaker—a latency period of about 70 years from theory to practical devices (Aquilina, 2006). In the ensuing six decades the devices have become increasingly simple and more effective. By 1996, the MADIT trial showed that implantable defibrillators increased survival, with a relative risk reduction of 59 percent compared with standard therapy (Kedia and Saeed, 2012). Today, Litt continued, pacemakers prolong life by 8.5–20 years, depending on the study. Their risk is low, the operation to implant the pacemaker is simple, and they are accepted almost universally, said Litt. The regulatory pathways governing them require clear evidence of safety for these complex systems where failure could be life threatening. This means, Litt continued, that each component of these devices (software, hardware, patient and caregiver interfacing systems, charging, long-term performance) must be carefully reviewed and approved. However, companies that regularly build and seek approval for these devices have a comprehensive understanding of these pathways and requirements and

they may also seek the advice of regulatory consultants who can provide additional guidance, he added. A pacemaker's total value is high in terms of decreased hospitalizations, decreased cost of medications, and of lives saved. This could be best exemplified by the indication for both pacemakers and defibrillators which is primary prevention, Litt said.

Litt summarized several lessons and observations from the pacemaker story: multiple factors drive adoption, the development cycle is shortening, knowledge of the biological circuits is increasing, double-blind, controlled trials that provide class I evidence supporting the therapy are necessary, and development takes time and money.

LESSONS LEARNED ACROSS THERAPEUTIC AREAS

Strategies for increasing the adoption of implantable brain stimulation therapies could be developed by leveraging insights gained from the adoption of other novel therapeutic approaches. To this end, a panel of four speakers discussed lessons learned from the use of different technologies for various disorders that might be applied to implantable brain stimulation: FDA-approved neuromodulation therapies,[1] cochlear and retinal implants, responsive neurostimulation for epilepsy, and DBS for OCD. Each speaker provided an overview of the therapy and the patient need that was being addressed and shared insights into why that particular therapy has or has not been adopted into clinical care.

Approved Neuromodulation Therapies

Vivek Pinto, the director of the Division of Neuromodulation and Physical Medicine Devices at the Center for Devices and Radiological Health (CDRH) at the FDA offered an overview of approved neuromodulation therapies.

The FDA has approved several neuromodulation devices under its premarket approval (Parkinson's disease, essential tremor, and epilepsy) or humanitarian device exemption (dystonia and obsessive-compulsive disorder) programs. On the "crossing the chasm" curve that Denison displayed, Pinto said that these devices tend to be in the early adopters' stage, which means that for most of them, significant work needs to be done before they can be adopted more widely. It is important to understand what barriers stand in the way of this broader diffusion of the technologies, he said.

Pinto laid out CDRH's vision for medical devices, saying, "Our goal is for patients to have access to high-quality, safe, effective medical devices."

[1] Neuromodulation therapies—which include deep brain stimulation—are therapies that use magnetic or electrical signals to modify nerve activity (Marjenin et al., 2020); the focus here was on such therapies that have already approved for use by the FDA.

Beyond that, CDRH would like the United States to be a world leader in regulatory science and device innovation and help facilitate device approval or clearance, and to ensure that consumers, patients, and their caregivers and providers have access to understandable science-based information about medical devices and that they use this information to make health care decisions. He emphasized the steps CDRH and FDA are taking to be proactive, saying "when we see things getting in the way, we want to look at policies, procedures, structures so we can do what we can do internally."

Showing an organizational chart of the Office of Neurological and Physical Medicine Devices, which contains his division, Pinto said that the Division of Neuromodulation and Physical Medicine Devices (DHT5B) had been recently reorganized in 2020, partly in response to concerns about how reviews were being conducted of technologies used in different therapeutic areas. For example, DBS was being tested as a treatment in a growing number of disorders. The new organization includes teams that focus on specific clinical areas and examine any treatments that are used in their area of responsibility. For example, Pinto's division has four teams: (1) neurostimulation—neurology, (2) neuromodulation—psychiatry, (3) physical medicine—acute injury, and (4) physical medicine—neurodegeneration. The neurostimulation–neurology team is responsible for DBS and noninvasive devices used to treat Alzheimer's disease, epilepsy, headache, and movement disorders. The office reorganization is only one part of the solution, he said, but "we want to adopt to things we see going on in the industry."

Pinto said that while DBS is recognized as having the potential to alleviate symptoms and improve the quality of life for patients with debilitating conditions, CDRH is experiencing some "short-term struggles" related to the technology. For instance, there are different risk-benefit profiles for different specific populations and subpopulations. There are also concerns about which are the most clinically meaningful assessment tools and outcomes. Importantly, Pinto emphasized that patient perspectives must be considered as well.

CDRH is looking for ways to accelerate the realization of its vision, Pinto said, and he listed three programs intended to help with that: collaborative communities,[2] the Breakthrough Devices Program,[3] and the Total Product Life Cycle Advisory Program, or TAP.[4]

[2] To learn more about the collaborative communities program, see https://www.fda.gov/about-fda/cdrh-strategic-priorities-and-updates/collaborative-communities-addressing-health-care-challenges-together (accessed November 26, 2023).

[3] For more information on the Breakthrough Devices Program, see https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program (accessed November 26, 2023).

[4] To learn more about the Total Product Life-Cycle Advisory Program, see https://www.fda.gov/medical-devices/how-study-and-market-your-device/total-product-life-cycle-advisory-program-tap (accessed November 26, 2023).

Pinto spoke on approval for studies involving the most vulnerable patients, those who do not have other options. In such cases, he said, the FDA wants to make sure that those patients who are willing to try a new technology or procedure will have access to it. One challenge for the FDA, Pinto continued, is that the agency does not get enough information on the patients' preferences and the level of risk they are willing to take. Additional patient information and having their voices be heard will be needed to help in FDA's decision making, said Pinto. Overall, he concluded, the FDA is dedicating effort and resources to hear from many different perspectives to inform its programming and strategic planning.

Cochlear Implants and Retinal Implants

Carla Mann Woods, the chief executive officer of Mann Healthcare, and a member of the board of counselors at USC Viterbi School of Engineering, spoke about the adoption of cochlear implants and retinal implants to gain insight and lessons that might apply to the adoption of implantable brain stimulation.

She first addressed the question of whether the adoption of cochlear implants should be seen as a success or a failure, and to answer that, she began by looking at the barriers that influenced that adoption. The first barrier was the regulatory system, which gradually expanded the population that could be fitted with cochlear implants, beginning with adults with profound bilateral hearing loss in 1984. Since then, the population of patients approved for cochlear implants has grown to include children older than 2 years with bilateral profound hearing loss (1990), children older than 18 months and adults with severe to profound bilateral hearing loss (1998), adults with moderate to profound bilateral hearing loss (2002), children older than 9 months (2020), and adults with unilateral hearing loss (2022; Figure 2-1). Given the slow pace of allowing access to the technology, Mann Woods said, those interested in implantable brain stimulation should be considering how regulatory approvals could be sped up.

A second major barrier in the adoption of cochlear implants is insurance and cost, Mann Woods said. With 21 percent of U.S. adults and 36 percent of U.S. children on Medicaid, she explained, lack of coverage has had a huge limiting effect in cochlear access. "To this day, 40 percent of states do not cover adult cochlear implants," she said. "All 50 states cover cochlear implants for children, but the coverage is so inadequate that it really is a disincentive for the programs." According to Mann Woods, this is because in most cases Medicaid reimburses about 10 percent of the cost of cochlear implants (which is around $80,000–$100,000, including the surgery), so most centers will not accommodate Medicaid patients who need the implants.

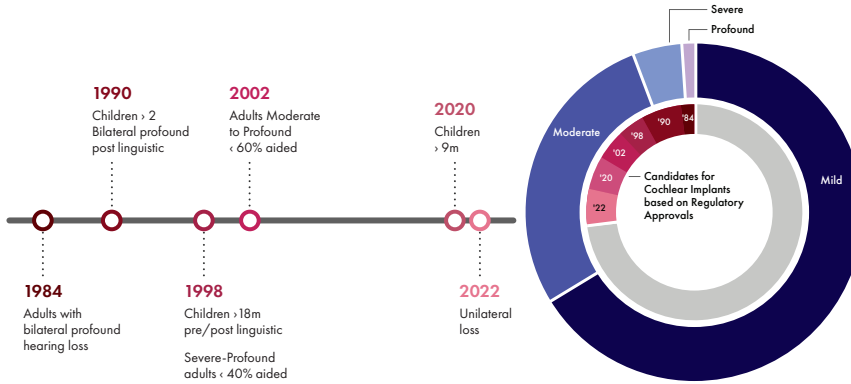

FIGURE 2-1 Chronology of regulatory approval for cochlear implants. (A) Timeline of regulatory approvals of cochlear implants. (B) The population of candidates who are approved to receive cochlear implants has increased with each regulatory approval but remain a smaller proportion of the total population of individuals with hearing loss.
SOURCES: Adapted from figure presented by Carla Mann Woods on October 31, 2023. Data from Goman and Lin (2016).

Another 18 percent of the U.S. population is on Medicare, and while the FDA approved cochlear implants for adults with moderate hearing loss in 2002, it was not until 2022 that Medicare allowed payment for cochlear implants for those patients. That was a huge number of people who would have been suitable candidates, Mann Woods said, which means that Medicare's refusal to pay for them had a huge impact.

Public insurance does not cover, inadequately covers, or limits access to all other cochlear implant services (e.g., postoperative care) as well, she added. Private insurance covers costs adequately, but it is up to employers and plans as to whether to include coverage.

All of this serves as a disincentive to providers, Mann Woods said. It is expensive to run a cochlear implant program, and, due to the reimbursement limits, the pool of patients who can afford the implants is limited. Furthermore, postoperative care, rehabilitation, and maintenance are also expensive, but all payers provide little support. Yet another issue is that many people with hearing loss end up at hearing aid dispensaries, where the workers are not trained, do not understand who a candidate for a cochlear implant is, and work on commission, resulting in minimal referrals for cochlear implants. As a result, there are fewer and fewer cochlear implant centers available to support the growing need.

A third barrier to the adoption of cochlear implants, Mann Woods said, has been the resistance to the technology expressed by some members of the

Deaf community. Early on, some members of the Deaf community would discourage hearing parents from implanting their young deaf children based on the belief that it was not parents' right to take that option to be deaf away from the children. This resistance "was a very significant obstacle the industry had to deal with," she said. Eventually, the stance of the Deaf community softened to insisting that clinicians should also advise patients of the option to have their child grow up with access to sign language. But to a certain extent the resistance still exists today.

A fourth barrier is the fact that the general population and even the medical community have low awareness of cochlear implants and who is an appropriate candidate.

Mann Woods explained the result of all these barriers is that there has been profoundly low penetration of the technology—less than 10 percent of candidates who would benefit from cochlear implants ever get one. So, she said, while many people think of cochlear implants as a success, and while it certainly is an accepted technology and a covered technology, it has not seen nearly the success that it could have. Only 200,000 Americans have received cochlear implants since 1985, compared with many millions who could have benefited and Mann Woods continued, even today, just 50 percent of candidate children receive an implant, and less than 5 percent of candidate adults do (Nassiri et al., 2022).

Mann Woods then spoke briefly about retinal implants, which were developed by Second Sight, a company that was founded in 1998 and filed for approval for its Argus-II retinal prosthesis in 2009–2010. It is mainly a regulatory story, she said. After the company completed its trials, the FDA changed the endpoints for approval and required that Second Sight conduct new trials designed around those new endpoints. The FDA then instructed the company to validate the new endpoints before going to new trials. This technology was novel, Mann Woods said, and there were no previously established endpoints to define the benefit in this patient population. Ultimately, the submission was withdrawn, new trials were done and submitted in 2011, and the FDA granted approval in 2013. But the after-the-fact change of approval endpoints may have depleted Second Sight of necessary resources and eventually, in 2020, the company became unable to move forward. The company is still in existence under another name and owned by another company, but it is unlikely to recover, she added.

Mann Woods closed with some takeaways. In terms of DBS, she said, it will be important to get devices approved earlier in the disease progression. "We tend to test on patients that will benefit [the] least," she said, referring to those at the end stage of their diseases. Carrying out clinical trials will help establish the benefit of these devices early in the paradigm and, Mann Woods continued, "as soon as possible will help open up the market in these applications."

The second takeaway concerned insurance. It is extremely important, she said, to have a dedicated industry organization whose mission is industry-patient advocacy. In the case of cochlear implants, she said, "some of the recent advances in opening up the Medicare candidacy coverage to meet the FDA candidacy labeling that was 20 years after the fact were driven by new, dedicated organization for cochlear implants." Furthermore, it is important to carry out cost-benefit trials early and in parallel with the regulatory trials. Developers will often see getting regulatory approval as the main milestone goal, she said, but it can take another 10 years to take care of the reimbursement component if one waits to start the cost-benefit trials until after obtaining regulatory approval.

Mann Woods said it will also be valuable to establish referral pathways and providers. "It is very important to understand how those pathways go," she said, and to understand the incentives or disincentives.

Finally, Mann Woods said, capital is crucial. "If you are spending too much redoing trials or unable to get reimbursement pay, then you lose capital." And without enough capital, companies will lose the ability to deliver and support their products, to educate people about them, and to conduct ongoing trials.

Responsive Neurostimulation for Epilepsy

Taneeta Mindy Ganguly, an assistant professor of clinical neurology at the University of Pennsylvania, discussed responsive neurostimulation (RNS), which is one of three approved devices for use in treating medically refractory focal epilepsy. The treatment is indicated for patients who continue to have seizures originating from up to two foci in the brain despite adequate trials of at least two seizure medications, she said. Placing the RNS device requires knowledge of the seizure onset zone, which typically involves sophisticated neuroimaging techniques. The device records the patient's electroencephalogram (EEG) and uploads it to the cloud, where it can be reviewed by the patient's doctor. The patient's doctor will then program the device to detect the patient's seizures, and the patient will have a series of visits to optimize the delivery of stimulation when the seizure activity is detected.

Less than 1 percent of the patients in the United States who are eligible for RNS are implanted, Ganguly said. A total of 3.4 million Americans has epilepsy,[5] of whom about 1 million have medically refractory epilepsy, and 575,000 have medically refractory focal epilepsy, making them candidates for RNS.[6] Yet of those, only 5,000 patients have been implanted with RNS, Ganguly explained.

[5] See, for example, Zack and Kobau (2017).

[6] For more information, see https://www.sec.gov/Archives/edgar/data/1528287/000162828021005481/neuropaces-1.htm (accessed February 28, 2024).

A major barrier to RNS is that simpler equivalents exist, Ganguly said. In many cases, surgical resection is the standard of care. And if a patient is not a candidate for surgical resection, neuromodulatory options such as vagal nerve stimulation, DBS, and responsive neurostimulation are considered.

Ganguly then compared RNS with DBS. The two devices' effectiveness is very similar. In controlled trials, both have a responder rate of about 75 percent (i.e., three out of four patients respond, and both have a 75 percent median reduction in the rate of seizures). DBS does not require an invasive presurgical workup, while RNS does. In real-world studies, RNS seems to perform better than DBS, Ganguly said. RNS uploads data to the cloud, while DBS does not. RNS has better a side-effect profile in terms of sleep and mood. But perhaps the biggest difference between them, Ganguly said, is that RNS records long term EEG recordings, as long as the patient reliably uploads data. RNS's data can be invaluable to clinicians as alternative methods of seizure tracking are often known to be unreliable, but this data also requires time from a clinician to interpret—time that the clinician may not have and that may not be properly reimbursed.

RNS's complexity is a barrier to scaling for a variety of reasons, Ganguly said. First, it demands a provider learning curve, and providers may not wish to invest the time. The complexity also implies that clinicians are at least initially dependent on highly trained clinical engineers who are familiar with the technology. Reimbursement is also an issue, she said, because "the billing does not represent the amount of time it takes to review this data." Furthermore, the device is implanted only at level 4 epilepsy centers in the United States.[7] And, finally, patient compliance is often poor, and clinicians rely on patients to upload their data.

Some of the challenges facing RNS can be overcome by valuing the long-term EEG data provided by the devices, Ganguly said. "Judging a device based on the number of seizures is short-sighted," she said. "We know that long-term EEG can inform better surgical plans, elucidate cycles, and inform medication response, yet we give more weight to patient complexity and cost and patient burden." Given the growing value of EEG data recording devices outside of clinical settings, she said, "why not start with existing [RNS] devices implanted long-term that reduce seizures by 75 percent?" Improving technology should increase the memory on these devices, Ganguly said, reducing the patient burden related to uploading the data to the cloud. Thinking of RNS not just as a way of helping reduce the number of seizures but also as a way of providing data that will help inform

[7] For more information on level 4 epilepsy centers, see https://www.naec-epilepsy.org/about-epilepsy-centers/what-is-an-epilepsy-center (accessed February 29, 2024).

the use of the device, the titration of medications, and the understanding of epilepsy as a disease could reshape clinicians' conceptions of RNS.

Litt asked whether RNS is on track to be adopted or if there must be some fundamental changes first. "I think time plays a role," Ganguly responded, "but I think we have a limited number of providers who can only take on so much." Moving to a world where RNS is much more widely available will require, for instance, implementing support systems using artificial intelligence or other technologies to review all the brain data and identify important information, "so we are not drowning in data." That in turn will require "a lot of intersectionality from programmers and engineers as we are moving more towards devices," she said.

Deep Brain Stimulation for Obsessive-Compulsive Disorder

Benjamin Greenberg, a professor of psychiatry and human behavior at Brown University who also directs the COBRE Center for Neuromodulation at Butler Hospital, offered some thoughts about the use of DBS in the treatment of OCD.

Self-referrals to health care providers for DBS are the norm for OCD, Greenberg said. Referrals from clinicians are relatively rare even if a patient's case is intractable and quality of life is poor.

The attitudes of clinician groups vary, he continued. Psychologists and psychiatrists vary in the degree to which they see OCD as a brain problem. In particular, he said, even some behavior-therapy-intensive programs—which his group refers patients to before surgery and after surgery—are not open to including neurosurgery of any sort in their treatment plans.

On the regulatory side, Greenberg said, it is useful to think about the different barriers that dystonia and OCD encounter despite both having FDA approval under the humanitarian device exemption.[8] He explained the barriers for referral and reimbursement are not as great for dystonia as they are for OCD.

Multiple access and workforce issues affect OCD care, even conventional care, he said. "You can't find an OCD expert psychiatrist." Even in large medical centers, the best places to offer OCD treatment, clinicians do not have adequate time or resources. "We also have a problem in the next generation of workforce coming in," he said. Clinicians who also conduct research face increasing difficulties in both clinical life and regulatory burden. "That makes life difficult, if you want to try to do this," Greenberg said.

[8] Dystonia is a "neurological movement disorder characterized by involuntary (unintended) muscle contractions that cause slow repetitive movements or abnormal postures that can sometimes be painful." For more information, see https://www.ninds.nih.gov/health-information/disorders/dystonia (accessed December 4, 2023).

In terms of needs for the future, Greenberg pointed to combined centers that perform neuromodulation and other procedures, such as laser interstitial thermal therapy (LITT) for lesions. "Maybe if there is alignment across fields, one could have adequate resources," he said. "We also desperately need long-term follow-up data to assess effectiveness, burdens, access to care, cost benefits, effects on functioning, and, what seems to be most important to patients, does this procedure, does this device in the case of DBS, help me to reach my life goals?"

In terms of advocacy, he pointed to the Focused Ultrasound Foundation as an "interesting model." It is aggressive, well organized, and well-funded in its advocacy for using ultrasound in various ways, he said.

Litt asked Greenberg about measuring outcomes from patients using psychiatric devices, which are currently difficult to objectively measure. He wondered if technology such as mobile phones or smart watches would become standard for monitoring symptoms and prognosis though there would have to be efficient, cost-effective ways to analyze and utilize these large data streams.

"I think all those things," Greenberg responded. "Digital phenotyping is promising," although questions remain about how activity is going to be monitored. Also, he continued, in addition to patient self-reports and reports from clinical observers, additional information is needed from "informants"—that is, people who know a patient well and can offer details about their symptoms and limitations. "I think we can do better than we do now," he said.

DISCUSSION

Funding Opportunities for Deep Brain Stimulation Procedures

Litt opened the discussion session by offering a question about funding to the panel: "If we are successful and there's increased uptake for these devices, how are we going to pay for it?"

"I would say, with difficulty," Greenberg answered. In the case of using DBS for OCD, it can be difficult to get reimbursement especially from Medicare, in his experience. "There is going to have to be a payment regime where the long-term benefit to a patient is key," he said, "and we don't have such a thing."

Mann Woods said that when funding is decided based on a cost-benefit paradigm, a strong case can be made for paying for surgery, particularly in the cases of patients who will go back to work. So, Mann Woods said, it will be important to get cost-benefit considerations to play a role in coverage decisions.

Current Barriers to the Adoption of Implantable Brain Stimulation

Litt asked the panel to provide short answers to another question: "What is the single biggest barrier to uptake of implanted neuro-devices?" "Lack of knowledge and fear," Greenberg said. "Lack of integration into standard of care," Ganguly said, with which Mann Woods agreed, and added, insurance coverage and awareness. Finally, Pinto spoke about patient acceptance of the procedures. Why are some patients more accepting of the technology, and what underlies the fear of the technology that some have? Litt raised the issue of effectiveness, suggesting that there may be a threshold that, once passed, could be a tremendous driver of adoption independent of other factors. Litt concluded that including participants in the conversations about implantable brain stimulation will also be important and this sentiment was reflected in the workshop's ensuing discussions with individuals with lived and living experience.

3

Perspectives from Those with Lived Experiences

HIGHLIGHTS

- Some patients benefit tremendously from implantable brain stimulation (McNasby, Nelson), while others experience little or no benefit. (Austin)
- Not all candidates for implantable brain stimulation choose to have the procedure. The reasons vary but often depend upon a weighing of the risks and benefits. A patient who initially declines such a procedure may later choose to undergo it as their condition and the technology evolve. (Garrido-Revilla)
- Some patients living with complex neurological or psychiatric conditions find that promising and even effective treatments are not covered by their insurance companies. This may prevent patients who could benefit from implantable brain stimulation from receiving them. (Austin, Nelson)
- One obstacle to more people getting implantable brain stimulation to treat mental illness is the lack of qualified practitioners in many parts of the country. Many patients end up moving to areas with first-class medical facilities and doctors in order to pursue deep brain stimulation treatment. (Garrido-Revilla, Nelson)

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

When considering optimal applications for deep brain stimulation and its broader adoption, a constructive approach may be understanding the technology from the perspective of patients who contemplate and undergo it. During the workshop, four individuals living in the United States with medical conditions that can be treated with implantable brain stimulation shared their perspectives. Their experiences ranged from having almost complete success in treating the condition to seeing very little improvement to deciding not to have a device implanted at all.

"Despite the success of neurostimulation in treating neurological disorders," said Laura Lubbers, the chief scientific officer at CURE Epilepsy, "it is often thought of as a last treatment option and not a first- or second-line treatment. [The] panelists have differing neurological conditions which require unique neurostimulation solutions, but perhaps by looking across them we may find commonalities that may help advance all of them." Workshop participants explored what patients need from implantable brain simulation for it to be considered a successful treatment, discussed how adoption of the technology can affect patients and their quality of life, and finally, highlighted some of the biggest challenges to applying this technology from the patient perspective "in hopes of finding solutions and pathways forward that might enable more people to adopt this as a treatment."

A DISAPPOINTING EXPERIENCE WITH THE TREATMENT OF EPILEPSY

Steve Austin, a member of the board of directors of CURE Epilepsy, was diagnosed with epilepsy when he was 12. Now, at 49, he takes approximately 15 medications to control it. Although brain surgery can be used in some epilepsy patients to stop or reduce the number of seizures, he chose not to pursue that option because in his case the surgery would require removing tissue from the motor cortex, which could result in paralysis of half his body. "I would rather have seizures," said Austin. Therefore, he decided on a procedure in which a device was implanted in his brain in an effort to use RNS to control the seizures.

Unfortunately, after 4 years of doctors experimenting with various settings on the device, they were unable to decrease the number of seizures. In fact, Austin said, the number increased, "which they absolutely did not expect." The clinicians and research doctors had known it was a possibility that RNS would not work, he said, but they were optimistic, so "it was basically disappointing for everyone."

Given that situation, Austin decided in collaboration with his clinician that it was probably best not to replace the device's battery after 4 years, which is the typical replacement time. He thought that if the doctors could not figure out how to reduce his seizures with the device during that time,

they probably were never going to get it to work for him. So, the device remains in his brain, but it is not mitigating the epilepsy.

Instead, Austin uses medication to help control the seizures. "What I have now manages the epilepsy well enough," he said. "You won't notice I'm having a seizure unless you know what to look for. I do have them, on average, two times a day." This means that sometimes he will go days without a seizure, and other days he will have multiple seizures. It prevents him from doing things like driving, and since one of the triggers for his seizures is body heat, he cannot do much physical exercise. "So, there are certain downsides that I have learned to live with over time," he said. Knowing that as he gets older the disease may lead to further complications, he had hoped that the brain implant would make a difference, but ultimately it did not.

SUCCESSFUL TREATMENT OF PARKINSON'S DISEASE

Jim McNasby, general counsel of the Michael J. Fox Foundation for Parkinson's Research, described his experience with DBS used to treat his Parkinson's disease. In 2019 he had been living with the disorder for 19 years, and he had reached the point where he was taking 20 to 27 pills a day to control it, but he was disappointed with the results. Thus, he chose to get DBS to alleviate his symptoms.

Instead of describing the results of DBS in words, he showed a video from the first time the device was turned on after implantation. At first, his hands were shaking noticeably, but as soon as the current began flowing through one side of his brain, the shaking in his right hand stopped. In the video he says, "I feel like the problem which was always there is not there—like somebody turned my right arm back on." His posture improves noticeably, and he reports to the doctor that he feels "speedy and less rigid." After the device is turned on in both sides of his brain, he can be seen jogging down the hall, taking great pleasure in an ability he had not had for many years.

McNasby actually had two devices implanted, one in each hemisphere, each with a battery and a lead into the relevant area of the brain. And each of the devices had a remote connection so that his doctor could adjust the settings remotely. This was particularly important, he said, in September 2022, when a wire on the left side broke. He knew something had happened, but he was not sure exactly what. He called the doctor to tell her what had happened. Although she was not in her office and the Abbot representative was in a parking lot in Hackensack, New Jersey, and McNasby was in the Catskill Mountains in southeastern New York State, the three of them were able to discuss what should be done. The Abbott representative was able to remotely turn the power on and off to the two devices and figure out what had happened. McNasby had to go back on his medication

until he could have the surgery to replace the wire, but otherwise everything turned out fine.

McNasby noted that the implants have not been a panacea. While they have remedied his tremors and dystonia, he is now taking seven pills to help control Parkinson's disease, and he has developed three categories of symptoms that he had never had, including REM sleep behavior disorder,[1] a syndrome that is common among Parkinson's patients, and balance issues, which have caused him to start festinating or sometimes needing to take smaller steps backwards in order to maintain an upright and balanced position.[2] Still, in spite of these new symptoms, McNasby views the procedures as a success.

LIFE-CHANGING RESULTS IN TREATING DEPRESSION

Jon Nelson was diagnosed with major depressive disorder (MDD) in 2012. Nelson, who is with Jon Nelson Advisors, LLC, began with a gripping description of the effects that major depression had on him.

Amid Nelson's depression, his self-esteem and self-confidence got increasingly lower. In the beginning he was able to work effectively in his job in the corporate world, he said, likening himself to a high-functioning alcoholic except that he was dealing with depression instead of alcoholism. On the surface he had everything, including three healthy children and an amazing wife, which made him question his behavior even more. "I didn't understand what was going on," he said.

What happened, he continued, is that he began thinking about dying by suicide more and more until it became nearly constant. "I still drive around my town, and I know exactly which trees would be the best to slam my car into," he said. Over time he became less and less functional, to the point that his wife had to take on all his responsibilities, including going back to work to support the family. He watched as her life crumbled and his own engagement with his children diminished. Although he had come to realize that he was suffering from a disease over which he had little control, he could not help but feel that everyone would be better off without him.

[1] A person with REM sleep behavior disorder, sometimes called dream-enacting behavior, will "physically act out vivid, often unpleasant dreams with vocal sounds and sudden, often violent arm and leg movements." For more information, see https://www.mayoclinic.org/diseases-conditions/rem-sleep-behavior-disorder/symptoms-causes/syc-20352920 (accessed November 26, 2023).

[2] Festinating or festinating gait is characterized by short, shuffled steps to prevent falling due to an individual's center of gravity being too far forward, sometimes caused by a stooped position. For more information, see https://parkinsonsdisease.net/symptoms/parkinsons-gait (accessed February 27, 2024).

"I started becoming extremely euphoric for death," he said, and thinking about ways he might accidentally die. "I was obsessed with it. The reason I wanted that to happen is, if I died of an accident, it solved my problems. My wife would get life insurance. My children would have a father who died of an accident, and I wouldn't have to suffer anymore. So that consumed me—so much so that I would hear about a car wreck, hear about an airplane crash, and I was jealous that it wasn't me. That is what it is like to live with this disease." At that point he counted a day as successful if he was able to take a shower, or if he slept for 12 hours plus a nap instead of sleeping for 16 hours.

He tried everything he could think of to survive, he said, including two residential treatment programs, more than 10 medications, three partial hospitalization programs (PHPs), two intensive outpatient programs, and even psychodrama therapy. Nothing worked. His depression was deemed treatment resistant.

Fortunately, though, he was able to get into a clinical trial at the Icahn School of Medicine at Mount Sinai that was using DBS to treat depression. Although he had no expectations that the treatment would work, he said, he was not concerned about any possible negative outcomes. Because nothing had worked to that point, he saw his two options for the future as being living in misery or dying by suicide, which made him willing to try what seemed to be a long shot.

The Mount Sinai physicians and care team were amazing, Nelson said, and they took good care of him. The implant was inserted during an eight-hour procedure, and the device was turned on the next day. The effect was instantaneous, with all the feelings of dread and the suicidal ideation vanishing. "I haven't had a single suicidal thought since the surgery, August 22, 2022, and haven't had a single feeling of depression," he said. "It is a complete miracle."

"Everything is new to this day," he continued. "I want to go on vacation, to be present, walk my dog. I couldn't do any of this stuff. To do that and go into an ocean and feel water on my body—just the most basic things you could ever imagine, I just feel extremely lucky to be here and extremely lucky for the technology and scientific development that has happened."

CHOOSING TO FORGO AN IMPLANT

Claudia Garrido-Revilla, a member of the patient council at the Michael J. Fox Foundation for Parkinson's Research, shared her perspective of choosing not to undergo DBS. Now a 58-year-old Parkinson's disease patient, she was diagnosed at the age of 45 in May 2010, after enduring 3 years of tests and scans to determine what was affecting her. "No one could diagnose me," she said. "I was a younger woman [and] Hispanic.

At some point I asked, 'Could it be Parkinson's? Do you think it could be Parkinson's?'" But the doctors would say, "'Oh no, no. Your characteristics don't qualify you. We are sure it is not Parkinson's.'"

At that point, she continued, she decided it would be a good idea to change clinics, and, indeed, when she went to a new clinic the doctors there quickly determined that she had Parkinson's disease. That diagnosis felt "like a bucket of ice water," she remembered. "It was a shock for everyone." A mother of two young, very active boys and a husband who traveled a lot, she wondered what she would do, how she would cope.

Under the guidance of her doctor, Garrido-Revilla began taking the basic medications used to treat Parkinson's disease. At some point her doctor suggested that if the medications stopped working, she could try DBS. "I was excited," she said, and willing to undergo DBS as an alternative treatment option that could help alleviate symptoms as the disease progressed.

Initially Garrido-Revilla was very positive about getting an implant for DBS, she said, but various things caused her to question whether it was right for her. Because of her advocacy, she attended various conferences and support group meetings and spoke with people about their experiences with Parkinson's disease and DBS. "I would ask their stories," Garrido-Revilla said. "They would tell me everything." She found that the men she spoke with generally had very positive experiences with that treatment, feeling as though it made a major difference in their symptoms.

But the women, Garrido-Revilla observed, did not seem to have such positive experiences with DBS. Some of them had certain speech issues or experienced confusion. "I started thinking, 'What if this is related to gender? Is there a clinical difference between Parkinson's in women and men?'" She found a couple of studies from the National Institutes of Health that found that there is a gender gap in having DBS, with more men having the procedure than women.[3] That made her concerned that there might be differences in the standard of care between men and women. She also noted that as a Hispanic woman she was treated differently from White women in various ways, such as nurses assuming that she might not speak fluent English and asking her if she needed a translator.

Ultimately, Garrido-Revilla could not shake the feeling that as a Hispanic woman she might not receive the same standard of care as a White man and thus might not get as good a result. This affected how she viewed the risks and benefits of the procedure enough that she has decided, for the moment at least, not to proceed with it. However, Garrido-Revilla has not ruled out the possibility that she might do it sometime in the future. She knows that many people have been very happy with the results, and she may still decide to move forward.

[3] See, for example, Sarica et al. (2023).

DISCUSSION

Unexpected Experiences

Lubbers asked the panelists each to talk about what was unexpected, in either a positive or negative way, in their experiences that they would want people to know about.

McNasby said that he was surprised by the lack of precision after the implantation for Parkinson's disease. There was so much rigor before the surgical procedure (e.g., multilayered brain scans and robotics to ensure the exact placement of the leads) that McNasby was surprised by the trial-and-error approach to adjust the electrical stimulation.

Nelson did not expect the DBS device to work as quickly as it did for his depression. But then once the implant was on and working well, he worried about what would happen if it stopped. In the clinical trial he participated in, the device was scheduled to be turned off for a week 6 months after the initial surgery. "I was so scared," he said, and he spent much of that 6-month period talking to the team about how he would handle it. He was heartened when one of the doctors on the team, a psychiatrist, told him that if he felt anything, it probably would not be until about 5 days after the device was turned off. That is exactly what happened. While he didn't experience any mental symptoms, the disease physically took over his whole body. He made it through that week, but it took him another 3 weeks to get back to baseline after the device was turned back on. Currently, he added, he now has an investigational device, which must be charged every 2–3 days. "I pretty much am worried at all times it is not working," he said, "so I have massive anxiety about that."

Nelson shared that he was also surprised by the size of the implants under his scalp—he did not realize they would be so prominent. While he does sometimes feel self-conscious about the implants, they represent his journey, and that is something Nelson is proud of.

Austin spoke about two things that surprised him after receiving RNS as a treatment for his epilepsy. First, he was surprised that the frequency of his seizures increased after the procedure. He was not really surprised that RNS did not work for him, he said, because "nothing has really ever worked," but he did not expect the increase in seizures. Second, he did not expect how much trial and error the process would involve on the doctors' part. "It is not as if they knew exactly what they were doing," he said. "They were actually learning as they went along." This did not feel really ideal to him, he added, but he hopes that at least the doctors learned something that might be able to help other people.

Clinical Management and Standard of Care

Given the different experiences among patients with their clinical care teams, Lubbers asked: "What does the gold standard look like? What do medical teams need to know to help improve patient care?"

The current standard of care leaves much to be desired for patients with severe mental illness, Nelson said. Most of the treatments he tried were not covered by insurance and had to be paid for out-of-pocket. It was extremely frustrating to get a letter from his insurance company refusing to pay for a treatment because it was "not medically necessary" when that treatment might help him not die by suicide, said Nelson. By contrast, he was treated exceptionally well by the Mount Sinai team. "I felt like a VIP," he said. "It was the most incredible patient experience you could have." Both his preoperative and postoperative care were incredible and served as examples of how mental illness should be managed. "I'm so grateful for the kindness and empathy of the entire clinical team," he said.

Garrido-Revilla, who has not yet received DBS for her Parkinson's disease, echoed Nelson's points on the difficulties with insurance coverage. The insurance supplied by her husband's employers did not cover several medications, and these added up to thousands of dollars a month. So she worried about the costs of getting an implant for DBS, and that is one of the factors she considers in thinking about whether to get the procedure.

By contrast, McNasby said he was very fortunate in his insurance coverage because as the former general counsel of one of the country's largest insurance brokers, he knew a lot about insurance and had advocates in the business helping him personally.

Austin said that he was able to get his procedure covered by insurance, although that coverage was not automatic. Initially his insurance company said it would not cover the procedure because it was not proven. "Fortunately for me, the neurosurgeon called his counterpart at the insurance company, and it got covered," he said. However, if an insurance company denies coverage to an individual, the individual may not have the same privilege or resources to convince the insurance company to provide them with coverage or reimbursement.

Access to Care

In response to a question from Lubbers about access-to-care challenges in different regions of the country, Garrido-Revilla said that many parts of the country need more neurologists, more movement disorder specialists, and neurosurgeons with experience in DBS. "The system is lacking the personnel to cover the needs of the patients," she said. "I used to live in central Illinois. The [single] provider was definitely not enough. I had to

go to Chicago to get my care." Although she has since moved to Houston to increase her access to care, she said that "the medical system is not prepared for the amount of Parkinson's disease patients out there," including potential DBS patients."

Nelson agreed and said that many patients relocate so that they can be close to doctors and clinics that know how to care for their conditions.

4

Patient Selection and Engagement

HIGHLIGHTS

- Success in deep brain stimulation depends to a great degree upon selecting the correct patient. (Candelario-Mckeown)
- It is vital to educate a patient on what to expect from the DBS surgery and afterward, as this can have a major effect on the patient's satisfaction and behavior. Clear communication between a patient and providers is crucial. (Perides, Wang)
- Support systems (e.g., family, caregiver, and friends) for a patient are also an important factor in the success of DBS. (Davis)
- Biomarkers can signal to clinicians and patients that a DBS surgery has had its desired effect even before the surgery's effects on the patient's symptoms are apparent. (Widge)
- DBS used for psychiatric disorders such as depression or obsessive-compulsive disorder may be seen as rehabilitative rather than curative. That is, in most cases it will not get rid of symptoms, but it may make them easier for a patient to manage. (Widge)

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Decisions regarding which patients should be offered the option to undergo deep brain stimulation can impact the overall effectiveness of the treatment, said Sarah Perides, a pediatric practitioner at the Evelina London Children's Hospital: "I think patient selection is one of the most important, if not the most important, aspect about managing patients with implantable devices." Furthermore, the decisions and actions of individual patients will also play a role in determining how widely adopted deep brain stimulation technologies may become in the future.

Good patient selection is very challenging, Perides continued. She said, "You need to find the right patient . . . clinically, phenotypically, biologically, psychologically, and socially. You also need to know what patients are not good for this type of surgery." Then, once a patient is selected, the clinician must build an effective relationship not only with the patient but also their family, partner, and local care team. The clinician must have open conversations with the patient about the procedure risks, potential benefits, and long-term implications. "No matter what the outcome is—good, bad, or ugly—you need to maintain that relationship. It is not a do-and-discharge therapy. You have a long-term relationship with the patient, whatever the outcome."

With that background, several workshop participants reviewed the challenges associated with patient selection and engagement to consider the ethics of ensuring access to all patients and demographics; explored the potential opportunities and collaborations needed to develop informed patient selection practices and equitable access to the technology; and reviewed patients' concerns about possible complications of implantable brain stimulation and how best to inform patients about those complications.

PATIENT SELECTION IN THE UNITED KINGDOM'S NATIONAL HEALTH SERVICE

Joseph Candelario-Mckeown is a nurse practitioner at the National Hospital for Neurology and Neurosurgery in London with more than 17 years of experience using deep brain stimulation to treat Parkinson's disease, among other areas. He said that success in DBS relies heavily on selecting the right patient at the right time in terms of when the surgery is carried out. Making the correct decision requires a multidisciplinary approach with expert clinicians who know what they are doing, Candelario-Mckeown said, and it is also important to listen to the patients in the time leading up to the surgery. In the United Kingdom there are specialized nurses to look after patients undergoing DBS and to serve as the first point of contact. "We have put the patient at the very center of their care," he said.

To determine which patients qualify for DBS surgery, the United Kingdom's National Health Service uses a number of objective clinical criteria,

Candelario-Mckeown said. In the case of Parkinson's disease, these include such things as the patient having had the disease for a minimum of 5 years, Levodopa responsiveness,[1] a cognitive and neuropsychology assessment, neuroimaging, and a psychiatric assessment. In addition to assessing the need for the surgery, the criteria are also meant to assess the likely short- and long-term outcomes of the surgery and whether it would offer the patient a positive or negative outcome. The predictive criteria include age, quality of life, the disease phenotype, genetic information, and comorbidities.

As a nurse practitioner, Candelario-Mckeown said, one of his jobs is to understand patient expectations and motivations. Why are they getting the surgery? What do they expect to gain? He also educates patients and their families about what they can expect from DBS, such as what improvements are likely and how long it will take to optimize the settings of the device.

BARRIERS TO RECEIVING DEEP BRAIN STIMULATION

Rachel Davis, an associate professor of psychiatry at the University of Colorado Anschutz School of Medicine, spoke about four main barriers to getting DBS surgery, using OCD as an example. One barrier is limited access to specialized prerequisite treatment. "It is hard for people to find psychiatric care covered by insurance, let alone specific OCD expert care," she said. "We in Colorado have one of the few centers that accept insurance and provide expert OCD treatment. However, the more patients we see, the more money we lose, and the more we are at the mercy of our hospital and our department of psychiatry to keep us afloat." Her department had about 100 people on its wait list for therapy at the time of the workshop, she added.

This barrier combines with two others—a lack of insurance authorization and reimbursement and a lack of access to specialized treatment centers—to dramatically limit the number of patients who receive DBS to treat OCD, Davis said. Since the FDA approved DBS for the treatment of OCD in 2009, there have been fewer than 400 DBS surgeries worldwide in patients with OCD. "You can compare this to approximately 160,000 surgeries for Parkinson's disease," she added. And without enough surgeries, it is impossible for doctors and clinics to develop expertise at treating OCD with DBS. "Right now, there are only a handful of centers in the U.S. that offer deep brain stimulation for OCD or psychiatric indications in general," Davis said.

[1] In most patients with Parkinson's disease, treatment with levodopa, the precursor to dopamine, acts to reduce various symptoms of the disease, such as bradykinesia, or the slowing of movement that is one of the disease's main symptoms. How a Parkinson's patient responds to levodopa provides information about the likely underlying neuronal deficits that are causing the disease. See Kempster et al. (2007).

The fourth barrier Davis mentioned was stigma and how stigma regarding surgery for mental health issues is still left over from earlier attitudes. In the mid-1900s, she explained, there were few medications to treat psychiatric illness, so doctors used brain surgery or lobotomy. "Brain surgery back then was often indiscriminately done, grossly destructive, and not very effective," she said, and "it became associated with inhumane treatment of people who were mentally ill." Brain surgery is very different today with much more attention being given to ethical and medically appropriate use, she continued, "but that stigma is still there." And that stigma probably ends up limiting referrals from some physicians who do not consider neurosurgery a reasonable option for the treatment of mental illness.

To conclude, she spoke briefly about the importance of support systems both pre- and post-operation. "DBS requires not only individual buy-in but family or support system buy-in," she said. "You want to make sure that the family [and support system] has all their questions answered. If the patient is on board but the family is suspicious, that can interfere with outcomes and impede recovery. You also want to be sure family is available for support postoperatively." For example, some patients with OCD have problems maintaining appropriate hygiene after the surgery because of their extensive shower rituals, which can increase infection. "Involving your family to ensure adequate hygiene, nutrition, and postoperative wound care can be important," she said.

HELPING PATIENTS DECIDE WHETHER TO HAVE DEEP BRAIN STIMULATION SURGERY

Doris Wang, an associate professor in the Department of Neurological Surgery at the University of California, San Francisco, is a neurosurgeon who specializes in providing deep brain stimulation for patient with movement disorders. She spoke about helping patients determine whether DBS surgery is right for them and how to optimize surgical outcomes.

"By the time patients get to me for surgical evaluation," she said, "they have been living with their movement disorders for many years. It is a big step to go from dealing with a chronic illness for which your symptoms may be partially managed by taking pills to having your head opened and all these electronics implanted in your brain." Some patients, particularly those who have spoken with others who have had good results from the procedure, cannot wait to get a potentially life-changing surgery. Others see it as a "big scary thing" that they are exploring at the request of their doctors or as a last resort.

In speaking with patients, she said, she has several goals. The first is to explain the surgery: what is being implanted, the steps of the surgical procedure, the risks, the length of the associated hospital stay, and so on.

Second, she wants the patient to have the correct expectations about what will and will not improve with the surgery. It is important that the patient understand, for instance, that DBS does not cure the disease or stop its progression. Third, she wants to learn about the patient's preferences in order to personalize the surgery. Would the patient prefer to be asleep or awake? Would the patient prefer the incision-less option? Or would the patient prefer to forgo the surgery altogether and choose a less invasive way to treat the symptoms?

Finally, Wang said, she has learned that there are several factors important to optimizing the outcome of DBS surgeries. The most important factor is patient selection—making sure, for example, that the patient has been diagnosed correctly, that the patient's major motor symptoms are at least somewhat responsive to medication, that psychiatric and neurological comorbidities are not too bothersome, and that the patient has adequate social support.

Second, she provides clear expectations so that the patient does not have unrealistic hopes for improvement. The third factor in optimizing outcome is practicing good surgical techniques. She does everything in her power, she said, to place the electrodes accurately and safely. "That comes from years of practice and surgical technique," she explained.

Fourth, she tries to anticipate potential problems and have contingency plans in place. Finally, she said, clear communication with patients is key to good outcomes. "Even if I do the perfect job, sometimes patients still don't have the perfect or expected outcome," Wang said. "If patients don't have what they need, then we go and explore what the issue is. Is it because the leads are not placed well? Is it because they haven't undergone adequate programming?" By communicating clearly with patients and other members of the team, such problems can be identified and solved, she added.

PROGRAMMING DEEP BRAIN STIMULATION IMPLANTS TO IMPROVE OUTCOMES

Alik Widge, an associate professor of psychiatry at the University of Minnesota, where he directs the Translational NeuroEngineering Laboratory, spoke about improving DBS outcomes by learning to do a better job of programming the implants. "If we really want to get patients enthusiastic and payers enthusiastic about scaling up innovative brain stimulation," he said, "we have to be able to tell people that we know when this is going to work for you, and we know we are doing it right." The key to that, he continued, "is to get way more objective about what we are doing with programming," and the key to that, in turn, is to use biomarkers to provide an objective measure of the results of DBS.

Widge offered an example of how biomarker use can improve results from deep brain stimulation. The example involved the treatment of MDD and OCD, but it is much more broadly applicable, he said.

One area in the brain that has been identified as a potential DBS target in treating MDD is the ventral capsule/ventral striatum. The FDA has approved DBS in that area for treating OCD (Denys et al., 2020), and several research groups have investigated it in the treatment of MDD, but the results have varied wildly. One industry-sponsored trial (Dougherty et al., 2015) saw no effect on depression from this treatment, Widge said, while another academic trial (Bergfeld et al., 2016) reported a large effect. What was the difference? The first trial lasted just 4 months and used a standard algorithm for DBS, almost "set it and forget it." The second one, by contrast, gave an expert clinician a year of trial and error to try to figure out how to help these patients, working with the settings and observing the results. The moral, he said, is that with time, experimentation, and clinical expertise, outcomes can get much better.

A major problem with such an approach is that it is very hard to measure outcomes, Widge said. In the best cases, such as the one described previously by Jon Nelson, the improvement may be obvious immediately, but more commonly, it will often take weeks to months for an effect to appear. "That means patients are sitting there saying, 'Am I going to get better? Do you have any clue? Do you really know what you are doing? Is my stimulator on? Is it in the right place?'"

Given this situation, Widge and his colleagues are looking for ways to measure changes in the brain that will predict improvement even if that improvement will not appear for weeks or months. In particular, they are focusing on a particular biomarker known as cognitive control, which is the ability to inhibit responses—in essence, a person's ability to refrain from what would be a default or habitual behavior, such as resisting the urge to eat a candy bar when on a diet. Cognitive control is impaired in a number of disorders, Widge explained, including depression, OCD, and addiction, and it can be measured objectively.

What Widge's team discovered is that DBS of the ventral capsule/ventral striatum improves cognitive control, and the effect is measurable within a few seconds of a change in stimulation (Basu et al., 2023; Widge et al., 2019). Thus, he suggested, it may serve as a biomarker that predicts whether DBS will improve psychiatric symptoms in a patient (Nagrale et al., 2023). This would provide a "decision support system" to a clinician that will indicate when the proper target in the brain has been fully engaged. It could also give patients confidence that a treatment has made a difference in their brain, even if they cannot yet sense the difference themselves.

Widge also spoke about the challenge of using biomarkers in a clinical setting. Clinicians often have to juggle many responsibilities, so a simpler technology can be important for usability in the clinic. However, academic doctors often seek out technologies that provide them with more control over the settings and output. This means that it is a challenge to figure out how to take complex knowledge and procedures developed by academic doctors—such as the use of biomarkers—and translate them into something that clinicians will use. Technology or biomarkers that are too complex may prevent widespread usability by clinicians and decrease accessibility to patients.

Finally, Widge said that it is important to see psychiatric DBS as rehabilitative. In treating something like tremors caused by Parkinson's disease, he thinks of it as curative, he said. "Put on the stimulator, turn it on, the symptom goes away." But, he continued, "in mental health we are learning it is not curative but rehabilitative. What we are doing is helping patients benefit from the intensive psychosocial therapies that you heard some patients talk about. This is a different model for psychiatry." Patients may feel more able to ignore their symptoms, even if the symptoms still exist. This is very different from classic ideas about changing mood or eliminating thoughts, he said, and it will be important to determine how best to talk to patients to explain to them what to expect.

DISCUSSION

Perides asked if poor patient selection affects outcomes and overall patient engagement and satisfaction. "Yes," Candelario-Mckeown responded, "I have seen patients I thought who would have done better if we were careful identifying problems we should have known." In particular, he mentioned nonmotor symptoms (e.g., mental health, pain, restless legs, speech and communication problems) that end up being overlooked because of the focus on motor symptoms such as trembling.

The Impact of Data Collection and Outcomes on Patient Perception

Perides then asked the panelists if DBS patients are worried about the fact that clinicians collect a great deal of data about them and their brain function and if perhaps such worries affect their decisions on whether or not to get the procedure. Widge said he did not think many patients are thinking about what happens to their data; they are more concerned with how that data is used to help improve their conditions. Davis echoed those sentiments, saying that many DBS patients have heard for years that they were not trying hard enough to get better and that somehow their issues

must be their fault, so they are just happy to get solid evidence that something is not working properly in their brains. However, both Widge and Davis agreed that consent is needed before beginning to collect patient information.

In response to an audience question, "Why is there a push for implantable psychiatric therapies [and] invasive surgeries that are costly and risky if outcomes are so ambiguous?" Davis said she does not agree that the outcomes are ambiguous. Deep brain stimulation for OCD has a 60–70 percent success rate, for instance, which is remarkable, she said, because these are patients who have not responded to any other standard treatments.

Widge agreed that the results are not ambiguous but said that patients who hear about, say, a 66 percent success rate still wonder what will happen to them. "Can you guarantee I won't be one of the 33 percent who has a suboptimal outcome?" A success rate of two out of every three is good, he said, but it will likely need to be better if DBS is to become the standard of care.

Financial Considerations for Deep Brain Stimulation Uptake

Ben Greenberg asked, given the problems with insurance that speakers had discussed, whether a single-payer health system such as exists in the United Kingdom would help DBS become more widely used. Candelario-Mckeown answered that in the United Kingdom's National Health Service, anyone who meets the criteria is allowed to have the surgery. However, he continued, referrals for DBS for the treatment of Parkinson's disease have been declining even though the rate of diagnosis of Parkinson's disease have been increasing, which means that the solution is not as simple as having a single-payer system. He said that it is important to work harder at educating patients and general practitioners about the procedure in order to increase the number of referrals. Another hurdle in the United Kingdom is that the National Health Service guidance specifies that a group can open a DBS service only if it includes a DBS nurse, neurologist, surgeon, psychiatrist, psychologist, and speech therapist, so only larger groups can perform DBS services.

John Krystal, the Robert L. McNeil Jr. Professor of Translational Research and a professor of psychiatry, neuroscience, and psychology at Yale University, asked how a DBS program in psychiatry can be grown and sustained, given that it is not always possible to get the procedures covered and the practice tends to lose money even when the procedures are covered and reimbursed. While the situations can vary geographically, Widge answered that his OCD program at the University of Minnesota can break even or even make a little profit. "I'm not going to say this is a moneymaker that I could sustain my life doing. . . . There are ways to make

a service like this sustainable, but it requires thought," he said. "I think it is possible but hard."

Davis expanded on that answer, stating that DBS is not necessarily money-losing, particularly once the implant is positioned: "We get reimbursed more for the programming codes than therapy codes." However, getting patients to qualify for the DBS surgery requires a great deal of effort. In some cases, for instance, her clinic spent more than a year on negotiating with the insurance company and on appeals, which require much time and effort from the clinicians. "Not just anyone can battle with the insurance companies," she said. "That is not a sustainable option for ongoing use of DBS."

Managing Patient Expectations

Tim Denison pointed out a contradiction in expectations between DBS and pharmaceuticals. Once a DBS device is implanted, he said, it is often expected simply to work without further adjustment. By contrast, people understand that doctors may have to spend significant time getting to the proper dose of a medication. "Why [do] you think there is a different perception?" Denison asked, and what might be done to help people understand that adjustments need to be made with DBS as well?

"I think it is all about education," Perides said. "I would say the majority of my patients know it is going to take a long time. Often, we see in pediatrics and dystonia it could take up to 2 years to find the sweet spot," and sometimes they never find it.

Wang agreed with Denison's observation. "Patients have this expectation of high risk, high reward, in some aspects. They think if you go through the evaluation and being a candidate, once you turn on the electricity, they sort of expect symptoms to go away." Part of it may be because patients have seen success stories on social media where the device is turned on and the tremor goes away, she said, and doctors themselves may be partly to blame. "When I counsel patients, I show the best case [of] what this device can do. So they kind of have that built into their mind that once they turn on the device it would help a good majority of symptoms." She is also careful to tell each patient multiple times that getting the optimal setting may take months, even as long as a year, but it is human nature to hope for the best.

5

Health Professional Education and Adoption

HIGHLIGHTS

- A major factor in the adoption of new technologies is the "activation energy," that is, the additional effort required to learn and put the technology in practice over and above the day-to-day work of a clinic. If the activation energy is too high, adoption is unlikely. (Hammer)
- Adoption of a new medical technology also requires community physicians to be aware of it and its benefits and be willing to recommend and to refer their patients to the appropriate specialists. (Hammer, Miravite, Okun, Pathak)
- Access is one barrier to new medical technologies, which can be limited by insurance companies and by the lack of qualified providers. (Miravite, Okun)
- Big data provided by medical devices could be useful in identifying which patients could benefit from new medical technologies. (Morrell)
- Educating patients and getting them involved in their own care could help push the adoption of new medical technologies. (Pathak)

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Moving from practical barriers involving patients to those involving clinicians and other practitioners, the workshop addressed barriers associated with health professional education and adoption. David McMullen, the director of the Office of Neurological and Physical Medicine Devices at the FDA, asked participants to discuss the current barriers to increasing training and engagement among health professionals on implantable brain stimulation and the barriers of current practices and, second, to explore what relationships might need to be developed across different specialties and clinical practices to facilitate referrals and the continuance of care. McMullen commented that he hoped the panelists would not just highlight and discuss the various barriers but would also think through some potential solutions. "What can we do as a community to come together and blaze a new path forward?" said McMullen. Clinicians will certainly be critical to greater adoption of the technologies, he added, with their roles including both patient education and patient selection.

FACTORS INFLUENCING CLINICIAN ADOPTION OF TECHNOLOGIES

Lauren Hammer, a movement disorders and neuromodulation research fellow at the University of California, San Francisco, discussed some of the factors influencing whether clinicians adopt new technologies.

"Even if regulators approve and payers cover [the procedure]," Hammer said, "adoption requires patients and the caregivers to buy in. That requires that the clinical benefit outweighs the perceived burden on the patients." A second factor is the so-called activation energy of learning this new technology (see Figure 5-1). How much additional burden is required to integrate the technology into the clinic? Even if the clinical process ultimately becomes easier once the new technology has integrated, it still may require a tremendous amount of effort to reach that point, learning the new technology and modifying various established processes to adapt to it. One must ask if that activation energy is too great to overcome. "I have a strong interest in seeing these technologies succeed," Hammer said, "and I still found it hard to integrate some of the most recent advances like image-guided[1] or physiology-guided programming[2]. Physicians are busy, stretched for time. Sometimes it is easier to do what we know works fairly well instead of trying something new."

[1] Image-guided programming is the collection of images during implantable brain stimulation surgery that allow the physician to see the exact location for the device leads and stimulation. For more information, see https://www.bostonscientific.com/en-US/medical-specialties/neurological-surgery/deep-brain-stimulation-system/image-guided-programming.html (accessed February 27, 2024).

[2] Physiological-guided programming is the collection of brain signals (e.g., local field potentials) simultaneously while delivering the stimulation treatment. Physicians can correlate the brain signals with the stimulation and the patient's symptoms to optimize care. For more information, see https://www.medtronic.com/us-en/healthcare-professionals/products/neurological/deep-brain-stimulation-systems/brainsense.html (accessed March 1, 2024).

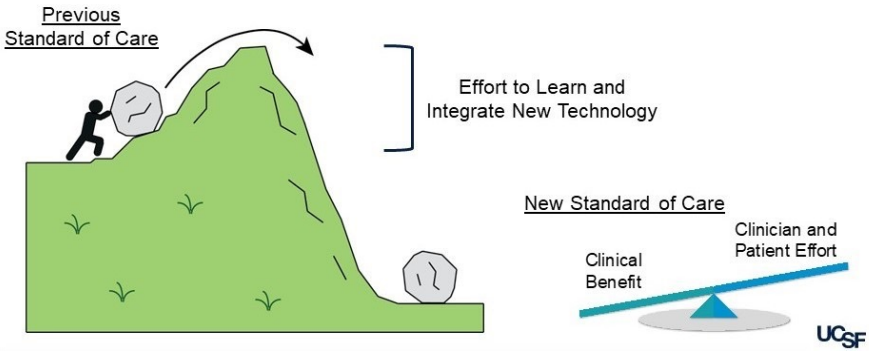

FIGURE 5-1 Manageable clinician workflows are needed to adopt new technology. SOURCE: Presented by Lauren Hammer on October 31, 2023.

A second factor in the adoption of new technologies is the role of doctors and other providers beyond the highly subspecialized clinicians who are most comfortable with such technologies. A recent paper reported that only about 10 percent of Medicare patients with Parkinson's disease had seen a movement disorder specialist within the previous year, with more than 50 percent of them being managed and seen by a general neurologist (Pearson et al., 2023). "These are the partners who are going to be identifying who is appropriate for referral," Hammer said. "And these are the partners who are going to be comanaging patients while stimulation is being optimized and, ideally, if we can make things simpler, even taking over stable management of these patients." So it is vital, she said, that the subspecialists find ways to educate these community providers and bring them into care teams. "This is going to be important if we want to expand these technologies to more people," she said.

A NURSE PRACTITIONER'S PERSPECTIVE

Joan Miravite, a nurse practitioner, assistant professor of neurology at the Icahn School of Medicine, and director of interdisciplinary clinical care for movement disorders at Mount Sinai, described herself as having several roles: a DBS programmer; an educator of patients, clinicians, and advanced practice provider; and an advocate both for patients and for the use of advanced practice providers in neurology to address the current shortage of neurologists, decrease wait times, and increase access to care.

She spoke briefly about barriers to care, mentioning both a lack of relevant training for clinicians and various knowledge gaps related to the procedure. A major barrier, said Miravite, is limited access to the procedure, particularly because of its treatment by insurance companies. "Some insurance companies deem DBS still experimental," she said, "and I've had some insurance companies deny me from programming patients because

I'm a nurse practitioner and not a physician." In New York, nurse practitioners are not able to bill Medicaid for any procedures they perform in Article 28 facilities,[3] Miravite said. So, despite her expertise, "I'm not able to use it to help all of my patients."

She listed several approaches to improving the current situation, including creating scalable models of care; building a consensus on DBS management; collaborating with foundations, organizations, payers, and industry to educate and streamline therapy; and using advanced practice providers in specialized care. The ultimate goals, Miravite added, are to foster health equity, increase the quality of care and patient access, and improve patient outcomes.

USING BIG DATA TO IMPROVE TREATMENT

Martha Morrell, the chief medical officer of NeuroPace, Inc., and a clinical professor of neurology at Stanford University, began by expressing her excitement about the progress that has been made in the field and her incredible optimism about its future. Just as clinicians need to manage the expectations of their patients, she said, they need to manage their own. "Do we think we are going to develop a therapy and it is going to come out fully formed?" she asked. "Of course it's not. It is not perfect yet." But there has been amazing progress in a variety of devices, and that progress should only continue.

Morrell then explored the utility of applying big data from medical devices to improve the treatment of brain disorders. She began by talking about some of the requirements that these data must fulfill in order to help improve such treatment. First, the data should be accessible and comprehensible to users, and in particular, the information derived from the large, complex datasets must be interpretable by the physician and the patient. Second, the data should be disease-relevant. "We shouldn't show all the data," Morrell said, "but only the data we have identified as important." This should include things like biomarkers to track how somebody is doing and help predict outcomes. Third, the data should enhance the efficiency of clinical care. "We have to make everybody's life easier," she said. And fourth, the data should contribute to treatment decisions that improve clinical outcomes. "Otherwise," she said, "none of this data is worth anything."

BARRIERS TO THE ADOPTION OF DEEP BRAIN STIMULATION TECHNOLOGIES

Michael Okun, the executive director of the Norman Fixel Institute for Neurological Diseases at the University of Florida and the medical advisor

[3] For more information on what is denoted as an Article 28 facility in New York, see https://www.health.ny.gov/facilities/hospital/regulations (accessed February 28, 2024).

of the Parkinson's Foundation, offered a few comments about the state of the DBS field.

First, he said, the word "adoption" implies a voluntary aspect, which is equally true for the adoption of a technology. But that means it is necessary to get buy-in from the community of users, and that has not proved to be easy in this case. "We can blame health care systems, regulatory agencies, health care payers, we can blame ourselves," he said, but there has not yet been the necessary buy-in.

"Second," he continued, "you have to actually want it to adopt it." A recent discussion at the most recent Deep Brain Stimulation Think Tank concerned whether the technology has been branded correctly: "There was a discussion about should we be calling this brain pacemaker, which is something . . . people can understand . . . better."[4]

Third, even if people want the technology, it will be necessary that we are able to provide it to those people. "So we have a lot of people in society across the world that want therapies we may not be able to deliver," Okun said. "We have to remember that it's bidirectional. The arrows go both ways."

Yet another potential barrier is the need for experts to operate the devices, he said, but he suggested that this issue may prove not to be a major barrier. In the case of Parkinson's disease, for instance, clinicians and nurses are sufficient. Although the initial trials may require experts, he said, it should be possible to eventually develop easier-to-use technologies. "Once you know the biology, there should be a simpler, more elegant path to the answer," he said. "So let's not get overwhelmed with that."

AN INDUSTRY PERSPECTIVE

Yagna Pathak, medical science manager at Abbott Neuromodulation, provided an industry perspective to the discussion.

In thinking about practical barriers to further use of DBS that are related to professional education and adoption, she said she sees the issue from three perspectives. The first is awareness of the current state of technology. To illustrate the problems related to that awareness, she told a story about an experience she had at the Consumer Electronics Show (CES) in January 2023. "The people that go to CES are probably the most in-the-know of cutting-edge technology," said Pathak. "They came to our booth. We were talking about deep brain stimulation, and they just looked at us like we were talking about something that was still being innovated on." They asked when the technology would become available for humans. "I just looked at them, and I said, 'This has been around for over 30 years.'

[4] For more information regarding the 2023 DBS Think Tank, see https://fixel.ufhealth.org/research/deep-brain-stimulation-think-tank (accessed November 26, 2023).

And it was the first time that it struck me that it is not nearly as ubiquitous to everyone as it is to us." The problem, then, is that many of the people who are shaping decisions about whether to adopt the technology are not familiar with it and may not even know it exists. By contrast, she said, everyone knows about cardiac pacemakers. "How do we make our technology as ubiquitous as pacemakers are?"

The second barrier relates to the referral pathway, she said. A patient goes to a doctor, gets referred to another doctor, and another, and eventually gets to a specialist who can recommend DBS. "By the time the patient even knows to go to a specialist, it may be too late," Pathak said. "At least for deep brain stimulation used for movement disorders, there is a very optimal window," which means that it is important to educate doctors along the referral pathway so that patients can get referred as soon as possible to appropriate providers.

Finally, Pathak emphasized the importance of educating patients and getting them involved. "Patients listen to patients," she said. "Their stories resonate with other patients. So I think we all need to spend a lot more time understanding our patients, listening to our patients, and making sure they have enough knowledge and education to spread it around in their communities so [other] patients are more empowered to ask their doctors for the therapies that they think they require."

DISCUSSION

To begin the discussion, McMullen asked Pathak whether the right people were at the workshop to address the DBS issue effectively. "I do think we have the right people," she said. "I think this is a multidimensional problem which requires multidimensional solutions." One sector that may be missing, she observed, are patient advocacy organizations (e.g., Parkinson's Foundation or Dystonia Medical Research Foundation) that can provide a patient-oriented lens on what progress is needed.

Okun disagreed and said that it would have been valuable to get a more international perspective from organizations like the World Health Organization. "If you could [solely] blame the problem on the FDA or the NIH or whomever, then why are all these other countries having the same problem?" he said. "I think we have to stop blaming and start thinking that maybe this is a global issue."

Barriers to Referrals

McMullen asked Okun about issues with referrals, specifically what barriers he saw that make it less likely that doctors will refer patients who might be helped by DBS to specialists familiar with the technology. It is

more a system problem than anything, Okun said. He explained, "We get upset at internal medicine doctors and geriatric doctors for mishandling Parkinson's disease, though they are tasked in 30 minutes with dealing with cholesterol calculator, cardiac risk, an examination of the lungs and counseling on, preventive measures . . . by the tail end of the visit they may notice, or the person may mention a shaking tremor. Those folks with Parkinson's disease may be the lucky ones as one in five [Parkinson's patients] don't have a tremor." Then a patient is referred to a neurology specialist who then may refer the patient to a sub-specialist. Generally speaking, Okun said, the health care system is not set up to incentivize the best care for a patient: "Everybody is playing their role within limited systems, limited amounts of time, limited amounts of resources. We have to figure out how to put those pieces together and incentivize them correctly so that the person gets the best possible treatment. And we don't do that."

McMullen then turned to Morrell and asked how her company, NeuroPace, had succeeded in convincing clinicians to adopt its technology. "We are all learning," she said. "The way you start out is figure out what you are doing well and what could be done better and just pick it off piece by piece." One thing that the company found success with was sponsoring programs available to fellows and trainees that allowed them to "come and in a nonpromotional way learn about the technology and apply it." Those programs were met with great enthusiasm, she said, adding that the younger generation seems to be more open to learning about and using new technologies and new treatments.

Educating Physicians About Deep Brain Stimulation

McMullen asked Hammer about the exposures to neurotechnology that neurologists get in their residency programs. Hammer said that neurological residents get relatively little exposure to technologies such as DBS, which is a problem. She suggested that ways should be found—such as 2-week programs—to help residents become more familiarized with these technologies. "It doesn't have to be long," said Hammer. "It just has to be enough that neurology trainees know [the technologies] exist so they can then potentially seek out further education themselves."

Okun agreed that such educational approaches could be important, particularly in helping newer physicians become familiar with DBS and other neurotechnologies. Another approach to addressing the issues with referrals, he said, would be to expand the use of navigators, who could help patients in health care systems to access the best possible care and get them more options quickly and connected with doctors and clinicians who can best address their needs. "I very much like this model and would advocate strongly for that," Okun said.

Expanding Access to and Use of Deep Brain Stimulation

A workshop participant asked what the panelists thought would work well to increase access to advanced care in community clinics, given the educational gap between academic centers and community clinics. Morrell offered an initial answer by saying that it is important to help community physicians better understand the needs of their patients and where those needs can best be met. One way would be to develop a system that takes all the information acquired by devices used in a patient's care, interprets it, and comes up with a solution. "Obviously," she said, "the holy grail would be to have a truly closed-loop device where the device is constantly collecting information and then acting upon it in a dynamic way. . . . If we had something that was truly closed-loop, then it would be pretty easy for that to be implemented at a level that did not require the ultimate specialist." Such a device does not yet exist, she said, but many people believe that it will sometime in the future.

Okun agreed and emphasized the importance of statistics and keeping in mind how individual patients are doing relative to everyone else. For many of the devices now being used, he said, about 80–90 percent of patients are doing well. Thus, if a patient falls at the 80th percentile, the physician should be told that this person is doing well; just keep an eye on it. Conversely, it is important to identify the 10–20 percent who are not doing well. "We need to work together to identify those people," he said, and send them to the appropriate clinicians, whether specialists or sub-sub specialists. In that way, community physicians will be able to obtain the assistance they need in determining which of their patients are doing okay and which need to see a more specialized provider.

Pathak suggested getting professional societies involved in educating their members on the benefits of implantable technologies and which patients can benefit from them. Awareness is a major problem right now, she said, but even when physicians are aware that these technologies exist, they often still prefer drugs and noninvasive therapies, even though studies have shown that as many as 70 percent of patients will benefit from DBS without complications. "I think that needs to be stressed a little more," she said. "This does need to not be the last resort, but it can come earlier."

Brian Litt added that the responsibility for identifying patients who can benefit from implantable brain stimulation does not need to be placed entirely on physicians. "There are enough biomarkers you can extract from the electronic medical record (EMR) which could easily come up and say, this patient meets these measures and these criteria and should be considered for brain stimulation." The University of Pennsylvania system performs such monitoring for hypertension, postnatal care, and the initiation of diabetes care. "We did an experiment through EMR where we

looked through medically refractory epilepsy patients at our own hospital seen by neurologists within our own system meeting criteria for presurgical evaluation," said Litt. "We found it was 15 per month. So, if that is what is happening in our system, what is happening out in the community?"

The Relationship Between Physicians and Future Technologies

McMullen asked Hammer about what can be expected with future technologies, including artificial intelligence (AI). Who will be delivering this care in the future? Will it be neurologists? Clinical engineers? Other members of the clinical teams? Some new type of specialists altogether?

Hammer answered that it will depend in part on how well AI is integrated into the new technologies. "If you have AI or machine learning take all the data and make a suggestion to the clinician that makes sense and has some sort of biologic or medical interpretation, then the need for human data scientists to make a patient-specific model or do specific data mining is a lot less important." A lot of clinicians, she said, would prefer some system that processes the data and makes reasonable recommendations. "So if there is no additional effort [for the clinician] to learn and interpret, those automated systems would be very powerful." Still, she added, there is a great deal of work that must be done to get to that point, and in the meantime, it will be necessary to have data scientists or other specialists bridge the gap. Community providers may find it challenging to independently handle the new technologies in their current form, thus so "having support from other trained professionals, like technicians focused on the neural data, would be useful."

Okun pointed out that if community physicians and others are going to rely on systems that interpret big data and make suggestions, they will have to be comfortable with the "black box" nature of those suggestions because there will be no indication of why the suggestion was made. The FDA could be helpful here by reviewing and approving algorithms, signaling to doctors that they can trust the recommendations.

Hammer commented that while the sorts of people who were attending the workshop would probably want to understand what the black box was doing, community physicians and many others may not necessarily be interested in all those details as long as the FDA signaled confidence in the recommendations.

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Reimbursement and Other Economic Considerations

HIGHLIGHTS

- How medical procedures are reimbursed plays a major role in how scalable they can be. New technologies often face problems in getting reimbursed because they do not fit well with established reimbursement codes. (Brown, Mahoney)
- The Centers for Medicare and Medicaid Services offer a variety of programs for covering and reimbursing innovative technologies. (Miller)
- In thinking about the adoption of new technologies, it is useful to view them not in isolation but as part of a system. (Mahoney, Silburn)
- To avoid as many issues as possible in obtaining coverage and reimbursement for a new technology, the best approach is to meet with regulators early in the development and testing process in order to understand the best path forward. (Miller)
- To get evidence for the cost-effectiveness of new technologies, it would be useful to establish an industry-wide system of collecting, storing, and analyzing patient data. (Mahoney)

NOTE: This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Throughout the workshop, participants explored practical barriers to the increased use of implantable brain stimulation, such as deep brain stimulation, with an examination of how reimbursement policies and other economic considerations affect the uptake of this and other medical technologies. Participants considered the current economic barriers and technological limitations that prevent implantable brain stimulation from becoming scalable, discussed what ongoing or future approaches need to be taken to improve the benefit-cost ratio and allow brain stimulation to be scalable for wider application in central nervous system disorders, reviewed the current status of reimbursement for implantable brain stimulation, and discussed opportunities to increase reimbursement.

BILLING AND REIMBURSEMENT

Julie Brown, senior director for health economics and market access at Spark Biomedical, began by discussing her previous experience at Abbott Neuromodulation, where she was involved with their virtual clinic, which offered telehealth services. It worked well, she said, but several issues arose concerning how clinicians using this remote clinic would bill for it. "We had a couple of questions," she said. "Do we take the current codes and we make those adaptable to telehealth, or do we go get a completely new set of codes?"

More generally, she said, working with reimbursement even when there are well-defined pathways can be like playing a board game. "If you read the rules, you can end up where you need to go," she said, "It might take you longer than you would have liked, but there are milestones to be achieved along the way." This board game–like nature makes it important to educate all the relevant stakeholders so that everyone understands what is necessary.

FUNDING A HEALTH CARE SYSTEM

Kevin Mahoney, chief executive officer of the University of Pennsylvania Health System (UPHS), spoke about that system's funding. Penn Medicine is the umbrella organization comprising both UPHS and Penn's Perelman School of Medicine, which together have a tripartite mission of clinical care, education, and research. UPHS includes six acute-care hospitals, multispecialty centers, and outpatient facilities in three states.

Echoing what Brown had said in the previous talk, Mahoney said, "it gets into a game with insurance companies as to how we get reimbursed," and the focus is on how to get their payments from public and private insurers. What is unusual about the funding model at the Penn Medicine, he said, is that 60 percent of the clinical margin is used to support the

organization's research mission, making up for its operating deficit and adding to its capital investment. Another 15 percent of the clinical margin goes to support its teaching mission, while the remaining 25 percent goes into clinical mission capital. "We made about $512 million last year, and $300 million of that or so went to supporting research," he said, explaining that much of that goes to supporting good research ideas that do not have enough data supporting them to get outside grants.

This approach has led to significant breakthroughs at Penn Medicine, Mahoney continued. Two dozen drugs developed there have received FDA approval in the past decade. Most recently, two researchers there, Katalin Karikó and Drew Weissman, were awarded the 2023 Nobel Prize in Physiology or Medicine. Initially, they experienced challenges with securing a grant, Mahoney said. "Then we set up a venture fund similar to what many of our colleagues across the country are doing."

The system's venture fund is focused on two things, he said: gene therapy and connected health. The goal of connected health is particularly relevant to implantable brain stimulation. "We are talking about patients being able to adjust technology over time," he said, "You don't want everyone coming into the hospital or the clinics, so how do we do that remotely?"

COVERAGE DECISIONS AT THE CENTERS FOR MEDICARE AND MEDICAID SERVICES

Susan Miller, a board-certified physiatrist who was in practice for more than 20 years, is now a medical officer at the Centers for Medicare and Medicaid Services (CMS). She spoke about the process CMS uses in determining coverage for medical procedures, particularly those involving innovative technology.[1]

Coverage decisions are made through an evidence-based policy, she began. "When we evaluate any item or service that has a benefit category, meaning that we are allowed to statutorily cover that item, we look for several factors to determine if it is reasonable and necessary for our beneficiaries." It is important to establish a causal relationship between the item or service and the desired outcome in a trial. Among the factors evaluated is the "the methodology of the study to see if it has done the best that it can to promote bias reduction," Health outcomes are also evaluated, Miller said. In particular, CMS is looking for health outcomes that are important to the

[1] For additional information on the CMS programs covered by Miller, see https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D5BD8054113521CFB0A96DA50D1CF13B578812D93C52?noSaveAs=1 (accessed February 28, 2024).

patient, such as morbidity and mortality, physical functioning and quality of life. The agency also looks for data on the durability of outcome, which is a very important piece of the information in making coverage decisions, as well as for information about whether the available item or service is actually generalizable to the Medicare patient population.

Miller also noted that this is a very high bar. CMS has a number of innovative programs or methods by which to promote coverage for new technologies. An example is the Program for Parallel Review of Medical Products done in collaboration with the FDA, in which the two agencies carry out simultaneous reviews of new medical devices to decrease the time to a CMS proposed coverage decision.

Miller also mentioned the coverage with evidence development paradigm, in which a promising item or service with a limited evidence base, specific to the Medicare population, is investigated within an approved study, or with the collection of additional clinical information. CMS also has a Clinical Trials policy and a proposed program for transitional coverage for emerging technology. "That [program] is sort of a combination of our parallel review program and coverage-with-evidence development program," she explained, "but it also brings in opportunities for the manufacturers [of Breakthrough Devices] to discuss benefit category and coding in addition to coverage."

Finally, for those situations where a new device does not qualify for any of these other programs, CMS has specialized payment programs. "We have tried very hard to expand these innovative programs at CMS," Miller concluded. However, it's still important to follow the correct procedures and regulations for each program.

THE ADOPTION OF DEEP BRAIN STIMULATION TECHNIQUES

Peter Silburn, the foundation chair in clinical neurosciences at the University of Queensland and codirector of the Asia-Pacific Centre for Neuromodulation at the Queensland Brain Institute, offered a couple of thoughts about the adoption of DBS technologies.

First, he said the concept of an ecosystem is useful when thinking about adoption of new technologies. In an ecosystem, he said, people get together and evolve in nodes, which can lead to some interesting outcomes because they evolve in parallel as well as sequentially and in an integrated way. "I think if we go to adopt DBS across the world and various geographies and battle with their various systems," he said, "we have to integrate health economics and also people who know how to get things across the line at the outset."

The fact that many people, even technologically savvy people, do not realize that DBS is an established technology can be seen as a failure of

marketing, Silburn said. Henry Ford, the founder of Ford Motor Company, said that he was not selling cars, he was selling experiences, and a similar approach can be taken with DBS.

Internationally, he continued, the biggest barrier is that each country has its own way of doing things. "What works in one country does not work in others." But by focusing on the patient's outcomes and safety and innovating at a fast pace, it should be possible to get an ecosystem of individuals working together to get the technology adopted around the world.

DISCUSSION

Barriers to Physician and Patient Adoption

Pathak asked the members of the panel to identify a current practice, activity, or economic issue that is a potential barrier to either physician or patient adoption of DBS.

"The biggest barrier we are facing with DBS or any new technology," Mahoney said, is that "we are held accountable for the unit price of one item as opposed to the ecosystem." People are "focusing on one sliver of a large pie." It is important to start seeing payment issues holistically rather than piece by piece. Silburn agreed, saying, "We need to shift the paradigm from one single device to the patient experience." He suggested partnering with marketing people to urge the public to focus on the overall experience rather than the specifics of any one piece of it.

Brown said that from a reimbursement perspective, DBS has good reimbursement, as there has been a national coverage determination for DBS in the United States for patients with essential tremor or Parkinson's disease since 2003. That is, Medicare will reimburse for a DBS procedure. "So, from my perspective," she said, "it is interesting to hear there are challenges." Yes, she continued, there are certainly challenges getting reimbursement for remote programming or for indications such as treatment-resistant depression or OCD. In those cases, CMS will need to see compelling evidence for efficacy before it provides a national coverage determination. She added, however, that from her perspective, and not in an official CMS position, the reimbursement situation for DBS is "ahead of the game" because the procedure is already covered by Medicare, and other insurers look to Medicare when making their coverage decisions. Because of that, she said, "I think DBS is already in a nice, enviable position to begin with."

More than just finances play a role in people's decisions about getting DBS, said Miller. For example, patients often must travel a long distance to get the surgery, and then must worry about who is going to take care of the implant after the surgery. "Is there a local physician able to take care

of that technology, or are you asking the patient to travel extra distances once or twice a year to make certain that their implant works?" In short, it is often not just a case of money, she concluded.

Adoption of Emerging Technologies into Health Care Systems

Reflecting on Mahoney's earlier comments that technologies such as DBS should be seen as an entire service line versus a single implant, Pathak asked what that implies for scalability. "The more steps you add to something, the less desirable it becomes for adoption, to physicians at least," she said. How is the tension resolved between how the business model works (and wanting to move beyond single items) versus the desire to do less because simpler things are easier to adopt?

Mahoney answered that this is an issue he wrestles with. One approach is to focus on innovations and improvements in treatments and technologies once they are being used in the clinic, something he described as a "lost art." Once something is in place, he said, "it's got a code, got a system, we have a way of doing it," which means that clinicians end up staying in one place. It is important that the medical system evolve instead. "As the reimbursement pressure continues downward," he said, "I think we will have to adopt a new tenet: there aren't unprofitable patients, just unprofitable delivery systems. The only way we will be able to successfully treat every patient without losing our shirts is to make the system more efficient. If we have 10 steps, can we get it to 9, to 8 . . . to 5? The patients, as Peter [Silburn] said, enjoy that experience, and costs will tumble down."

Examining Meaningful Measurable Outcomes

Pathak asked panelists for their thoughts on which measurable outcomes are of the upmost importance, in their opinion. Miller offered a perspective about how CMS thinks of outcomes. "It is important for people to realize that . . . we are looking for those outcomes that are important to the patient. . . . What we are looking for is [does the patient] feel better, and what can they do today that they weren't able to do yesterday." Miller also mentioned patient-centric scales such as pain levels, function, sleep, and the amount of medication the patient needs to take. A similar approach is true for neurological treatments, she said: "If the patient is treated with a device that is supposed to make them better, how is that manifested in the patient's world? That's the kind of thing we look for."

Following Miller, Silburn said that beyond that, it would be useful to find biomarkers that are objective rather than subjective. Even the Unified Parkinson's Disease Rating Scale, a standard in the field, depends on when the examination is given, he noted.

Brown commented that in the United States it has been difficult to make remote programming reimbursable because there has not been sufficient peer-reviewed, published evidence on it. "We have to be patient-centric," she said, "but we also have to make sure we are committed to really good science, having these publications, having it peer-reviewed, and being able to present that to CMS." That can be seen as a hurdle to reimbursement. "You can't just get coverage," Brown said. "You have to have evidence that speaks to the outcomes and to the benefits."

Exploring How to Encourage Innovation

Pathak wondered how innovation can continue to be encouraged, specifically in digital health and telemedicine. Miller offered the perspective of regulatory agencies. The best thing for innovators to do, she said, is to meet with CMS early to discuss plans for trials. CMS will tell you what they are interested in. "I really think that coming in early to the regulatory agencies in our country is a huge step that you can take in order to be able to scale up your innovative technology," said Miller.

Mahoney responded to a question about how to demonstrate that a particular therapy brings benefits in terms of health economics when the illnesses being addressed are chronic, so that the benefits may stretch out over decades and may involve many people other than the patient, such as caregivers and employers. Without years of patient history and with the patient potentially switching from system to system, it can be very difficult to provide information that proves the benefits of a new therapy. Mahoney agreed that it is a difficult problem to solve. People do switch health systems and insurance companies every 2 or so years, he said. "Unless you are on Medicare, you are switching quite often." He said that health care should begin collecting long-term, follow-up clinical data across medical centers that is put into a central repository not owned by any one institution. "That is what airlines do and so many industries do," he said. "They share their back room. I think that would make it much more effective."

Tim Denison noted that reimbursement codes can be an obstacle to innovation. Suppose, for example, he said, that someone came up with an innovation that made programming more efficient, so that what used to take 30 minutes could now be done in 15. Unfortunately, there is no reimbursement code for a 15-minute programming, which means that people will not adopt the new, more efficient method because they cannot get reimbursed for it. "Now you could say, 'Let's go invest and come up with the new reimbursement code,' but for startups that could actually be a killer," he said. "Little startups desperately try to match their technology to existing codes, artificial as it may be." What models, he asked, might make

it possible to move to a more shared incentive "so everyone can economically benefit and truly be patient-outcome focused"?

"There isn't an easy answer to this question," Brown said. The coding system does have many advantages, such as the fact that it is brand-agnostic so that all devices, regardless of the manufacturer, use the same codes. But, she said, innovation often does outpace the current mechanisms in place, and there is not an obvious way to address this.

Miller reiterated that innovators should speak to regulators early in the process of development. "You don't want to be at the end of your pivotal trial and then start asking these sorts of things," she said. "We try to educate people on this whole process. The thing the innovators have to do is avail themselves of that education."

7

Potential Next Steps to Move the Field Forward

HIGHLIGHTS

- Many patients who could benefit from deep brain stimulation must fight stigma and a system that is not always set up to direct them to the proper providers. (Ellis)
- Socioeconomic and demographic disparities in the use of implantable brain stimulation will need to be addressed if the technology is to become fully adopted into the standard of care. (Pulliam)
- It will be vital to educate the various stakeholders, including not only patients but clinicians, researchers, and engineers, to have a more accurate and complete understanding of the technology and the barriers it faces. (Hammer)
- How an innovation gets through the regulatory system is vital to its success, and innovators should be working with regulators from early in the innovation cycle to smooth the new technology's path to market. (Kelly, Lisanby)
- Reimbursement issues should be handled in parallel with regulatory issues. (Kelly, Lisanby)
- There is a need for more objective outcome measures, such as with biomarkers, in both the research and the regulatory arena. (Lisanby)

- Through collaboration, innovation, and optimism, the system can be changed. (Mahoney)

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Helen Mayberg and Tim Denison asked participants to reflect on the core themes and takeaways from the workshop and explore creative approaches or collaborations needed to move the field forwards toward the adoption of implantable brain stimulation into the standard of care across central nervous system disorders. Workshop participants also discussed the implications of comorbidities and opportunities to develop technologies and treatments to holistically treat patients.

A PATIENT PERSPECTIVE

Brandy Ellis, a neuromodulation patient advocate who has a deep brain stimulation implant, shared her journey to treatment and perspectives on what's needed to move the field forward. Before she received the implant as part of a clinical trial, she said, she had had 4 years of treatment-resistant depression. "I had tried 25 different medications, not including different dosages, different combinations." She had also had 24 electroconvulsive therapy treatments, and she had been dropped as a patient by a half dozen psychiatrists.

"For me in the trial it was very much *not* flipping a switch," she said, unlike the experience that Jon Nelson had described in Chapter 4. "I became a responder, which meant my depression rating scale had been reduced by 50 percent at 6 months." By 21 months she was in full remission. She added that she agreed with Alik Widge's comment about the treatment not being curative but rather rehabilitative (Chapter 4). She has to work to maintain her mental health every day.

"I will say that the one side effect I did not expect was a nearly pathological desire to talk to anybody about patient advocacy, mental health, and DBS," Ellis said. "I am now a fully functioning, healthy, happy, mood-appropriate, functional adult who supports herself and has good relationships, and has a full-time job. This is my bonus life, and I went from absolutely terminal treatment-resistant depression to this life that I have now."

AN ENGINEER'S PERSPECTIVE

Chris Pulliam, an assistant professor of biomedical engineering at Case Western Reserve University, offered a few thoughts about increasing the use of DBS. First, he said, it will be important to address the presence of socioeconomic and demographic disparities in the use of invasive neurologic systems. "I don't think there is a path toward broad adoption if we don't wrestle with that topic," he said.

Referring to Claudia Garrido-Revilla's remarks (Chapter 3), he said that her observations about sex differences in DBS treatment are true. "That is something we understand is an issue, where women are maybe 20 percent or 30 percent less likely to receive DBS after they have been screened as good candidates," he said. "And as a Black American, I'm much less likely to be a DBS recipient." Geographical disparities also exist, with people from rural areas much less likely to receive these treatments than those living in major urban areas, particularly those with major medical centers such as Cleveland or Boston or Houston. "Grappling with [these] topics is something we have to take seriously," he said.

Finally, as an engineer, Pulliam said he believes it is important to advance technological capabilities in a way that lines up with user need. New technological capabilities will make it possible to do many things that were not previously possible, such as data from sensors offering unique insights into physiology, but the emphasis should always be on improving care for patients.

A REGULATORY PERSPECTIVE

Doug Kelly, deputy director of the Center for Devices and Radiological Health of the FDA, began by describing his background, which included being a venture capitalist in Silicon Valley, starting several companies himself, and working as a physician and in a laboratory.

One thing about the workshop that struck him, he said, is how much it paralleled his own experience. "I know from a lot of therapy that I'm primarily driven by fear and anger," he said. "When I hear Jon [Nelson]'s story, it makes me angry that he has to fight for his own care. It's dehumanizing to do that. That drives a lot of my motivation to change a lot of things at the Food and Drug Administration."

Then Kelly spoke about the FDA's Total Product Life Cycle Advisory Program, or TAP. The idea behind it, he said, is to bring different sectors together from the beginning to provide early opportunities to collect input and feedback. He based the TAP program on lessons he had learned starting his own companies, he said, particularly the importance of answering

significant questions about a product and how it will make a profit early in the development process. He described TAP as "a consultancy inside the FDA" that helps innovators maximize their chances of bringing a useful and valuable product to market. For instance, he said, "Often the fastest way through the FDA may not be the best to get you the evidence you need. The evidence you generate is your biggest strategic advantage, your biggest competitive advantage. It may take a little more time to generate that, but you will suffer so much less failure and so much less time in unprofitability. You can't have a product that makes it out to patients unless it is profitable, and people make money doing it." The goal of TAP, he said, is to "figure out those things up front and figure out the most efficient path forward."

A FUNDER'S PERSPECTIVE

When reflecting on the workshop discussions, Sarah Hollingsworth Lisanby, the director of the Noninvasive Neuromodulation Unit and the Division of Translational Research at the National Institutes of Mental Health, organized the themes into the four R's: research, regulation, reimbursement, and real world. "When we think about the idealized pathway," she explained, "you start with research, [then] get regulatory approval, reimbursement approval, and achieve real-world impact." But the various opportunities and gaps discussed at the workshop complicate that simple picture, she said. "We need to redraw arrows. They are not just linear. Some have feedback loops."

She then offered some of important things she had heard at the workshop relating to each of the four R's. In the research arena, she said there is a need for better targets and objective outcome measures, perhaps with biomarkers (Alagapan et al., 2023; Deng et al., 2020). Concerning regulation, she emphasized how the FDA has programs such as TAP that accelerate the development of new technologies. "At the level of reimbursement," she continued, "we have learned that it really should be done and thought about in parallel with regulatory approval," noting that there are programs for parallel review at FDA and CMS. Another regulatory issue, she said, is the importance of looking at functional improvement, not just symptoms.

And at the level of real-world impact, she said, "I thought of the three Cs: clinicians, communities, and care disparities." Clinicians need training and support, biomarkers that are scalable and reliable for guiding their decisions, and interdisciplinary collaboration. Concerning communities, she continued, "we have heard about lived experience and how that should really be centered in all of our thinking in this regard." It is also

important to think about whether a device meets the needs of a community and as was seen in the example of the Deaf community's response to cochlear implants, whether it is culturally sensitive. Concerning care disparities, she said, "we learned there are disparities in access, diagnosis, and treatment along lines of gender, race, and ethnicity." Mental health or other health conditions can also impact a patient's access to treatment, she said. "When we think about how that real-world impact should be informing the research that we do," she said, "we should begin with the end in mind, so we end up with something that does have real-world impact."

A CLINICAL RESEARCHER'S PERSPECTIVE

Lauren Hammer named three things she had identified as important during the workshop. The first was a "focus on broad education and communication among all the stakeholders here." Certainly, the public needs to have a better understanding of what brain stimulation is and to realize that it is not "mad science" but something that has been around for decades, she said. In particular, patients need better education so that they can advocate for themselves and recognize when a procedure might be appropriate. Clinicians need to be better educated about how to integrate this technology into their own practice, added Hammer.

Second, she said, engineers need to work on making things simpler, not just for today's technologies but for those in the future. As it exists today, DBS technology is not scalable. Making things more efficient is not always the most exciting thing to work on, said Hammer, "but it is something I think is really important for us to be focusing on."

The third topic she identified was economic considerations. Overcoming the financial hurdles facing the technologies will require various approaches, including creating various incentives and making the devices more efficient, noted Hammer.

A HEALTH SYSTEM PERSPECTIVE

Kevin Mahoney agreed with Martha Morrell's comments that people in the field should be optimistic. "We created this system, we can fix this system," he said. "But it means we all have to . . . look across the aisle and not just maximize our position but [that of] all the stakeholders involved."

A major hurdle to more widespread use of deep brain stimulation is inertia, he said. "We are used to the way things are," he continued. "I think if we change—we, the health system at large—I think we can bring more advances quicker and faster to the globe."

DISCUSSION

Exploring the Importance of Patient Inclusion

Kelly highlighted that many people who work in health care do so to help their communities, which is why he participated in the workshop—because communication and putting the patient first are important. "One of the first things they teach in medical school," he said, "is if you do tests and at the end of the day still don't know what is wrong with the patient, ask. They will almost always tell you. It is a matter of listening." That lesson applies to the development of implantable brain stimulation and other technologies as well. "People do not ask the patient enough, 'What does this mean to you? Is this okay for you? Is this good for you?'"

Ellis responded to a question about what can be done to support giving a voice to patients and their groups. Patients absolutely can provide information about health-care-related issues that is important to hear, she said. "There are some hard truths here," she said. "The truth is that a lot of the burdens that are preventing adoption of DBS [from becoming] more widespread are because those burdens are put on the patients. The stigma of DBS is one of those things that is put on the patients. . . . We currently have to prove to our providers all the time that we really are sick. You know, they don't believe us. We do have to jump through a lot of hurdles. When our symptoms don't perfectly align, we are told we are wrong. . . . I have yet to meet a person with depression who has not been told they were malingering . . . that they just don't want to get well." Furthermore, she said, there is no incentive among providers to not just write prescriptions for the drugs that are pushed by pharmaceutical representatives. "I could not get a provider to write me a [prescription for] transdermal MAOI [monoamine oxidase inhibitor],[1] which has been around for decades." But if she went to too many providers, she was assumed to be provider-shopping or drug-seeking. "I was getting fired by my psychiatrists when everything they tried didn't work. I was not referred for additional treatments for new technologies." She was literally told that nothing was going to work for her.

Ellis also said that she found very few support options. People in her situation tend to get referred to the National Alliance on Mental Illness[2]

[1] Monoamine oxidase inhibitors are a class of effective and well-studied drugs that include the first antidepressants developed. They work by inhibiting the action of monoamine oxidases, enzymes that remove dopamine, serotonin, and norepinephrine from the brain; thus, MAOIs act to increase the levels of dopamine, serotonin, and norepinephrine in the brain.

[2] For more information about the National Alliance on Mental Illness, see https://www.nami.org (accessed January 18, 2024).

or the Depression and Bipolar Support Alliance,[3] she said, but those organizations "don't have resources for the atypical people." They also cannot provide a list of providers who will provide acute care. "Try finding a psychiatrist right now who will take your call when you are in crisis," she said; they will direct you to call 911. "As someone who watches the news, I'm not real confident in the 911 response to a mental health emergency."

Even once she was enrolled in a clinical trial, Ellis said, she faced many obstacles. "My parents had to be willing to sign a payer agreement for over $75,000 for me to be admitted in case my insurance didn't cover my inpatient stay." Furthermore, her parents paid for her to move to Atlanta and supported her while she was out of work because clinical trial participants are not compensated. "So how do you get people who can't work because they have to go to three doctor appointments a week?" she asked. "The assumption that we'll be on disability is not accurate. The ability to get disability is a nightmare." While acknowledging that she got incredible care and that she is "so thankful for this bonus life that I have," Ellis noted that she had to agree to be experimented on and be awake during brain surgery to get that quality of care. "I got no quality of care before then," she concluded. "That is what is preventing people from getting to DBS; [it's] because we are killing them before they can."

Kelly followed Ellis's comments with a statement that it is important to make sure that patient advocacy is as effective as it can be. "Oftentimes patient advocacy is not very effective in changing the course of what therapies get adopted, how they are adopted," he said. "Part of it is the way a lot of patient advocacy groups are founded. There's some on one end of the spectrum that are hypercompetent and really good at getting message out, in Parkinson's disease and diseases like that. There are others where the voice is much weaker. Part of the goal with TAP program as well is make sure we help those patient advocacy groups become better at having a big impact on what technologies get developed and how they develop."

In response to Ellis's comments, Mayberg spoke about the things researchers can learn from people who take part in clinical trials. "I see patients as collaborators," she said. "I'm doing something to you, and you are giving something to me." She also said that every patient in a clinical trial should get rehab to learn how to live with the implant. "Nobody gets a heart pacemaker and doesn't get cardiac rehab," she said. "Nobody gets their knee replaced or hip replaced or gets an insulin pump and doesn't learn how to control their diet, learn how to exercise, get a physical therapist." The same is true for implantable brain stimulation.

[3] For more information about the Depression and Bipolar Support Alliance, see https://www.dbsalliance.org (accessed January 18, 2024).

Reflecting on Opportunities to Move the Field Forward

A workshop participant asked what each panelist is planning to do as a result of participating in this workshop and how the workshop changed their perspective on what the field needs to do going forward.

Lisanby answered first and spoke about the need for objective biomarkers. In psychiatry, she said, when researchers doing clinical trials rely exclusively on subjective symptom-based diagnosis and outcome measures, it often leads to a significant amount of heterogeneity within diagnoses and comorbidity across diagnoses and fails to map well onto brain circuitry. Objective biomarkers can be used to reduce that heterogeneity and inform treatment decisions. She mentioned a paper published by researchers at Mount Sinai who identified an electrophysiological fingerprint associated with recovery from depression after deep brain stimulation (Alagapan et al., 2023). That fingerprint was used to inform dosing so that the clinicians were no longer reliant exclusively upon subjective reports.

Kelly answered next and spoke about speeding up the approval process at the FDA and other regulators. "There's lots of functions that happen serially that dramatically increase the time to get patient access to devices," he said. "If we can integrate some of those things into FDA studies early on, . . . it is our responsibility to do that. Our public mission at FDA is timely patient access to safe and effective medical devices. We really need to redouble our efforts on that timely patient access. It is not okay when you have a process that takes 20 years from product ideation to accessibility." The question, he said, is how to reduce those 20 years to ideally under 10 years, making the process similar in length to what venture capitalists are used to and thus making it more attractive to invest in this area. "Today really makes me want to redouble my effort and really dig into those relationships," he said.

Hammer said that hearing some of the patients' stories made her want to find ways to ease their burden. "I'm just starting my career and seeing patients, trying to build a research program," she said. "I have always thought of community education as something that I will get to later." Now, she continued, hearing about the importance of first-line providers such as general neurologists and psychiatrists being knowledgeable about these technologies, "I personally will probably change in terms of what I view as a priority."

Pulliam said that the workshop discussions convinced him that the adoption of implantable brain stimulation or any other new intervention into the standard of care is not just about the research, but it is also influenced by factors beyond research, such as the health care system and the payer system. "What I would do differently, then, is to increase communication with our fellow agencies," he said. "It is going to take all of us to

cooperate. No one of us can solve this." He added that he would also be looking for ways to integrate the patient into all levels of the field, including the research level.

"I'm going to continue to cheer every single one of you on," Ellis said. "I'm going to also continue to talk to anybody who will listen about . . . bioethics, post-clinical-trial responsibility, mental health care, patient advocacy." She ended by saying, "I want all of you to continue to do the work you are doing because this is absolutely meaningful treatment that absolutely is critical for people to survive and enjoy life."

Mahoney closed out the discussion period. "I'm inspired by opportunities and want to keep pushing forward," he said. "I will do a better job with my colleagues across the country pushing them towards total value of care and little less [toward] fee for service. What I heard was, rather than following the scientific evidence, people like me follow the reimbursement evidence, so [I'll be] trying to lead more on that." Finally, he said, "Recognizing the importance of the patient is one of my biggest takeaways from today."

CONCLUDING REMARKS

In her concluding remarks, Mayberg said, "My takeaway bullet point is angry but optimistic." "Anger is a representation of impatience with things that are obvious and that you have the data, and nobody is listening. That is what makes people angry." However, she said, seeing the individuals with lived and living experiences at the forefront of these conversations gives her optimism. While the path ahead may not be straightforward, she said, "we need to figure out how to capitalize [on the optimism]."

A second takeaway, she said, is the importance of getting all the clinicians, researchers, and engineers working together—psychologists, neurologists, physiologists, engineers, and so forth. "I'm inspired by Kevin [Mahoney] that there is a mechanism to set up pilot programs in this space," she said. "That is my advocacy now—to do the science but to figure out how to actually get this into practice."

Denison then offered his own takeaway. "The analogy floating around in my head for the day is, we have a jazz band where we have all the members of the band on the stage, but we are not yet playing the tune together. That requires us to do a lot more listening. Like a good jazz band, you are listening and building and going with the flow with your companions and accentuating but also giving up the stage as well and giving that notion of a band as being an ecosystem and being mindful. That is my takeaway, making sure I'm listening and not trying to have my trombone overpower the ensemble."

Denison closed the workshop by acknowledging the patients who make his work and that of other researchers and clinicians possible. "The real

pioneers . . . are actually those first research subjects who volunteer to be the very, very first," he said. "I think it is appropriate to close out the workshop to recognize them. They are the true pioneers supporting this entire ecosystem."

Appendix A

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Appendix B

Workshop Agenda

EXPLORING THE ADOPTION OF IMPLANTABLE BRAIN STIMULATION INTO STANDARD OF CARE FOR CENTRAL NERVOUS SYSTEM DISORDERS

The Keck Center, 500 Fifth Street, NW
Washington, DC 20001

OCTOBER 31, 2023
ROOM 100

9:00–9:05 Welcome
Frances Jensen, *University of Pennsylvania*; Co-chair, Forum on Neuroscience and Nervous System Disorders
John Krystal, *Yale University*; Co-chair, Forum on Neuroscience and Nervous System Disorders

SESSION 1—CROSSING THE CHASM: LESSONS LEARNED ACROSS TECHNOLOGIES

- Review the current state of knowledge regarding the clinical utilization of implantable brain stimulation across various CNS disorders and consider the future potential to improve quality of life for patients.
- Discuss the lessons learned from other technologies that have or have not "crossed the chasm" to be adopted into clinical care.

- Consider how these lessons learned might be applied to implantable brain stimulation.

9:05–9:15 Workshop Overview
Tim Denison, *University of Oxford*; Workshop Co-chair
Helen Mayberg, *Icahn School of Medicine at Mount Sinai*; Workshop Co-chair

- Share the scope of the workshop and what will not be covered.
- Introduce technology adoption theory as the theme for this workshop.
- Highlight that scalability, technology, comorbidities considerations, and opportunities to overcome these barriers will be implicit throughout the workshop.

9:15–9:20 Setting the Stage: Where Do We Want to Be
Brian Litt, *University of Pennsylvania*

- What does it mean to be a part of the standard of care?
- Provide a brief history about cardiac pacemakers and defibrillators.
- What would be required for implantable brain stimulation to be adopted into the standard of care?

9:20–9:45 Lessons Learned Across Therapeutic Areas

- Provide an overview of the therapy and the patient need that was being addressed.
- Share insights into why the therapy has been or not been adopted into clinical care.
- What are some of the lessons learned that should be considered for any new implantable brain stimulation therapy?

Overview of Approved Neuromodulation Therapies
Vivek Pinto, *U.S. Food and Drug Administration*

Cochlear Implants and Retinal Implants
Carla Mann Woods, *Adventus Ventures*

Responsive Neurostimulation for Epilepsy
Mindy Ganguly, *University of Pennsylvania*

Deep Brain Stimulation for Obsessive-Compulsive Disorder (OCD)
Benjamin Greenberg, *Brown University*

9:45–10:00 Moderated Discussion
Moderator: **Brian Litt,** *University of Pennsylvania*

SESSION 2—BENEFITS AND CHALLENGES EXPERIENCED BY INDIVIDUALS WITH LIVED EXPERIENCE

- Explore what patients need from implantable brain stimulation to define it as a successful treatment.
- Discuss how adoption of this technology can impact patients and their quality of life.
- Consider what challenges and barriers prevent patients from selecting this treatment or causes patients to perceive the treatment as a failure.

10:00–10:05 Session Overview
Laura Lubbers, *CURE Epilepsy*

10:05–10:25 Speaker Remarks
Steve Austin, *CURE Epilepsy*
Jim McNasby, *Michael J. Fox Foundation for Parkinson's Research*
Jon Nelson, *Jon Nelson Advisors, LLC*
Claudia Garrido-Revilla, *Michael J. Fox Foundation for Parkinson's Research*

10:25–10:55 Moderated Discussion

10:55–11:05 Break

SESSION 3—PRACTICAL BARRIERS I: PATIENT SELECTION AND ENGAGEMENT

- Review the challenges associated with patient selection and engagement and with managing expectations of patients and their families.
- Consider the ethics of ensuring equitable access to all patients and demographics.
- Explore the potential opportunities or collaborations that are needed to develop informed patient selection practices and equitable access to the technology.
- Review the concerns of patients regarding the possible complications and side effects of implantable brain stimulation and potential educational campaigns to increase patient awareness of and comfort with the technology.

11:05–11:10 Session Overview
Sarah Perides, *Evelina London's Children Hospital*

11:10–12:10 Moderated Panel and Audience Q&A
Joseph Candelario-Mckeown, *National Hospital for Neurology and Neurosurgery*
Rachel Davis, *University of Colorado Anschutz School of Medicine*
Nita Farahany, *Duke University* (*Zoom*)
Doris Wang, *University of California, San Francisco* (*Zoom*)
Alik Widge, *University of Minnesota*

12:10–12:55 Lunch

SESSION 4—PRACTICAL BARRIERS II: HEALTH PROFESSIONAL BARRIERS AND ADOPTION

- Discuss the current barriers to increase training and engagement among health professionals on implantable brain stimulation and barriers of current practices.
- Explore what relationships might need to be developed across different specialties and clinical practices to facilitate referrals and continuance of care.

12:55–1:00 Session Overview
David McMullen, *Food and Drug Administration*

1:00–2:00 Moderated Panel and Audience Q&A
Lauren Hammer, *University of California, San Francisco* (*Zoom*)
Joan Miravite, *Icahn School of Medicine at Mount Sinai*
Martha Morrell, *NeuroPace, Inc.*
Michael Okun, *University of Florida*
Yagna Pathak, *Abbott Neuromodulation*

2:00–2:10 Break

SESSION 5—PRACTICAL BARRIERS III: REIMBURSEMENT AND OTHER ECONOMIC CONSIDERATIONS

- Consider the current economic barriers and technological limitations that prevent implantable brain stimulation from becoming scalable.

- Discuss what ongoing or future approaches need to be taken to improve the benefit-cost ratio and allow brain stimulation to be scalable for wider application in CNS disorders.
- Review the current status of reimbursement for implantable brain stimulation and discuss opportunities to increase reimbursement.

2:10–2:15 Session Overview
Yagna Pathak, *Abbott Neuromodulation*

2:15–3:15 Moderated Panel and Audience Q&A
Julie Brown, *Spark Biomedical* (*Zoom*)
Kevin Mahoney, *University of Pennsylvania Health System*
Susan Miller, *Centers for Medicare and Medicaid Services* (*Zoom*)
Peter Silburn, *Queensland Brain Institute* (*Zoom*)

3:15–3:25 Break

SESSION 6—SYNTHESIS OF WORKSHOP THEMES

- Review the core themes and takeaways shared across the previous sessions.
- Based on previous discussions, explore creative approaches or collaborations needed to move the field forwards toward the end goal of adoption of implantable brain stimulation into the standard of care.
- Discuss the implications of comorbidities and opportunities to develop technologies and treatments to holistically treat patients.

3:25–3:30 Session Overview
Tim Denison, *University of Oxford*; Workshop Co-chair
Helen Mayberg, *Icahn School of Medicine at Mount Sinai*; Workshop Co-chair

3:30–4:25 Moderated Panel and Audience Q&A
Brandy Ellis, *Neuromodulation Patient Advocate*
Lauren Hammer, *University of California, San Francisco* (*Zoom*)
Doug Kelly, *Food and Drug Administration*
Sarah Hollingsworth Lisanby, *National Institute of Mental Health*
Kevin Mahoney, *University of Pennsylvania Health System*
Chris Pulliam, *Case Western University*

4:25–4:30 Synthesis and Concluding Remarks
Tim Denison, *University of Oxford*; Workshop Co-chair
Helen Mayberg, *Icahn School of Medicine at Mount Sinai*; Workshop Co-chair