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Therapeutic advances in the management of neurodegenerative diseases

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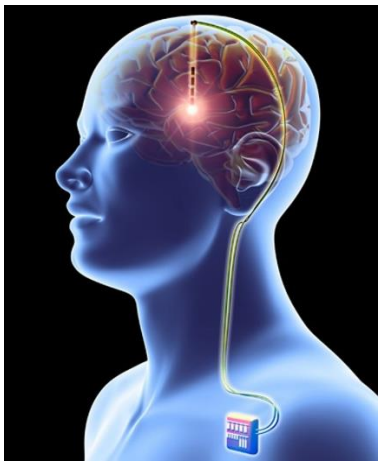

HiRes Deep brain stimulation Science Photo Library,Alfred Pasieka

Abstract

- *No treatment is currently available that is capable of interrupting neuronal cell death. For certain neurodegenerative diseases there are not even any symptomatic treatments available. Nevertheless, great advances have been made in recent decades towards understanding these diseases.*
- *Technological advances (medical devices, biotechnology) have made it possible to foresee the development of new, innovative treatments in the medium term.*
- *The arrival of new immunotherapies for Alzheimer's disease has brought hope, but also the risk of disrupting care pathways; careful consideration is necessary in order to promote diagnosis and allow for the treatment of eligible patients; these therapies will help to alleviate the burden of this disease on patients, their families and on society as a whole.*

Florence Lassarade, Senator

Neurodegenerative diseases[1] are caused by the death of certain neuronal cells in the brain. The underlying pathophysiological mechanisms differ from one disease to another and involve different regions of the brain. They constitute a very significant burden for society, because most of these ultimately lead to a substantial degree of dependence. In France, Alzheimer's disease affects 1.2 million people, Parkinson's disease 200,000, and multiple sclerosis more than 115,000.[2] These numbers will continue to increase with the aging population.

Pending the development of more effective curative or symptomatic treatments, much hope has been placed in recent decades in immunotherapies, but it is only very recently that two antibodies have finally shown effectiveness on the cognitive symptoms of Alzheimer's disease. New therapies continue to be tested: classic, based on small molecules, or innovative, such as cell or gene therapies.[3] Neurology is the second most dynamic clinical research area worldwide.[4]

Specialists agree on the need for earlier treatment, because symptoms begin to appear when the brain is already being affected by neuronal death, the effects of which it may conceal for some time.

Available therapeutic strategies and recent advances

Chemical modulation of signalling pathways

In the brain, the death of a group of neurons leads to defective stimulation of downstream neurons in communication networks. Since neurons communicate via molecules (neurotransmitters), this defect may be compensated by restoring neurotransmitter levels. In Parkinson's disease, these disappearing neurons' signalling pathway can be chemically modulated by administering dopamine precursors (L-DOPA) or analogues, or dopamine degradation inhibitors.[5]

The only symptomatic treatments available in France for Alzheimer's disease are chemical modulators as well. However, the National Health Authority (Haute Autorité de Santé) has determined that the risk-benefit ratio of these treatments was not favourable enough to continue to justify their reimbursement.[6] Patients, doctors and learned societies have all expressed regret at this decision,[7] as the consequences of halting these treatments are poorly understood.[8]

Brain-stimulating medical devices

Deep brain stimulation consists of applying stimulation in the subthalamic nucleus by means of electrodes.[9] This treatment effectively reduces the

motor symptoms of Parkinson's disease by restoring the excitation/inhibition balance.[10]

Over the past 30 years, the operation time for laying the device has been shortened with the help of technology,[11] and is now carried out under general anaesthesia, which is more comfortable for patients. A rechargeable version of the device has now been developed, increasing its lifespan to 25 years, whereas traditional devices need to be changed once every 4 years,[12] and directional electrodes allow more precise targeting of the area to be stimulated. Devices are currently being tested that can record brain activity and adjust correspondingly in order to deliver stimulation tailored to suit patient needs, in the hope of thereby reducing side effects.

Only 500 patients are operated on per year, though specialists estimate that five times that many are likely eligible. The procedure is still relatively inaccessible to populations far from hospital centres performing it on a regular basis.[13]

Modulation of inflammation

Immunomodulatory and immunosuppressive treatments have been developed to successfully control the inflammatory flare-ups associated with multiple sclerosis. These include monoclonal antibodies directed against actors in the patients' immune system in order to inhibit them. The inevitable progression of brain damage, gradually leading to disability, could be counteracted by stimulating the regeneration of myelin, which is neuroprotective.[14]

Control of genome expression

In the case of diseases of genetic origin, the mutation of a gene can lead to the expression of a dysfunctional protein. Antisense oligonucleotides are designed to prevent the expression of the mutated gene, therefore preventing the synthesis of the toxic protein.[15] Tofersen has just been authorised in the United States for certain patients suffering from amyotrophic lateral sclerosis.[16] These therapies are also being tested in Huntington's disease.

Passive immunotherapy

The administration of antibodies against protein aggregates in neurodegenerative diseases has been tested for several decades.[17] Two therapies have recently proven effective in bringing about improvement in Alzheimer's patients both biologically (elimination of senile plaques in the brain) and clinically (slowdown of cognitive and functional decline).[18] The improved targeting of patients eligible for the tested treatments[19] and early treatment[20] have likely contributed to this advancement, as well as the precision with which antibodies are directed at their targets.[21]

However, these treatments are associated with adverse effects: cerebral oedema and microhaemorrhages occurred in 13 to 31% of treated patients,[22] though most showed no symptoms.[23] Since patients are very attentive to adverse effects and reluctant to experience them as long as their cognitive state is not deteriorating too greatly,[24] the enthusiasm generated by the arrival of these new treatments has been somewhat muted.

Non-drug therapies

Cognitive and physical stimulation of patients has achieved results, but access to this care is impeded by the lack of physiotherapists, speech therapists, psychologists, and psychomotor therapists.[25]

In institutions, the Paro robot (stuffed animal seal) is used to reduce anxiety in patients with dementia. Humanoid robots, on the other hand, are used to improve their engagement in psychomotor type activities. Professionals report a keen interest in robots. Technological tools, whether intended as aids for everyday life[26] or for cognitive stimulation,[27] can supplement human intervention, but they suffer from a lack of referencing and evaluation.[28]

One-third of Alzheimer's disease cases are linked to risk factors that can be changed, such as smoking, depression and social isolation.[29] Interventions combining cognitive stimulation, physical activity and nutrition,[30] as well as meditation,[31] have also shown promise in terms of prevention in persons at risk of developing the disease.

In multiple sclerosis or Parkinson's disease, providing therapeutic education to patients can help them to better understand their illness and eventually to improve how they live with it. Patient-experts, trained by associations, share their experiential knowledge with caregivers to help improve care.

■ Possible areas for future development

Diagnosis, a preliminary to treatment

The arrival of immunotherapies will sharpen the need for early diagnosis in Alzheimer's disease, which is still prone to diagnostic delay.[32] Diagnosis is based in part on searching out biomarkers in the cerebrospinal fluid (CSF).[33] These markers can be looked for in the blood, but their concentration is much lower there. The roll-out of routine detection techniques by the industrial diagnostics sector will facilitate the development of blood tests.

These tests should help in the short term to produce preliminary information on the benefit of conducting a lumbar puncture. In the medium term, specialists hope that general practitioners might be able to prescribe them as a diagnostic orientation test before referring patients to specialists. They nevertheless warn of the need to regulate the deployment of these tests, which could lead to a slide toward commercialism.[34]

In the long term, questions arise about the relevance of screening for the disease in order to provide better treatment in the absence of symptoms. However, no reliable diagnosis exists based on amyloid biomarkers alone.[35] Furthermore, the benefit of treating subjects with brain lesions in the absence of symptoms is unknown, but the hypothesis is currently being tested.[36]

Though the Aβ and Tau peptides are specific to Alzheimer's disease, other non-specific markers are useful as well for characterising brain damage.[37] Progress has been more modest with regard to markers for other diseases.[38]

Technological advances helping to open up possibilities

Increased permeability of the blood-brain barrier

The brain is isolated from the rest of the body by what is known as the blood-brain barrier. The relatively reinforced wall of blood vessels allows very few molecules to penetrate the brain tissue – too little for the desired therapeutic action, thus thwarting many drug strategies.

By applying ultrasound to the surface of the skull focused on a specifically defined area of the brain, it is possible to destabilise this barrier for a few hours and deliver intravenous treatment to the patient, achieving optimal penetration into the tissues. This technique is still being tested in primates, but may make it possible to reconsider numerous treatments that have been abandoned due to lack of penetration into the brain. Several French teams are working to develop such a tool, which would also be useful in oncology.[39]

Photobiomodulation

Inspired by deep brain stimulation, researchers are now seeking to develop a technique to stimulate *in situ* the neurons that degenerate in Parkinson's disease, by applying light stimulation. Near-infrared light can stimulate neuronal activity, and may be able to slow or even stop neuronal death.[40] This neuroprotection technique, unique in the treatment of Parkinson's disease, is currently being tested.

Gene therapy

With the aim of compensating for the consequences of neuronal death, gene therapy strategies consist of giving other neurons the capacity to produce the defective neurotransmitter. In the case of Parkinson's disease, researchers insert genes involved in dopamine synthesis into the neurons in the striatum.[41] This brain structure is located downstream in the neuronal circuits from where neurons are dying. Normal dopamine levels can thus be restored.

Cell therapy

For the same purpose, stem cell transplantation is now being tested for use in Parkinson's disease, Huntington's disease and multiple sclerosis.[42] Encouraging results have been obtained for the latter, since such transplantation can promote remyelination: the transplanted cells have a neuroprotective action, replacing damaged cells and providing factors stimulating spontaneous remyelination *in situ*.[43]

The discovery of induced pluripotent stem (IPS) cells, obtained by reprogramming epithelial cells (skin cells, for example), has opened new horizons for this technique, which was previously dependent on embryonic stem cells.[44]

Organoids, a new research model

The development of these new therapies has been limited by a heavy dependence on research models. The brain being a particularly complex organ, the models that have been traditionally used, such as rodents, have limitations, hence the interest of the field in the use of primates, which are required for the clinical translation of these technologies. However, the recent rise of IPS cells has made it possible to develop an intermediate model: cerebroids.[45]

These structures, although far removed from the complexity of the animal brain, have the advantage of being made up of human cells, which makes them a choice model for testing gene and cell therapies. They also show promise in terms of drug screening. "Brain-on-a-chip"[46] and grafts on hosts[47] type approaches offer new prospects for the study of these structures in the long term.

■ Barriers to research

Difficulties associated with the organisation of care

Patients with neurodegenerative diseases suffer from the difficulties faced by our healthcare system. In the case of Parkinson's patients, it can be difficult to hold a consultation quickly to adjust symptomatic therapies properly or organise their administration at a fixed time at medical facilities due to understaffing.

The role of advanced practice nurses could be expanded with regard to these patients.[48]

In addition to the lack of effective treatment, the lack of caregivers can also contribute to the underdiagnosis of Alzheimer's disease in certain regions. However, the need to organise the patient's life alone justifies diagnosis as early as possible, and the arrival of immunotherapies will accentuate this need.

If these therapies are administered under the same conditions as applied in clinical trials (bimonthly, intravenously), their availability to the population of eligible patients – 1 to 2 million – will require the involvement of personnel whose numbers are currently insufficient.[49] The medical community has begun discussions regarding the organisation of care to prepare for the arrival of these treatments; it considers it urgent that these discussions include all stakeholders.[50]

Difficulties associated with clinical research

Stakeholders in clinical research are disappointed by the difficulties faced by the entire biohealth sector, in particular funding that is too short-term, and unsuitable for the duration of the research projects and risks involved,[51] and the relative unattractiveness of careers in the field.[52]

They have also expressed dissatisfaction about the cumbersome administrative and legal procedures and multiple administrative supervisors.[53] Research ethics committees (CPP) are often perceived as too cautious and as a barrier to clinical research initiatives. Specialisation of committees would make it possible to limit the issuance of excessively heterogeneous decisions from one committee to the next.[54]

In the case of rare diseases for which the national numbers are low, it is a very complicated matter, if not impossible, to cooperate with foreign cohorts because of the territorial attachment rule applicable under the Computing and Civil Liberties law.[55] More generally, stakeholders have expressed a strong desire to see the conduct of clinical research facilitated. Measures taken in this regard during the Covid-19 pandemic were appreciated, with the establishment of platform trials such as Discovery. Support provided by the F-CRIN network[56] for the organisation of clinical trials has been very welcome.

■ Conclusions

The incidence of neurodegenerative diseases has been increasing in the population as it ages, but the avenues being studied are promising and offer hope for the appearance of curative treatments. The immunotherapies and antisense oligonucleotides authorised this year[57] illustrate the fact that the few treatments available so far for these diseases do not reflect the current state of knowledge. They also demonstrate the need for long-term investment in this research.

In light of their experience at the forefront of research in the context of the first "Alzheimer plan," the community of researchers, doctors and associations take the position that these diseases are not being given due consideration in light of their consequences for society. Expectations regarding the newly updated Neurodegenerative Diseases roadmap, particularly with regard to the financial resources to be allocated, are quite high.

Innovation needs to be facilitated and freed from overly restrictive administrative constraints. Patient access to innovation must be secured.

■ Recommendations

- Efforts must be made to reduce the underdiagnosis and diagnostic delay all too often seen in diseases such as Parkinson's and Alzheimer's, to the extent that therapeutic care currently exists and future treatments are likely to allow improvements to care, with the full participation of family medicine.
- Access to medical device implantation for Parkinson's patients must be secured by bringing together experienced, technologically advanced teams at dedicated centres.[58]
- The development of blood tests intended to search out biomarkers linked to neurodegenerative diseases will need to be regulated, initially restricting their prescription to memory centres.
- Among the preventive check-up appointments as provided for in the Social Security budget for 2023, the one planned at age 65 should be made a key moment for the prevention of neurodegenerative diseases.
- Preparations must be made now for the likely arrival of new amyloid immunotherapies, so that every interested eligible patient can access them.

OPECST website:
http://www.assemblee-nationale.fr/commissions/opecst-index.asp
http://www.senat.fr/opecst

Persons consulted

- Gaël Chételat, research director at Inserm, head of the "Multimodality imaging and lifestyle factors in aging and Alzheimer's disease" team within the Cyceron platform at Université Caen Normandie;
- Emmanuel Roux, director of market access and institutional relations, Emmanuelle Baloche, senior medical manager of neurology, and Anouch Mouradian, senior market access manager at Eisai's French subsidiary;
- Prof. Stéphane Chabardès, head of the neurosurgery department at Grenoble Alpes University Hospital and medical director of the Clinatec centre (CEA-Leti, Grenoble);
- Prof. Anne-Sophie Rigaud Monnet, head of gerontology department no. 2 at Broca hospital (AP-HP, Paris), professor of geriatric medicine, director of the "Alzheimer's disease, risk factors, and care management for patients and caregivers" university research unit, co-facilitator of the Southern Ile-de-France Memory Resources and Research Centre;
- Prof. Béchir Jarraya, neurosurgeon at Foch hospital (Suresnes), director of the "Primate Consciousness and Cognition" team at the Neurospin centre at CEA Paris-Saclay, professor of neurology and member of the Opecst Scientific Council;
- Persons encountered at a round table dedicated to the activities of patient associations:
    - Amandine Lagarde, general director of France Parkinson, accompanied by Marie Fuzzati, medical director;
    - Lorène Gilly, public policies monitoring manager for France Alzheimer and related diseases, and Kevin Rabiant, studies and research manager;
    - Sophie Tortosa, general director of the French League against Multiple Sclerosis, accompanied by Marine Petit, patient-expert;
- Persons encountered at a round table dedicated to blood biomarkers:
    - Prof. Olivier Hanon, head of gerontology department no. 1 at Broca hospital (AP-HP, Paris), head of the "Vascular and genetic risk factors" team within the "Alzheimer's disease, risk factors and care management for patients and caregivers" unit, coordinator of the Baltazar cohort;
    - Prof. Claire Paquet, neurologist at Lariboisière hospital (AP-HP) and at the Northern Ile-de-France Memory Resources and Research Centre, member of the Inserm "Biomarkers and neurocognition" research unit, former scientific co-supervisor of the Ministry of Health neurodegenerative diseases mission, and president of the scientific committee of Fondation Vaincre Alzheimer;
    - Prof. Sylvain Lehmann, head of the clinical biochemistry-proteomics laboratory at Montpellier University Hospital and director of the Montpellier centre of excellence in neurodegenerative diseases;
- Persons encountered during the visit to the Bordeaux Institute of Neurodegenerative Diseases:
    - Thomas Boraud, director of the Institute, research director at CNRS, hospital practitioner;
    - Erwan Bezard, former director of the Institute, research director at Inserm;
    - Prof. Wassilios Meissner, director of the neurology – neurodegenerative diseases department at Bordeaux University Hospital, director of the clinical branch of the Bordeaux Neurodegenerative Diseases Institute and of the reference centre for multiple system atrophy, professor of neurology;
- Persons encountered during the visit to the Paris Brain Institute:
    - Prof. Alexis Brice, general director of the Institute, accompanied by Corinne Fortin, general secretary and Jean-Louis Da Costa, communications director;
    - Prof. Catherine Lubetzki, medical director, head of the "Remyelination in multiple sclerosis: from biology to clinical translation" team;
    - Prof. Richard Lévy, director of the "Frontlab: functions and dysfunctions of frontal systems" team, professor of neurology, head of the Memory and Alzheimer's Disease Institute and the Behavioural Neurology Unit within the department of neurology at Pitié-Salpêtrière hospital (AP-HP);
    - Prof. Jean-Christophe Corvol, head of the "Molecular pathophysiology of Parkinson's disease" team and director of the neurology department at Pitié-Salpêtrière Hospital;
    - Céline Louapre, head of the Clinical Investigation Centre, associate professor of neurology at Sorbonne University;
    - Louise-Laure Mariani, head of the Neurotrials clinical trial platform, associate professor of neuropharmacology;
    - Séverine Boillée, head of the "Causes of amyotrophic lateral sclerosis and mechanisms of motor neuron degeneration" team, research director at Inserm;

- François Salachas, researcher in the "Causes of amyotrophic lateral sclerosis and mechanisms of motoneuronal degeneration" team, neurologist at the Pitié-Salpêtrière hospital, head of the centre of reference for amyotrophic lateral sclerosis;
- Prof. Alexandra Durr, head of the "Fundamental and Translational Neurogenetics" team and professor of medical genetics at Sorbonne University;

- Persons encountered during the visit to the François Jacob Institute of Biology of the Atomic Energy and Alternative Energies Commission:
  - Simone Mergui, deputy director of the Institute;
  - Philippe Hantraye, director of the MIRCen (Molecular Imaging Research Centre) department;
  - Anselme Perrier, director of the Cellular Interactions in Neurodegenerative Diseases team: models and therapies;
  - Julien Flament, head of the NMR (nuclear magnetic resonance) platform;
  - Jean-Philippe Deslys, head of the Department for the Study of Prions and Atypical Diseases (SEPIA);
  - Frank Yates, research professor at Sup'Biotech and researcher at SEPIA;
- Written contribution from LEEM.

■ **Appendix**: summary of the characteristics of the main neurodegenerative diseases

Disease	Lesions	Aggregated protein	Origin	Prevalence/ Incidence	Temporality
Alzheimer's disease	fibrillar tangles in the hippocampus	phosphorylated tau proteins	1 to 5% of cases of genetic origin and the rest sporadic	5% of over 65s – 1.1 to 2 million people	Diagnosis around age 73 on average, then progression of the disease over several years or even decades
	amyloid plaques in the cortex	amyloid peptides			
Parkinson disease	aggregates (Lewy bodies) in the substantia nigra	α -synuclein	5 to 15% of cases of genetic origin and the rest sporadic	1% of over 65s – 200,000 people – annual incidence of nearly 40 cases per 100,000 inhabitants	Diagnosis around age 75 to 80, evolution over several decades with an initial phase of good symptom control through symptomatic treatments
Multiple sclerosis	destruction of the myelin sheath in the white matter and spinal cord		sporadic illness	115,000 people – annual incidence of 5 to 7 cases per 100,000 inhabitants	Phase of inflammatory flare-ups and parallel progression of lesions leading to disability. Disease detected most of the time in young adults
Amyotrophic lateral sclerosis	death of motor neurons in the brain and spinal cord	TDP-43, FUS	10% of cases of genetic origin and the rest sporadic	5000 to 7000 people – annual incidence of approximately 2.5 cases per 100,000 inhabitants	Progressive paralysis with fatal outcome, beginning on average around age 55-60: patient dies within 3 to 5 years
Huntington's disease	death of neurons in the cortex and striatum	huntingtin	genetic disease	6000 people	Abnormalities may appear in early development but symptoms do not begin until around 30 to 50 years old

Sources: Ministry of Health Neurodegenerative Diseases Roadmap, thematic dossiers from Inserm, Association for Amyotrophic Lateral Sclerosis Research

Références

[1] See table in appendix for a summary of the characteristics of the primary neurodegenerative diseases.

[2] 2021 – 2022 Neurodegenerative Diseases Roadmap from the Ministry of Health: https://sante.gouv.fr/IMG/pdf/plan_pmnd_version_longue.pdf

[3] 72% of therapies for neurological diseases in phase I testing are small molecules, 16% are biological molecules (such as antibodies), 4% are cell therapies, 4% are gene therapies, and 3% are therapies aimed at modifying the expression of the genome by acting on RNA (LEEM – IQVIA data).

[4] After oncology, the largest number of phase I clinical trials being conducted worldwide are in the field of neurology. The four most common neurodegenerative diseases are listed among the top 5 diseases in number of therapies being tested: Alzheimer's, Parkinson's, multiple sclerosis and amyotrophic lateral sclerosis (LEEM – IQVIA data).

[5] Generally administered via the oral route; they may also be administered via subcutaneous pump (apomorphine pump) or transdermally (patch). Haute Autorité de Santé: "La maladie de Parkinson: critères diagnostiques et thérapeutiques." Accessed 11 April 2023. https://www.has-sante.fr/jcms/c_272069/fr/la-maladie-de-parkinson-criteres-diagnostiques-et-therapeutiques, and VIDAL: "Le traitement médicamenteux de la maladie de Parkinson." Accessed 11 April 2023. https://www.vidal.fr/maladies/systeme-nerveux/maladie-parkinson/traitement.html.

[6] In particular, these treatments have failed to demonstrate effectiveness on behavioural disturbances, quality of life, time to institutionalisation, or caregiver burden (a). Some scientists even believe that they should be taken off the market: "Médicaments de la maladie d'Alzheimer: enfin non remboursables en France!" (b):

(a) Transparency Commission, National Health Authority. "Rapport d'évaluation des médicaments indiqués dans le traitement symptomatique de la maladie d'Alzheimer"; https://www.has-sante.fr/upload/docs/application/pdf/2016-10/annexe_-_rapport_devaluation_des_medicaments.pdf

(b) https://www.prescrire.org/fr/3/31/55116/0/NewsDetails.aspx.

[7] The learned societies in the fields of neurology and geriatrics in particular expressed a fear that this delisting for reimbursement would result in delays in the diagnostic process. Only three European countries, including France, have taken this step. Elsewhere, these therapies remain recommended; "Déremboursement des traitements symptomatiques dits 'anti-Alzheimer': une injustice difficile à comprendre". France Alzheimer ; https://www.francealzheimer.org/deremboursement-des-traitements-symptomatiques-dits-anti-alzheimer-une-injustice-difficile-comprendre/ ; Opinion column by Serge Bakchine, "Non au déremboursement des médicaments symptomatiques de la maladie d'Alzheimer", 17 June 2018. https://www.lefigaro.fr/sciences/2018/06/17/01008-20180617ARTFIG00034-non-au-deremboursement-des-medicaments-symptomatiques-de-la-maladie-d-alzheimer.php.

[8] Results vary from study to study. A Cochrane systematic review dating from 2021 concluded that the interruption of these symptomatic treatments is in fact rather harmful for patients, but found only a relatively modest level of evidence. Parsons, Carole et al. "Withdrawal or Continuation of Cholinesterase Inhibitors or Memantine or Both, in People with Dementia." Cochrane Database of Systematic Reviews, no. 2 (2021). https://doi.org/10.1002/14651858.CD009081.pub2.

[9] Invented in the 1990s, deep brain stimulation is today a standard technique in the treatment of Parkinson's disease. It was originally a product of French research : the technique was first developed by Prof. Alim-Louis Benabid and Pierre Pollak in Grenoble, based on preliminary work carried out by Abdelhamid Benazzouz in Bordeaux.

[10] The subthalamic nucleus is a structure nested in a communication loop with other basal ganglia that control motor skills, including the substantia nigra, whose neuronal cells degenerate in Parkinson's disease. This degeneration and the resulting lack of dopamine lead to an imbalance of stimulation that causes the motor symptoms observed in the disease. High-frequency stimulation of the implanted area allows the effective reduction of said symptoms by restoring the excitation/inhibition balance. With this intervention, a substantial reduction in the dosages of adverse effect-prone dopamine precursors and analogues can be achieved ; Benazzouz, Abdelhamid. Stimulation à haute fréquence du noyau sous-thalamique dans la maladie de Parkinson." médecine/sciences 20, no. 4 (1 April 2004): 397-98. https://doi.org/10.1051/medsci/2004204397.

[11] The electrode is implanted using a robotic arm. The use of a scanner and visualisation software makes it possible to identify the target structure more precisely. These innovations have contributed to reducing the duration of the procedure from 20 hours around twenty years ago to around 4 hours today.

[12] Device change procedures thus account for over 2/3 of hospitalisations involving deep brain stimulation.

[13] Being less of a priority than oncology care or emergencies, this activity has in fact suffered the consequences of the difficulties experienced by hospitals. Although previously this procedure was offered at 22 healthcare institutions in France, only around ten now continue to perform it on a regular basis with a high level of expertise.

[14] The myelin sheath is a sheath made of lipids, surrounding the axons and allowing the propagation of nerve impulses over distances that on the scale of these cells are quite large. In sick patients, this sheath is attacked by the immune system. Remyelination is one strategy potentially able to limit neurodegeneration and the resulting disability. Many molecules as well as cell therapies are currently being tested for this purpose, as described below.

[15] Antisense oligonucleotides are small fragments of RNA complementary to certain parts of the targeted messenger RNA. By binding there, they prevent the cellular machinery from translating the messenger RNA into a dysfunctional protein. These molecules must be administered intrathecally, i.e., directly into the cerebrospinal fluid, which the practitioner accesses at the lumbar level (such as in a spinal tap). For more details, see the Inserm file "Les thérapies à ARN – un domaine thérapeutique en pleine expansion" (2022); https://www.inserm.fr/dossier/therapies-a-arn/.

[16] Tofersen targets the gene coding for the SOD1 protein, a dysfunctional enzyme involved in the 10% of cases of amyotrophic lateral sclerosis that are of genetic origin. "FDA Grants Accelerated Approval for QALSODY™ (Tofersen) for SOD1-ALS, a Major Scientific Advancement as the First Treatment to Target a Genetic Cause of ALS | Biogen." Accessed 1 June 2023. https://investors.biogen.com/news-releases/news-release-details/fda-grants-accelerated-approval-qalsodytm-tofersen-sod1-als.

[17] These are exogenous antibodies, administered to patients intravenously. They direct the patients' immune system against the elements to be eliminated – i.e., amyloid plaques, in the case of Alzheimer's disease. In addition to the immunotherapies described in the paragraph, others are being tested to target the Tau protein involved in Alzheimer's disease or the misfolded α-synuclein involved in Parkinson's disease.

[18] These are Lecanemab (Leqembi®) from the Eisai-Biogen consortium and Donanemab from Eli Lilly. Positive results from phase III clinical trials for these therapies were disclosed respectively in September 2022 and May 2023. Patients receiving the antibodies showed reduced cognitive and functional decline compared to control patients. Cognitive decline was reduced by 27% with Lecanemab and by 40% with Donanemab, but these results are not comparable because they use two different measurement scales for cognitive abilities in different populations. "Lecanemab Confirmatory Phase 3 Clarity AD Study Met Primary Endpoint, Showing Highly Statistically Significant Reduction of Clinical Decline in Large Global Clinical Study of 1,795 Participants with Early Alzheimer's Disease." https://media-us.eisai.com/2022-09-27-LECANEMAB-CONFIRMATORY-PHASE-3-CLARITY-AD-STUDY-MET-PRIMARY-ENDPOINT,-SHOWING-HIGHLY-STATISTICALLY-SIGNIFICANT-REDUCTION-OF-CLINICAL-DECLINE-IN-LARGE-GLOBAL-CLINICAL-STUDY-OF-1,795-PARTICIPANTS-WITH-EARLY-ALZHEIMERS-DISEASE and "Lilly's Donanemab Significantly Slowed Cognitive and Functional Decline in Phase 3 Study of Early Alzheimer's Disease | Eli Lilly and Company." https://investor.lilly.com/news-releases/news-release-details/lillys-donanemab-significantly-slowed-cognitive-and-functional.

[19] The definition of Alzheimer's disease has varied over time and remains heterogeneous from one country to another. In France, the diagnosis is based on clinical criteria (neuropsychological assessment, notably allowing an objective determination of memory loss) and the search for biological markers: amyloid peptides and Tau proteins from a sample of cerebrospinal fluid, or visualisation of senile plaques (amyloid peptides) in PET-scan imaging. Examination of MRI imaging also makes it possible to characterise cerebral atrophy and identify a possible vascular component. In the past, patients suffering from vascular dementia, for example, which may be independent of an amyloid pathology, have been included in clinical trials seeking to evaluate the effectiveness of antibodies targeting amyloid peptides.

[20] Patients included in the clinical trials presented either mild cognitive decline associated with Alzheimer's disease lesions or a mild form of Alzheimer's disease.

[21] Lecanemab targets protofibrillar forms of amyloid peptides. The study of the so-called Swedish mutation of Alzheimer's disease made it possible to identify this form, the most toxic of those adopted by Aβ peptides. As for donanemab, it targets the truncated forms of peptides, starting with a pyroglutamate. Leveraging the action of brain cells with this function, monoclonal antibodies developed against these different Aβ peptides help clean out senile plaques in the brain.

[22] Phase III trials report the occurrence of edema-type events (detected by MRI) in 13% of patients treated with lecanemab (the incidence of symptomatic events was less than 3% of patients) and 24% of patients treated with donanemab (including 6% symptomatic events), and microhaemorrhage type events in 17% of patients who received lecanemab (including only 0.7% symptomatic events), and in 31% of patients who received donanemab. With donanemab, only 1.6% events were severe. "Lecanemab Confirmatory Phase 3 Clarity AD Study Met Primary Endpoint, Showing Highly Statistically Significant Reduction of Clinical Decline in Large Global Clinical Study of 1,795 Participants with Early Alzheimer's Disease." https://media-us.eisai.com/2022-09-27-LECANEMAB-CONFIRMATORY-PHASE-3-CLARITY-AD-STUDY-MET-PRIMARY-

ENDPOINT,-SHOWING-HIGHLY-STATISTICALLY-SIGNIFICANT-REDUCTION-OF-CLINICAL-DECLINE-IN-LARGE-GLOBAL-CLINICAL-STUDY-OF-1,795-PARTICIPANTS-WITH-EARLY-ALZHEIMERS-DISEASE and "Lilly's Donanemab Significantly Slowed Cognitive and Functional Decline in Phase 3 Study of Early Alzheimer's Disease | Eli Lilly and Company." https://investor.lilly.com/news-releases/news-release-details/lillys-donanemab-significantly-slowed-cognitive-and-functional.

[23] These events may be linked to the frequent deposition of amyloid peptides in the walls of blood vessels. The action of the antibodies then weakens these vessels. The presence of amyloid deposits in the lining of cerebral blood vessels is called cerebral amyloid angiopathy; it is very common in elderly people suffering from Alzheimer's disease. Raposo, Nicolas, et al. "Angiopathie Amyloïde Cérébrale: avancées récentes et perspectives." Bulletin de l'Académie Nationale de Médecine 205, no. 2 (1 February 2021): 180-91. https://doi.org/10.1016/j.banm.2020.12.005.

[24] Results of a patient consultation requested by the European Medicines Agency's Committee for Medicinal Products for Human Use, distributed by Alzheimer Europe to European patients.

[25] Adapted physical activity - popular in Parkinson's disease and multiple sclerosis - is however not reimbursed by Assurance Maladie (Public Health Insurance). It may sometimes be reimbursed by local governments, pension funds or mutual insurers. Interventions by speech therapists and physiotherapists can be covered by social security in the context of a long-term illness (LTI) The same applies for interventions by occupational therapists and psychologists for multiple sclerosis, and by psychomotor therapists for Alzheimer's disease.

Description of the activities and services covered for the corresponding LTI:

- 15 - Alzheimer's disease and other types of dementia: https://www.has-sante.fr/upload/docs/application/pdf/2009-07/lap_alzheimer_finale_web_juin2009.pdf
- 16 - Parkinson's disease: https://www.has-sante.fr/upload/docs/application/pdf/syndromes_parkinsoniens_liste_actes_presta.pdf
- 25 - Multiple sclerosis : https://www.has-sante.fr/upload/docs/application/pdf/lap_ald_25_sep_actualisation.pdf

[26] Such as connected watches or pill boxes, remote alarms, etc.

[27] Such as software, video games, virtual reality, etc.

[28] For this reason they remain little known to families and caregivers, though they are essential to learning about these tools and their proper use. Assistive Technology Lending Library initiatives are to be welcomed, but they are still too few in number. The EqLAAT (Local assistive technology support teams), organised by the National Solidarity Fund for Autonomy, could play a role in the spread of assistive technologies helpful in the everyday life of patients suffering from neurodegenerative diseases. See the report on recent progress in disability management technologies prepared by Member of the National Assembly Huguette Tiegna on behalf of Opecst (2022): https://www.assemblee-nationale.fr/dyn/15/rapports/ots/l15b5145_rapport-information, https://www.senat.fr/rap/r21-561/r21-561.html.

[29] The risk factors differ depending on age: first, education level plays the primary role; then it is hearing problems, hypertension or head injuries; and over the age of 60, smoking, depression and social isolation are preponderant. Livingston, Gill, et al. "Dementia Prevention, Intervention, and Care: 2020 Report of the Lancet Commission." The Lancet 396, no. 10248 (8 August 2020): 413-46. https://doi.org/10.1016/S0140-6736(20)30367-6.

[30] Ngandu, Tiia, et al. "A 2-Year Multidomain Intervention of Diet, Exercise, Cognitive Training, and Vascular Risk Monitoring versus Control to Prevent Cognitive Decline in at-Risk Elderly People (FINGER): A Randomised Controlled Trial." The Lancet 385, no. 9984 (6 June 2015): 2255-63. https://doi.org/10.1016/S0140-6736(15)60461-5.

[31] Meditation helps specifically target emotional risk factors such as depression, stress and anxiety. Lutz, Antoine, et al. "The Protective Effect of Mindfulness and Compassion Meditation Practices on Aging: Hypotheses, Models and Experimental Implementation." Ageing Research Reviews 72 (1 December 2021): 101495. https://doi.org/10.1016/j.arr.2021.101495.

[32] As discussed below on page 4 in the paragraph "Difficulties associated with the organisation of care ," Alzheimer's disease in particular is often subject to delayed diagnosis. Several factors contribute to this, including lack of treatment, lack of access to care, and lack of time and knowledge among general practitioners – particularly among older generations. Patient associations refer for instance to Landes, a French region that would appear very little affected by Alzheimer's disease, which they say is an aberration linked to a grievous lack of neurologists in the region. Delayed diagnosis is a problem because it can lead to iatrogenics (adverse effects of treatments, occurring, for example, in patients who no longer remember whether or not they had already taken medications prescribed to them for another pathology), accidents on the road or at home, and problems managing personal finances.

[33] Practitioners look for the Aβ amyloid peptides that make up senile plaques – specifically, Aβ40 and Aβ42 peptides – as well as total Tau protein and Tau protein phosphorylated at position 181 (P-Tau181). When a lumbar puncture is contraindicated, a PET-scan imaging examination can be performed, which allows the amyloid plaques to be observed.

[34] It is important for precautions to be taken in advance of routine clinical use, in particular regarding the definition of thresholds distinguishing normal and pathological values, since plasma concentrations of Aβ and Tau peptides exhibit greater interindividual variability than concentrations in cerebrospinal fluid, particularly in connection with the patient's renal function. Actors in the diagnostics sector are still cautious: the small difference between the plasma concentration of Aβ peptides in healthy subjects and that in patients does not make it possible to guarantee sufficient diagnostic quality, so some companies have stopped working toward the development of a routine diagnostic for these peptides. In any case, the diagnosis of Alzheimer's disease, in the short and medium term, will certainly continue to be based on a triad of cognitive tests, imaging and biomarkers; the search for blood biomarkers should be restricted to a role of diagnostic testing for orientation purposes only.

[35] Indeed, nearly a third of people over the age of 70 have amyloid deposits and no symptoms. The study cited below found that 28% of people over 70 years old had amyloid deposits, but did not show symptoms as a result. After 2.5 years of follow-up, less than 5% presented symptoms, and these presented aggravating risk factors (their cognitive scores were lower at inclusion in the trial, and 3 out of 4 were carriers of the APOE ε4 allele, known to be a risk factor for the disease). Dubois, Bruno, et al. "Cognitive and Neuroimaging Features and Brain β-Amyloidosis in Individuals at Risk of Alzheimer's Disease (INSIGHT-PreAD): A Longitudinal Observational Study." The Lancet. Neurology 17, no. 4 (April 2018): 335-46. https://doi.org/10.1016/S1474-4422(18)30029-2.

[36] This hypothesis is currently being tested for the two immunotherapies that have shown effectiveness in patients with mild symptoms of Alzheimer's disease. The two clinical trials now underway (a and b) are being conducted in patients with normal cognitive functions but who present a biomarker (Tau or Aβ) suggesting lesions due to Alzheimer's disease. The arrival of other new neuroprotective treatments could increase the interest of such screening.

(a)Eisai Inc. "AHEAD 3-45 Study: A Study to Evaluate Efficacy and Safety of Treatment With Lecanemab in Participants with Preclinical Alzheimer's Disease and Elevated Amyloid and Aaso in Participants with Early Preclinical Alzheimer's Disease and Intermediate Amyloid." Clinical trial registration. clinicaltrials.gov, 17 April 2023. https://clinicaltrials.gov/ct2/show/NCT04468659

(b)Eli Lilly and Company. "A Study of Donanemab versus Placebo in Participants at Risk for Cognitive and Functional Decline of Alzheimer's Disease." Clinical trial registration. clinicaltrials.gov, 16 May 2023. https://clinicaltrials.gov/ct2/show/NCT05026866

[37] Neurofilaments are used routinely in the context of multiple sclerosis or strokes ; GFAP markers, associated with astrocytes - non-nervous cells of the brain - provide information on inflammation status ; or synaptic markers, which provide a clear reflection of cognitive symptoms, insofar as they are affected by the loss of these neuronal communication structures. Advances in blood biomarkers whether specific to Alzheimer's disease or otherwise have greatly benefited from work carried out using large French patient cohorts, such as Memento and Baltazar.

[38] Notably, in Parkinson's disease, the detection of misfolded α-synuclein is a delicate matter and is not possible in routine clinical tests. Progress has nevertheless been made in the identification of markers that can be used in PET-scan imaging for better characterisation of the disease and a better understanding of the pathological mechanisms.

[39] https://joliot.cea.fr/drf/joliot/Pages/Actualites/actualites/actualites_scientifiques/2018/Ultrasons-acces-medicaments-cerveau.aspx

[40] Near-infrared light stimulation has the effect of stimulating the mitochondria in neurons, the "power plants" of these cells. Restoring normal energy levels helps protect neurons against death by apoptosis; near-infrared light thus may have a neuroprotective effect. Moro, Cécile, et al. "Photobiomodulation inside the Brain: A Novel Method of Applying near-Infrared Light Intracranially and its Impact on Dopaminergic Cell Survival in MPTP-Treated Mice." Journal of Neurosurgery 120, no. 3 (March 2014): 670-83. https://doi.org/10.3171/2013.9.JNS13423.

[41] Despite encouraging preclinical and clinical results, the development of gene therapy to combat the symptoms of Parkinson's disease has been halted. Bryson, Steve. "Development Halted on Parkinson's Therapy Candidate AXO-Lenti-PD," 2 February 2022, Parkinson's News Today. https://parkinsonsnewstoday.com/news/sio-gene-therapies-oxford-biomedica-therapy-candidate-axo-lenti-pd-parkinsons/.

[42] Opecst report on cloning, cell therapy and the therapeutic use of embryonic cells, prepared by Member of the National Assembly Alain Claeys and Senator Claude Huriet (February 2000); https://www.assemblee-nationale.fr/11/rap-off/i2198.asp, https://www.senat.fr/rap/r99-238-1/r99-238-1.html.

[43] Genchi, Angela, et al. "Neural Stem Cell Transplantation in Patients with Progressive Multiple Sclerosis: An Open-Label, Phase 1 Study." Nature Medicine 29, no. 1 (January 2023): 75-85. https://doi.org/10.1038/s41591-022-02097-3.

[44] For ethical reasons, stem cells of embryonic origin are subject to strict legislation. See the Opecst report on the evaluation of the implementation of law no. 2011-814 of 7 July 2011 on bioethics, prepared by Member of the National Assembly Jean-François Eliaou and Senator Annie Delmont-Koropoulis (2018); https://www.assemblee-nationale.fr/dyn/15/rapports/ots/l15b1351_rapport-information, https://www.senat.fr/notice-rapport/2018/r18-080-notice.html.

[45] Cerebroids or cerebral organoids are made up of cultured cells, differentiating into neural cells and agglomerating into a spherical structure; this has led to their being referred to as mini-brains.

[46] Organoids have benefited from the development of microfluidics. These mini organs can be installed on a microfluidic chip, where capillaries allow controlled irrigation by physiological solutions, and can even be nested within a network of mini organs. See also the Opecst report on the use of animals in research and alternatives to animal experimentation, prepared by Member of the National Assembly Cédric Villani and Senator Florence Lassarade (2019); https://www.assemblee-nationale.fr/dyn/15/rapports/ots/l15b1794_rapport-information, https://www.senat.fr/rap/r18-400/r18-400.html.

[47] Organoids can be grafted onto a genetically immunocompromised animal host, in order to grow the organoid in an environment more favorable than the culture medium and study its characteristics in the long term. This was recently done in rats, and the cerebroid was found to have established functional connections with the animal's brain. Jgamadze, Dennis, et al. "Structural and Functional Integration of Human Forebrain Organoids with the Injured Adult Rat Visual System." Cell Stem Cell 30, no. 2 (2 February 2023): 137-152.e7. https://doi.org/10.1016/j.stem.2023.01.004.

[48] Specialists are of the opinion that advanced practice nurses have a role to play in the care of patients with common neurodegenerative diseases. Their training, however, does not give enough attention to these diseases, addressed only as part of "stabilised chronic pathologies," which, moreover, does not include multiple sclerosis. Order of 18 July 2018 establishing the list of stabilised chronic pathologies provided under article R. 4301-2 of the Public Health Code; https://www.legifrance.gouv.fr/loda/id/JORFTEXT000037218197

[49] Though only 400,000 people are registered under ALD 15 in France (a), the country likely has at least 1.2 million people suffering from the disease (b). One manufacturer in the sector even estimates the number of people eligible for anti-amyloid immunotherapies at 2 million. This would be 1.65 million people living with mild cognitive impairment associated with the disease and just over 300,000 people living with Alzheimer's disease at a mild stage (c).

(a) CNAM. Numbers, prevalence and characteristics of persons treated for ALD30-31-32 under the General Social Security scheme in 2021, by ALD30-31-32 condition type and modality; https://assurance-maladie.ameli.fr/sites/default/files/2021_ald-prevalentes_serie-annuelle.xls.

(b) Ministry of Health Neurodegenerative Diseases Roadmap 2021 – 2022: https://sante.gouv.fr/IMG/pdf/plan_pmnd.pdf.

(c) Gabelle, Audrey, et al. "Forecasting the Prevalence of Alzheimer's Disease at Mild Cognitive Impairment and Mild Dementia Stages in France in 2022." The Journal of Prevention of Alzheimer's Disease 10, no. 2 (1 February 2023): 259-66. https://doi.org/10.14283/jpad.2023.22.

[50] This will also need to involve access to MRI imaging infrastructure to conduct examinations before and during treatment to monitor the appearance of adverse effects such as microhaemorrhages and cerebral oedema. It should be noted that intravenous treatment can be administered on an outpatient basis or even at home, as was authorised during the clinical trial conducted by Eisai, which took place during the Covid-19 health crisis. Specialists advocate for the treatment of willing patients at memory centre facilities, since they are accustomed to hosting such treatment, having participated in the clinical trials. Memory resources & research centres and memory consultation facilities perform diagnosis and provide therapeutic and medical-social care for Alzheimer's and related diseases throughout the country; https://www.centres-memoire.fr/presentation-de-la-federation-des-centres-memoires/.

[51] As highlighted as well by the National Academy of Medicine during the Opecst hearings on the financing and organisation of biohealth research (June 2021); https://www.assemblee-nationale.fr/dyn/15/rapports/ots/l15b4373_rapport-information, https://www.senat.fr/rap/r20-770/r20-7700.html.

[52] Since the positions of researchers and technicians recruited for research projects are contractual, it is impossible to keep teams together for more than 6 years, which leads to a loss of expertise and hampers the pursuit of long term research projects. The Research Planning Law introduced project-based indefinite employment contracts (CDI de mission), but this

does not seem to have resolved the problem of these positions' unattractiveness. The status of University Professor - Hospital Practitioner (PU-PH), which allows a hospital doctor to conduct research, is losing its attractiveness due to major constraints (in terms of working time, responsibilities and administrative burden) and a retirement determined on the basis of the university salary alone; https://www.le-shu.fr/recours-aupres-du-conseil-detat/.

[53] The delays in implementing collaborations with manufacturers, which are far too great, are often singled out as well. Inserm Transfert has also been criticised on this subject by the Court of Auditors (a). Stakeholders interviewed expressed hope that the new Health Innovation Agency would provide solutions, since one of its missions is to simplify procedures to stimulate innovation in healthcare.

(a)"Accounts and management of Inserm and Inserm Transfert | Court of Auditors", 23 January 2023. https://www.ccomptes.fr/fr/publications/les-comptes-et-la-gestion-de-linserm-et-dinserm-transfert.

[54] It would in particular be impossible at this time to conduct clinical trials in persons with a mutation that condemns them to developing a neurogenetic disease while they have no symptoms, although early treatment could be key, as suggested by recent work conducted on Huntington's disease. French researchers have shown that correcting neuronal abnormalities caused by Huntington's disease (the symptoms of which are only observed in adults) in the first days of a mouse's life makes it possible to delay the appearance of symptoms. See "Huntington disease: restoring neuronal transmission at birth could prevent adult onset of the disease." Inserm press room, 22 September 2022. https://presse.inserm.fr/maladie-de-huntington-restaurer-la-transmission-neuronale-a-la-naissance-pourrait-prevenir-lapparition-de-la-maladie-a-lage-adulte/65676/ and Braz, Barbara Yael, et al. "Treating early postnatal circuit defect delays Huntington's disease onset and pathology in mice." Science 377, no. 6613 (23 September 2022): eabq5011. https://doi.org/10.1126/science.abq5011.

[55] The Computing and Civil Liberties law (a) applies to all clinical trial sponsors working with data from French patients. According to the researchers, French law is too restrictive compared to European law (b).

(a)Law No. 78-17 of January 6, 1978 on Information Technology, Data Files and Civil Liberties. https://www.legifrance.gouv.fr/loda/id/JORFTEXT000000886460

(b)Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (Text with EEA relevance), 119 OJ L § (2016). http://data.europa.eu/eli/reg/2016/679/oj/fra.

[56] This network is made up of themed research and clinical investigation networks, including one dedicated to multiple sclerosis, one to amyotrophic lateral sclerosis and one to Parkinson's disease; https://www.fcrin.org/infrastructure/organisation.

[57] A marketing authorisation request has been submitted to the European Medicines Agency for lecanemab (a). Eisai has already obtained an accelerated approval from the FDA (b), the United States health agency. While awaiting the decision of the European Medicines Agency, Eisai could make a request for early access from the National Health Authority to ensure the accelerated availability of the treatment for certain patients. Tofersen, an antisense oligonucleotide, has obtained a marketing authorisation from the FDA (c).

(a)Eisai Co., Ltd. "Marketing authorisation application for Lecanemab as treatment for early Alzheimer's disease accepted by European Medicines Agency | News Release：2023." https://www.eisai.com/news/2023/news202311.html

(b)"FDA Grants Accelerated Approval for Alzheimer's Disease Treatment." FDA. 1 June 2023. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment.

(c)"FDA Grants Accelerated Approval for QALSODY™ (Tofersen) for SOD1-ALS, a Major Scientific Advancement as the First Treatment to Target a Genetic Cause of ALS | Biogen." Accessed 1 June 2023. https://investors.biogen.com/news-releases/news-release-details/fda-grants-accelerated-approval-qalsodytm-tofersen-sod1-als.

[58] Steps will need to be taken to organise care for patients located at a distance from these specialised centres, and increase the total accommodation capacity of these centres to meet demand.