Neurology Future Forecasting Series

Diagnostics in 2035

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Author Contributions

Dr. Ciccarelli: Design of study, drafting of manuscript

Dr. Pandolfo: Design of study, revision of manuscript

Word Count: 3,982

Abstract word count: 98

Title character count: 19

Study funding: None

Disclosures

OC is Deputy Editor for Neurology, for which she received an honorarium.

MP has served as a consultant for Voyager Therapeutics, Chiesi Canada, Minoryx, Design Therapeutics and Exicure in the last 12 months. He is Deputy Editor for Neurology: Genetics, for which he received an honorarium.

Abstract

Innovations and advances in technologies over the last few years have yielded faster and wider diagnostic applications to patients with neurological diseases. This article focuses on the foreseeable developments of the diagnostic tools available to the neurologist in the next 15 years. We are convinced that clinical judgment is and will remain the cornerstone of the diagnostic process, even if assisted by novel technologies, such as artificial intelligence (AI) and machine learning. The future generations of neurologists must be educated to develop, cultivate and rely on their clinical skills, while becoming familiar with novel, often complex, assistive technologies.

Current State of Diagnostic Technologies

Assistive diagnostic technologies in medicine, and neurology in particular, are evolving at a fast pace. This review comprises a selection of those that are most influencing current clinical practice, and our forecasts for the future of neurologic diagnostics in 2035.

Genomics, epigenetics, transcriptomics and proteomics

Genomics

Next generation sequencing (NGS) technologies allow to rapidly sequence millions of base pairs of DNA[1]. NGS can be used to sequence the whole genome of an individual (whole genome sequencing, WGS) or specific portions of it, such as the exons of all protein-coding genes (whole exome sequencing, WES), of all genes known to be mutated in monogenic diseases (clinical exome), or just in a group of diseases (gene panels). NGS can also estimate the abundance of specific sequences by counting the number of reads they generate. This way, it can be used to detect amplified or deleted regions in the genome and to generate gene expression profiles by quantifying the number of copies of each RNA present in cells or tissues (RNAseq)[2]. Another use of NGS is the identification of the organisms present in a biosample by sequencing their genomes (metagenomics)[3].

Until a few years ago the diagnostic use of NGS was controversial because of technical and cost issues. NGS has since become more powerful, more reliable and cheaper, so it is now generally used for genetic diagnosis in advanced health care systems, mostly as gene panels, clinical exomes and WES. However, these approaches have limitations. First, the explored portion of the human genome is only about 0.25% for a clinical exome and 1% for WES. Then, some

mutation types, as disease-causing repeat expansions, are not efficiently sequenced and need to be separately tested when indicated. And even with optimal coverage, data interpretation may be challenging. When no previously reported mutation(s) are found, demonstrating pathogenicity of suspicious genetic variants is subject to strict criteria[4] that are often not attainable in a diagnostic context, so their status remains uncertain (Variants of Unknown Significance, VUS). For all these reasons, currently less than half of the cases of suspected monogenic diseases are solved by WES, even after re-analysis of data in the light of more recent advances[5].

In addition to neurogenetics, NGS has an expanding role in neuro-oncology, where classification of many brain tumors currently relies on genetic profiling[6]. In neuro-infectivology the identification of pathogens by metagenomics[3] is an emerging approach, though still limited to specialized centers.

Epigenetics

Epigenetics explores the processes determining whether a gene is active, at what level, in what cells, at what time, in response to what stimuli. In addition to DNA methylation and of post-translational modifications of histones that determine binding of transcription-activating and repressive factors, the roles of non-coding RNAs, chromosomal architectures and gene position in the nucleus are emerging as major epigenetic mechanisms[7]. Though the study of disease-associated epigenetic changes is still mostly a research subject, tests for specific changes in DNA methylation are already being used in neuro-oncology[8] and for the diagnosis of some rare genetic diseases[9].

Transcriptomics and proteomics

Transcriptomics and proteomics are large-scale analyses of the RNAs and proteins contained in biological samples. Technologies have evolved in transcriptomics from hybridization microarrays to RNAseq, and in proteomics from 2-D gels to sophisticated mass spectrometry approaches[10]. These studies, by identifying disease-linked profiles of proteins and RNA expression, provide potential diagnostic, prognostic, and treatment response biomarkers. Some have already entered clinical practice, as levels of beta amyloid, tau and phosphorylated tau protein in biofluids to support the diagnosis of Alzheimer disease (AD) and other dementias[11]. Others, as levels of neurofilament proteins, in particular neurofilament light chain (NfL), in CSF and blood, are moving into the clinical space as neurodegeneration markers, though further research is needed to establish their power and reliability[12]. The need for ultra-sensitive assays for some of these markers, still very expensive and demanding specialized expertise, is a limitation.

Imaging

Radiology has quickly moved from X-ray films to digital image acquisition, which is currently the standard for all types of diagnostic imaging, including angiography, computed tomography and magnetic resonance imaging (MRI). This innovation has led to faster acquisitions, thereby reducing motion artifacts and improving image quality. Further advancements in computing technology have led to more accurate diagnoses and better patient care.

Magnetic Resonance Imaging and initial applications of Artificial Intelligence (AI)

One of the most important MRI advances has been the ability to go beyond the assessment of structure in order to map the function of brain regions, which has led to important applications, such as preoperative localization of motor and language cortices for neurosurgery. Advanced imaging techniques, including diffusion-weighted imaging, when interpreted with perfusion imaging, allow the detection of mismatch between infarction and hypoperfusion, thereby estimating the presence of salvageable ischemic tissue and guiding the selection of patients who may benefit from endovascular reperfusion[13]. Alongside these advancements, we have witnessed a widespread use of PET/MRI from presurgical assessment to diagnosis of neurological disorders (e.g., AD, PD and epilepsy).

At the same time as increased digitization of the information contained in the medical images, AI methods have become available outside computer science centers. These have led to the growing field of radiomics, which is an approach aiming to use AI to extract textural features from images, through analysis of spatial distribution of signal intensities and relationships between pixels, mostly applied to neuro-oncology[14]. The application of radiomics to clinical MRI scans have allowed the identification of thresholds for quantitative values, which lead to diagnosis of neurological diseases, especially in uncertain cases; for example, thresholds for hippocampal volume help the diagnosis of dementia[15], and those for hippocampal volume and T2 signal the diagnosis of hippocampal sclerosis[16].

The analysis of radiomic features using AI can be used to support clinical decision-making. An AI system, which was constructed to support the differential diagnosis of common and rare disorders (e.g., toxic leukoencephalopathy), approached neuroradiologists' diagnostic performance. Additionally, AI has been used to identify new disease subtypes, based on the evolution of abnormalities on MRI scans, which can be used to stratify patients for interventional trials and to monitor treatment response.

Research into AI-based computer-aided systems for the diagnosis of neurological disorders, using not only brain MRI, but also physiological images and EEG, has grown over the last few years[17], and has the potential of assisting clinicians in making the correct diagnosis. However, the sample size of AI studies is often small, and the reproducibility of radiomics studies is often poor, indicating the need for larger databases and externally validated algorithms.

There have been many applications of machine learning (ML), which is a subset of AI, to MRI for imaging analysis tasks, such as lesion segmentation in traumatic brain injuries, brain tumors, ischemic stroke and MS[18]. The main advantage of these applications is that the data are analyzed automatically, thus saving investigators' time and improving interpretive accuracy. However, only a small proportion of imaging studies using ML have evaluated their algorithm on external datasets. ML applied to large amount of data captured from soft wearable sensors can automatically detect neurological symptoms and then inform clinicians about the progression of diseases, such as PD[19] and MS[20]. Therefore, the use of ML to extract information on neurological functions among independent-living neurology patients has the potential to complement clinical assessment to monitor disability progression.

Deep learning (DL) is a subset of ML and is able to handle large data sets using its multilayer architecture, which is inspired by the human brain. The advantage of deep learning is that it allows avoiding subjective decisions about which features are important; however, it requires more training data, which is a limitation, for example in medical imaging. The application of DL to MRI scans has led to the prediction of chronological age[23], which is the first step towards distinguishing healthy ageing from the early stages of neurological diseases. Interestingly, a convolutional neural network, which is a deep learning algorithm, applied to a large database of conventional MRI scans of healthy persons, has detected different aspects of the ageing brain, and identified healthy and unhealthy ageing[21]. This approach can lead to recognition of early manifestations of neurological diseases, which may guide early treatment initiation. Data-driven deep learning models have been used with MRI scans to re-define disease subgroups on the basis of the development of MRI abnormalities over time in patients with MS[22] or describe the propagation of pathology in MS, AD and normal ageing[23].

The rise of data-driven biomedicine

Medicine is being transformed by the exponential growth in radiological, genetic, molecular, biometric, and chemical data being collected via a burgeoning array of technologies, mobile sensors and medical devices. This has paralleled the development of deep learning, where its application to biomedical data has led to improved understanding of how genetic variation affects cellular processes and prediction of pathology on the basis of imaging data[24].

A combination of images, demographic and clinical data, and "omics" data have been used in applications of AI to neurological diseases, more often to help diagnosis or prognosis, rather than to optimize treatment. Recent efforts have been aimed at predicting individual patient response to therapy; for example, high-dimensional models based on routine MRI scans can enhance the detection of MRI response to therapies in MS[25] and in stroke[26].

However, the application of AI to health care data has gone beyond the area of diagnosis, prognosis, monitoring and treatment optimization, and it has started to involve many operational aspects of hospital care, such as prediction of attendance for scheduled appointments, which may lead to selective and cost-effective interventions aimed to improve hospital attendance[27].

Forecasted Developments: the most likely innovations

Genomics, epigenomics, transcriptomics, proteomics

By 2035 WGS should be widely available, possibly via emerging technologies such as nanopore sequencing[28], already successfully used in neurogenetics to detect mutations that escape WES, such as intronic expansions in adult familial myoclonic epilepsy[29]. These powerful technologies will allow to detect pathogenic variants in non-coding elements, in non-coding RNAs and their targets, and RNA modifications. Advanced bioinformatic tools will support data analysis, using ML and AI[30]. Much deeper knowledge of human genetic variability, essential for interpreting genomics data, is expected as large numbers of WGS from individuals of different ethnicities will be stored in public databases.

Epigenomics, in addition to genome-wide and locus-specific data on DNA and histone modifications, will be coupled with transcriptomics and proteomics to obtain an integrated picture of the genetic, gene regulation and gene expression profile of an individual, with diagnostic and prognostic implications in domains as neuro-oncology[31], neurodegenerative diseases[32], and stroke[33]. Importantly, and following already existing trends, findings in non- or minimally invasively accessible biosamples, "liquid biopsies"[34] will be used to infer pathological processes occurring in the brain, whose characterization will then be completed with advanced structural, functional and metabolic imaging.

Imaging and artificial intelligence applications

Forecast developments include the wider use of novel, low-field scanners that are portable and compatible with ferromagnetic materials. This will increase use of brain MRI examinations at the bedside, even in complex clinical care settings, thereby overcoming the issue of limited access to timely MRI in intensive care units[35]. This achievement will increase the number of point-of-care examinations and holds promise as a more inclusive and efficient technology. However, it is expected that these highly portable, cloud-enabled MRI scanners will lead to new ethical, legal and social issues, such as privacy concerns and reliance on cloud-based AI for data analysis[36].

Reduced scan times, reduced scanning noise, and improved image quality will improve patients' experience and accessibility, while increasing the accuracy of the diagnosis. Shorter time in the

scanner will improve the financial and operational aspects of the MRI centers. New technology will allow running several protocols simultaneously, thereby leading to time savings.

Operational whole-body human 7T ultra-high MR units, currently available in less than 100 centers worldwide, will increase in number and geographical distribution. They will be used in routine clinical settings and will be associated with improved confidence of neurological diagnoses, mainly because of their high spatial resolution and contrast. The applications of 7T MR imaging to the work-up of neurovascular diseases in the neurosurgical setting will also increase.

We expect further developments in big data and data mining, leading to algorithms that will automatically analyze images, supply radiologists with clinically relevant measures contextualized with normative data and generate more consistent reporting across levels of radiologist experience[15]. This new framework will result in more accurate diagnoses and reduced inequalities in MRI reports between centers; this, in turn, could lead to a more 'scattered' expertise, since even the most challenging diagnosis and prognosis could be made in small and non-academic centres. However, the use of imaging assessment tools to assist MRI reporting will be widely used in the clinical setting only if they are integrated into the clinical reporting workflow, and this is more likely to be achieved in academic, large centres, thereby leading to a more centralized knowledge (and medicine).

Data-driven biomedicine

AI, and in particular DL, will be integrated seamlessly into a health management system. DL is the most promising technology for intelligently incorporating huge amounts of data, and

modelling complex systems with clinically relevant measures, contextualized with normative data.

What will be the use of these approaches in neurological diagnosis?

The power to diagnose monogenic disorders will be increased by access to WGS and -omics data to support the potential pathogenicity of identified variants. Platforms for efficient functional testing of VUS in model systems may be available in reference centers. The delay between symptoms onset and diagnosis, which in 2021 may still be substantial, will be greatly reduced. In addition, the use of high-throughput genomics for neonatal screening of genetic diseases will allow pre-symptomatic diagnosis of later-onset disorders, a necessary step for the implementation of preventive therapies currently under (mostly) pre-clinical or clinical development.

Genomics, epigenomics and biomarker profiling will provide early specific diagnoses of common multifactorial diseases. The identification and functional characterization of a large number of predisposing variants, common and rare, will improve understanding of biology underlying risk of diseases, improving therapeutic development as well as personalized screening strategies on large scales[37]. As an example, polygenic risk scores (PRS) that estimate the overall effect of many genetic variants on an individual's phenotype[38,39] will likely become a standard assessment.

Extensive availability of -omics data from large clinical cohorts will identify sex differences that modulate the effect of genetic variants and responses to treatment, bringing to maturity an area that is currently at a relatively early stage of development.

In imaging, radiomics will be accessible and integrated in the routine clinical practice to improve diagnosis, prognosis, and treatment prediction. For example, radiomics will be used routinely in patients with brain tumors to extract information from routine imaging data, and, in combination with molecular markers and genomics, will predict response to surgery or prognosis. The correlation of imaging features with genetic, mutational and expression patterns (radiogenomics) will be used to monitor tumor evolution over the course of treatment, thereby leading to improved patient management and treatment optimization.

The use of genomic data in combination with imaging data, and any other biomarker contributing to define the profile of the disease at the individual level, will help to predict treatment response and susceptibility to side and toxic effects, leading to the choice of the most effective and safest therapy for each patient, achieving true precision medicine.

We expect that the framework able to facilitate diagnosis of neurological disorders may not be widely available in non-specialized health care centers. Therefore, it is possible that patient data, such as MRI scans, are going to be transmitted to a cloud-based computer-assisted system that will run the AI models. The results of the models may be sent to the mobile device of the clinician for a preliminary diagnosis, together with the probability of error associated with such diagnosis and advice on the next step.

Implications: developments which affect the practice of neurology

Practice changes

These diagnostic developments will affect the nosology of neurological diseases, leading to redefinition or refinement of diagnostic entities and the introduction of new ones. While this has been happening since the start of modern medicine, new challenges relate to the faster pace of change, combined with the need for understanding and interpreting data obtained with complex technologies and modeling algorithms.

All subspecialties will be affected. For example, in epilepsy, decision algorithms will be fed by multiple data sources for improved diagnosis as well as for treatment selection and outcome assessment. These will include devices and wearables for automated seizure detection, clinical and electrical, using automated reporting and alarms, as well as automated detection of non-convulsive seizures in ICU based on EEG and other physiological parameters. Diagnosing specific syndromes and identifying underlying etiologies will be assisted by developments in imaging, with improved lesion detection, e.g. subtle cortical dysplasias, and the use of automated classifiers, as well as by advanced neurophysiology and -omics data. This will require an increasing involvement of multidisciplinary teams in the diagnostic process, including imaging, genomics, engineering and IT specialists, but the overall coordination will remain the responsibility of the neurologist, who must have the necessary competencies to fruitfully interact with the whole team.

Advanced practice providers (APPs) in their position at the interface between the specialized medical team and the patient will become more and more relevant in this landscape, so it will be essential for them to acquire knowledge about diagnostic advances and data interpretation as well as the necessary communication skills to communicate with patients about these issues.

Furthermore, it is likely that the direct availability to the public of diagnostic services such as medical images, genome data, diagnostic tests, risks of side effects and treatment response, will continue to expand. Neurologists have to prepare to confront with this issue, assuring that findings are properly interpreted and contextualized and providing advice in the best interest of patients.

Education

Training and continuing medical education (CME) programs will need to include new knowledge required by these practice changes. Neurologists will need to gain sufficient familiarity with diagnostic, data analysis and interpretation technologies to act as informed advanced users.

Learning and retaining basic clinical skills will remain essential. Neurologists will be able to use these advances properly only if they retain their traditional skills in obtaining an accurate history and detecting abnormalities on face-to-face, hands-on neurological examinations. This will also be necessary for the appropriate interpretation of complex diagnostic datasets, which although supported by machine learning and AI approaches, will eventually still rely on clinical judgment. As mentioned above, changes in the definition, description and diagnostic criteria of disease entities will continue to change, imposing regular updates.

The diagnostic process is not limited to giving a name to a disease and obtaining patient-specific information to select a personalized treatment. Equally important is the assessment of the effect of the disease state on a patient's well-being and functionality, and what is most important for both patient and provider to address. This aspect will remain entrusted to the

neurologists' competence, experience and empathy, which cannot be replaced by any type of AI or machine learning algorithm.

Economic consequences

Any advanced diagnostic requires general, affordable access to influence practice beyond highly specialized centers. Experience tells us that the cost of new technologies may be prohibitively high initially, but as the technology matures and diffuses its cost goes down. NGS and advanced imaging techniques are recent examples. However, the delay between initial development and generalized application takes years, during which access is limited and unequal. Furthermore, direct costs are just part of the overall cost of these technologies, as they often require specific infrastructure and, even more important, the diffusion of specific competences via training and continuing education programs, again creating a gap between the most advanced and the bulk of health care providers. This will likely be a continuing issue both within health care systems and on a global scale. Different systems also have different reactivities, and different ways to assess, accept and accommodate these changes. Eventually, a balance needs to be struck between the cost of new technologies and their benefits in terms of increased patient well-being and of savings in other areas, such as ending unnecessary, expensive investigations.

Planning for the Future

There are long-term uncertainties that need to be addressed. It is important to start planning for the acquisition of competencies and partnerships needed for the practice changes that have been discussed above. Training programs must adapt to the evolving scenarios and do it in a coordinated manner. Providing tools and resources to promote exchanges and collaboration

among training programs directors. Professional societies like the AAN and the European Academy of Neurology (EAN) play a key role in this regard, so they must continue and expand these activities. Professional societies also have a fundamental role in reducing inequalities by their continuing engagement to affect public policy and health care reform. Individual engagement of every practitioner is equally necessary for translating stellar advances in science into better practice and better health for all, avoiding dystopic scenarios of exploding inequalities.

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