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Review article

Precision neurology

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ABSTRACT

Over the past several decades, high-resolution brain imaging, blood and cerebrospinal fluid analyses, and other advanced technologies have changed diagnosis from an exercise depending primarily on the history and physical examination to a computer- and online resource-aided process that relies on larger and larger quantities of data. In addition, randomized controlled trials (RCT) at a population level have led to many new drugs and devices to treat neurological disease, including disease-modifying therapies. We are now at a crossroads. Combinatorially profound increases in data about individuals has led to an alternative to population-based RCTs. Genotyping and comprehensive "deep" phenotyping can sort individuals into smaller groups, enabling precise medical decisions at a personal level. In neurology, precision medicine that includes prediction, prevention and personalization requires that genomic and phenomic information further incorporate imaging and behavioral data. In this article, we review the genomic, phenomic, and computational aspects of precision medicine for neurology. After defining biological markers, we discuss some applications of these "-omic" and neuroimaging measures, and then outline the role of computation and ultimately brain simulation. We conclude the article with a discussion of the relation between precision medicine and value-based care.

1. Introduction

With our increasing knowledge about individual differences in human biology, it has become apparent that scientific medicine (Osler, 1902) is in the midst of a radical new evolution. During the first evolutionary period, scientific truths and the clinical-pathological method changed the way we perceived neurological disease and the opportunities for treatment. We are now entering a second evolutionary period during which major new technologies are helping refine the generalities about biology and behavior that were discovered in the first wave. In neurology, we have learned through functional and structural brain imaging that although there are commonalities to brain organization across individuals, there are also marked differences, and these differences can be considered when developing prognoses and treatments for diseases. The normal human brain differs across individuals at all levels of description, from macroscopic to microscopic and in between (mesoscopic) (Freeman, 2000), and disease processes increase these differences. Also affecting susceptibility to disease and treatments are the profound individual differences in genome and epigenome, proteome and metabolome, and microbiome.

As we learn more and more about these differences across all aspects of individuals, the more we can use them to personalize care for each patient at a more quantitative and "precise" level than ever before. Certainly, personalization is not completely new. Indeed, Hippocrates is said to have stated that "it's far more important to know what person the disease has than what disease the person has" (Abrahams and Silver, 2010). The excitement that exists now reflects the dramatic increase in quantitative personalized information combined with the ability to process it with high performance computers. Indeed, with such precise personalized data about the brain, spinal cord, and peripheral nervous system, we are in an era of "precision neurology".

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2. Personalized medicine

2.1. Overview

The term "precision medicine" has a number of synonyms, including "personalized medicine" and "individualized medicine", and does not have a single universally agreed-upon definition. The first use of any of these terms decried the waning of the personal touch in medicine (Gibson, 1971). Their first use to characterize the contemporary notion appears to have occurred in 1979 in a Chinese journal discussing acupuncture (Wei, 1979). In fact, whereas later uses of the term have emphasized genomics, this earlier article focused on electrical signals. Since 2006, more than 25,000 articles have been indexed in Medline that include the phrase "personalized medicine".

Many of the current concepts of precision medicine focus on the ancient dichotomy of nature and nurture: The National Institutes of Health called precision medicine an "emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person" (National Library of Medicine, 2017). A systems biology perspective emphasizes predictive, personalized, preventive, and participatory (P4) medicine (Hood and Friend, 2011; Sagner et al., 2017). In the body of this paper, we will survey these initiatives in neurology.

3. Biomarkers and disease markers

3.1. Disease markers

Disease markers are measurements related to an individual that either alone or in some multivariate combinations can predict the outcome of a disease. These measures can be biological, behavioral, environmental, or otherwise. One of the first uses of the concept came in an early paper on aging, in which it was stated that such a marker would, "in the absence of disease, better predict functional capability at some late age than will chronological age" (Baker et al., 1988). Such markers have been conceived as surrogate end points for clinical trials. In pulmonary hypertension, one early surrogate marker was the distance walked in six minutes (Kawut and Palevsky, 2004). Clearly, this functional deficit is neither specific nor unique as a cause of the disease: If a patient with the disease develops a second or third process that affects the same function, e.g., infection, fatigue, its value as a surrogate measure erodes.

3.2. Biomarkers

A special type of disease marker has a close anatomical and/or physiological relationship to the disease process, and ideally, is causally involved in disease pathophysiology (Sharon et al., 2010). Such "biomarkers" are critical to the development of a true precision neurology. Since biomarkers have an integral causal relationship with a disease process *per se*, they can be used as surrogate measures of outcome, progression, or treatment efficacy and will reflect the nature of the underlying biology.

Specifically, biomarkers are biological measurements (e.g., blood, cerebrospinal fluid, genome) that relate in a predictable and regular biological manner to the progression of a disease and/or the outcome of an intervention for that disease. In this way, biomarkers are disease markers with specific physiological meaning that can be used both as surrogates for the disease and as tools for discovery of novel interventions. Thus, whereas all biomarkers are disease markers, the reverse is not true.

The value of such biomarkers as surrogate measures of therapeutic effectiveness in clinical trials has been appreciated for at least two decades, as has concern about their validation and interpretation (Katz, 2004). Ultimately these robust biological markers are uniquely suited to choosing therapies in a highly personal way based on specific biological characteristics of individual patients.

The most traditional form of biomarker is the human genome, where genotypes are known to respond differently to certain interventions than others. A vast array of other personalized information obtained through "deep phenotyping" (e.g., (Misiak et al., 2023; Tang et al., 2022; Xu et al., 2022)) can now be used to complement the genome for precision medicine. For neurology, the concept of biomarker expands the pathophysiological underpinnings from the microscopic – cellular and molecular function — to the mesoscopic (e.g., local field potentials) and the macroscopic (e.g., structural and functional networks).

3.3. Clinical trials

In addition to their role as surrogate outcome measures, biomarkers have a crucial role in the overall design of clinical trials. It is increasingly clear that individuals with neurological diseases are complex and different from each other, and that the significant heterogeneity across participants in traditional clinical trials has been underestimated (Duan et al., 2024), leading to "costly trials with high failure rates" (Krainc et al., 2023). By using genomic and phenomic biomarkers that have physiological validity, a new era of clinical trials is emerging that creates groups of patients who share similar characteristics ("stratification") and evaluates therapeutic efficacy at a subgroup level. By using "deep genotyping" and "deep phenotyping", with biomarkers that have an essential causal relationship with the disease process, such stratification will ultimately lead to data on personalized therapeutic efficacy.

The vastly increasing array of disease biomarkers is leading to rapid evolution of clinical trials. Innovative trial designs, such as "master trials" (Woodcock and LaVange, 2017), which include "basket", "umbrella", and "platform" trial designs, recruit patients in carefully characterized groups based on molecular, genetic, or immunologic features, and evaluate one or more equally characterized treatments that have causal relationships with the target (Fountzilas et al., 2022; Park et al., 2020). Particularly important for investigations in rare neurological diseases are "N-of-1" studies — randomized, controlled, multiple crossover trials in a single patient that are also built on the causality between patient and target biology (Fountzilas et al., 2022; Müller et al., 2021). Many additional innovative approaches are in development. For example, the "Max Impact" design selects a particular population based on biomarkers, and then aims to "optimize population impact once the trial is completed" (Zhao and LeBlanc, 2019). The explanatory power of such stratified clinical trials will make statistical inferences far more precise (Abdelnour et al., 2022; Jogia et al., 2021; Seif et al., 2019).

One caveat to the implementation of these selective trials relates to equity. To the extent possible, it is important to attend to both biomarker-positive and biomarker-negative groups, i.e., if a meaningful — if not maximal — benefit is possible in the biomarker-negative patients, then it would be ideal to create a more stratified experiential design to determine more precisely the group(s) that might benefit (Polley et al., 2019). These advanced efforts in precision clinical trials are already being aided by artificial intelligence and machine learning, particularly with respect to subject recruitment, simulation of interventions, and management of novel biomarker-based designs (Miller et al., 2023).

In summary, new trial designs across medicine aim to use predictive biomarkers to characterize patients sensitive to specific targeted therapies (Polley et al., 2019), with important benefits for personalized health. The results of such trials in neurodegeneration, neuro-oncology, rare diseases, epilepsy, stroke, and related diseases will empower precision neurology.

4. -Omics in precision neurology

4.1. Genomics

The most discussed biomarkers are in the realm of genes, their

expression (transcriptomics), products (proteomes), and modifications (epigenomes) (Han et al., 2014). Overall, genomic analysis has played the most significant role in the diagnosis and treatment of brain tumors but is playing an increasing role in a number of neurological diseases.

4.2. Neuro-oncology (Brain Tumors)

In neuro-oncology, the emphasis has been on molecular biomarkers, with particular attention to the most virulent and least treatable brain tumor, the grade 4 astrocytoma, or glioblastoma (GBM), a molecularly heterogeneous tumor with a generally poor prognosis (median survival of ~15 months for patients who enroll in clinical trials) (Stupp et al., 2009).

As one of the first cancers to be profiled in the NIH Cancer Genome Atlas, GBM is one of the most molecularly profiled of all human cancers (Cancer Genome Atlas Research, 2008), and this has led to discovery of a number of molecular features that could be targeted in the development of novel treatments (Weathers and Gilbert, 2017). Unfortunately, these molecular features are not static within a particular tumor and undergo spatiotemporal evolution (Kim et al., 2015). Despite the spatiotemporal changes, recent progress has led to certain biomarkers having a role in helping choose among initial treatment options (Weller et al., 2012).

Perhaps the earliest and most successful example is methylation of the O-methylguanine methyltransferase gene, which predicts response to alkylating agents (Weller et al., 2010), and is the most widely used existing molecular biomarker (Holdhoff et al., 2012). Although most clinical neuro-oncologists believe in the promise of personalized neurology for glioblastoma, and despite significant advances in the characterization of GBM genomics, biomarker-based targeted efforts have shown minimal efficacy in clinical trials (Prados et al., 2015).

4.3. Epilepsy

More than half of all epilepsies have been identified as having a genetic origin, some of which have been associated with single gene defects in ion channels or neurotransmitter receptors (Striano and Minassian, 2020). These rare monogenic epilepsies, which account for only 5 % of all cases, are amenable to genetic testing and precision treatment (Ellis et al., 2020; Thakran et al., 2020), including CRISPR-Cas9 gene editing performed in model systems (e.g., Zebrafish, induced pluripotent stems) and then used for drug screening (Demarest and Brooks-Kayal, 2018).

On the other hand, even though as many as 70 % of the most common types of epilepsy (Fisher, 2017) have a genetic component (Myers and Mefford, 2015), they typically have complex inheritance with multiple genetic variants that are modulated by environmental factors, making precision care not yet viable (Thakran et al., 2020). However, another way in which precision neurology impacts epilepsy care involves the extremely common presence of adverse effects of treatments. For example, pharmacogenetic screening can prevent serious adverse side effects (e.g., Stevens-Johnson syndrome) in patients with certain HLA proteins, by avoiding carbamazepine (Walker et al., 2015).

4.4. Traumatic brain injury

Traumatic brain injury (TBI) is highly prevalent (Frost et al., 2013) and can lead to long-term effects in physical, cognitive, behavioral, and emotional functioning (Mostert et al., 2022), even in mild cases (Giza and Kutcher, 2014). Individuals who experience TBI can have markedly different long-term consequences (Dean et al., 2012), with similar head impacts causing markedly different outcomes (Reddi et al., 2022). Having a genetic basis for this difference could help inform individualized treatments and prognosis (Carmichael et al., 2021; Reddi et al., 2022).

Several single nucleotide polymorphisms (SNPs) have been evaluated with limited success. The presence of the apo-ε4 allele, known to be a risk factor for the development of Alzheimer Disease (Neu et al., 2017), seems to be a risk factor for poor outcome in severe TBI, and possibly for increased symptomatology in moderate (Chamelian et al., 2004; Merritt et al., 2018) and mild TBI (Merritt and Arnett, 2016).

Individuals with two Val alleles (homozygotes) in the gene coding for brain-derived neurotrophic factor (BDNF) are less likely to have long-term psychological symptoms than those carrying a Met allele (Gabrys et al., 2019; Wang et al., 2018).

4.5. Parkinson disease

Some patients with Parkinson Disease (PD) have a definite hereditary basis to their disease (Brüggemann and Klein, 2019), and a number PD risks genes have been identified (Bandres-Ciga et al., 2020). This suggests the possibility that clinical trials might benefit from stratification of subgroups by genetic criteria (Gasser, 2016; Schneider and Alcalay, 2020). Two important PD risk genes are those encoding the enzymes leucine-rich repeat kinase 2 (LRRK2) and glucocerebrosidase (GBA) (von Linstow et al., 2020). There is significant hope that GBA-associated and LRRK2-associated PD will be amenable to personalized therapy, with a number of ongoing studies (Schneider et al., 2020). However, the vast majority Parkinson disease (PD) cases are idiopathic (Troisi et al., 2019), and thus require other types of disease markers to permit therapeutic personalization.

4.6. Metabolomics

For some neurological diseases, including Parkinson Disease, biological markers can be identified in metabolic products that are produced as a direct consequence of disease pathogenesis or as co-occurring manifestations. The field of metabolomics involves the high-throughput identification and quantification of these small molecule metabolites (molecular weight < 1.5 kDa), and, when possible, linking them to disease biology (D'Alessandro et al., 2012; German et al., 2005; Wishart, 2007). As with all "-omics", metabolomics rely on complex computational analysis to make multivariate statistical inferences, i.e., to determine which combinations of metabolites relate to the biological consequences in question. In neurology, metabolomics — including lipidomics — are playing an increasingly important role in precision medicine for neurodegenerative diseases.

4.6.1. Parkinson disease

With Parkinson Disease most often considered multifactorial in origin, PD was an early candidate for developing metabolomic markers for precision medicine. To capture the interplay between genetic predispositions ("nature") and environmental experiences ("nurture"), it has been suggested that the metabolome is ideal, as it is thought to reflect the interaction between genes and the environment (Dunn et al., 2011; Greuel et al., 2020; Troisi et al., 2019).

Given that the metabolic pathways in Parkinson Disease remain unknown, investigation of PD employs untargeted (rather than targeted) metabolomics (Manier et al., 2019). In this method, advanced statistical analysis is used to compare the patterns of spectroscopic peaks that occur between two or more investigated groups, e.g., one group with PD and another without (Worley and Powers, 2013). The earliest untargeted metabolomic studies in PD were not particularly revealing and were inconsistent, possibly due to different methods and/or patient characteristics (Lei and Powers, 2013). More recent studies are stratifying patients more precisely and/or correlating metabolic differences with phenotypes, such as disease stage (Luan et al., 2015; Trezzi et al., 2017; Troisi et al., 2019), drug treatment (LeWitt et al., 2017), motor progression (Roede et al., 2013), and cognitive ability (Dong et al., 2021; Han et al., 2017).

4.6.2. Alzheimer disease

It is widely believed that the onset of Alzheimer Disease (AD) begins

as many as twenty years before the appearance of symptoms (Hunsberger et al., 2020; Reiman et al., 2012), and early treatment may be the critical factor for efficacy of novel agents (Dubois et al., 2016; Gauthier, 2005; Sperling et al., 2013). Early detection of AD has emphasized brain imaging of the neuropathological hallmarks of disease, but there has also been considerable effort on metabolic changes in cognitively impaired individuals that may be diagnostic of AD neuropathology. It has been pointed out that neuroimaging, metabolomics, and genetics can be used synergistically ("multi-omics") to characterize disease progression on an individual basis (Badhwar et al., 2020). One early untargeted metabolomic study in AD demonstrated lower plasma levels of serotonin, phenylalanine, proline, lysine, phosphatidylcholine, taurine and acylcarnitine in individuals who converted from amnestic MCI to AD compared to those who did not (Mapstone et al., 2014). Subsequent untargeted (Sun et al., 2020) and targeted (Huo et al., 2020; van der Velpen et al., 2019) metabolomic studies have implicated various metabolites in AD pathogenesis.

4.6.3. Other dementias and traumatic brain injury

Metabolomic studies are just getting underway in several other neurodegenerative dementias, such as Lewy body disease (Luchsinger and Zetterberg, 2020) and Frontotemporal dementia (FTD) (Swift et al., 2021), with one goal being able to distinguish the different neurodegenerative dementias from each other. In the case of FTD, the goal is to identify primary tauopathies or TDP-43 proteinopathies, with promising biofluid elements such as neurofilament light chain (NfL), progranulin, and dipeptide repeat proteins (Swift et al., 2021). In TBI, there has been a paucity of research thus far on "-omics" (Zeiler et al., 2021). The extreme heterogeneity of TBI (Kabadi and Faden, 2014) enhances the potential value of personalized approaches (Abu Hamdeh et al., 2021).

4.7. Microbiomics

More than half the cells and 99 % of the unique genes found in our bodies are from micro-organisms, many of which reside in the gut (Tremlett et al., 2017). In 1907, Élie Metchnikoff postulated a role for colonic bacteria in the pathogenesis of human disease, including neurological disease (Durgan et al., 2019; Metchnikoff, 1907; Podolsky, 2012). These gut microbes are now known to influence host metabolism through secretory elements, e.g., immune factors (cytokines, chemokine), and on the brain through vagus nerve input and/or through neurotransmitters and metabolites that cross the blood brain barrier (BBB) (Adamantidis, 2022; Giridharan et al., 2022). Further, the microbiome has emerged as a key regulator of brain development and the modulation of behaviors (Benakis et al., 2020), including formation of the BBB, myelination, neurogenesis, and microglia maturation (Sharon et al., 2016).

The most actively studied brain-gut interactions have been in the context of neurodegenerative disease (Tremlett et al., 2017), particularly PD (Pavan et al., 2022; Wallen et al., 2021) and AD (Jiang et al., 2017; Seo and Holtzman, 2020), but also in multiple sclerosis (Bhargava and Mowry, 2014; Mirza et al., 2020; Preiningerova et al., 2022), stroke (Tan et al., 2020), TBI (Urban et al., 2020), ALS (Nicholson et al., 2021), epilepsy (Cui et al., 2021; Ding et al., 2021; Fusco et al., 2022), migraine (Kang et al., 2022), and neuropathic pain (Chen et al., 2021). Research in this area has used microbiome characteristics as a precision biomarker for disease risk, activity, progression (Tremlett et al., 2017), or therapy (Josephson and Wiebe, 2020), or to alter the microbiome itself as a therapeutic tool (Seo et al., 2019; Winek et al., 2016).

4.7.1. Neurodegenerative diseases

In Parkinson Disease, it is increasingly recognized that constipation and other gastrointestinal symptoms are common in early or prodromal PD and can arise much earlier than motor manifestations (Klingelhoefer and Reichmann, 2017; Stirpe et al., 2016). The enteric nervous system (ENS) is significantly affected in PD (Pfeiffer, 2018), with autopsy studies of patients with PD showing enteric α-synuclein (αSyn) aggregates (Elfil et al., 2020). It is thought that an altered gut microbiome (Shen et al., 2021; van Laar, 2019) may play a role in PD pathogenesis (Braak et al., 2006; Cersosimo and Benarroch, 2008), with some dysfunction in the gut-brain axis leading to misfolding of α-synuclein in the ENS (Bu et al., 2016; Mayer et al., 2015; Rhee et al., 2009; Shannon et al., 2012), contributing to disease progression (Minato et al., 2017).

In Alzheimer Disease, the taxonomic groups of bacteria are different from that of healthy controls (Vogt et al., 2017; Wang et al., 2022b), with lower numbers of short-chain fatty acids producing microbes correlating with increased amyloid and p-tau (Verhaar et al., 2021). Other neurodegenerative diseases, including Huntington's Disease and amyotrophic lateral sclerosis (ALS) are also affected by the microbiome (Tremlett et al., 2017).

4.7.2. Other neurological diseases

The microbiome has also been implicated in pathogenesis (Esmaeil Amini et al., 2020) and progression of multiple sclerosis (MS) and neuromyelitis optica (NMO), possibly by its interaction with the immune system (Bhargava and Mowry, 2014). Some patients with MS have differences in their microbiome compared to controls (Navarro-López et al., 2022; Yadav et al., 2022), and these differences may be altered with therapy (Jangi et al., 2016).

Patients with epilepsy also have an altered microbiome (Cui et al., 2021; Şafak et al., 2020), and it is possible to use this as a predictive biomarker (Cui et al., 2021). The ketogenic diet has benefits for children (Lyons et al., 2020; Martin-McGill et al., 2020) and adults with epilepsy (Klein et al., 2010), perhaps by modulating inflammation and/or changing the composition of the gut microbiome (Pietrzak et al., 2022).

In stroke, gastrointestinal problems are not uncommon, suggesting some potential role of the microbiome-gut–brain axis (Tan et al., 2020). Stroke in animals (Stanley et al., 2018) and humans (Xu et al., 2021) lead to an altered microbiome (Stanley et al., 2018), with changes in functional brain networks (Aswendt et al., 2021) and cognition (Wang et al., 2022a), and impacting recovery (Cirillo et al., 2020; Stanley et al., 2018; Xia et al., 2021). Patients with TBI (Urban et al., 2020) and chronic pain (Chen et al., 2021; Kang et al., 2022) also show microbiome changes.

4.8. Proteomics

Protein expression in the brain, cerebrospinal fluid, and other neural tissues tissue also have a biomarker role in neurology (Cookson, 2019).

4.8.1. Neurodegenerative diseases

Protein markers are definitional to the diagnosis of neurodegenerative diseases (Alzheimer, 1907; Alzheimer et al., 1995; Engelhardt, 2017; Lewy, 1912). Alzheimer Disease is diagnosed post-mortem (McKhann et al., 1984) by the presence of extracellular neuritic plaques composed of amyloid-β (Aβ) protein and intracellular neurofibrillary tangles containing (hyper-) phosphorylated tau protein (p-tau) (King et al., 2020; Zhang et al., 2021). The hallmark neuropathological feature of Parkinson Disease, the intracellular Lewy body (Lewy, 1912), contains the protein α-Synuclein (α-Syn) (Tofaris, 2022). PD is now considered the paradigmatic example of a "synucleinopathy", others of which include PD with dementia, dementia with Lewy bodies, and multiple system atrophy (MSA) (Koga et al., 2021).

A number of other neurodegenerative diseases are considered "tauopathies" and are marked neuropathological by the presence of one or more types of tau protein (Virgilio et al., 2022) that differ from those present in AD. These include ALS, FTD, progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) (Sengupta and Kayed, 2022). Most ALS and about half of FTD cases present with accumulation of transactive response DNA binding protein of 43 kDa (TDP-43) (McGurk et al., 2020).

With respect to precision medicine, the importance of these proteins

leads to the natural quest to find *in vivo* biomarkers for early detection and improved (stratified) clinical trials (Kovacs, 2016) and identification of targets for vaccination or therapeutic intervention (Valera et al., 2016).

Currently, β-amyloid and p-tau can be identified in brain imaging studies with positron emission tomography (PET) and with cerebrospinal fluid (CSF) measurement, with Aβ42 correlating well with 11C-PiB status, particularly with Aβ40 as a reference (Ehrenberg et al., 2020). Recent approaches focus on plasma proteins, including Aβ42/Aβ40, three species of p-tau (pTau181, pTau217, pTau231), neurofilament light (NfL), and glial fibrillary acidic protein (GFAP) (Brum et al., 2024), although at this time, PET measurements remain the standard (Bouteloup et al., 2024; Shi et al., 2021).

4.8.2. *Other neurological diseases*

Protein biomarkers are also present in other neurological diseases and sought out for use in prediction and stratification (Png et al., 2021). CSF measurement is used in MS (Sandi et al., 2022) to assess inflammation, cellular damage, and blood-brain-barrier integrity (Fitzner et al., 2015). In stroke, early work suggests that NMDA peptide and antibodies may be present in ischemic but not hemorrhagic stroke (Maestrini et al., 2016). Brain natriuretic peptide, matrix metalloproteinase-9, and D-dimer suggest the presence of ischemic rather than hemorrhage stroke (Misra et al., 2020), and GFAP seems to index hemorrhagic stroke (Bustamante et al., 2021; Maestrini et al., 2016; Misra et al., 2020). In mild TBI, many proteins have been explored as tentative biomarkers of injury, such as S100 calcium-binding protein B (S100β), neuronal Neuro-Specific Enolase (NSE), Ubiquitin C-terminal Hydrolase L1 (UCH-L1), NfL, and tau, in addition to GFAP (Zeiler et al., 2021; Zetterberg et al., 2013). Recent data from healthy athletes demonstrated increased salivary NfL but not S100β after significant head contact (Monroe et al., 2022).

5. Imaging in precision neurology

Besides the -omics, brain imaging represents the most important class of disease markers for clinical trials and precision medicine in neurology. Particularly valuable have been imaging of brain structure with high-resolution magnetic resonance imaging (MRI), task-dependent (fMRI) and resting state functional MRI (rs-fMRI), white matter imaging with isotropic or anisotropic diffusion weighted imaging (DWI), vascular imaging using computed tomography (CT) and MRI, and molecular techniques using PET and single photon emission computed tomography (SPECT). Electrophysiological techniques, such as electroencephalography (EEG) and magnetoencephalography (MEG) are also playing increasing roles as disease markers and biomarkers for individualizing treatment.

5.1. *Surrogate outcome measures*

The successes and failures of a number of recent clinical research efforts can be partly attributed to the use of brain imaging as surrogate outcome measures. These outcome measures are “surrogate” because they are faster, cheaper, and/or more reliable and consistent than assessments of the truly desired outcomes, i.e., neurological signs and symptoms.

The overall goal of surrogate imaging outcome measures is to find indices that are more reliable than clinical parameters, with lower intra-subject variability, thereby enabling clinical trials with lower sample sizes (Jack et al., 2003). The statistical value and valid use of such markers has been discussed in an influential paper by R. L. Prentice (> 1300 citations) that defined “a surrogate endpoint to be a response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint.” (Prentice, 1989).

5.2. *Imaging biomarkers*

5.2.1. *Multiple sclerosis*

Imaging has played a crucial role in the explosion of new therapies for multiple sclerosis in the past decade, with initial interest focusing on T2 weighted imaging, which was known from the earliest stages of MRI to show sensitivity to the plaques of MS (Ormerod et al., 1987). The volume of T2 hyperintensity (Elliott et al., 2019; Fisniku et al., 2008) and/or presence of a T2 hypointense rim (Cacciaguerra et al., 2023) have been particularly useful. The presence of active lesions in MS has relied on MRI scans conducted after the administration of glatiramer acetate (gadolinium), i.e., contrast-enhanced MRI (Michielsens et al., 1990).

An early study in relapsing-remitting multiple sclerosis suggested that a combination of (i) the number of new enhancing lesions on contrast-enhanced MRI and (ii) the percentage change in lesion volume on T2-weighted MRI was an effective biomarker (Sormani et al., 2002) and fulfilled the Prentice operational criteria for surrogacy (Prentice, 1989). In a recent article, Calabresi and colleagues (Calabresi et al., 2021) suggest that combining imaging with clinical and metabolic measures leads to better prediction and treatment monitoring than clinical measures alone.

5.2.2. *Parkinson disease*

PET or SPECT scanning with ligands specific for dopamine receptors (Thobois et al., 2001) can evaluate dopamine concentrations in the basal ganglia (Cummings et al., 2011), and this can be valuable in helping to confirm or refute a clinical diagnosis of idiopathic PD compared to other related disorders (Brücke et al., 2000), such as the “atypical Parkinson” syndromes PSP (Brooks, 1994; Whitwell et al., 2017), CBD (Klaffke et al., 2006), or MSA (Kaasinen et al., 2021). In hereditary PD, such imaging is a helpful adjunct to genetic testing for individualized intervention (Bu et al., 2016; Weingarten et al., 2015). Although imaging has not yet had success as surrogate endpoints for clinical trials in PD (McGhee et al., 2013; Morrish, 2003), a combination of such markers may ultimately have meet this need (Saeed et al., 2017; Saeed et al., 2020).

5.2.3. *Alzheimer disease*

Interest in imaging measures as surrogate outcome measures for AD clinical trials has been intense (Fox et al., 2000) because of the unreliability of clinical evaluations, which are marked by inter-individual variability (Devi and Scheltens, 2018), intra-individual performance variability (Gorus et al., 2008; Murtha et al., 2002), and heterogeneity of clinical progression (Devi and Scheltens, 2018). Unfortunately, from the early efforts to use structural markers of brain atrophy (Jack et al., 2003) until very recently, no surrogate measure was adequate for clinical trials (Growdon, 2001). This lack of surrogate biomarkers very likely impeded progress in drug discovery for AD (Beach, 2017; Cozachenco et al., 2023).

Nevertheless, progress in molecular imaging with PET has changed this situation, initially involving regional metabolic deficiencies measured with fluorodeoxyglucose (FDG) tracers (Hoffman et al., 1989), and now with Aβ imaging of neuritic (amyloid) plaques and p-tau imaging of neurofibrillary tangles (Wang et al., 2023). Imaging is now incorporated into the standard diagnostic criteria for AD (Jack et al., 2018; McKhann et al., 2011) and imaging outcome measures are now fundamental to clinical trials (Perneczky et al., 2024).

Pittsburgh Compound B (Klunk et al., 2004), a carbon-11 (^{11}C) ligand that binds to cortical areas containing β-amyloid, was the first specific radiotracer for AD, and remains the gold standard for Aβ imaging (Myburgh and Solingapuram Sai, 2024). Because ^{11}C has a short (20 min) half-life, its use requires an on-site cyclotron and experience in ^{11}C radiochemistry. The subsequent discovery (Choi et al., 2009) and FDA approval (SNM Newsline, 2012) of florbetapir, an ^{18}F ligand, followed by ^{18}F-florbetaben and ^{18}F-flutemetamol (Filippi et al., 2018) has

led to more widespread availability of Aβ imaging. Finally, the discovery and approval of the p-tau ligand ^{18}F-flortaucipir (Chien et al., 2013; Mattay et al., 2020; Schwarz et al., 2016) has significantly advanced *in vivo* diagnosis and treatment monitoring in AD (Tian et al., 2022; Wang et al., 2024), including staging via the Braak criteria (Braak and Braak, 1997; Naude et al., 2024).

Over the past several years, three monoclonal antibodies directed against aggregated forms of Aβ have been approved by the FDA, aducanumab, lecanemab, and donanemab (Rabinovici and La Joie, 2023). Both the lecanemab and donanemab trials relied heavily on imaging biomarkers, with entry criteria depending on proven Aβ on amyloid PET imaging and a secondary endpoint involving decreased amyloid burden (Sims et al., 2023; van Dyck et al., 2023). Studies are also examining whether the degree of PET Aβ and p-tau at entry affects clinical efficacy (Sims et al., 2023).

5.2.4. Other Neurological Diseases

Imaging has played a role in precision medicine for other neurological diseases as well, although not yet to the same extent as those for MS, AD, or PD. In epilepsy, for example, a number of efforts are underway to incorporate artificial intelligence (AI) to perform statistical inferences from brain images to distinguish individuals with epilepsy from those without, to lateralize (or localize even more precisely) seizure foci, and to make predictions about outcome in the context of different therapies (Sone and Beheshti, 2021; Yao et al., 2019). The use of "digital twins" (Acosta et al., 2022) for assessing therapeutic outcome in epilepsy will be discussed below in the context of The Virtual Brain (Jirsa et al., 2010).

Cerebrovascular disease is among the most common neurological diseases (Feigin et al., 2021; Tong et al., 2019), and the use of intravenous recombinant tissue plasminogen activator (rTPA) (Hacke et al., 1995) and intra-arterial thrombectomy for acute large vessel stroke (Berkhemer et al., 2015; Campbell et al., 2015; Goyal et al., 2015) has dramatically improved therapy in recent decades. Individualized brain imaging has been critical to these developments. CT and CT angiography (CTA) were used to select (and exclude) patients for the ESCAPE trial based on the nature of the lesion and presence of good collateralization (Goyal et al., 2015). Vessel imaging of any type (CTA, MR angiography, digital subtraction angiography (DSA)) was used to choose participants for MR-CLEAN (Berkhemer et al., 2015), and in EXTEND-IA, DSA was supplemented with CT perfusion imaging to demonstrate the presence of salvageable tissue (Campbell et al., 2015).

6. Computation and Precision Neurology

Computation has an overarching role in virtually all of precision neurology and can be viewed as one of the main contributors to its viability. The advent of high-performance computing (HPC) enables us to probe enormous sets of data and ask novel questions and seek out answers that would not previously been accessible (Bender, 2015). There are two aspects to computation in precision medicine: First is the processing and integration of large and complex sets of genomic and phenomic data (Yue and Dutta, 2022), including the network anatomy of the human brain ("connectome") (Sporns et al., 2005) and massive data sets obtained from devices and wearables (Chawla and Davis, 2013; Cobos Gil, 2019). Second is construction of predictive models (Hunter, 2016; Luo et al., 2020) and "digital twin" (Cen et al., 2023; Sen et al., 2024) and "virtual brain" simulations (Jirsa et al., 2010; Ritter et al., 2013).

6.1. Computation and -omics

The -omic disciplines discussed above all generate huge amounts of data that can only be processed with advanced computational methods (MacInnes, 2020). As sequencing and other biomarker technologies continue to improve, the sheer quantity of -omic data has led to computational challenges (Zhang and Liu, 2013) and to questions about reliability and reproducibility (Altmäe et al., 2014; Boertien et al., 2019; McKay et al., 2017). The most advanced precision neurology will require integration of multiple sources of -omics data (multi-omics) with data of many other types, leading to even greater needs for bioinformatics methodology and computing (Bhinder et al., 2021; Gujar et al., 2020; Karkossa et al., 2020; Katz, 2018; Li et al., 2022; Merelli et al., 2014; Prosperi et al., 2018).

6.2. Computation and brain imaging

Functional imaging using PET and MRI (fMRI) as well as high-resolution structural imaging of grey and white matter produce enormous multidimensional matrices of data. The elements of such a matrix (i.e., voxels) are often then processed into connected networks, which at the maximal scale involve the pairwise (or more) relations among millions of voxels. In reality, the voxels are often clustered, and hypotheses refine the number of relations, but the computational scale remains enormous.

6.3. Computation, measurement, and wearable sensors

Precision medicine is increasingly building on the collection of personal physiological data, and the proliferation of watches and other wearable devices that tout health benefits has been rapid and widespread. Given the sampling rate of most physiological data, e.g., EEG data at 16 kHz (Lei et al., 2022), there is no way to monitor and assess manually these enormous volumes of data by human inspection.

It is still the norm for patients with advanced smartwatches to have their pulse checked manually at the physician's office even when they could probably provide hundreds of readings over time. Using data from such "wearables" for prediction, prognosis, or clinical trial selection, for example, requires advanced computational methods, such as deep learning (Egger et al., 2022), which can introduce errors (Varga et al., 2020) or raise ethical concerns (Erickson et al., 2019). In PD, wearable devices can be used to assess both motor and non-motor symptoms in real time and can lead directly to interventions or can supplement other biomarker data (Bu et al., 2016). An Israeli start-up company is now marketing a device that uses radar technology to detect falls (Hrubý and Černý, 2023), and a Korean group has a wearable closed loop EEG system (Shin et al., 2022). In MS, wearable technology can collect large amounts of dynamic activity data with high resolution (Dillenseger et al., 2021). In stroke rehabilitation, wearable sensors help increase the amount (dose) of needed therapeutic practice and its monitoring by professionals (Burridge et al., 2017).

7. Computational brain simulation

7.1. Connectomes

Unique to precision medicine in neurology (and neurosurgery, psychiatry, and anesthesiology) is the organization of the human brain, which shares many features across individuals, but also has many points of differentiation, particularly in the unique set of white matter connections that link together the neuronal components (e.g., cortical regions, subcortical nuclei) of the central nervous system. These unique patterns of connectivity can be measured with diffusion weighted MRI (Behrens et al., 2003; Le Bihan et al., 2001), and with constantly improving tract tracing algorithms (Jeurissen et al., 2019) can be used to produce personalized structural "connectomes" (Gordon et al., 2017; Sporns et al., 2005), which can be used in multi-scale (i.e., cellular, local circuit, systemic) contributions to precision neurology.

7.2. The Virtual Brain

The development of quantitative integrative tools to take advantage

of "big data" for precision medicine is just beginning. One such effort, The Virtual Brain (TVB) (Jirsa et al., 2010; Sanz Leon et al., 2013; Sanz-Leon et al., 2015), is a computational neuroscience platform for simulating brain network function at multiple levels of description. TVB simulations are personalized based on unique individual connectomes, and link large-scale brain dynamics with biophysical parameters at the mesoscopic (local field) level. Many of the inferred biophysical parameters represent biomarkers of disease pathogenesis, and consequently targets for therapy. Although a nascent technology, and applied only experimentally in the clinical setting, TVB modeling has thus far been investigated in epilepsy, stroke, and Alzheimer Disease.

7.2.1. Epilepsy

The investigation of epilepsy was the first exploration of personalized medicine using TVB simulations and was chosen because of its inherent nature as a disease manifested by abnormal network dynamics (Jirsa et al., 2017). The first precision TVB model involved a 41 y.o. woman with bi-temporal complex partial epilepsy. Her digital twin, a "Virtual Epileptic Patient" model, was constructed based on her own phenotypic conditions, including structural brain connectivity assessed by diffusion weighted MRI, epileptogenic zone determined by extracranial EEG and direct intracranial recording (using nine focal stereotactic EEG electrodes), and structural abnormalities assessed with MRI. The resulting simulation demonstrated spatiotemporal seizure evolution closely aligned with the empirical data (Jirsa et al., 2017). With this proof of concept, personalized TVB models were constructed for 15 patients to simulate individual seizure propagation patterns and validated by comparing simulated EEG data to pre-surgical stereotactic EEG data (Proix et al., 2017). These data led to a clinical trial (EPINOV) to see if these "virtual epileptic patients" can improve localization of the epileptogenic zone in pre-surgical patients and improve outcome (Jirsa et al., 2023; Naddaf, 2023).

7.2.2. Stroke

A TVB study in stroke patients compared structural connectomics with dynamic TVB simulation to assess long term changes that might be therapeutic targets. Individuals with stroke and healthy controls differed in global efficiency (Falcon et al., 2015), with simulations showing that stroke alters local dynamics (indexed by long-range coupling) and decreases efficiency of the system (indexed by global efficiency) (Falcon et al., 2015). Furthermore, these biophysical parameters change with therapy (Falcon et al., 2016), with local excitatory coupling negatively correlated with motor outcome, and global coupling positively correlated with motor outcome. This led to the conclusion that poor recovery may be a consequence of more localized dynamics with increased local excitatory influences whereas better recovery relates to values closer to controls.

7.2.3. Alzheimer disease

The first TVB simulation work in neurodegenerative disease focused on Alzheimer Disease, comparing patients without symptoms, with amnestic MCI, and with probable AD, finding (i) a high correlation between simulation parameters and cognitive test data, and (ii) high variability among the patients in the amnestic MCI group than the other groups (Zimmermann et al., 2018). A follow-up study showed that simulation differences in local excitation/inhibition balance (i.e., hyperexcitation) correlated with PET evidence of β-amyloid deposition (Stefanovski et al., 2019).

In summary, the Virtual Brain and other computational simulation methods have enormous potential for prediction at the individualized level, and for use as model systems for examination of treatment efficacy at the personal level prior to potentially risky or ineffectual application in the individual. As such, these methods represent an important future for precision neurology.

8. Precision neurology and value-based care

One economic model for funding health care associates an amount of payment with an amount of administered care ("fee-for-service"), an approach used by health care systems around the world to varying degrees (Emanuel, 2020). Although these models, and the variations in between, differ in incentives, costs, and potential rewards for health systems and providers, they all index payment to volume, whether at the level of the individual service (e.g., EMG), event (e.g., acute stroke), disease (e.g., epilepsy), or the patient (e.g., health young adult, post-stroke senior with seizures).

Value-based care differs in that the relevant quotient is no longer costs per volume, but instead relates costs to "value", leading to reimbursement based on not just the number of units served but also on the "quality" of those units. For precision neurology, it will be necessary to assess quality and value at the individual level, rather than solely at the aggregate group level. For example, the population-based expected mortality does not help (much) to inform the expected mortality of a particular individual at a particular hospital at a particular time with a large vessel ischemic stroke, status epilepticus, or glioblastoma.

This is where value-based care and precision neurology intersect. For example, an individual with a particular genetic allele, e.g., val → met substitution in the single nucleotide polymorphism (SNP) for brain derived neurotropic factor (BDNF), might be predicted to have a more rapid stroke recovery than someone without (Kim et al., 2016; Liu et al., 2021). Likewise, someone with a genetic disease, such as Huntington's Disease (HD) or spinocerebellar ataxia 6 (SCA6), may have a wide range of poly-Q repeats, which relates directly to the degree of symptomatology. Thus, expected outcomes for certain individuals will be different from others, affecting assessment of quality and value, and impacting cost.

Value-based care is also entering the marketplace of drugs and procedures. In one scheme, the payer agrees to pay more for a drug if it works than if it doesn't. For example, a drug to treat epilepsy that reduces the frequency of recurrent seizures should keep these patients out of the hospital, thus reducing overall hospital costs for the bundled reimbursement for that diagnosis or that person-year. With precision neurology, individuals could be identified who should be treated with particular drugs or surgical interventions, and providers could choose the best therapies at the outset, reduce costs, and decrease expenses. In a value-based reimbursement setting, in which payer and payee share risk, both payer and payee benefit from this precision neurological approach.

9. Summary and conclusions

Neurological diagnosis and treatment will increasingly depend on detailed data-intense characterizations of individuals that will enable highly personalized care. Both nature and nurture determine disease risk, course, and response to treatment, and increasingly, we can measure the myriad components of each on a personal basis and apply them to neurological care. Using examples from a variety of neurological diseases, we have shown that the early efforts to quantify and use massive amounts of genomic and phenomic data are yielding incremental results, but that the field appears to be rapidly accelerating. We have also shown how computation is critical to this effort, and that in neurology, computational simulation of brain function plays a particularly unique and important complementary role to more biochemical phenomic information. Finally, we argue that the combination of precision neurology with value-based care will lead to an incredible future for neurological health.

Declaration of Competing Interest

None

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Data availability

No data was used for the research described in the article.

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