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EDITORIAL

Precision and translational neurology: From mechanistic insight to personalised care

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Neurological disorders are now the leading contributor to the global burden of disease. The Global Burden of Disease 2021 analysis estimated that 3.4 billion people, more than 40% of the world's population, were living with a neurological condition, with the greatest burden concentrated in low- and middle-income countries.[1] Historically, however, neurology has been characterised by considerable precision in anatomical localisation but limited therapeutic specificity. Diagnoses were syndromic and often confirmed only at autopsy, and therapies were largely symptomatic and applied uniformly to heterogeneous patient populations. Precision medicine offers a means of changing this paradigm.

Precision medicine is defined as the tailoring of prevention and treatment to individual variability in genes, environment, and lifestyle.[2] It shifts care from population averages to biologically defined subgroups, using molecular, imaging, and clinical data to match the right intervention to the right patient at the right time. This approach first gained clinical traction in oncology, where imatinib for *BCR::ABL1*-positive chronic myeloid leukaemia and trastuzumab for human epidermal growth factor receptor 2-positive breast cancer showed that targeting a defined molecular driver can transform outcomes.[3,4] Its foundations have since broadened, including large-scale sequencing, multi-omic profiling, biobanks linked to electronic health records, and advanced analytics, allowing disease to be classified by mechanism rather than by symptoms alone.

Neurology is now undergoing a similar transformation, driven by four enabling pillars that are moving the field beyond one-size-fits-all approaches: omics-driven diagnostics, gene- and cell-based therapies, digital health tools, and stratified clinical trial designs (Figure 1). These pillars inform an iterative translational continuum in which knowledge moves from discovery through validation and clinical trials to implementation in routine practice, centred on personalised patient care. Within this continuum, the transition from validation to clinical trials represents the translational "valley of death," where many promising neurological candidates fail. Reverse translation, in which clinical observations and real-world experience generate new hypotheses, closes the cycle.

Omics-driven diagnostics integrate genomic, transcriptomic, proteomic, and metabolomic data to resolve disease at the molecular level. Exome sequencing establishes a diagnosis in roughly one-third of individuals with neurodevelopmental disorders. It is now recommended as a first-tier test,[5] while proteomic profiling of cerebrospinal fluid is uncovering molecular subtypes within clinically uniform syndromes such as Alzheimer's disease.[6] Blood-based biomarkers are extending molecular diagnosis beyond specialist centres. For instance, plasma phosphorylated tau 217 distinguishes Alzheimer's disease from other neurodegenerative disorders with accuracy comparable to cerebrospinal fluid

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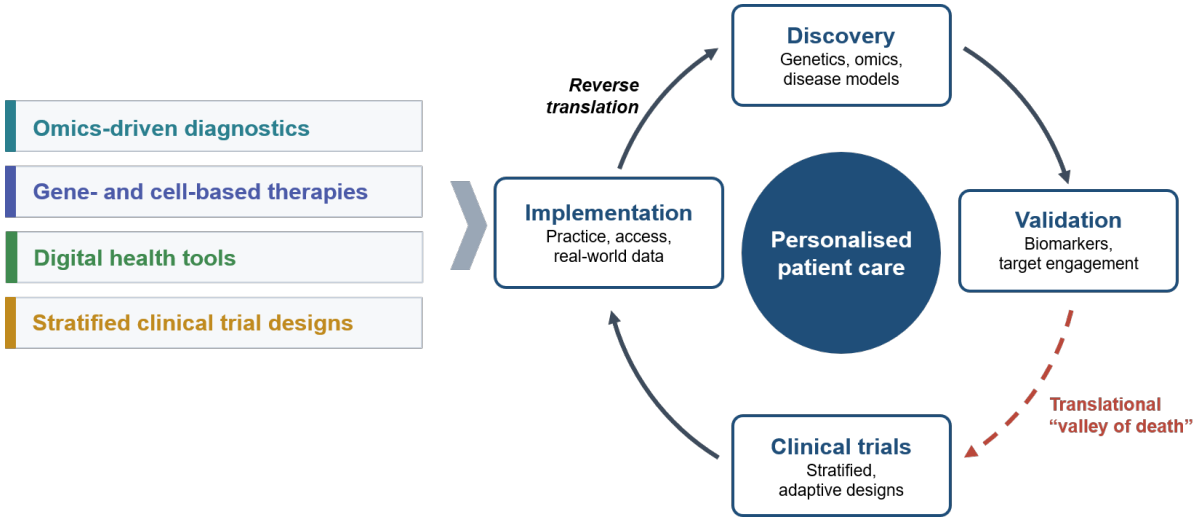


Figure 1. A framework for precision and translational neurology

and positron emission tomography measures.[7] Single-cell technologies are further resolving cell type–specific disease mechanisms and potential therapeutic targets.[8] In epilepsy, multi-omic approaches are beginning to bridge the gap between genotype and phenotype, although candidate biomarkers still require clinical validation.[9]

Gene- and cell-based therapies act directly on disease mechanisms. Viral-vector gene replacement, antisense oligonucleotides and RNA interference can restore deficient or silence pathogenic gene products.[10-12] Gene-replacement therapy has transformed the natural history of spinal muscular atrophy,[10] and RNA interference has produced disease-modifying effects in hereditary transthyretin amyloidosis with polyneuropathy.[11] In amyotrophic lateral sclerosis associated with superoxide dismutase 1 (*SOD1*) mutations, the antisense oligonucleotide tofersen did not meet its primary clinical endpoint but reduced cerebrospinal fluid SOD1 and plasma neurofilament light chain concentrations, a biomarker response that supported its accelerated approval by the United States Food and Drug Administration (FDA).[12] Cell-based approaches are also gaining traction in refractory neuroinflammatory disease. Autologous haematopoietic stem cell transplantation markedly reduced disability progression compared with continued disease-modifying therapy in relapsing-remitting multiple sclerosis.[13] Anti-B-cell maturation antigen chimeric antigen receptor T-cell therapy has shown encouraging early results in relapsing aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder.[14] Nevertheless, delivery across the blood–brain barrier, adequate distribution within the nervous system and immunogenicity remain critical constraints.

Digital health tools, from wearable sensors and smartphone-based assessments to remote monitoring and teleneurology, enable continuous, real-world measurement of symptoms that clinic visits capture only episodically.[15] Machine learning applied to imaging, electroencephalography, and electronic health records can support earlier detection and prognostication. For instance, an artificial intelligence model trained on more than 30,000 clinical electroencephalograms achieved diagnostic accuracy comparable to that of human experts in identifying and classifying abnormalities in independent test datasets.[16] Regulators have also begun to accept sensor-derived measures as trial endpoints: stride velocity 95th centile, captured by a wearable device, was the first such digital endpoint to be qualified by the European Medicines Agency (EMA) for use in Duchenne muscular dystrophy trials.[17]

Stratified clinical trial designs enrol participants according to molecular or biomarker profiles rather than clinical phenotype alone, and include biomarker-enriched, basket, umbrella, and platform trials, often conducted under a master protocol.[18] Umbrella trials evaluate several targeted therapies within a single disease, whereas basket trials test one targeted therapy across multiple diseases or disease subtypes that share a common molecular feature.[18] Platform trials extend the umbrella concept by running continuously, with investigational therapies added or discontinued over time according to prespecified decision rules.[18] These designs are increasingly complemented by pharmacometrics approaches that use pharmacokinetic–pharmacodynamic, exposure–response, and disease-progression models to integrate prior knowledge, inform

dose selection, optimise sample size and trial duration, and simulate trial outcomes before patients are enrolled.[19] In Alzheimer's disease, a model-based clinical trial simulation tool has been formally endorsed by the FDA and EMA.[20]

These advances share a common thread: each has depended on translation, the iterative movement of knowledge between laboratory, clinic, and population. Translation, however, remains the principal bottleneck. The gap between promising preclinical findings and approved therapies is especially wide in neurology, where limited blood–brain barrier penetration, slow and variable disease progression, and a shortage of validated surrogate endpoints conspire against success.[21] Precision and translational neurology are therefore not separate ambitions but two sides of the same endeavour: precision defines whom to treat, when, and with what, whereas translation determines whether those answers ever reach patients.

Closing this gap will require more predictive human models, such as induced pluripotent stem cell-derived neurons and brain organoids; experimental medicine studies that confirm target engagement in humans before large efficacy trials; and greater emphasis on reverse translation, whereby clinical observations feed back into discovery. Longitudinal open-science cohorts that share data, biosamples, and imaging, exemplified by the Parkinson's Progression Markers Initiative, together with public–private partnerships, demonstrate how pre-competitive collaboration can de-risk development.[22] Looking ahead, neurology is poised to shift from reactive to anticipatory care: identifying at-risk individuals with accessible blood-based biomarkers, intervening at preclinical stages, and monitoring response with digital measures and blood- or cerebrospinal fluid-based biomarkers. Realising this will require sustained collaboration among scientists, clinicians, patients, industry, regulators, and payers to ensure that the benefits of precision neurology reach patients wherever they live.

Conflict of interest

Kheng-Seang Lim is a member of the Editorial Board of this journal but was not involved, either directly or indirectly, in the editorial decision-making or peer-review process for this manuscript. The other author declares no conflict of interest.

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