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Editorial

Editorial: The Foundation and Architecture of Personalized & Precision Medicine (PPM) in Clinical Autoimmunity Conditions: Towards Neurodegenerative Disease-Modifying Treatment

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INTRODUCTION

A new systems approach to diseased states and wellness result in a new branch in the healthcare services, namely, ***personalized*** and ***precision medicine (PPM)***[1-4] (Figure 1).

Precision medicine identifies differences in individuals, categorizing based on environmental, biological, and psychosocial factors.

Personalized medicine takes these differences and implements preventions/treatments tailored to the individual [5].

Individualizing patient and/or person-at-risk treatment is a core objective of PPM. Reaching this objective has been elusive owing to the complex set of factors contributing to both disease, pre-illness conditions and health; many factors, from genes to proteins, remain unknown in their role in human physiology. Accurately diagnosing, monitoring, and treating disorders requires advances in biomarker discovery, the subsequent development of accurate signatures that correspond with dynamic disease states, as well as therapeutic interventions that can be continuously optimized and modulated for dose and drug selection. In this context, PPM-driven methods identify phenotypes of patients and/or persons-at-risk with less-common responses to treatment or unique healthcare needs. Meanwhile, bioinformatics leverages sophisticated computation and inference to generate insights, enables the system to reason and learn, and empowers clinician decision making through augmented intelligence.

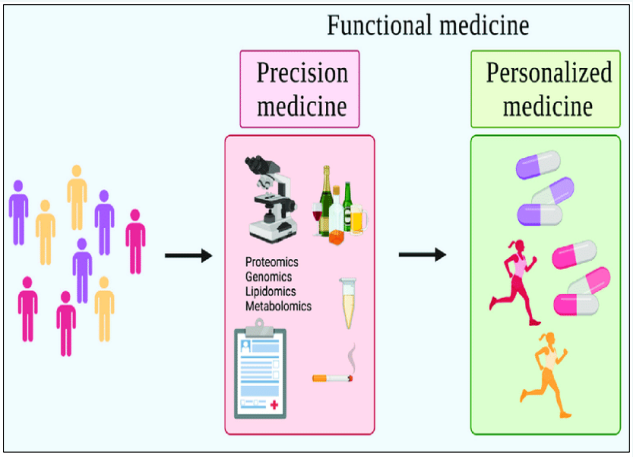

Figure 1 Precision & personalized medicine (PPM)

Individualizing patient and/or person-at-risk treatment is a core objective of PPM. Reaching this objective has been elusive owing to the complex set of factors contributing to both disease, pre-illness conditions and health; many factors, from genes to proteins, remain unknown in their role in human physiology. Accurately diagnosing, monitoring,

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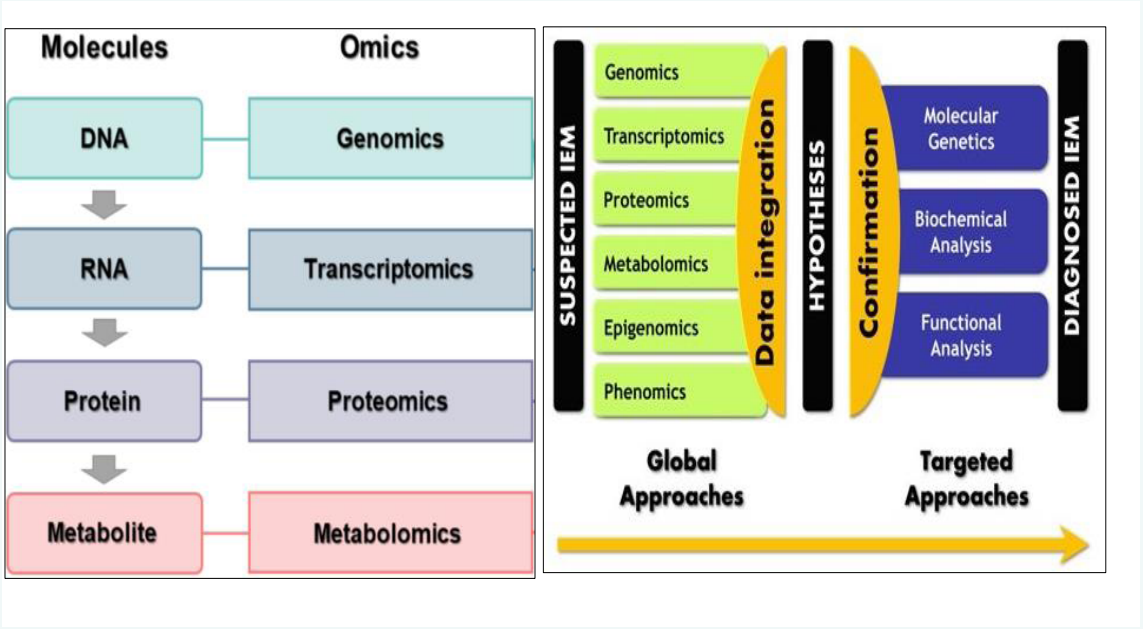

Figure 2A,B: OMICS Technology Development as applicable to Personalized & Precision Medicine

and treating disorders requires advances in biomarker discovery, the subsequent development of accurate signatures that correspond with dynamic disease states, as well as therapeutic interventions that can be continuously optimized and modulated for dose and drug selection. In this context, PPM-driven methods identify phenotypes of patients and/or persons-at-risk with less-common responses to treatment or unique healthcare needs. Meanwhile, bioinformatics leverages sophisticated computation and inference to generate insights, enables the system to reason and learn, and empowers clinician decision making through augmented intelligence.

To achieve the implementation of PPM concept, it is necessary to create a fundamentally new strategy based upon implementation of OMICS technologies (Figure 2A,B).

Multi-OMICS data are initially collected from patients and integrated to create their individual molecular profiles. These profiles are then matched to previously defined disease profiles that can guide the selection of treatment. This is achieved either through a match to known biomarkers, OMICS signatures or network/pathway signatures. OMICS technologies are enabling the simultaneous measurement of a huge number of biochemical entities, including genes, genes expressions, proteins, and metabolites. The appropriate drug is then selected based on this match, to improve the chance of successful treatment and reduce the probability of side effects. OMICS technologies have had a huge impact on the discovery of next-generation diagnostics, biomarkers, and drugs in the PPM-driven era. High-throughput OMICS technologies allow the retrieval of comprehensive and holistic biological information, whereas computational capabilities enable high-dimensional data modeling and, therefore, accessible and user-friendly visualization. Furthermore, bioinformatics has enabled comprehensive multi-OMICS and clinical data integration for insightful interpretation. With the advancement of the OMICS technologies, multi-OMICS research has emerged as one of the most promising venues for a deeper understanding of biological problems. Upgrading laboratory informatics infrastructures and a new medical workforce trained in biomedical big data management are necessary for the successful integration of OMICS-based strategies [6,7].

IT algorithms and bioanalytical platforms (Figure 3), and the recognition of biomarkers long before the disease clinically manifests itself.

PPM relies on advancements in OMICS technologies, as well as bioinformatics and data analysis, to identify bio markers that can help anticipate disease risk, diagnose conditions, and guide treatment decisions.

Molecular diagnostics is a collection of techniques to analyze the biomarkers in the genes and proteins of bilological entities. These techniques are used to diagnose and monitor disease, identify risk, suggest which therapies are most suitable for individual patients. The biomarkers are useful in clinical practice for: (i) diagnosing and predicting the risk of patient's diseases; (ii) identifying the signs of early-stage diseases from healthy human beings; (iii) deciding current treatment sufficient or not for the patients, and (iv) identifying specific target people who will help for a particular drug. To achieve PPM for each patient, the potential biomarkers need to be identified, verified and evaluated [8] (Figure 4A).

PPM is an emerging approach to healthcare that aims to optimize medical treatment by tailoring it to the specific characteristics of each patient, person-at-risk and/or healthy person. PPM is based on the idea that individuals differ in many aspects, including their genetics, phenotype, lifestyle, and environment, and that these differences can have a significant impact on disease development and response to treatment. Therefore, by taking into account these individual differences, PPM can help to identify the most effective treatment strategies for each patient (canonical treatment) and/or person-at-risk (preventive and prophylactic approaches) (Figure 4B) [9,10].

Neurological disorders are the leading cause of disability and the second leading cause of death worldwide. The rise in absolute numbers of people affected suggests that advances in prevention and management of major neurological disorders are not sufficiently effective to counter global demographic changes [11]. Meanwhile, technological development of PPM has paved the way for accelerated OMICS-driven discovery and is bringing PPM resources into a scope of applications in clinical neurology. The goal of PPM is to deliver optimally targeted and timed interventions tailored to an individual's molecular drivers of disease.

Neurodegenerative disorders (NDDs) are promisingly suited models for PPM because of the rapidly expanding genetic knowledge

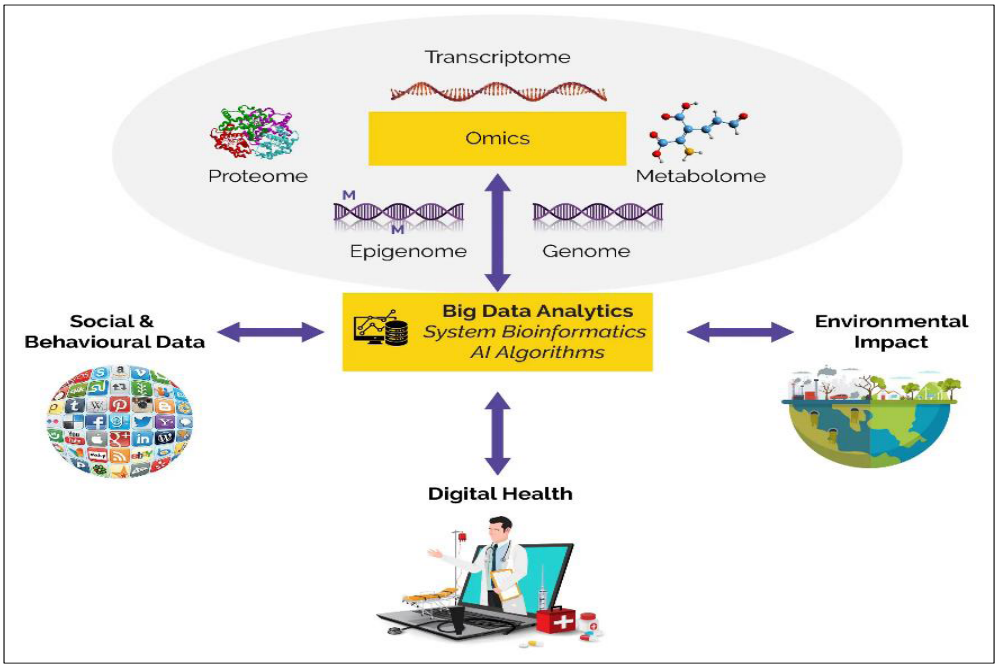

Figure 3: OMICS technologies, bioinformatics, IT-driven algorithms and datasets as principal tools of personalized & precision medicine (PPM)

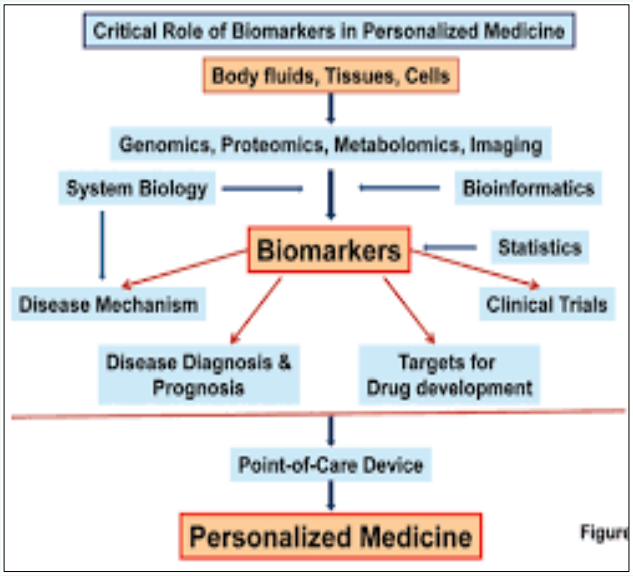

Figure 4A: The Role of Biomarker in Personalized & Precision Medicine (PPM)

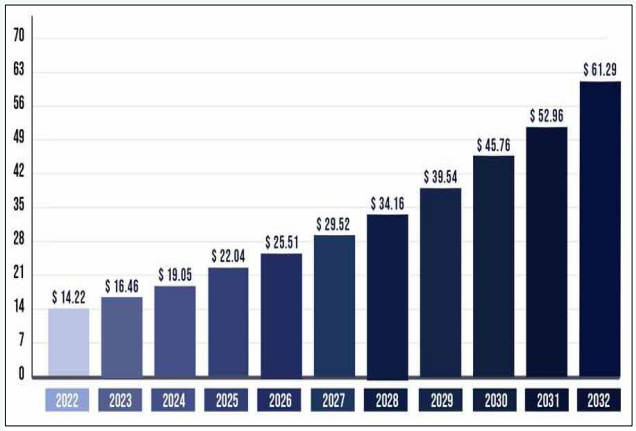

Figure 4B Personalized & Precision Medicine (PPM) Biomarker Market size in 2023-2032 (in US dollars)

base, phenotypic classification, the development of biomarkers and the potential modifying treatments. And the considerations make it clear that PPM could transform clinical care in the field of NDDs, and could lead to a new treatment framework for NDDs diseases [11-20].

The main goal of PPM is to deliver optimally targeted and timed interventions tailored to an individual's molecular drivers of disease. By understanding the unique characteristics of a patient's NDD-related condition, such as genetic predispositions, biomarkers, and disease mechanisms, PPM aims to optimize treatment outcomes and improve patient care. Taking a more precise, personalized approach to NDDs will give rise to a breadth of targeted drugs and therapies that can be effectively used in combination to treat specific NDD-related impairments that present uniquely in NDDs, including canonical patients and pre-illness persons-at-risk.

The NDD-related field has enjoyed extremely limited success in the development of effective therapeutics. Standard clinical trials have pre-determined a single treatment modality, which may be unrelated to the primary drivers of neurodegeneration [21,22].

The potential benefits of PPM in the area of NDDs are significant. By identifying biomarkers and disease subtypes, PPM can help to diagnose the disease earlier and more accurately, as well as predict disease

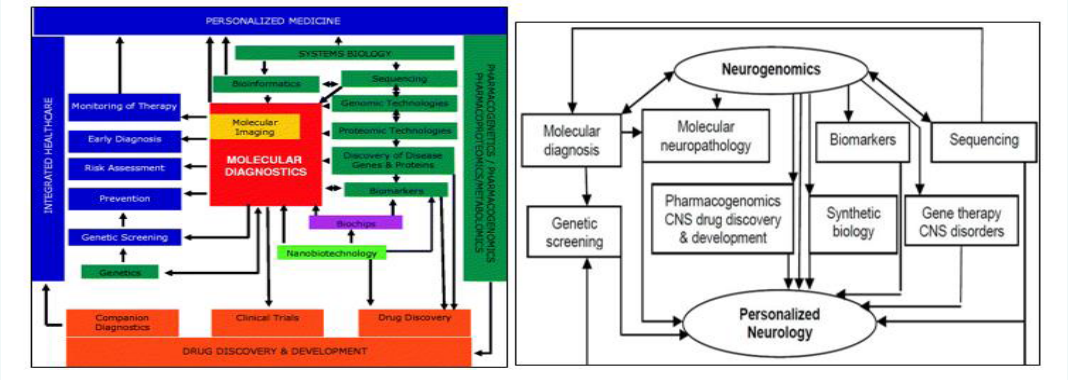

Figure 5A,B: Personalized & precision medicine (PPM) as applicable to neurology

course and response to treatment. Furthermore, by developing targeted therapies, PPM can improve treatment efficacy and reduce the risk of adverse effects (Figure 5A,B).

PPM-guided manipulations mean the prescription of specific treatments and therapeutics best suited for an individual taking into consideration both genetic and environmental factors that influence response to therapy. A PPM-guided approach will improve the management of NDDs. PPM-guided neurology stands at the threshold of a revolutionary transformation with the advent of PPM. Neurological diseases are promisingly suited models for precision medicine because of the rapidly expanding genetic knowledge base, phenotypic classification, the development of biomarkers and the potential modifying treatments. Moving forward, it is crucial that through these integrated research platforms to provide analysis both for accurate personal genome analysis and gene and drug discovery. The intricate tapestry of neurological disorders, long characterized by heterogeneity and complexity, is now being unraveled at the molecular level. By delving into the genetic underpinnings of NDDs, we uncover the potential for tailored interventions that promise not only to improve treatment outcomes but also to reshape our understanding of NDDs [23].

Precision diagnostics is a critical component of PPM in NDDs and is essential for the successful implementation of PPM in the field of NDDs. The identification of accurate and reliable biomarkers and imaging techniques can help to diagnose the disease earlier and more accurately, predict disease course and response to treatment, and monitor disease progression. However, the implementation of precision diagnostics in the field of NDDs also requires addressing several challenges, including the development of affordable and accessible technologies and the standardization of diagnostic criteria. In recent years, significant progress has been made in the development of biomarkers and imaging techniques for monitoring NDDS and MS, in particular.

Meanwhile, precision in therapeutic focus aims to determine the best approach to prevent, diagnose, and treat NDD, in which what is measured is linked to outcomes and relevant clinical unmet needs. By delivering differentiated therapies in areas of critical unmet need and by creating and leveraging advances in PPM-driven neurology across several key areas, we aim to lead the precision revolution in neuroscience to reduce the burden and disability caused by serious NDDs [22].

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive NDD affecting upper and lower motor neurons, with death resulting mainly from respiratory failure three to five years after symptom onset. Despite decades of research, the pathogenesis of ALS is still un-elucidated. And thus currently, there is no cure for ALS and the foundation of ALS management revolves around symptomatic and palliative care [24].

Pre-early (subclinical) diagnosis offers the best prognosis for a longer, quality life while living with the disease. Even though curative treatment options, able to prevent or stop disease progression, are still unknown, recent breakthroughs, especially in the field of targeting genetic disease forms, raise hope for improved care and therapy for ALS patients [18]. With the lack of effective and reliable treatment options, it is imperative for healthcare professionals to understand the nuances of using riluzole and edaravone to optimize therapy and quality of life for patients with ALS [25,26].

Meanwhile, most clinical trials have focused on testing small molecules and monoclonal antibodies (MAbs) affecting common cellular pathways in ALS: targeting glutamatergic, apoptotic, inflammatory, and oxidative stress mechanisms among others. More recently, clinical trials utilizing stem cell transplantation and other biologics have emerged. This rich and ever-growing pipeline of investigational products, along with innovative clinical trial designs, collaborative trial networks, and an engaged ALS community', provide renewed hope to finding a cure for ALS [27-30].

To date, only supportive care is provided for ALS patients, and no effective treatment or cure has been discovered. For instance, the therapeutic potential of cell-based therapies in ALS has not been fully evaluated, given the paucity of high-quality clinical trials. Based on data from preclinical studies, cell-based therapy is a promising treatment for ALS/MND [18,21,30-32].

The lack of successful treatments can be well explained by the complex and heterogeneous nature of ALS, with patients displaying widely distinct clinical features and progression patterns, and distinct molecular mechanisms underlying the phenotypic heterogeneity. Thus, stratifying ALS patients into consistent and clinically relevant subgroups can be of great value for the development of new precision diagnostics and targeted therapeutics for ALS patients.

In the last years, the use and integration of high-throughput "OMICS" approaches have dramatically changed our thinking about ALS, improving our understanding of the complex molecular architecture of ALS, distinguishing distinct patient subtypes and providing a rational foundation for the discovery of biomarkers and new individualized treatments. Anyway, modern neurology urgently needs panels of productive and informative biomarkers, biomarker-driven targets and targeted drugs of the next step generation with newer indications in the treatments of ALS. Many biomarkers and treatments for ALS have been discovered, and current concerns are to affirm their therapeutic effects. In future clinical trials, a good trial design will be the most promising approach to achieve desired outcomes in alleviating incurable NDDs [24,33].

The current molecular mechanism of ALS, including immune disorders, redox imbalance, and autophagy dysfunction, propose some

unique biomarkers (including RNA-binding proteins), and discuss therapeutic strategies including biomarker-driven targeted drug therapy, immunotherapy, and stem cell-exosomal therapy to bale to secure as the newest therapeutic strategies more or less slowing down the progression of the disease.

A growing body of evidence from the biodesign-driven studies demonstrate the safety and efficacy of therapies based on different cell types such as mononuclear cells, neural progenitors, and mesenchymal stem cells (Figure 6A,B).

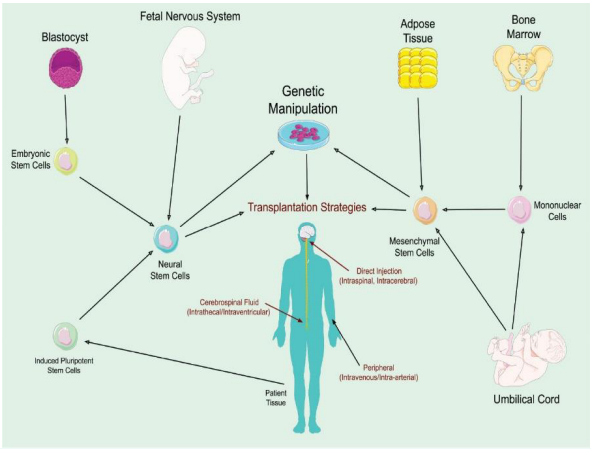

Figure 6A Therapeutic strategies using cells in ALS

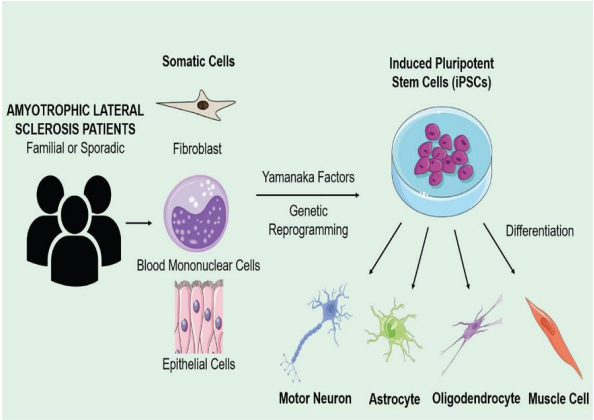

Figure 6B iPSCs as applicable inALS pathologic mechanisms
iPSC-derived cell can also be used in drug screenings and possibly in future cell replacement therapies.

Neural stem cells from different sources could be used to replace motoneurons or glial cells, while mesenchymal stem cells or mononuclear blood cells have been tested mainly as immunomodulators. Genetic manipulations, such as growth factors superexpression, can improve cells therapeutic potential.

As you see from the Figures, the advent of induced pluripotent stem cells (iPSCs) has enabled the development of patient-specific cell lines, a valuable tool to investigate *in vitro* molecular mechanisms of the disease and create cell-driven therapies of the future. Moreover, preclinical studies and clinical trials indicate that cell therapy might be considered as a hopeful therapeutic alternative to ALS patients. But despite the encouraging results in preclinical studies, cell therapy-based clinical trials for ALS have achieved only modest results so far [34]. And thus further studies are required to determine ideal cells candidate, doses, and delivery routes, since the great heterogeneity in ALS clinical and genetic presentation makes it difficult to standardize a unique therapeutic protocol for cell transplantation. In this context, stem cells and their derivatives emerge as a promising tool for the optimization of clinical trials, helping to stratify patients and design effective personalized therapies. Meanwhile, identification of novel therapeutic strategies for ALS management is urgently needed. And thus PPM-guided prognostic models with use of predictive biomarkers may identify patients with ALS for whom a specific therapeutic strategy may be expected to be more successful [28,35-40].

Finally, the rapid application of emerging clinical and biomarker strategies may reduce heterogeneity, increase trial efficiency, and, in turn, accelerate ALS drug development [32,41].

The quest for disease-modifying therapies in ALS has several obstacles, the most important being the sub-optimal quality of the design of clinical trials, and the clinical and pathological heterogeneity of the disease. As there is no cure for ALS right now, the field of design-inspired and biotech-driven translational research and applications in the field is very important for human beings [39].

Recent proof-of-concept clinical trials using a PPM-guided approach suggest a new model of ***Alzheimer's disease (AD)*** as a chronic innate encephalitis that creates a network insufficiency. Identifying and addressing the multiple potential contributors to cognitive decline for each patient may represent a more effective strategy [21,42-45].

Meanwhile, many therapeutic strategies have been explored for several decades; including studies showing the promising role of nanoliposomes and exosomes as smart drug delivery systems able to penetrate the blood-brain barrier and target AD-related sites. However, there is still no curative treatment for AD management, and the priority remains prevention [46-48].

The underlying heterogeneous etiology and diverse symptoms of AD suggest that a PPM-driven and guided strategy is required, which would take into account the complex genetic, epigenetic, and environmental landscape of each AD patient and/or person-at-risk. Their specific patterns could represent the basis for novel individually tailored approaches aimed to optimize PPM-guided strategies for AD prevention and treatment.

Currently, diagnosis and management of pre-early (subclinical) AD are largely guided by clinical symptoms. The efficacy of a treatment could be better evaluate if efficient biomarkers are available. FDA-approved biomarkers can aid detection and diagnosis, but the clinical implementation of these testing modalities is limited because of availability, cost, and perceived invasiveness. Meanwhile, blood-based biomarkers may enable earlier and faster diagnoses as well as aid in risk assessment, early detection, prognosis, and management.

As a result of translational research and applications, ***aducanumab***, being in the phase IV trial, first FDA approved moiety that surpasses the blood-brain barrier (BBB) and reduces amyloid plaques in the brain, thereby reducing associated cognitive decline. Other drugs such as ***lecanemab*** are also under clinical trial and has recently been approved by the FDA and is also discussed here. Some other design-driven therapeutic modes including active and passive immunotherapy for AD as well as several vaccines, such as amyloid-beta epitope-based vaccines, amyloid-beta DNA vaccines, and stem cell therapy for AD, which are in clinical trials as well [44,49,50]. The latter means that the successful application of PPM to AD demands a further extensive research of underlying pathological processes, as well as clinical and biological complexity of this multifactorial neurodegenerative disorder.

The clinical course of ***multiple sclerosis (MS)*** is highly variable among patients, thus creating important challenges for the neurologist to appropriately treat and monitor patient progress. Despite some patients having apparently similar symptom severity at MS disease onset, their prognoses may differ greatly [51-55].

The improved understanding of MS neurobiology alongside the development of novel markers of disease will allow PPM to be applied to MS patients, bringing the promise of improved care. Combinations of clinical and paraclinical data are currently used for diagnosis and prognosis. The addition of advanced magnetic resonance imaging and biofluid markers has been strongly encouraged, since classifying patients according to the underlying biology will improve monitoring and treatment strategies [56].

Therapeutic armamentarium in MS has radically changed in the last few decades due to the development of disease-modifying treatments (DMTs) with highly selective mechanisms of action [57,58]. Honestly, DMTs for MS are widely used given their proven efficacy in the relapsing form of the disease, while biomarker-driven ***siponimod*** and ***ocrelizumab*** (Figure 7), have been approved for the progressive forms of the disease

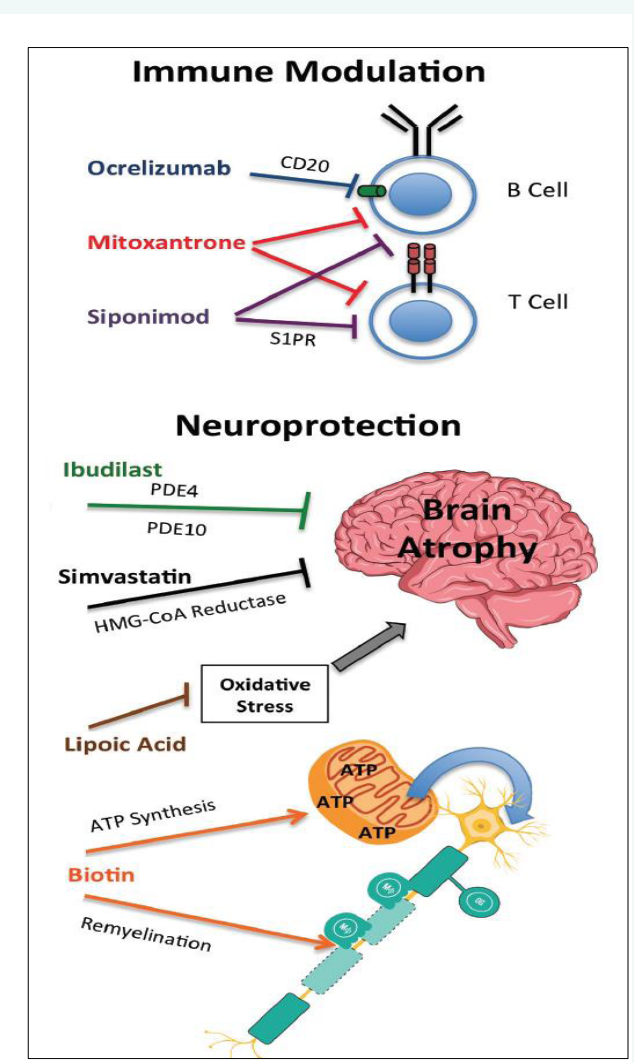

Figure 7: Therapies in use and under investigation for progressive multiple sclerosis (MS) are immunomodulators or neuroprotective agents with a variety of mechanisms of action

[59,61,62].

There are reasons to be optimistic about filling the unmet need of preventing disability for persons with progressive MS, including patients who may not be ideal candidates for an effective immunomodulator. A number of agents with putative neuroprotective effects have shown promise in recent clinical trials.

Siponimod, a selective sphingosine-1-phosphate1,5 receptor modulator. Much of the treatment effect from siponimod is attributable to decreased inflammation, which favors younger patients with shorter disease duration. Such patients represent a fraction of those with progressive MS, making these results difficult to generalize to real-world patient populations.

Ocrelizumab is a humanized anti-CD20 monoclonal antibody approved for the treatment of adults with relapsing forms of MS (RMS) or primary progressive MS (PPMS). In patients with PPMS, ocrelizumab reduced measures of progression relative to placebo.

Ocrelizumab and siponimod continue to represent a generally well-tolerated, high-efficacy disease-modifying therapy (DMT) for relapse MS and is a valuable treatment for delaying disease progression in patients with primary progressive MS (for whom there are currently no other approved DMTs) [59,60].

And along with biomarker-driven OMICS technologies, computational biology and data bioanalytics, which involve the use of computational tools to answer biomedical questions, may provide the basis for novel healthcare approaches in the context of MS. The rapid accumulation of health data, and the ever-increasing computational power and evolving technology have helped to modernize and refine MS research. From the discovery of novel biomarkers to the optimization of treatment and a number of quality-of-life enhancements for patients and persons-at-risk, computational biology tools are shaping the field of MS diagnosis, management and treatment.

The precise pathogenesis and etiology of MS are still a mystery despite many studies that have been aimed to identify biomarkers of the next step generation. There is urgently needed for biomarkers, which could clarify pathology, monitor disease progression, enable pre-early diagnosis, guide targeted therapy and monitor the active ty and therapeutic responses across the diseases, response to treatment, and prognosis in MS. In this sense, proteomics analysis are powerful tools to identify putative and novel candidate biomarkers and thus a rapidly evolving discipline which may fulfill this dire need for the discovery of molecular biomarker. And development of new and improvement of existing therapeutic strategies therefore require a better understanding of MS pathogenesis, especially during the progressive phase of the disease. Proteomics is thus a powerful and promising tool to accelerate biomarker detection and contribute to novel therapeutics [63-65].

As you might see from the above-mentioned, the identification of reliable and specific biomarkers for MS can be challenging [66,67]. Among the best-validated predictive biomarkers are autoimmunity-related ones to predict and prognosticate risks of the chronification, complications and thus disabling. The latter is so much valuable and important since chronic autoimmune inflammation course is structured to consist from different stages including subclinical and clinical ones. In this sense, MS is just one of the chronic tissue-specific autoimmune diseases resulting in a destruction of myelin by different tools, including autoAbs of very broad specificity (Figure 8).

Along with canonical Abs, some of the families proven to occur are Abs possessing with catalytic activity (***abzymes***), and thus to belong to Abs with ***functionality*** (Figure 9) [68-73].

Abs against myelin basic protein/MBP endowing with proteolytic activity (***Ab-proteases***) are of great value to monitor demyelination to

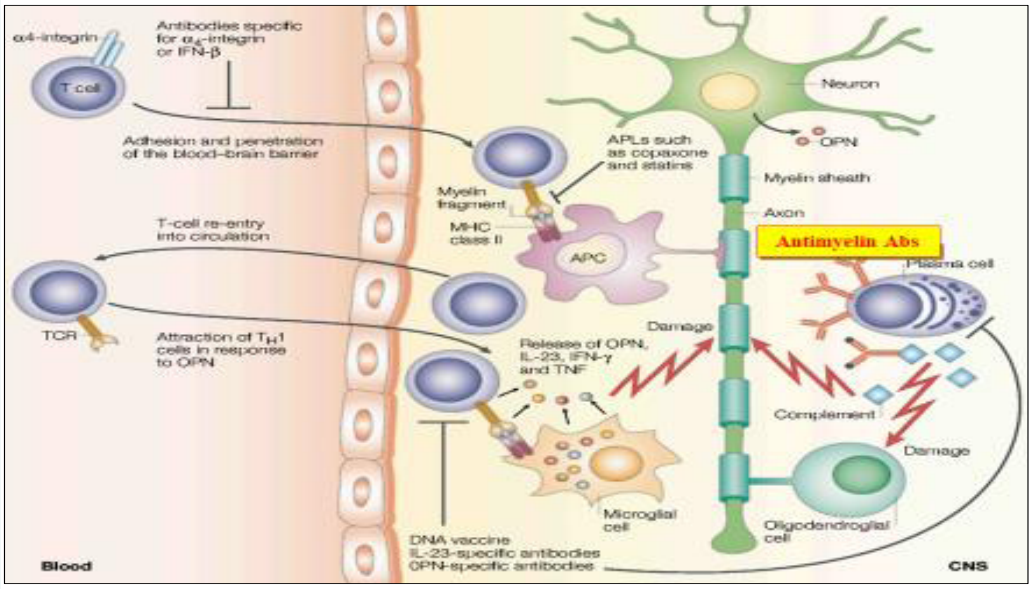

Figure 8: Multiple sclerosis (MS): autoimmunity, demyelination and neurodegeneration - anti-myelin autoAbs and autoreactive CTLs are able to make oligodendrocytes and axons damaged in direct and indirect ways to result in demyelination and neurodegeneration, respectively

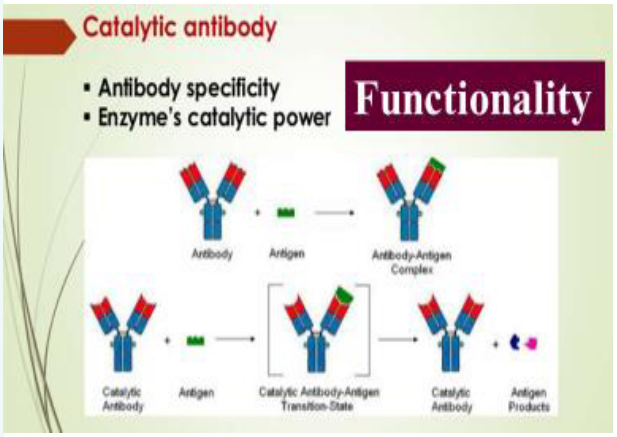

Figure 9: Antibodies (Abs) possessing with catalytic activity (*abzymes*) and thus to belong to Abs with functionality

Indexes	MS patients (n=332)	Healthy controls (n=128)
Ab-proteases (68%)	154,66 ±72,40	1,99 ±0,71

Figure 10A: The activity of antibody (Ab)-proteases in MS patients and healthy controls [79]

illustrate the evolution of MS. Anti-MBP autoAbs from MS patients exhibit specific proteolytic cleavage of MBP, which is specific for MS patients only, and markedly differs between clinical MS courses and EDSS scales of demyelination to correlate with the disability of MS patients to predict the transformation prior to changes of the clinical course (Figure 10A-C) [74-78].

Ab-mediated proteolysis of MBP being sequence-specific and located within the immunodominant regions of MBP were shown to differ in its sequence specificity between the sites of MBP-targeted proteolysis (Figure 11) [80].

Antibody-mediated proteolysis of MBP results in generating a set of peptides with MW ranged in various but fixed boundaries to suit common principles of the molecular architectonics of MBP. The final statistical data revealed FIVE sites of preferential proteolysis (indicated by ***yellow*** color) [81].

Number of MS patients		Serum presence of Ab-proteases	Ab-mediated proteolytic activity
Of type	*at a stage of*		
Remittent	Exacerbation	24 (18%)	97,3±30,1
	Remission	7 (5%)	8,8±2,5
Secondary-progradient	Progression	20 (15%)	288,9±39,9
	Stabilization	5 (4%)	25,3±15,0
Primary-progradient	Progression	18 (14%)	93,2±21,2
	Stabilization	8 (6%)	20,1±10,2

Figure 10B: The correlation of activity of MBP-targeted Ab-proteases with scales of demyelination [79]

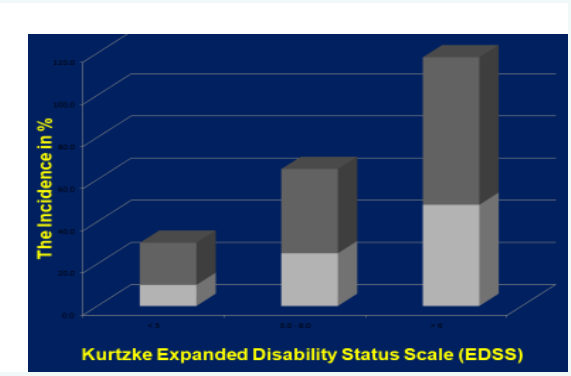

Figure 10C: The correlation of activity of MBP-targeted Ab-proteases with neurological deficiency and the disability of the patients [79]

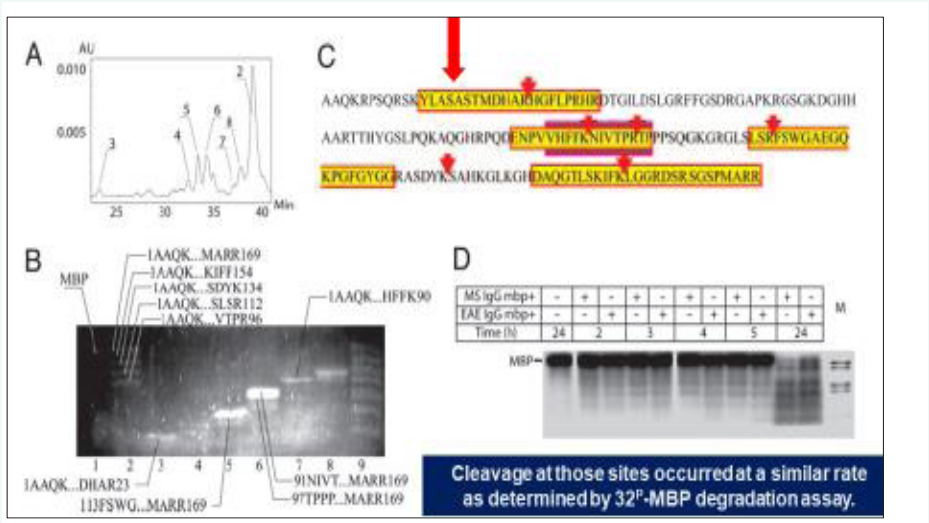

Figure 11: Antibody-mediated sequence-specific proteolysis of targeted MBP

Some of the sites (with the highest encephalitogenic properties) were proved to be attacked by the MBP-targeted Ab-proteases in MS patients with the most severe (progradient) clinical courses. The other ones whilst being less immunogenic were shown to be attacked by Ab-proteases in MS patients with moderate (remission-type) courses.

71% and 18% of the MS patients and MS relatives were initially seropositive for canonical anti-MBP autoAbs with no proteolytic activity ("disarmed" Abs) (Figure 12).

And less than 2% of the MS relatives were initially seropositive for low-active Ab-proteases. Neither of the seropositive relatives (regardless to type of Abs) demonstrated neither clinical nor instrumental or laboratory MS manifestations initially. Meanwhile, a substantial proportion (around 34%) of MS relatives demonstrating low-active Ab-proteases initially but with no trends to grow had had subclinical evidence of latent autoimmunity without developing clinically overt disease in the future to come.

The activity of Ab-proteases was first registered at the subclinical stages prior to the clinical illness. And the registration in the evolution of highly immunogenic Ab-proteases would illustrate either risks of transformation of subclinical stages into clinical ones, or risks of exacerbations to develop. And the "escalation" illustrating re-orientation of the sequence specificity to focus on the more important targeted sites for proteolysis might be an early prognostic and/or predictive sign to

Indexes	MS patients (n=332)	Relatives of MS patients (n=1448)	Healthy controls (n=128)
Anti-MBP autoAbs cases (in %)	71.4±7.8	17.7±4.8	0
Activity of Ab-proteases	154,66±72,40	3,04±2,59	1,99±0,71

Figure 12: The activity of Ab-proteases and anti-MBP autoAb-positive cases among MS patients, their direct relatives and healthy volunteers (at a starting point of monitoring) [81].

monitor demyelination progressing and thus the clinical illness to come. The activity of Ab-proteases in combination with the sequence-specificity would confirm a high subclinical and predictive (translational) value of the tools as applicable for personalized monitoring protocols [76,82,83].

Sequence-specific Ab-proteases have proved to be greatly informative

and thus valuable biomarkers to monitor MS at both subclinical and clinical stages! And the translational potential of this knowledge is in the rational design of new diagnostic tools and new therapeutics based on principles of design-driven artificial biocatalysts [84,85]. So, further studies on Ab-mediated MBP degradation and other targeted Ab-mediated proteolysis may provide biomarkers of newer generations and thus a supplementary tool for assessing the disease progression and predicting disability of the patients and persons-at-risks.

Overall, OMICS approaches can develop different therapeutic and diagnostic aspects of NDDs, from biomarker discovery to PPM. In this sense, as you might see, DMTs and targeted therapies aim to modulate specific immune pathways involved in NDD-related pathogenesis, with the goal of reducing disease activity and preventing further damage to the CNS. In recent years, significant progress has been made in the development of targeted therapies for NDDs [86,87].

The primary targets of therapies in MS and other types of NDDs are immune cells and cytokines involved in the immune response. For example, MAbs targeting CD20, such as rituximab and ocrelizumab, have been shown to reduce B-cell activity and disease activity in MS [86,87]. Similarly, Abs targeting alpha-4 integrin, such as natalizumab and vedolizumab, have been shown to reduce T-cell activity and disease activity in MS. Other targeted therapies, such as sphingosine-1-phosphate receptor modulators, have been shown to reduce lymphocyte migration and prevent further CNS damage.

One of the main challenges of PPM-guided treatment in MS is the identification of reliable and specific biomarkers and disease subtypes [88]. The identification of biomarkers and disease subtypes can be complex, requiring the use of expensive and sophisticated technologies. Furthermore, the identification of reliable biomarkers and disease subtypes may require large-scale studies involving diverse populations, which can be time-consuming and costly. Another challenge of PPM-guided treatment in MS is the development of targeted therapies that can address the specific characteristics of each patient. The development of targeted therapies can be time-consuming and costly, and the efficacy of these therapies may vary depending on disease stage and patient characteristics [89,90].

In this context, of special interest is ***masitinib***, being a selective tyrosine kinase inhibitor, whose therapeutic efficacy in MS have explored and proved to have the potential therapeutic benefits in various NDDs, such as AD) ALS, and MS, whilst demonstrating in preclinical and clinical studies promising results via inhibition of microglia, astrocytes, and mast cell activity in both central and peripheral nervous systems (Figure 13A,B) [91-95].

A potential strategy, currently under investigation, is to target cell-signaling pathways associated with neurodegeneration, in order to decrease neuroinflammation, excitotoxicity, and to improve cognitive functions, centering on the role of neuroinflammation and NDD pathophysiology. In this context, masitinib administration could be considered a new pharmacological approach to control detrimental neuroinflammation. Masitinib downregulates the proinflammatory cytokines, indirectly reduces inflammation, and induces neuroprotection [95,96].

Masitinib is a potent and selective phenylaminothiazole-type tyrosine kinase inhibitor which is currently in Phase III studies for the treatment of NDDs with the aim of modifying its evolution and with multiple pharmacological targets, inhibition of microglia activation, profiled signaling pathway and prevention of synaptic damage. All research studies revealed positive effects concerning the cognitive functions in AD and generally with good safety and tolerability [97].

As you see from the above-mentioned, masitinib emphasizes the neuroinflammatory activity in a broad spectrum of NDDs by targeting macrophages, mast cells, and microglia cells. Masitinib downregulates the proinflammatory cytokines, indirectly reduces inflammation, and induces neuroprotection. Masitinib could be a promising actor in the treatment of ALS, AD and MS patients.

Targeted therapies (including DMTs) represent a promising approach to the management of NDDs. The development of the therapies in the field of NDDs is guided by the identification of specific biomarkers and disease subtypes, and the use of targeted therapies can improve treatment efficacy and reduce the risk of adverse effects [20,98,99]. However, the implementation of DMTs and targeted therapies in NDDs also requires addressing several challenges, including the development of affordable and accessible therapies and the standardization of treatment guidelines.

The final goal in NDDs and MS, in particular, as such a complex disease would be PPM-guided approaches, i.e., providing healthcare services that are tailored to the individual patient and/or persons-at-risk, in accordance to the particular biology of their disease and the environmental factors to which they are subjected. For MS, the prevention of progression and the preservation of quality of life play a crucial role over the entire therapy period. In MS, patients tend to become ill at a younger age and are so variable in terms of their disease course that there is no standard therapy. Therefore, it is necessary to enable a therapy that is as personalized

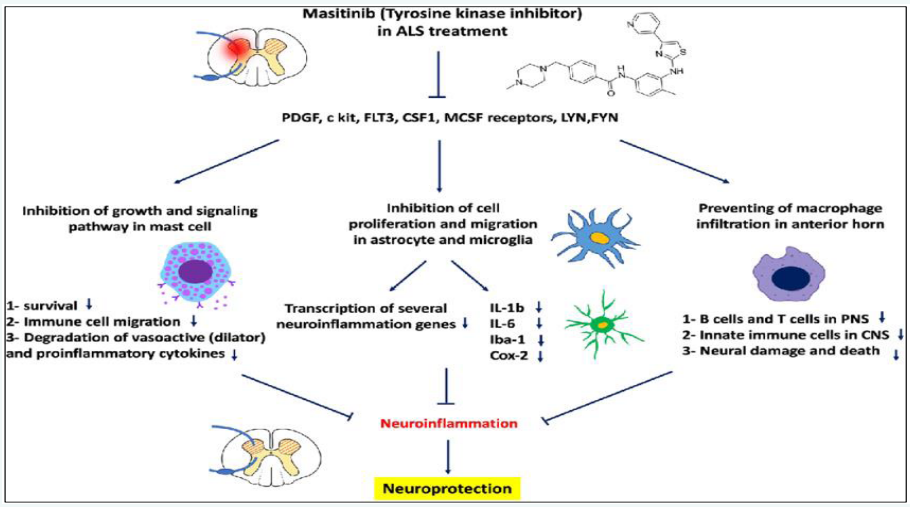

Figure 13A: Mechanisms of masitinib on neuroinflammation

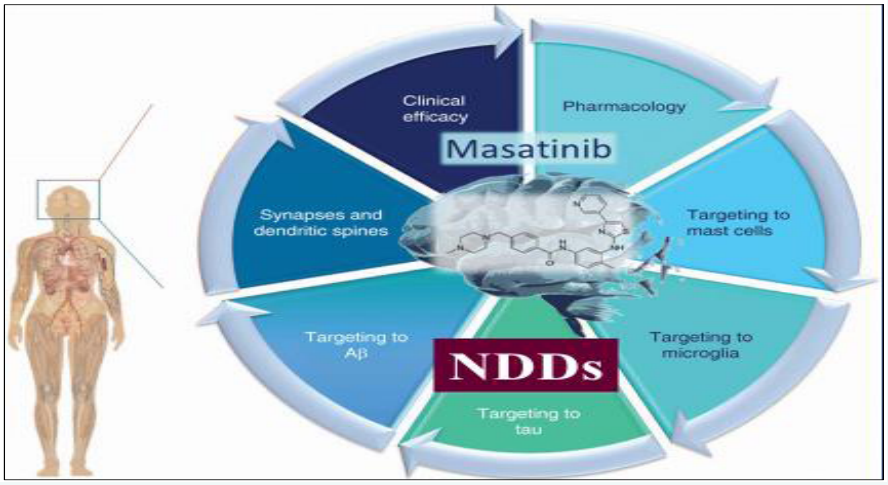

Figure 13B: Masitinib for the treatment of NDDs

as possible and to respond promptly to any changes, whether with noticeable symptoms or symptomless [100]. So, further research, involving traditional and adaptive trial designs, should strive to halt, repair or protect against central nervous system damage. To personalize new treatments, their selectivity, tolerability, ease of administration, and safety must be considered, while to personalize treatment approaches, patient preferences, risk-aversion, and lifestyle must be factored in, and patient feedback used to indicate real-world treatment efficacy [56].

As you might see, applying PPM-driven resources to diagnose and treat NDDs involves several key steps:

(i) biomarker-driven OMICS-guided molecular profiling: analyzing the molecular characteristics of a patient's neurological disorder or a pre-illness in a person-at-risk;

(ii) clinical evaluation: conducting a comprehensive assessment of the patient's medical history, symptoms, and neurological examination to gather relevant clinical information;

(iii) personalized diagnosis: integrating OMICS-related and clinical information to make a precise diagnosis and classify the specific subtype of the NDD;

(iv) targeted treatment and DMT selection: using the patient's unique characteristics to guide the selection of treatments that are most likely to be effective and minimize adverse effects;

(v) monitoring and adjustment: regularly monitoring the patient's response to treatment using personalized biomarkers or clinical indicators, and adjusting the treatment plan as needed to optimize outcomes.

By applying these steps, precision medicine enables more accurate diagnoses, personalized treatment plans, and better management of neurological disorders, leading to improved patient outcomes. And thus the improved patient (or persons-at-risk) outcomes with the application of the biomarker tests must consider not only increased survival or quality of life, but also improved ***clinical decision support (CDS) & making*** leading to the avoidance of unnecessary therapy or toxicity [101-104]. For instance, there is growing consensus that MS exists on a continuum, with overlap between relapsing-remitting and secondary progressive phenotypes. Evidence demonstrates that neuroaxonal loss occurs from the outset, that progression can occur independent of relapse activity, and that continuous underlying pathological processes may not be reflected by inflammatory activity indicative of the patient's immune response. So, pre-early (subclinical) intervention can benefit patients and persons-at-risk, and there is a need for a tool that assists physicians in rapidly identifying subtle signs of MS progression.

Moreover, data from multiple sources are being combined to create more personalized neurological disease diagnoses and prognoses. These data sources range anywhere from family history and whole genome sequencing to the whole body and brain magnetic resonance imaging and computed tomography imaging. So, bioinformatics, dataset-related management and biostatistics will be crucial in translating those Big Data into useful applications, leading to improved diagnosis, prediction, prognostication and treatment. The future of PPM in neurology lies in multimodal digital data, enabling the principles of PPM to be applied in neurological disease diagnostics, treatment, and monitoring at scale, expanding the benefits to everyone [105].

Meanwhile, the clinic-pathologic model that defines NDDs has remained unchanged for over a century. According to it, clinical manifestations are defined and explained by a given pathology, that is, by the burden and distribution of selected biomarkers and targets. There are two logical consequences from this model:

(1) a measurement of the disease-defining pathology represents a biomarker of that disease in everyone affected, and

(2) the targeted elimination of that pathology should end that disease.

But success in disease modification guided by this model has remained elusive. So, understanding the pathophysiology and genetic background of NDDs increases the likelihood of developing effective DMT-guided strategies. We believe that an effective model of PPM as applicable to NNDs must be prioritized in the near future providing key insights into their role in guiding the decision-making process for NDDs in daily clinical practice. In this sense, multimodal analysis and modeling approaches can guide neuromodulation by combining molecular networks, functional signal analysis, and cognitive neuroscience paradigms in single subjects. So, biological subtyping is becoming the key developmental milestone needed to launch PPM for patients living with neurodegenerative disorders and persons-at-risk with the proper suspicions [20,106,107].

The implementation of PPM in the field of NDDs also requires addressing several challenges, including the standardization of diagnostic criteria and treatment guidelines, the development of affordable and accessible technologies and therapies, and the ethical and legal considerations of personalized treatment. PPM represents a promising approach to the management of NDDs, with the potential to improve

diagnosis, prognosis, and treatment outcomes. Together, these data-driven insights enable the design of more precise therapeutic interventions in targeted patient populations. And future directions of PPM in the field of NDDs should aim to address these challenges and improve the integration of precision medicine in clinical neurology-related practice [42,107,108].

Advances in disease modeling and methodological design have paved the way for the development of personalized neurology. So, PPM-guided neurology is the application of principles of PPM, ie, the prescription of specific therapeutics best suited for an individual taking into consideration both genetic and environmental factors that influence response to therapy. The aim is to improve the efficacy and reduce the adverse effects of various therapies. Biomarkers, biomarker-driven targeting and integration of diagnostics with therapeutics are important for the selection and monitoring of treatments of neurologic disorders, covering: molecular profiling, clinical evaluation, personalized diagnosis, targeted treatment selection, monitoring and adjustment.

For instance, MS, AD and/or ALS, being chronic, autoimmune, demyelinating disease of the central nervous system, are now main biomarker-driven targets for implementation of PPM-related resources and search for specific biomarkers of the disease subtypes. PPM in those disorders include the development of targeted therapies that aim to modulate specific immune pathways involved in the pathogenesis.

PPM-guided neurology stands at the threshold of a revolutionary transformation with the advent of PPM. And OMICS-driven and IT-supported potential to advance ***personalized precision neurology (PPN)*** hinges on resolving core challenges across four pillars-models, data, feasibility/equity, and regulation/innovation-through concerted pursuit of targeted recommendations. The intricate tapestry of NDDs, long characterized by heterogeneity and complexity, is now being unraveled at the molecular level. By delving into the genetic underpinnings of neurological conditions, we uncover the potential for tailored interventions that promise not only to improve treatment outcomes but also to reshape our understanding of NDDs. And a journey from genomics and related OMICS-driven technologies to personalized therapies is not only transforming clinical neurology-related practice but also offering hope to individuals and families affected by NDDs (Figure 14).

The advent of PPM demands, besides the detailed patient clinical profiles, data of different types such as biological, sensor data, clinical, physiological, environmental, etc. Data collection and integration creates big data profiles of patients, leading to the need for advanced analytical approaches in order to reach meaningful results. The objectives of this Figure are: (i) to demonstrate the diversity of healthcare information that arise from the wide range of the data science methodologies built on data-driven research and (ii) to describe the application of these methodologies in different types of NDDs. The implementation and use of this novel approach offer the opportunity to combine traditional datasets, including data from the electronic health record, with emerging big data sources, such as continuous patient monitoring and real-time laboratory results [109].

It heralds a new era of neurology where treatments are tailored to the individual, leading to improved outcomes, reduced side effects, and a deeper understanding of disease mechanisms [20,21,110,111].

By understanding the unique characteristics of a patient's neurological condition, such as genetic predispositions, biomarkers, and disease mechanisms, PPM aims to optimize treatment outcomes and improve patient care. Overall, PPM in neurology holds the promise of advancing our understanding of neurological diseases and transforming healthcare by tailoring interventions to the unique needs of each patient. So, to fully harvest the unique potential of PPM-guided neurology, new generations of new precision diagnostic, predictive, prognostic, preventive, prophylactic, therapeutic, rehabilitative and digital products will need to be matched with new thinking and new practice on the part of all the participants in the clinical neurology-related practice.

When large quantities of digital neurocognitive function data sets from healthy individuals and those impacted by specific NDDs are combined with strong analytical tools, we can determine new links, patterns, and complex disease signatures associated with a breadth of

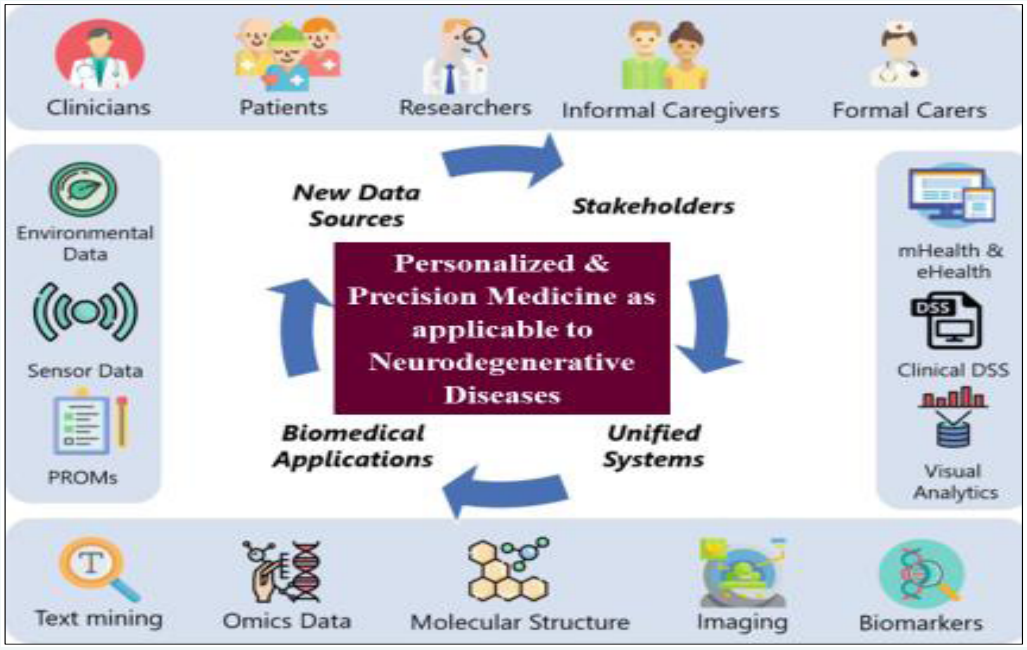

Figure 14: Biomedical Applications of Personalized & Precision Medicine (PPM) in Neurodegenerative Diseases.

NDDs. This method offers a highly accessible, cost-efficient, and non-invasive approach for diagnosing NDDs early, placing an individual precisely along a disease continuum, and providing the most effective possible treatment pathway.

It would be extremely useful to integrate data harvesting from different databanks for applications such as prediction and personalization of further treatment to thus provide more tailored measures for the patients resulting in improved patient outcomes, reduced adverse events, and more cost effective use of the latest health care resources including diagnostic, prognostic, preventive and therapeutic (targeted) etc [3].

The future of PPM-guided neurology lies in multimodal digital data, enabling the principles of PPM to be applied in NDD-related diagnostics, treatment, and monitoring at scale, expanding the benefits to everyone. This approach offers a highly accessible, cost-efficient, and non-invasive approach for diagnosing neurological diseases at their clinical and subclinical stages, placing an individual precisely along a disease continuum, and providing the most effective possible canonical and preventive treatment pathways.

The prospect of applying PPM concept broadly has been dramatically improved by the recent development of large-scale biologic databases, powerful OMICS-methods for characterizing patients, and computational tools for analyzing large sets of data. And PPM in neurology holds the promise of advancing our understanding of NDDs and transforming healthcare by tailoring interventions to the unique needs of each patient. This is the reason for developing global scientific, clinical, social, and educational projects in the area of PPM to elicit the content of the new branch.

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