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Review

Regulatory-accepted drug development tools are needed to accelerate innovative CNS disease treatments

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ABSTRACT

Central Nervous System (CNS) diseases represent one of the most challenging therapeutic areas for successful drug approvals. Developing quantitative biomarkers as Drug Development Tools (DDTs) can catalyze the path to innovative treatments, and improve the chances of drug approvals. Drug development and healthcare management requires sensitive, reliable, validated, and regulatory accepted biomarkers and endpoints. This review highlights the regulatory paths and considerations for developing DDTs required to advance biomarker and endpoint use in clinical development (e.g., consensus CDISC [Clinical Data Interchange Standards Consortium] data standards, precompetitive sharing of anonymized patient-level data, and continual alignment with regulators). Summarized is the current landscape of biomarkers in a range of CNS diseases including Alzheimer disease, Parkinson Disease, Amyotrophic Lateral Sclerosis, Autism Spectrum Disorders, Depression, Huntington's disease, Multiple Sclerosis and Traumatic Brain Injury. Advancing DDTs for these devastating diseases that are both validated and qualified will require an integrated, cross-consortium approach to accelerate the delivery of innovative CNS therapeutics.

1. The need for data sharing and cross-consortia biomarker development

Challenges to deliver CNS Therapeutics have been longstanding [1], and the industry's ability to deliver effective treatments for neurologic diseases has been particularly disappointing [2]. As the general population continues to age, the growing economic burden of neurodegenerative diseases is looming – which is becoming unsustainable [3]. With many advances in other aspects of healthcare, many individuals are living longer, only to succumb to age-related CNS diseases without any existent cures. There are 5.4 million Americans living with Alzheimer disease (AD); every 66 s someone new is diagnosed with the disease. The 2016 economic burden was estimated at $236 billion – thus consuming nearly $1 of every $5 Medicare dollars spent [4]. When expanded to a global perspective, the economic and emotional burden is daunting. If left unaddressed, AD alone will cripple the healthcare budget of many countries.

Molecular biomarkers are a cornerstone of the precision medicine initiative, and enable an approach to tailor treatments to the biochemical phenotypes/fingerprints of individual patients. In March 2016, ten recommendations were put forward by the Institutes of Medicines to advance this field [5]. When approved as drug

Abbreviations: ACR, American College of Radiology; AD, Alzheimer disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; ALS, Amyotrophic Lateral Sclerosis; ASD, Autism Spectrum Disorder; BBB, Blood-Brain-Barrier; BEST, Biomarkers, Endpoints and other Tools; BLA, Biologics License Application; BMD, Biometric Monitoring Device; CAMD, Coalition Against Major Diseases; CDER, Center for Drug Evaluation and Research's; CDEs, Common Data Elements; CDISC, Clinical Data Interchange Standards Consortium; CDRH, Center of Devices and Radiologic Health; CFAST, Coalition for Accelerating Standards and Therapies; CHMP, Committee for Medicinal Products for Human Use; CMS, Centers for Medicare & Medicaid Services; CNS, Central Nervous System; COAs, Clinical Outcome Assessments; COU, Context-of-use; CPAD, Critical Path for Alzheimer's Disease; C-Path, Critical Path Institute; CPP, Critical Path for Parkinson's; CSDR, Clinical Study Data Repository; CSF, Cerebral Spinal Fluid; DMD, Duchenne Muscular Dystrophy; EMA, European Medicines Agency; EU, European Union; FDA, U.S. Food and Drug Administration; FNIH, Foundation for the National Institutes of Health; FR, Federal Register; HD, Huntington Disease; ICFs, Informed Consent Forms; IDEAS, Evidence for Amyloid Scanning; IND, Investigational New Drug; iPS, Induced Pluripotent Stem Cells; IVD, In Vitro Diagnostic; LOS, Letter of Support; MDDT, Medical Device Drug Development Tool; MDIC, Medical Device Innovation Consortium; MJFF, Michael J Fox Foundation; MND, Motor Neuron Disease; MRI, Magnetic Resonance Imaging; MS, Multiple Sclerosis; MSOAC, Multiple Sclerosis Outcome Assessment Consortium; NCATS, National Center for Advancing Translational Sciences; NDA, New Drug Application; NIH, National Institutes of Health; NINDS, National Institute of Neurological Disorders and Stroke; PD, Parkinson Disease; PET, Positron-emission tomography; PKD, Polycystic Kidney Disease Consortium; PMDA, Japanese Pharmaceutical Medical Devices Agency; PPMI, Parkinson's Progression Marker Initiative; PPP, Public-Private-Partnerships; SAWP, Scientific Advice Working Party; SOD, Superoxide Dismutase; TAUGs, Therapeutic Area User Guides; TBI, Traumatic Brain Injury; TDI, Therapy Development Institute; TED, Traumatic Brian Injury Endpoint Development Initiative; TRACK-TBI, Transforming Research and Clinic Knowledge in Traumatic Brain Injury

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Table 1
Lexicon of key biomarker-related terms.

Term	Definitions
Drug development tools (DDT)	A measurement or method (and associated materials) that aids drug development. DDTs include, but are not limited to, biomarkers, clinical outcome assessments, and animal models. DDTs should be intended for potential use, over time, in multiple drug development programs
Biomarker	A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives
Diagnostic biomarker	A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.
Monitoring biomarker	A biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent
Predictive biomarker	A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent
Prognostic biomarker	A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.
Pharmacodynamic/response Biomarker	A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent
Safety biomarker	A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect
Surrogate endpoint	An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence
Susceptibility/risk biomarker	A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition

development tools by regulators, they can be used by all sponsors for a defined context-of-use (COU). These COUs range from preclinical safety biomarkers, to patient stratification biomarkers, and ultimately, to surrogate endpoints that are reasonably likely to predict clinical outcomes. Biomarker qualification can be defined as an acceptance by the U.S. Food and Drug Administration (FDA) that, within the stated context-of-use (COU), the biomarker can be relied on to have a specific interpretation and application in drug development and regulatory review. Once qualified, the biomarker information is made publicly available (through an FDA Guidance Document) and the biomarker can be used in multiple drug development programs under its qualified COU. This greatly reduces the time and effort that each individual company could take to have a specific biomarker linked to a specific treatment. The National Institutes of Health (NIH) and the FDA recently published an open access textbook: the Biomarkers, EndpointS and other Tools (BEST) Resource containing a glossary that is focused on clarifying important definitions, capturing the distinction between biomarkers and clinical assessments, and describing some of the hierarchical relationships, connections, and dependencies among the terms. Table 1 describes the types and definitions of biomarkers that are used in clinical development as DDTs [6,7].

Indeed, evidence across thousands of trials from numerous other therapeutic areas showed real benefit in using biomarkers for patient selection decisions in drug development [8]. The report highlighted the benefit of biomarker use raises the likelihood of approval from Phase 1 to one-in-four compared to less than one-in-ten when no selection biomarker was used. Use of selection biomarkers increased the likelihood of approval at all four phases of clinical development. Moreover, biomarkers used in this way spare patients unlikely to respond to treatment from unnecessary exposure to experimental drugs. Overall, patient selection biomarkers increase statistical power and the likelihood of observing treatment responses in clinical development. This later point is key, as it has been reported that most CNS trials are underpowered, and assume higher than realistic effect sizes for the treatment arms [9].

Remarkably, at the writing of this article (January 2018) the FDA does not have a single regulatory-accepted biomarker for use in clinical trials for neurological diseases Table 3. (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm) or as an outcome (https://www.fda.gov/%20Drugs/DevelopmentApprovalProcess/%20DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535926.htm). Even the approved use of Amyloid PET is restricted for use as a criterion for trial entry exclusion when not present, and is not approved for use as a clinical outcome measure. Although, limited in extent, the European Medicines Agency (EMA) has provided qualification opinions for the following (see Table 2) (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp#section8).

Moreover, efforts to collectively coordinate common lessons learned across CNS diseases are minimal to non-existent. For the most part, funding is provided by distinct patient-advocacy groups or NIH-allocated funding lines (e.g., Alzheimer disease, Aging, Schizophrenia, Depression, etc.). Unfortunately, funding incentives are not in place to foster learnings across disease states. While there are some independent efforts seeking common biochemical threads across diseases [10–12] given the high degree of co-morbidities and disabilities across diseases, it is shocking that more is not being done to understand both, the common and differentiating features for these debilitating diseases. The reality is that most of the neurodegenerative diseases share a number of common aspects of impaired function (Fig. 1). Where these overlap in terms of biochemical and functional markers will be discussed in Section 3.

Understanding the dynamics of these signs and symptoms across the disease continuum would be particularly insightful in building drug development tools (e.g., biomarkers, clinical outcome assessments, disease progression models) that could potentially be leveraged across these diseases, and even be used to objectively identify or stratify patients for specific clinical trials. However, even within AD, where the unmet need is high, there remains a reluctance to widely share data, or to focus on advancing the regulatory science required to gain acceptance of these DDTs. The Critical Path for Alzheimer's Disease (CPAD) consortium recently completed a landscape analysis utilizing Consortiapedia (a resource established by FasterCures: http://consortiapedia.fastercures.org/) to understand the different foci of these efforts in order to identify the greatest gaps that may exist in moving the field forward, and to understand some potential root causes of the lack of therapeutic progress (manuscript in preparation). Three key findings were evident:

Table 2
Alzheimer disease: regulatory-accepted biomarkers and DDTs.

Endorsement Level	FDA (U.S. Food and Drug Administration)	EMA (European Medicines Agency)
Letter-of-Support	• Cerebral Spinal Fluid (CSF) Analyte Biomarkers: Aβ1-42, Total tau, Phosphotau as a prognostic biomarker for early AD clinical trials (https://c-path.org/ programs/camd/) • Magnetic Resonance Imaging (vMRI) Biomarker: Low Baseline Hippocampal Volume as a prognostic biomarker for early AD clinical trials (https://c-path.org/ programs/camd/)	
Fit-for-Purpose	• Clinical Trial Simulation Tool	• Clinical Trial Simulation Tool
Qualification	• None	• Cerebral Spinal Fluid (CSF) Analyte Biomarkers: Aβ1-42, Total tau, Phosphotau as a prognostic biomarker for early AD clinical trials (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2011/02/WC500102018.pdf) • Magnetic Resonance Imaging (vMRI) Biomarker: Low Baseline Hippocampal Volume as a prognostic biomarker for early AD clinical trials (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2011/10/WC500116264.pdf) • Amyloid PET-absence of label in cognitively impaired patients excludes AD as the probable cause of dementia (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2011/12/WC500118364.pdf)
Approval	• Amyloid PET-absence of label in cognitively impaired patients excludes AD as the probable cause of dementia (https://www.accessdata.fda.gov/drugsatfdadocs/label/2012/202008s000lbl.pdf)	

1. Not all relevant consortia are represented in Consortia-pedia;
2. While many consortia have overlapping scientific objectives, the sharing of data across consortia is limited to < 20% of consortia. Remarkably, some of these consortia do not share data outside of their consortium; and
3. < 4% of consortia represented focus on advancing the regulatory science required to increase the efficiency of clinical development.

Increasing the efficiency of clinical drug development will require the global sharing of actionable, standardized data. Creation of a global, standardized database across a majority of consortia would enable the scientific community to better understand all the sources of variability

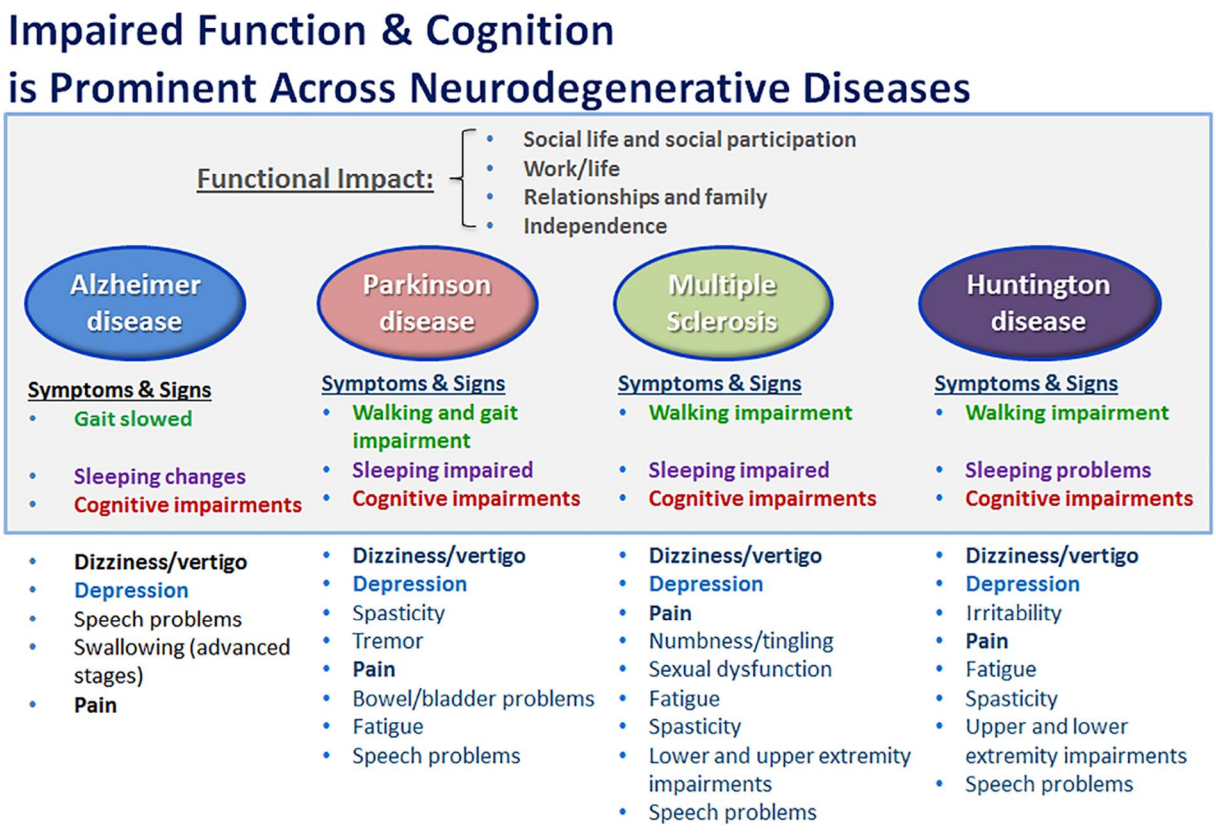

Fig. 1. Shared Disabilities Across Key CNS Diseases. Despite having distinct clinical criterion for disease diagnosis, Alzheimer disease, Parkinson Disease, Multiple Sclerosis and Huntington Disease share very similar core symptoms. This may represent an opportunity to understand how treatments for one disease may be useful in other. It also represents a call to action to work more collaboratively across CNS disease. References: Alzheimer's info: http://www.alz.org/documents_custom/2016-Facts-and-Figures-Fact-Sheet.pdf; Parkinson's info: http://www.parkinson.org/Understanding-Parkinsons/Causes-and-Statistics/Statistics; Multiple Sclerosis info: http://www.healthline.com/health/multiple-sclerosis/facts-statistics-infographic; Huntington info: https://www.mayoclinic.org/diseases-conditions/huntingtons-disease/symptoms-causes/syc-20,356,117.

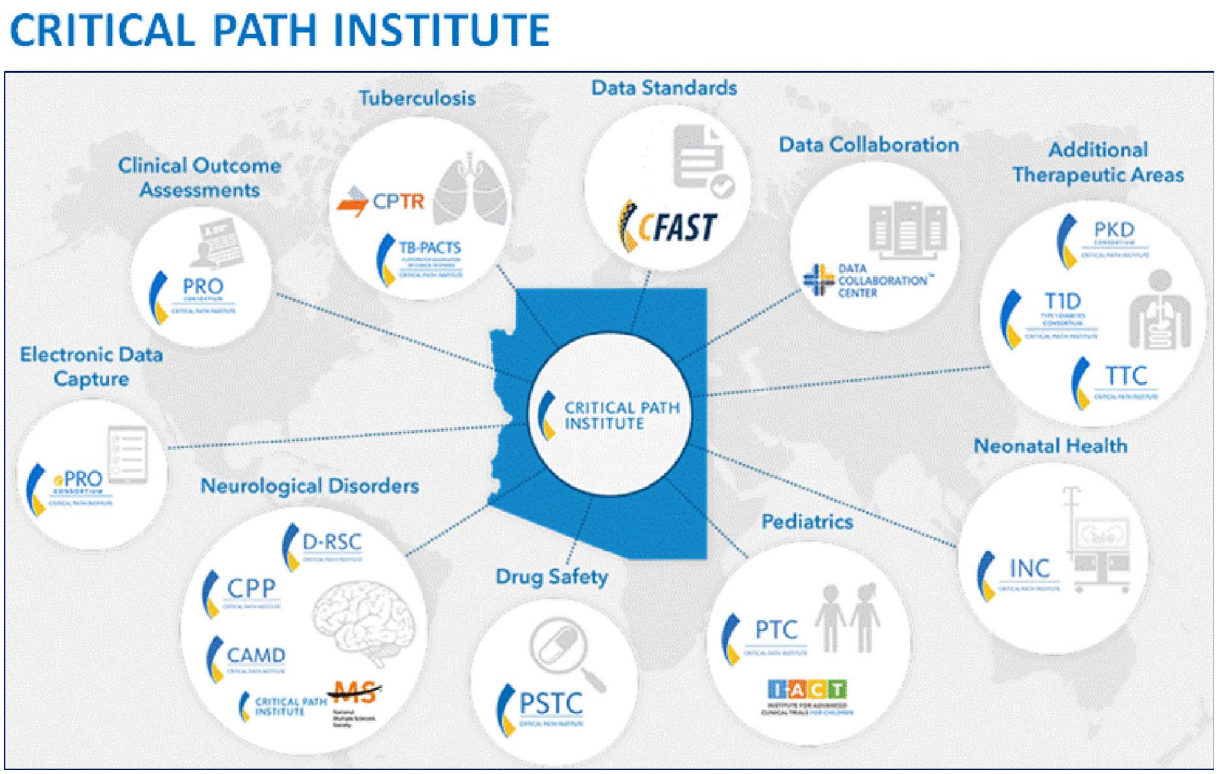

Fig. 2. The Critical Path Institute, which is based in Tucson, Arizona, USA, has global reach to advance consensus regulatory science for DDTs. The focus of C-Path is the advancement of regulatory science including data standards; clinical trial simulation tools from actionable data, disease progression models; biomarkers; and clinical outcome assessment instruments [LINK: https://c-path.org/].

in disease progression and treatment responses required to advance regulatory science, and inform the delivery of innovate treatments for AD, and other CNS diseases.

Across all CNS diseases, there has been a reluctance to share critical data, which may be one root cause to the exceptionally high failure rates of drugs in development. For example, the clinical trial failure rate for late-stage AD therapies from 2002 to 2012 was 99.6% [13,14]. A recent comprehensive study aimed to assess clinical development success rates by measuring the likelihood of FDA approval over ten years (2006–2016, n = 9985 transitions). The compound probability of progressing from Phase 1 to FDA approval revealed that only 9.6% of drug development programs successfully "make it to the market" [8]. Consistently, the lowest transition success rate was in Phase 2 (30.7%), with the second lowest phase transition success found in Phase 3 (58.1%). This is significant in that the longest and most-costly trials to conduct are at these late stages of development. The clinical success evaluation reported that neurology and psychiatry represent disease areas that have lowest likelihood of approval [8]. Moreover, the duration of time for regulatory review and approval of drugs for neurology is the longest across all disease areas; for example neurology drugs took on average two years to approve, while oncology drugs were approved in nearly half the time (1.1 years). A recent analysis of FDA-approved drugs for neurological disorders indicates that 72% of these drugs have been focused on the treatment of seizures (39%), Parkinson disease (23%) and neuromuscular disorders (20%) [2]. Collectively, these facts pose serious pharmacoeconomic challenges for pharmaceutical companies to continue to invest, given the current limited return on investment.

2. Developing standardized, actionable databases for drug development and approvals

With the aim at accelerating the review process, FDA has issued guidance (https://www.fda.gov/downloads/Drugs/…/Guidances/UCM292334.pdf) that requires that all new drug applications (i.e., New Drug Applications [NDAs] and Biologic License Applications [BLAs]), submitted after December 2016, to adhere to CDISC format. These standards also serve to enable integration of clinical trial data into a fully-integrated, actionable database for the scientific community to utilize.

This need arose from FDA's 2004 Critical Path Initiative report [15] where the importance of improved efficiencies in drug development and translational biomarker development was recognized as a top priority. Today, biomarkers are the foundation of precision medicine and their successful implementation in drug development has been transformational [16] and has been integrated into the 21st century cures legislation in catalyzing drug development. Both, FDA and EMA, have formal mechanisms for identification, evaluation and qualification of biomarkers for use in drug development [17–21].

The Critical Path Institute (C-Path) is a nonprofit organization founded in 2005 to lead and facilitate the FDA's Critical Path Initiative. The mission of C-Path is to catalyze medical innovation and regulatory science advancement of DDTs. This is achieved by leading teams that share data, knowledge and expertise resulting in sound, consensus-based science. In its 12-year history, C-Path has created fourteen consortia that focus on expediting drug development in many therapeutic areas. These global consortia (see Fig. 2) include over 1450 scientists from 84 global pharmaceutical companies and government agencies such as the FDA, the EMA and the NIH. C-Path's consortia are partially funded by the FDA as part of the Critical Path Public Private Partnerships [22], and partially by patient-advocacy and pharmaceutical industry members.

Core competencies of C-Path include: 1) development of consensus data standards with CDISC, 2) acquisition and integration of patient-level data, and 3) advancement of regulatory science paths for the endorsement of drug development tools. Public-private partnerships, like C-Path, have enabled efficiencies in regulatory acceptance of biomarkers [23,24]. Compiling databases using CDISC standards enables the cross-validation of the DDTs derived from these studies that may

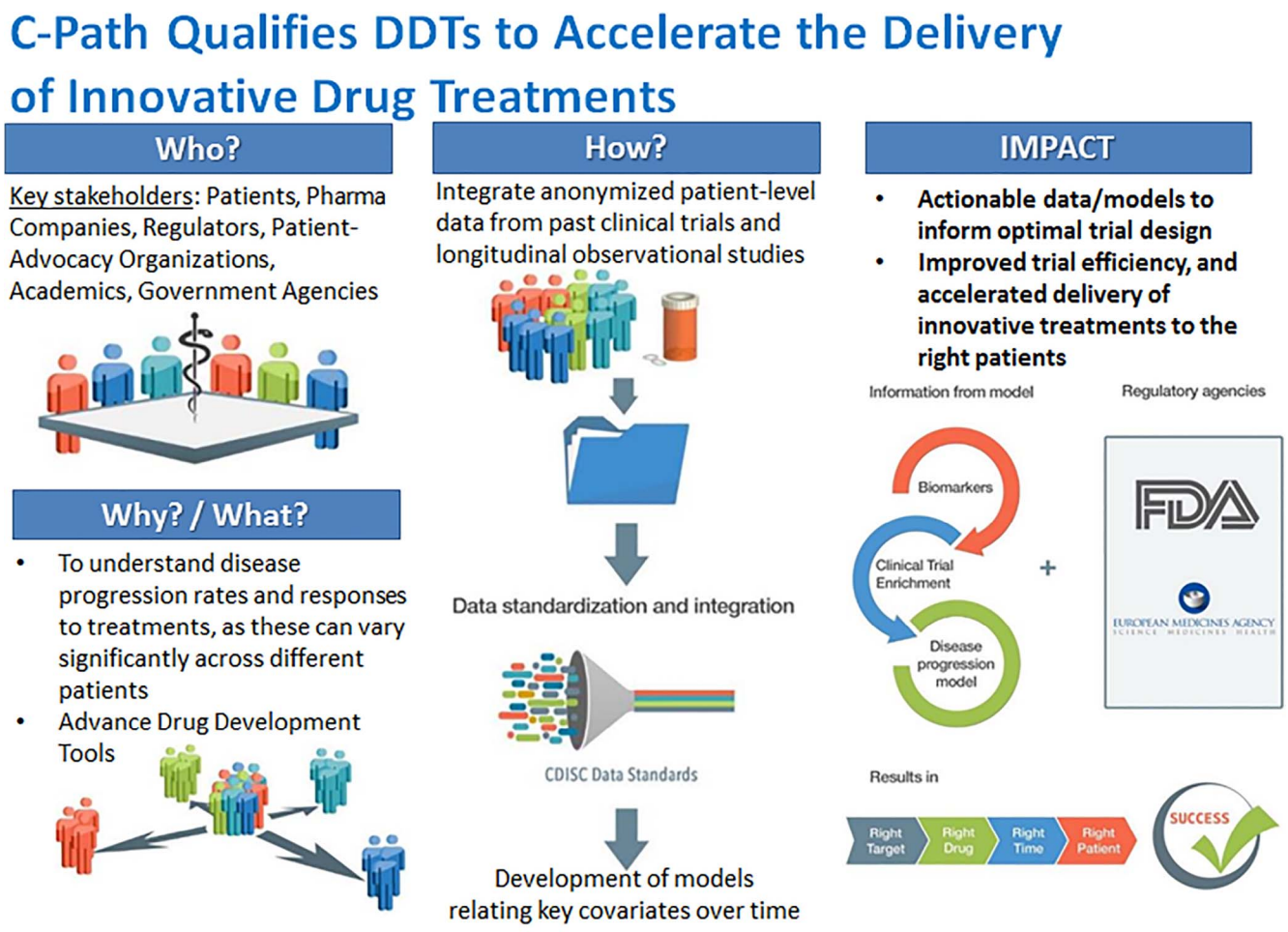

Fig. 3. Consortia work to build consensus science to advance regulatory approved biomarkers to ensure that the 'right patients' receive the 'right treatments'. The level of evidence required to validate these DDTs depends upon the clinical decision being made by the given assessment (e.g., biomarker, clinical endpoint) has on the patient. For example, on one end of the spectrum is the DDT being used as a prognostic biomarker to decide whether a patient is included or excluded from trial enrollment. On the other end of the spectrum is the DDT being used to assess treatment response. More details on these considerations are reviewed by Leptak and co-workers, 2017 (19). Specific accomplishments for select C-Path consortia are shown in Table 3.

increase the efficiency of future clinical trials. A high-level depiction of the process that C-Path consortia use to accomplish their mission is shown in Fig. 3.

The Coalition For Accelerating Standards and Therapies (CFAST) was launched in October 2012 as a partnership between CDISC and C-Path to accelerate clinical research and medical product development by facilitating the creation and maintenance of data standards, tools, and methods for conducting research in therapeutic areas important to public health. CDISC (Clinical Data Interchange Standards Consortium; https://www.cdisc.org/) is a non-profit organization with approximately 300 supporting member organizations from across the global clinical research and healthcare arenas. CDISC catalyzes productive collaboration to develop industry-wide data standards enabling the harmonization of clinical data and streamlining research processes from protocol through analysis and reporting, including the use of electronic health records to facilitate the collection of high quality research data.

CDISC Foundational Standards are the basis of the complete suite of standards, supporting clinical and non-clinical research processes from end to end. Foundational Standards focus on the core principles for defining data standards and include models, domains and specifications for data representation. Therapeutic Area (TA) Standards extend the Foundational Standards to represent data that pertains to specific disease areas. TA Standards include disease-specific metadata, examples and guidance on implementing CDISC standards. CDISC Standards specify how to structure the data; they do not specify what data should be collected or how to conduct clinical trials, assessments or endpoints (https://www.cdisc.org/standards).

CDISC standards and innovations have substantially decreased the time and cost of medical research and improved quality, thus contributing to the faster development of safer and more effective medical products. Many of the CDISC clinical standards for brain diseases were developed from foundational elements originating from National Institute of Neurological Disorders and Stroke (NINDS) common data elements (CDEs) [25]. In the absence of having these standards in place, there will be clear gaps achieving future regulatory approval of products, or the necessary biomarker drug development tools to speed their delivery.

Unfortunately, comparable, comprehensive, open-access databases for preclinical studies advancing most CNS targets do not exist. However, some interest in the development of preclinical data standards has been developed for TBI [26], spinal muscular atrophy [27] and in ALS [28]. Similarly, expanding big data approaches and standardization of preclinical data for CNS diseases, may help resolve, or refute, the relevance of its translation to human disease.

It is not well recognized that, even if a trial is positive and using an outcome without corresponding CDISC standard, it may take another 12–18 months post-study completion to convert data from these studies to CDISC standards to support a registration submission. This is the approximate time required to gain consensus feedback on what constitutes the appropriate CDISC standard.

As the neurodegenerative field has been moving towards conducting trials at the earlier pre-symptomatic stages, they have been using outcome measures that have greater sensitivity to detect changes at early stages. The hope for these trials is that, by providing intervention earlier in the disease process, a more prominent effect to prevent progression of disease and corresponding symptoms evolution is achieved. While CDISC standards do exist for many AD biomarkers and outcomes, the following are specific examples where this is not the case for two key Clinical Outcome Assessments (COAs) that are currently being recommended for use in the pre-symptomatic stages of AD:

1. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [29], recommended by the European Prevention of Alzheimer's Dementia (EPAD)
2. The Preclinical Alzheimer Cognitive Composite (PACC) [30].

A number of ongoing studies sponsored by the Innovative Medicines Initiative (IMI) and the Harvard Aging Studies, respectively, are using these clinical outcome assessments (COAs). Though promising as outcomes, the time required to detect statistical changes in these measures still often takes 18–24 months. Critically, at this point in time, neither of these outcomes has corresponding CDISC standards. Thus, trials that are completed with these COAs, will not be eligible as registration studies in the U.S. until the data are converted to CDISC standards.

Of rapidly growing interest is the integration of data from wearable smartphone devices and other remote biometric monitoring devices (BMDs) that continuously measure performance across physiologic and behavioral assessments [31–34]. A key advantage of this approach is the objective collection of data that can lead to the detection of change in the timeframe of weeks to months, which would reduce the overall number of individuals and cost of the trials required to detect change, and would accelerate the delivery of timely medicines [35]. However, one current impediment in the application of these leading technologies for use in registration trials is that CDISC standards for BMDs have not been created.

In summary, a key gap that needs addressing are consensus data standards that are openly available and comply both, with CDISC clinical data and NIH's common data elements (CDE) initiative [26,27]. Aggregation of these actionable datasets into integrated databases will facilitate a greater understanding of disease progression, and provide the foundation for advancing the regulatory science required to develop drug development tools that accelerate the delivery of innovative treatments. Both FDA and EMA have identified quantitative disease models as a drug development tool platform to accelerate drug development. Quantitative pharmacometric modeling of CDISC standardized data will enable sponsors to analyze data from integrated multiple sources to accurately design prospective clinical trials [36]. All of this would help foster improvements in biomarker utilization independent of disease area, and enable translational (forward and backwards) cross-species validation.

Critically, not all CNS diseases have CDISC standards in place to accommodate the new FDA requirements for registration studies (i.e., NDAs and BLAs). However, free access to all existing CDISC Therapeutic Area User Guides is available (https://www.cdisc.org/standards).

3. The landscape of CNS disease biomarkers

Highlighted below are some of the key publications of biomarkers used for Alzheimer disease, Amyotrophic Lateral Sclerosis, Autism Spectrum Disorders, Depression, Huntington disease, Multiple Sclerosis, Parkinson disease, Schizophrenia, Traumatic Brain Injury and other Rare Diseases. A review by Cedarbaum and co-workers [37] highlights many of the common challenges across clinical assessments for many of these diseases.

3.1. Alzheimer disease (AD)

AD serves as a key example of how biomarkers have driven evolution in both our understanding of the onset and pathophysiology of disease. Such advances have profoundly shaped the landscape of drug development. The growing sense of urgency and recognition for the unmet need in disease-modifying therapies has paved the way for recognition that public–private-partnerships are key to success in collectively approaching the barriers that face all stakeholders in tackling treatments for this devastating disease [38]. The Alzheimer's Disease Neuroimaging Initiative (ADNI), formed in 2004, represents one of the flagship public–private-partnerships focused on discovery of biomarkers that has provided foundational results in understanding the progression of AD. The principles of open access data and sample sharing have spawned the launch of other consortia and expansion of ADNI to worldwide efforts [39]. Scientific advances in the field include recognition of the stages along the AD spectrum as defined by biomarker trajectories, new diagnostic criteria and clinical trial designs and new targets.

Biomarkers are now used in AD research, development, and diagnosis with the ultimate goal of improving patient care. Comprehensive assessments of the leading biomarkers and how they are used to assess staging of the disease has been reviewed extensively [10,40,41]. Leading biomarkers for AD that have been used extensively in clinical trials include Amyloid-PET, Tau-PET, FDG-PET, CSF Aβ, CSF tau and p-tau [42]. Additional biomarkers under investigation include fMRI, DTI, ASL, CSF proteomic biomarkers, blood biomarkers, TMS and optical biomarkers [43,44]. Refinements to increase the precision of clinical diagnosis that combines clinical and biomarker data are evolving [45]. The regulatory landscape for CSF Biomarkers has been recently reviewed by Arnerić and co-workers [46].

Continued advances in regulatory science will be required to accelerate the successful implementation of additional biomarkers in AD drug development. The evolution of regulatory science in AD is a pivotal example that other brain disease areas can learn from. Active participation of regulatory agency representatives in consortia is an impactful way to seek alignment throughout phases of development [47].

Both, FDA and EMA, have developed draft guidance that communicates the Agency's recognition of the evolution of the field, specifically related to the recognition that AD dementia treatments need to evolve to recognition that the disease is a spectrum with different needs for various stages of the disease. Notably, the EMA has issued a total of five qualification opinions for AD, most of which relate to the use of biomarkers in AD clinical trials (see Table 3). Despite the lack of disease-modifying treatments to date, the regulatory agencies can serve to reduce the risk for drug developers and incentivize further investments in new trials. It is well recognized that biomarkers are needed to choose patients, particularly for early stage disease. Efficacy response biomarkers are oftentimes considered the "holy grail", yet effective treatments will be required to advance to this goal. Clearly, there remains a translational gap between basic science-driven discovery of novel promising biomarkers and the regulatory acceptance of biomarkers for use in clinical trials for decision making.

The Critical Path for Alzheimer's Disease (CPAD; formerly known as the Coalition Against Major Diseases [CAMD]), a consortium of the Critical Path Institute, has a mission to develop new technologies and methods to accelerate the development and review of medical products for AD and related neurodegenerative diseases with dementias. CPAD targets drug development in patients with dementias at very early stages, and advances tools to accelerate and streamline drug review [48]. The consortium focuses on sharing precompetitive patient-level data from the legacy clinical trials, developing new tools to be submitted to the regulatory agencies, and developing consensus data standards. Since February 2008, when CPAD (formerly CAMD) launched initial technical activity in these areas, significant milestones have been accomplished:

Table 3
C-Path's data successes in CDISC standards and integrated databases.

Consortium	Disease Area	Accomplishments
CPAD (Critical Path for Alzheimer's Disease)	Alzheimer disease (AD) and related dementias	• First CPAD (formerly CAMD) standard • First publicly-available database for AD in CDISC standards • First clinical trial simulation tool for AD endorsed by FDA and EMA LINK: https://c-path.org/programs/camd/
CFAST (Coalition for Accelerating Standard for Therapies)	Multiple therapeutic areas	• Delivery of 21 Therapeutic Area User Guides for CDISC standards LINK: https://c-path.org/programs/cfast/
CPP (Critical Path for Parkinson's)	Parkinson disease (PD)	• First CDISC standards for PD • Initiation of an integrated database for PD LINK: https://c-path.org/programs/cpp/
D-RSC (Duchenne Muscular Dystrophy-Regulatory Science Consortium	Duchenne Muscular Dystrophy (DMD)	• First CDISC standards for Duchenne • Initiation of first publicly-available database for Duchenne using CDISC standards LINK: https://c-path.org/programs/d-rsc/
HD-RSC (Huntington Disease-Regulatory Science Consortium)	Huntington Disease (HD)	• First CDISC standard for HD under review • Initiation of first publicly-available database using CDISC standards LINK: https://c-path.org/critical-path-institute-and-chdi-foundation-Inc.-establish-a-consortium-to-expedite-approval-of-huntingtons-disease-therapeutics/
MSOAC (Multiple Sclerosis Outcome Assessment Consortium)	Multiple Sclerosis (MS)	• First CDISC standard for MS LINK: https://c-path.org/programs/msoac/
PKD (Polycystic Kidney Disease Consortium)	Polycystic Kidney Disease (PKD)	• First CDISC standard for PKD • First publicly-available database and imaging biomarker approved by FDA for prognostic use LINK: https://c-path.org/programs/pkd/
PSTC (Predictive Safety and Toxicology Consortium)	Safety/Toxicology	• First regulatory support for liver and skeletal muscle biomarkers LINK: https://c-path.org/programs/pstc/ • First Data and Sample Repository initiative with FDA LINK: https://c-path.org/programs/bmdr/

- *Consensus data standards:* CPAD (formerly CAMD), in partnership with CDISC, have co-developed therapeutic specific clinical data standards for Alzheimer disease (v1.0, 2010 and v2.0, 2013)
- *Unified clinical trial database:* CPAD (formerly CAMD) members contributed clinical data at the individual patient-level from placebo arms of clinical trials available to qualified researchers to fulfill goals of consortium and address research gaps in the field [49,50]
- M*odel-based based drug development tool for clinical trial design in Alzheimer disease*: A clinical trial simulation tool designed to aid in trial design for mild and moderate AD was endorsed by both FDA and EMA representing the first example of regulatory endorsed drug disease trial [51]
- *Imaging biomarker qualified by EMA for Alzheimer's disease clinical trials*: Low baseline hippocampal volume was qualified for use by EMA as an enrichment biomarker for clinical trials in predementia stages of AD [52].

These achievements were made possible by the consortium approach of a large network of stakeholders, sharing of anonymized, patient-level data, shared costs and risks, and continuous engagement with the regulatory agencies. Fundamental to the mission of CPAD is the sharing of non-competitive patient-level data from legacy clinical trials, and transformation of those data into generalizable and applicable knowledge to advance new drug development tools.

There remains an urgent need to share biomarker data to enable FDA qualification of AD biomarkers and expand the existing quantitative disease models of mild-to-moderate AD to earlier stages of AD. Not sharing patient-level biomarker data from AD clinical trials has been a significant barrier and, if continued, would perpetuate the gaps in knowledge and prevent the necessary advancement from the tremendous investments already made. Meta-analyses have been recently reported on [53] and AlzForum has developed the AlzBiomarker database aimed at performing *meta*-analyses across large sources of data (http://www.alzforum.org/alzbiomarker).

Despite the remarkable advances in biomarker development since the last approved new molecular entity (NME) for AD product (circa 2004), AD trials continue to fail at an unprecedented rate of greater than 99.6%. Another recent disappointment came in December 2016 with the failure of Lilly's Solanezumab [54] Phase 3 study.

More recently, the AD community has been proposed a classification of AD based on three types of biomarkers [55]. The "A/T/N" classification system uses seven major AD biomarkers divided into three binary categories based on the nature of the pathophysiology that each measures. "A" refers to the value of a β-amyloid biomarker (amyloid PET or CSF Aβ42); "T," the value of a tau biomarker (CSF phospho tau, or tau PET); and "N," biomarkers of neurodegeneration or neuronal injury ([^{18}F]-fluorodeoxyglucose–PET, structural MRI, or CSF total tau). While, at face value, this classification is helpful in broadly classifying that an individual may have AD, it does not take into account the needed specificity for a diagnosis. For example, with this classification scheme, individuals with Lewy Body Dementia would be incorrectly included as AD patients unless an additional screen for dopamine transporter were to be performed [56], reinforcing the need for enhanced communication across the CNS disease communities. Although not yet considered for inclusion in the "A/T/N" classification, Neurofilament Light (NfL) has been shown to have very promising stage-dependent increases in plasma and CSF exposure [57].

The challenges detailed in Table 4 should not be underestimated. As we continue to fight the battle of overcoming this devastating disease, the AD community must pull together to understand what the root cause of these failures truly are: ineffective therapies, poor patient selection, insensitive outcome assessments, lack of sharing foundational data that would drive better decision making.

3.2. Amyotrophic Lateral Sclerosis (ALS)

Advancement in the discovery of candidate biomarkers for ALS have not been as rapid as in other brain disorders, both because of factors related to relatively low incidence of this disease, and because of limited funding opportunities. However, understanding of the clinical and pathological heterogeneity of ALS has become increasingly evident in the last several decades.

Recent reviews highlight that biomarker work is being focused into the following areas listed [58–60]: 1) Tissue and Fluid Markers for blood–brain barrier (BBB) dysfunction, neuroaxonal degeneration, neuroprotection, inflammation and immune activation, and glial

Table 4
Challenges and Opportunities in Developing CNS Therapeutics.

Challenge	Gaps	Opportunities
Patient Heterogeneity	• Heterogeneity of patient populations • Heterogeneity of co-morbid symptoms • A standardized database of anonymized, patient-level CNS clinical trial data	• Embed blood biomarkers/ genotyping and biometric monitoring device (BMD) assessments in annual health care check-ups • Actively share and aggregate data across CNS diseases to build greater understanding of converging and divergent patient characteristics and disease progression
Patient Selection/Study Design	• Recruitment speed • Patients without disease • Underpowered studies	• Create patient registries • Use data from screen-failures as baseline normal aging cohort • Use continuous assessments from biometric monitoring devices to increase statistical power
Mechanism	• Limited understanding of the neurobiology of disease	• Use concise informed consent that enables use of data/ samples for beyond single studies to understand disease progression across all CNS disorders
Treatment Initiation	• Increasing rationale to treat in pre-symptomatic stages of the disease	• Leverage objective biomarker and BMD annual check-up data to inform impeding need for treatment
Clinical Outcome Assessments	• Subjective, relatively insensitive outcome measures • Outcome assessments in pre-symptomatic stages take years to detect change	• Validate BMD assessments that reflect objective Performance Outcomes (PerfOs) • Utilize PerfOs that can detect change over weeks to months to accelerate drug approval process
Economic	• Reimbursement issues/payers; uncertainty in terms of what is needed by payers to facilitate adoption and coverage (e.g., IDEAs study for AD imaging) • High cost of trials due to imaging, ancillary assessments, and chronic nature of trials	• Reimbursement dependent on favorable impact to patients and overall reduction in health care maintenance • Accelerate the development of low-cost blood biomarkers and BMD PerfOs that improve patient selection and detection of meaningful change • Use of BMDs can reduce numbers needed to treat by 80%
Regulatory	• Need for qualified Drug Development Tools to accelerate the development process • Infrequent use of CDISC standards across individual trials that would enable the ability to pool and analyze data across all trials	• Require data sharing early as a condition of future reimbursement • Require all organizations, including NIH funded studies, to have clinical data aggregated into CDISC standards

activation; 2) Physiologic markers of motor neuron number, axonal excitability, electrical muscle impedance, and responsivity to transcranial stimulation; 3) Imaging markers for neurotransmitters and metabolism, voxel and surface-based MRI morphometry, diffusion tensor imaging (DTI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS), and spinal cord MRI. While many of these biomarkers are emerging with the potential to refine the diagnosis of ALS, to stratify patients prognostically, and to facilitate the development process for therapeutics, none have been endorsed by regulators.

However, one impactful example of validating back translation has been carried out by the Amyotrophic Lateral Sclerosis (ALS) community. The ALS Therapy Development Institute (TDI) nonprofit organization embarked on an intensive initiative to evaluate the predictive accuracy of the most commonly used mouse model of ALS, experimental animals carrying human Superoxide Dismutase (SOD) mutations. The G93A mouse genetic mouse model of motor neuron disease has been used extensively to evaluate candidate therapies for ALS with no efficacy found to date from all trials despite promising results in animals. Investigators gathered in 2006 to agree on standard operating procedures for preclinical research in ALS/MND as a way to foster translatability and consensus by applying learnings from independent investigators [61].

The ALS TDI investigators tested more than 100 potential drugs in the most commonly used mouse model of ALS using defined experimental conditions (http://www.nature.com/news/ preclinical-research-make-mouse-studies-work-1.14913). No treatment benefit was observed in the experiments carried out by ALS TDI investigators, despite the fact that many of the drugs tested included those that had been previously reported to slow down disease in the same mouse model. Eight of these compounds ultimately failed in clinical trials. In a disease, as rare and devastating as ALS, eight trials represent a relatively large population subjected to experimental treatments with no benefit or learnings to apply to future patients. Parallel initiatives, focused on data integration of patient-level data from human ALS patients into an open source data repository, are underway with focus on enabling discovery of novel therapeutic targets and biomarkers [62].

As has been seen for AD, more recently, there is growing evidence for the use of Neurofilament Light (NfL) as a biomarker in ALS. Elevation in NfL levels in patients with upper motor neuron involvement might reflect the corticospinal tract degeneration. Low NfL levels in patients with lower motor neuron signs might be a prognostic indicator of milder phenotypes of disease [63,64].

3.3. Autism Spectrum Disorder (ASD)

Drug development in ASD has lagged behind most all CNS disease. A major challenge in studying autism centers around its heterogeneity, which poses major hurdles in developing treatments. Other difficulties relate to the need for early intervention, perhaps even in infancy, the complex genetics, paucity of known druggable targets, and lack of knowledge of disease trajectories. Despite advances in the molecular genetics of autism, translational preclinical models are lacking to evaluate new targets [65]. Distinct subtypes of autism exist and subgroups are likely in need of different treatments. Precision medicine strategies will be essential to successful drug development and enabling translational research [66,67].

Stratification biomarkers hold promise in defining distinctive subtypes of autism; candidate biomarkers have been identified and are being investigated longitudinally in a European Autism Project. The EU-AIMS consortium (https://www.eu-aims.eu/) represents the largest multidisciplinary study on autism and has been deemed one of the most successful initiatives under the umbrella of IMI [68,69]. The study includes hundreds of patients with ASD, ranging from 6 to 30 years as well as typically developing participants and twin pairs. Comprehensive assessments on each subject include symptoms, cognitive function and neuroimaging biomarkers, biofluid biomarkers and genetics.

The project has made impressive progress since its inception in 2011. In addition to advancing the understanding of the underlying neurobiology of the disease, the impact has implications for researchers and drug developers. The consortium took unique steps to define paths to regulatory science and endorsement of novel candidate biomarkers and outcome measures. Academic and industry investigators consulted with representatives of the EMA to review the parameters of the EU-AIMS longitudinal study and define paths to use of biomarkers in clinical trials.

In 2016, the EMA issued a total of five letters of support for biomarkers and outcome measures (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp#section15) that included:

- EEG utility to measure deficits in social cognition for ASD patient stratification
- MRI methodology for ASD patient stratification
- Eye tracking to stratify patients with ASD
- Measures of executive function and basic emotions to stratify patients with ASD
- Methods to identify clinical outcome assessments utility to measure clinical symptoms in people with ASD.

Regulatory agencies have launched the biomarker letter of support mechanism as a way to encourage the use of particular promising biomarkers in clinical trials. Autism represents the most number of letters of support allocated to a specific disease across both FDA and EMA. Laying a regulatory path for biomarkers serves to incentivize their use in prospective trials and reduce the risk of individual sponsors in advancing new therapies to the clinic. Leading candidate biomarkers for Autism were outlined by consortium participants of EUAIMs in conjunction with members of the EMA Scientific Advice Working Party (SAWP) [70]. Eye tracking, fMRI, DTI all hold promise in defining patient endophenotypes and monitoring progression and recovery. Hopefully, in the near future, these biomarkers will acquire sufficient evidence to be qualified or approved by EMA for use as in clinical drug trials. Similar encouraging advances have not yet been achieved with the FDA.

Databases and quantitative disease progression models are urgently needed for ASD. Targeting specific needs of each individual on the spectrum, with the strategy of advancing the right drug for the right patient at the right time, will be critical for success. It is likely that challenges will continue in attempts to model the complex neurophysiological connectivity deficits of autism in animals and more attention to big data analytics will be critical for the future development of validated biomarkers and therapeutic interventions.

3.4. Depression

Depression is a debilitating and chronic disease. A string of promising, but ultimately unsuccessful studies on single biomarkers for depression has left many psychiatrists skeptical about the feasibility of a single test to diagnose depression. Other experts, however, believe that a recent shift towards studying multi-biomarker panels that reflect depression's true complexity could become an unexpected breakthrough for certain patient populations.

While not yet approved by any regulatory agency, there are two notable recent efforts on biomarkers for depression. The first [71], investigated sex differences in Major Depressive Disorder (MDD) markers using multiplex immunoassay measurements of 171 serum molecules in individuals enrolled in the Netherlands Study of Depression and Anxiety (NMDD = 231; Ncontrol = 365). They found 28 sex-dependent markers of MDD, as quantified by a significant interaction between sex and log2-transformed analyte concentration in a logistic regression with diagnosis (MDD/control) as the outcome variable ($p < 0.05$; $q < 0.30$). Among these were a number of male-specific associations between MDD and elevated levels of proteins involved in immune response, including C-reactive protein, trefoil factor 3, cystatin-C, fetuin-A, β2-microglobulin, CD5L, FASLG receptor, and tumor necrosis factor receptor 2. The second [72], is work using functional magnetic resonance imaging (fMRI) in a large multisite sample (n = 1188) with out-of-sample replication datasets. Patients were shown to be subdivided into four neurophysiological subtypes that were not associated with differing clinical-symptom profiles. Remarkably, however, the novel subtypes transcended current diagnostic boundaries to show the subset of individuals who were most likely to benefit from target neurostimulation therapies. Identifying this type of predictive response biomarker represents the "holy grail" to ensure effective treatments.

3.5. Huntington Disease (HD)

Drug development in Huntington disease holds tremendous promise, particularly for early intervention. Targeting therapies in premanifest disease stages is viable due to the advances in genetic testing that reliably predict with 100% reliability the development of the disease [73]. The key challenge for this disease is which symptoms will manifest, and when. Disease-modifying targets are being aggressively pursued, particularly in the biotech space [74]. Biomarker development in HD includes CSF Huntingtin [75] for assessing target engagement, volumetric MRI of striatum [76], MRS and Molecular imaging of PDE10, a specific marker of striatal medium spiny neurons now with specific PET ligands [77]. Challenges facing this disease area center around the lack of an accurate disease progression model that takes into account the co-variates that influence both, the timing and heterogeneity in the expression of the clinical symptoms.

One of the most-promising recent biomarkers that has shown correlation both with the degree of clinical manifestation of the disease and the prominence in the expression of the Huntington gene is Neurofilament Light, a marker of degenerating neurons that can be measured both in plasma and CSF [78].

Consortia, such as the Huntington's Disease-Regulatory Science Consortium (HD-RSC), are being launched to fill gaps and define collaborative strategies for the future (https://c-path.org/critical-path-institute-and-chdi-foundation-Inc.-establish-a-consortium-to-expedite-approval-of-huntingtons-disease-therapeutics/).

3.6. Multiple Sclerosis (MS)

Multiple sclerosis serves as a rare example in neurology illustrating that therapeutic development that modifies the course of the disease can be successful. The past 10 years have led to the approval of clinically-effective medicines for relapsing-remitting MS. To date, the FDA has approved a total of 13 medications for the treatment of relapsing forms of MS. It is well acknowledged that biomarkers have been key in catalyzing success in delivering effective treatments for patients. At present, gaps remain in treatments for primary progressive forms of the disease yet progress is advancing rapidly. This progress represents a candid success story of personalized medicine in neuroscience. Biomarkers are being used to assess risk/benefit in terms of safety for individual patients to manage potential autoimmune mechanisms that may underlie adverse responses to specific therapies [79].

All approved MS therapies have been shown to reduce the number of and number of new plaques as assessed by MRI [79]. Biofluid biomarkers that assess immune status are being used to aid in monitoring pharmacodynamic responses, target engagement and safety monitoring [80].

Precompetitive consortia, data sharing and biomarker research advances have a role in catalyzing successful advancement of therapies in MS [81]. C-Path's Multiple Sclerosis Outcomes Assessments Consortium (MSOAC) has successfully launched a unified clinical trial database consisting of patient-level data from placebo arms of MS clinical trials (https://c-path.org//wp-content/uploads/2014/06/CDISC-data-standard-for-multiple-sclerosis-spurs-sharing-of-clinical-data-press-release.pdf). The MS placebo database is targeted for researchers and industry. A MS data registry, open to all practicing neurologists called MSBase, represents a unique international database dedicated to sharing, tracking and evaluating outcomes data in MS [82]. The database has been used successfully

to investigate gender differences, geographic location, therapeutic responses and outcome measure optimization.

As is true for most chronic disease conditions, early intervention is believed to be key in MS. Most MS experts recommend that individuals consider starting one of the approved medications as soon as the diagnosis of relapsing remitting MS has been confirmed. Furthermore, neuroimaging biomarkers can enable effective treatment decisions when carried out early in the disease course [83]. Gaps exist at the present time in terms of therapies to treat primary progressive forms of MS, yet multiple strategies are underway including therapeutic targets aimed at neuroprotection and neurorestoration.

Two additional candidate biomarkers for MS include optical coherence tomography [84] and serum Neurofilament Light (NfL), as a marker to monitor for subclinical MRI activity and even treatment response in Relapsing Remitting MS [85]. Thus, in clinically stable patients, serum NfL may offer an alternative, cost-effective way to monitor for subclinical disease activity.

In conclusion, the tremendous success in approved treatments for MS, including disease modification, provides hope that similar advances can be achieved in other CNS conditions.

3.7. Parkinson Disease (PD)

Evaluation of the long-term trends on the incidence of PD indicates that the number of new cases has grown every 10 years since 1976, particularly in men older than 70 years of age [86]. Advances in the understanding of the pathogenesis of PD are occurring at a rapid pace. Novel candidate genes and new therapeutic candidates are emerging. There is increasing attention on the importance of non-motor symptoms as key feature that precedes onset of motor disability and may contribute to disease pathogenesis in ways that were not anticipated years ago [87,88].

Drug development in PD is being pursued aggressively by industry, biotech and nonprofit organizations. Challenges in drug development include prolonged duration of disease progression, heterogeneity of the patient population, risk of adverse drug reactions in an elderly patient population and absence of biomarkers to differentiate subtypes of parkinsonism. Furthermore, as with AD, the field is moving to early intervention with new diagnostic criteria [89] and strategies for intervention where biomarkers will be increasingly important [90,91].

There is an urgent need for biomarkers as tools that can be successfully employed in trials to enable patient selection, proof of mechanism and to monitor effects of new candidates on disease progression. Yet, the field of PD has lagged behind in terms of biomarker discovery and validation. Rich, data-driven approaches, focused on biomarker identification, have been well underway for several years [92,93] and many clinical trials employing candidate biomarkers exist. Leading candidate biomarkers for patient selection and target engagement are under active investigation. Examples include CSF biomarkers [94,95] and neuroimaging of dopamine function [96].

Other promising biomarkers are at an exploratory stage with further work needed to confirm initial findings [97,98]. Overall, data sharing in PD is at its infancy, particularly when one compares the field relative to that of other disease areas such as AD [99] and oncology [100]. A call to action to incentivize such a shift in mindset is underway [101,102] that also includes patients [103].

Regulatory status of candidate biomarkers has focused on imaging of the dopamine transporter DAT. This biomarker received letters of support from FDA and EMA as patient selection/enrichment biomarkers for early stage patients. The heterogeneity of PD poses challenges for drug developers. Even with DAT employed successfully, not all subjects with DAT deficiency will end up having true PD (e.g., DAT deficiency is also a feature of Multiple System Atrophy and Progressive Supranuclear Palsy and Lewy Body Dementia). It is unlikely that a single biomarker will identify a purely homogeneous patient population, so studies aimed at combinatorial strategies are important for the future [104].

At present, there are still gaps and barriers that pose substantial risk to those advancing new treatments, despite the progress with genetically defined targets. There is strong interest in early intervention, yet challenges still exist on many levels. 1) There is a lack of consensus across all stakeholders in terms of adopting diagnostic criteria and consensus taxonomy definitions; 2) precise subpopulations of PD subjects with prognostic fates are not yet defined (consensus on endophenotypes is lacking); 3) biomarkers are lacking that can accurately identify precise subcategories; and 4) the current accepted outcome measures are antiquated and lack the measurement properties to track progression of many disabilities that impact patient's quality-of-life.

Like AD, there is increasing recognition that novel disease-modifying therapies will be most efficacious if treatment is initiated very early in the course of the disease. Significant challenges exist in advancing treatments for very early stage PD subjects in that it is difficult to accurately diagnose patients based upon clinical evaluations alone. Clinical symptoms of early motor PD overlap with many different conditions and the true percentage of atypical parkinsonism or other non-PD cases in legacy PD clinical trials is still not known. Novel biomarker approaches are needed to accurately identify PD patients for subject selection in clinical trials. Pharmaceutical companies, in conjunction with academic experts and advocacy organizations, are exploring a multitude of biomarkers and risk factors that promise to aid in diagnosis, prognosis, target engagement and clinical response.

PD-centric consortia are far fewer in number as compared to AD consortia. Cross discipline alliances consisting of experts have been put in place to support defined initiatives [105]. In 2015 the Critical Path for Parkinson's consortium was launched as a precompetitive initiative aimed at sharing resources, data and advancing novel regulatory-endorsed tools aimed at early intervention [102]. The premise was aimed at replicating the success of CPAD (formerly known as CAMP) in Alzheimer disease by integrating data from global sources and advancing disease progression modeling tools to regulatory agencies for endorsement. Alignment of emerging precompetitive initiatives in PD will be key to enable shared learnings and costs so as to increase the chances of success of all new therapeutic candidates.

Finally, there is an urgent need for identification and validation of disease progression biomarkers and refined approaches to classifying PD that take into account current tools and technologies that enable continuous remote monitoring of patient functions using more sensitive measurements [106]. The recent example of sharing of data acquired from the PD community in the digital technology application mPower is noteworthy in driving increased direct patient engagement [107]. A remaining challenge is to motive patients to remain engaged over multiple years to build further understanding in disease progression.

In summary, the biomarker landscape in PD is advancing, yet it has not reached the point of expediting clinical trials. The National Institute of Neurological Disorders and Stroke (NINDS) launched in 2012 the Parkinson's Disease Biomarker Platform (PDBP) which has collected biospecimens and clinical data from more than 1000 individuals. Samples are stored in a central repository and made available for discovery efforts by the neuroscience research community [108]. The role of government and advocacy organizations is key in that NIH is leading PDBP and the Michael J. Fox Foundation (MJFF) is the primary funder of the Parkinson's Progression Markers Initiative (PPMI). These and other global efforts are advancing to biomarker discovery at earlier stages of the disease and in genetically defined cohorts (PPMI, EU cohort biomarker paper(s)). Leading candidate PD biomarkers include molecular neuroimaging of dopaminergic function, structural neuroimaging, MRS, CSF synuclein, plasma proteomics, microRNAs, fMRI/DTI, and more recently Neurofilament Light, NfL [109–111].

3.8. Schizophrenia

Identifying biomarkers that can be used as diagnostics or predictors of treatment response (theranostics) in individuals with schizophrenia will be an important step towards being able to provide personalized treatment. A recent study suggested that blood-based biomarkers for schizophrenia may be a viable, cost effective approach [112]. This is evidenced by a *meta*-analysis of six studies involving 330 patients and 202 healthy controls that were included for *meta*-analysis examining the role of microRNAs. The pooled sensitivity, specificity and diagnostic odds ratio were 0.81 (95% CI: 0.75–0.86), 0.81 (95% CI: 0.72–0.88) and 18 (95% CI: 9–34), respectively; the positive and negative likelihood ratio was 4.3 and 0.24 respectively; the area under the curve in summary ROC was 0.87 (95% CI: 0.84–0.90). Validation revealed that miR-181b-5p, miR-21-5p, miR-195-5p, miR-137, miR-346 and miR-34a-5p in Peripheral Blood Mononuclear Cells (PBMNCs) had high diagnostic sensitivity and specificity in the context of schizophrenia diagnosis.

Finally, as has been demonstrated for other areas, there is growing interest to run pilot studies to understand whether biometric monitoring with smartphones could be useful in understanding and managing schizophrenia [113].

Unfortunately, to date, no diagnostic or theranostic biomarkers have been approved by regulatory agencies.

3.9. Traumatic Brain Injury (TBI)

Worldwide, TBI is recognized as a leading cause of mortality and morbidity (https://www.cdc.gov/traumaticbraininjury/severe.html). The long-term consequences of TBI are gaining visibility with highly publicized attention on the impact of concussion and repetitive head impact exposure [114,115]. Unfortunately, no therapeutic drugs have been approved for the treatment of TBI.

The field of therapeutic development for TB faces unique challenges. Key factors to solve include the heterogeneity of the injury itself, the lack of precise diagnostic criteria, the heterogeneity in time-course of pathophysiological changes following TBI (depending upon the severity of insult), the current status of outcome measures (which are not sensitive to measure change or therapeutic response), spontaneous recovery rate (which is known to vary according to unknown factors), unknown blood brain barrier permeability of test agents, need for demonstration of target engagement and central activity (proof of mechanism), and the lack of existing data (that can be used to accurately estimate duration of treatment required for detecting measurable treatment effects). Clinical trials to date have included subjects with a broad range of severities and trial-specific parameters (inclusion/exclusion criteria, time for onset of treatment, dose, etc.). Furthermore, the existing tools employed in TBI trials do not permit selection of patients with injury mechanisms that may preferentially respond to targeted therapies. Precision medicine strategies are envisioned to be transformative. Biomarker development and validation is progressing with promising leading candidates including neuroimaging modalities [116,117] and biofluid proteins measurable in plasma [118,119]. Promising new fluid biomarkers have been recently reviewed [120,121]. These biomarkers promise to aid in patient selection and potentially to aid in assessing response to novel interventions.

Until recently, clinical research in TBI has been hampered by lack of data standardization and was undertaken with limited multidisciplinary collaboration. New initiatives are paving the way to successfully address these issues in ways that hold promise for the future. For example, the TBI community is championing comprehensive data standardization [122–125] including the preclinical stage [26]. Additional impactful initiatives include the TRACK TBI study, a longitudinal study designed (similarly to ADNI) for biomarker identification, and the Traumatic Brain Injury Therapeutic endpoints development initiative [125]. The Department of Defense funded the TBI Endpoint Development (TED) initiative as a consortium-led project aimed at development of clinical trials leading to more precise diagnosis and effective treatments for TBI. The unique attributes of the TED project include its focus on regulatory science with the aim at defining leading biomarkers and outcome measures that can be endorsed by regulatory agencies to accelerate drug and device development. The TED initiative was built to leverage the expertise and experience of academia, philanthropies, patient-advocacy organizations, and a committed cadre of pharmaceutical, imaging, and emerging technology industry members, with contribution of financial and in-kind resources by all participants to enable a precision medicine focus. The aims of the TED initiative are to gain consensus as to TBI outcome measures and biomarkers as drug development tools through formal regulatory endorsement. TED fosters early and iterative collaboration with FDA to: 1) assess the regulatory readiness of, and 2) by consensus, choose from a set of TBI COAs, proteomic and neuroimaging biomarkers, and emerging technologies that can be validated for use in TBI clinical trials [123].

Finally, the Center of Devices and Radiologic Health (CDRH) within FDA continues to support a number of efforts to advance biomarker development for monitoring TBI (https://www.fda.gov/EmergencyPreparedness/%20Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm440520.htm).

3.9.1. Spinal Muscular Atrophy (SMA). SMA is the most common genetic cause of death in infants. Remarkably, in 2016, the FDA approved the first effective treatment for this devastating disease (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm534611.htm). This landmark achievement is notable as it represents disease modification via gene therapy (http://www.sciencemag.org/news/2016/12/novel-drug-rescues-babies-fatal-neurodegenerative-disease), accomplished before the mandatory registration submissions requiring the use of CDISC standards.

3.9.2. Frontal Temporal Dementia (FTD). FTD represents a heterogenous set of diseases that lack approved drugs. Regulatory frameworks are lacking to guide various drug development programs sprouting up across the U.S. and the European Union (EU), which increases the risk for drug developers. Guidance documents that have been developed for AD by FDA or EMA and for rare diseases (FDA) do not specifically address FTD. Research suggests that biomarker profiles in FTD are distinct from that of AD [10]. More recently, shared genes have been discovered overlapping FTD with AD and PD [129]. Biomarkers in FTD hold potential to identifying patients, for assessing target engagement and for monitoring disease progression. In fact, regulators communicate that finding biomarkers that allow to discriminate between etiological types of FTD and positively identifying the presence of the underlying pathology hallmark lesions *in vivo* are factors that would propel drug evaluation in FTD (Alzforum: http://www.alzforum.org/news/conference-coverage/regulators-tell-frontotemporal-dementia-community-we-play-your-teamhttp://www.alzforum.org/news/conference-coverage/regulators-tell-frontotemporal-dementia-community-we-play-your-team). Sharing resources and data is key to success in this arena. Precompetitive efforts in this area are emerging (e.g., Tau Consortium and FTD Treatment Study Group).

3.9.3. Duchenne Muscular Dystrophy (DMD). DMD represents a class of inherited diseases that are characterized by weakness and wasting away of muscle tissue. Current and emerging treatments are underway with focus on molecular targeting [130]. Recent regulatory issues in the field of DMD are notable and emphasize the importance of biomarkers as well as the role of the external patient-advocacy community. The first global approval of a drug for the treatment of DMD took place in 2016

[131]. The antisense oligonucleotide Eteplirsen, designed to induce exon skipping, received accelerated approval by the FDA with orphan drug designation in the U.S. and the EU. Results were primarily based on Phase III data showing elevation of dystrophin levels from baseline in muscle tissues from twelve patients with DMD after 48 weeks of treatment. The external patient community was instrumental in highlighting the unmet needs for rare pediatric disease designation. Of the many factors that weighed into the final decision, data demonstrating changes in dystrophin expression in muscle biopsies was at the core of the decision by FDA leadership to approve the drug under the accelerated approval path. This experience emphasizes the importance of biomarkers in regulatory decision making in a unique way.

Regulatory guidance, developed by both FDA and the DMD external scientific community, led by Parent Project MD (PPMD), have attended to the importance of biomarker validation as critically important, with specific emphasis on dystrophin measurements (FDA Briefing Document: https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm481911.pdf). Increased muscle membrane fragility occurs as a result of loss of dystrophin expression in muscle results from DMD gene mutations distribution of the dystrophin glycoprotein complex. Relative to other biomarkers, the invasiveness of muscle biopsies, when combined with the rare prevalence in a pediatric population, poses challenges for reliable and reproducible longitudinal quantitative measures in humans. Indeed, evidence of dystrophin production in muscle biopsies has been inconsistent [132]. The challenges associated with the approval of Eteplirsen would have been reduced if additional studies had been carried out that proved the reliability and reproducibility as well as clinical relevance of dystrophin measurements in muscle biopsies.

FDA leadership has recommended that drug developers aim to first develop a comprehensive data-driven effort to understand the natural history of the disease. Indeed, a key priority for FDA's future strategies is to allocate funding to support natural history databases, particularly of rare diseases. It is advised that patients be consulted in addition to expert consultants. All biomarkers and outcome measures should ideally be qualified by regulatory agencies for use before starting to rely on them in decision making for new drug candidates (link to FDA presentation: https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM525805.pdf). For non-qualified biomarkers that are critical to a development program, performance aspects and validation studies should be explored in humans as thoroughly as possible prior to initiating human clinical trials. If the biomarker is to be used for a critical purpose, for example patient selection or pharmacodynamics readout, remaining uncertainly should be addressed as part of the development program.

While this section summarizes many of the key biomarkers assessments used in understanding CNS diseases, unfortunately, most have not gained regulatory acceptance.

3.10. Other rare diseases

A staggering 95 percent of orphan diseases have no FDA approved drug [86,126,127]. Challenges in advancing new treatments for rare diseases include small and heterogeneous patient populations, poorly-defined disease natural history, understanding and agreement concerning validated outcome measures and biochemical biomarkers for research and clinical trials. Nonetheless, orphan diseases and indications represent a major growth area for pharma and biotech companies. Collective resources of industry, government and patient-advocacy communities are tackling new frameworks for shaping the landscape of drug development. Orphan diseases of the nervous system frequently are progressive and fatal conditions that are devastating to families, patients and caregivers. Examples include Spinal Muscular Atrophy (SMA), Duchenne Muscular Dystrophy (DMD), and Frontal Temporal Dementia (FTD).

A co-evolution of science and regulatory guidance has taken place in recent years facilitating collaborative research and health policies. Stakeholder engagement drive deliberative processes have taken place across a wide variety of orphan diseases. For example, in DMD, the advocacy community submitted the first ever community-led disease-specific guidance [128]. Key areas highlighted in the consensus guidance included outcome measures and biomarkers. FDA followed up with their own guidance that was shaped by input from the DMD driven community.

The regulatory incentives for drug developers in this arena are catalysts for small and large pharma, and many pharmaceutical companies put in place rare disease units to focus on unique approaches to clinical development paths. Regulatory landscape and incentives have been enabled including guidance documents, accelerated approval processes, patient-centered outcomes, drug repurposing, patient compassionate access and adaptive trial designs. Model-informed drug development is a key platform to be scaled to provide better treatment for more orphan drug patients. A draft guidance was issued in October 2015 focused on drug development for rare diseases: http://www.regulations.gov/contentStreamer?documentId=FDA-2015-D-2818-0002&attachmentNumber=1&disposition=attachment&contentType=pdf.

4. Conclusions and recommendations for the future

The high failure rate of drugs to treat CNS diseases has led to business decisions by some large pharmaceutical companies to discontinue drug development in this space [133]. A sense of urgency is needed to collectively work together to solve complex problems associated with drug development [134]. Patients suffering from brain diseases are waiting and oftentimes do not survive the length of time to advance a new target or biomarker for use that will benefit them in their lifetime. Existing outcome measures may not be reflective of what is truly important to patients in their daily lives.

Public-private-partnerships represent a unique platform to share costs and risks. Policymakers have engaged themselves in raising issues and recommendations that are aimed at bridging the gap between precision medicine and FDA regulation. The total costs for biomarker-related initiatives, currently covered by industry, health insurance programs, philanthropists, and federally-funded research institutions, is far less than what is needed to advance innovative treatments across CNS diseases.

There is increasing recognition that regulators and payers require that clinical studies demonstrate not only statistical significance of an effect but even more importantly, clinical and pharmacoeconomic significance [135]. These types of standards also apply to biomarkers. A case example of this issue is focused on amyloid PET imaging. PET imaging is very costly and challenging to implement successfully in multisite global trials and in routine clinical care, particularly in rural communities. Regardless of the successful approval by regulatory agencies of multiple amyloid PET neuroimaging ligands to aid in the detection of amyloid in living human brain, the Centers for Medicare and Medicaid Services (CMS) will not cover the costs of PET imaging. The main concerns center around insufficient evidence that there is a beneficial impact on improving patient outcomes.

With the expansive landscape in human healthcare and focus on big data analytics, the attentiveness to data sharing is growing at a rapid pace. Real-world examples exist of Public-Private-Partnerships (PPPs) focused on data sharing, pathway based analysis, crowdsourcing and mechanistic modeling 5 generating substantial impact for CNS diseases. Yet, significant barriers still exist around privacy, consent, intellectual

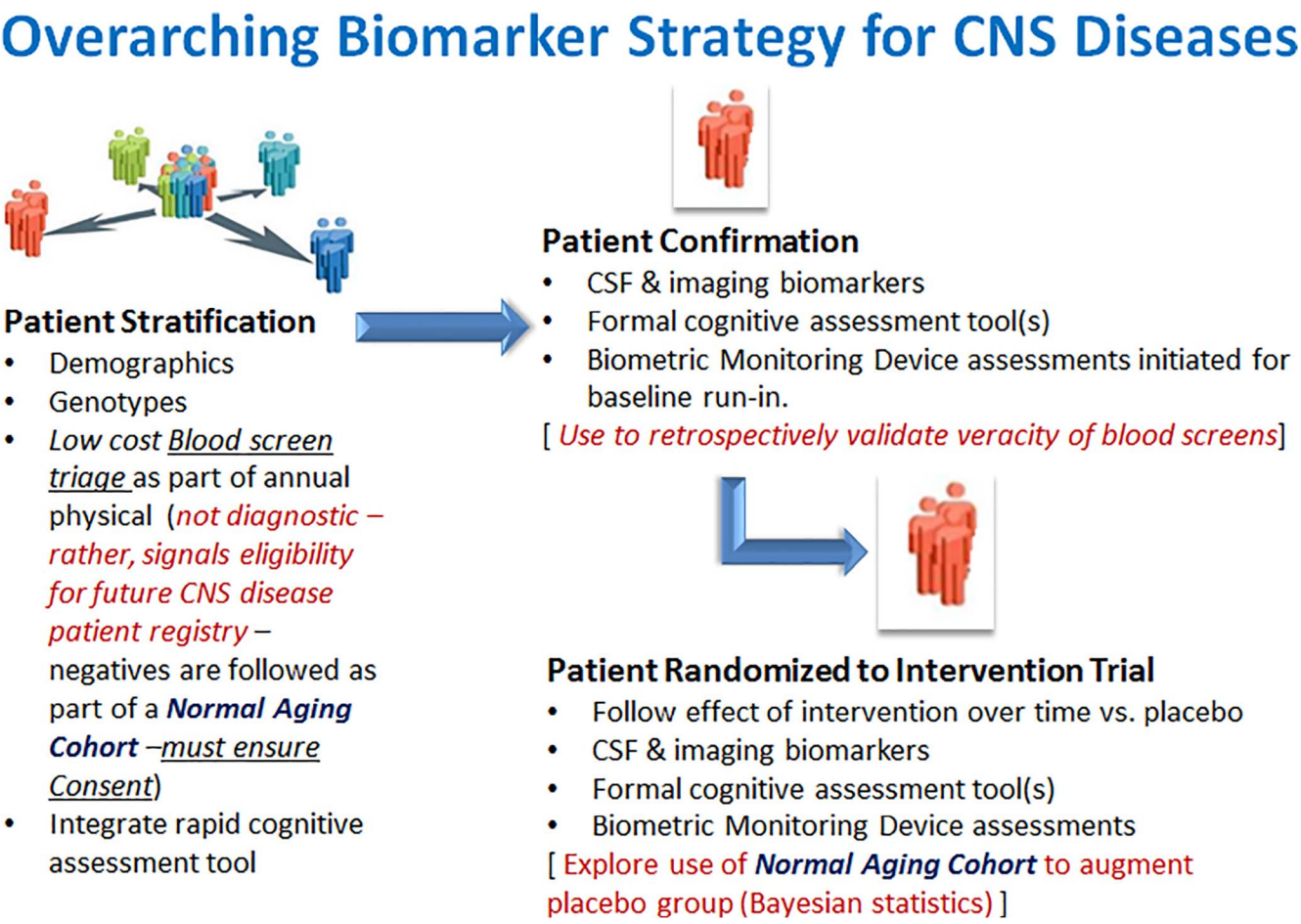

Fig. 4. In order to implement a viable biomarker strategy for CNS Disease, the following actions require implementation: Promote the development of a sustainable and feasible data sharing infrastructure that uses consensus data standards (e.g., CDISC). Create incentives that ensure data sharing for those who contribute patient-level data to support biomarker development. Improve compliance with sharing of clinical trials that have been completed (clinical trials.gov, peer reviewed publications), and improve communications of results of data sharing initiatives, especially those related to clinical trials [46]. Study sponsors should use concise informed consent forms (ICFs) that will enable sharing of data beyond a specific trial [136]. Leverage the framework already created for the cardiovascular, diabetes, and oncology fields to implement biomarkers not only into clinical trials, but as a means to understand on an annual basis the maintenance of brain health [137].

property, costs, enabling competitors, infrastructure, and potential inappropriate or false conclusions. Efficiencies will be gained by sharing learnings across organizations that host data repositories and engaging legal representatives from various stakeholder groups to define true risk vs benefit. While the field is clearly advancing, it is clear that it has not kept pace with plea from patients who are eager to share their data [101,103].

The gaps and the opportunities to successfully catalyze advancement of disease understanding and achieve regulatory acceptance of biomarkers for use in clinical trials of CNS diseases are highlighted in Table 4 and a roadmap for implementing these opportunities is depicted in Fig. 4**.** While individual consortia are attempting to close these gaps, data sharing both within neurologic disease areas, and across these diseases is not happening. This summary is a call to action to work together, rather than create understanding within disease state silos. In doing so, this will facilitate the scientific communities ability to accurately diagnose and treat the right patients with the right treatments.

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