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The Coalition Against Major Diseases: Developing Tools for an Integrated Drug Development Process for Alzheimer's and Parkinson's Diseases

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Aiming to emulate the successful accelerated development of HIV/AIDS drugs, the Critical Path Institute (C-Path), in collaboration with the Engelberg Center for Health Care Reform at the Brookings Institution, has formed the Coalition Against Major Diseases (CAMD). Members include 6 nonprofit groups representing patients' interests, 15 leading pharmaceutical companies, the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), 2 institutes of the National Institutes of Health (NIH)—the National Institute on Aging (NIA) and the National Institute of Neurological Disorders and Stroke (NINDS)—and representatives from academia. The coalition's purpose is to transform the drug development paradigm for neurodegenerative diseases and serve as a model for other major diseases.

Background

In recent years, the development of drug models that incorporate characteristics such as genetic polymorphisms of cytochrome P450, membrane pumps, and receptor sensitivity has become standard

in drug development. Integration of drug and disease progression models has been proposed but has been limited by the lack of contemporary and robust data for creation of disease models and incorporation of biochemical or imaging biomarkers.¹

Contribution from patient communities

The integration of nonprofit groups representing patients' interests into each of the coalition's work groups brings the patients' perspective to the setting of priorities for gathering and interpreting data. These groups also focus on providing information to aid patient care and enrolling participants into clinical trials and have a prominent role in the external communications.

Contribution from industry members

In 2004, the FDA's Critical Path Initiative identified neuropsychiatric diseases and disease models as priority areas of active research opportunities.² The work of the coalition will focus on member companies' sharing of precompetitive data, which may include data from placebo groups from clinical trials not submitted as part of a New Drug Application, disease models, and/or protocol elements. In addition, industry will contribute scientific expertise that will lead to improved knowledge across disciplines; an important component in the development of treatments for Parkinson's and Alzheimer's diseases. Improved management of existing knowledge will be aimed at qualifying for use in drug development, novel imaging or biochemical markers (here, both are referred to as biomarkers), and quantitative disease progression models. The CAMD will intentionally avoid using terms such as "valid" or "surrogate" to describe biomarkers. Instead, the coalition will seek to develop methods that are "qualified for use" based on a rigorous review of scientific data by scientists from industry, academia, and regulatory agencies. These "qualified" methods are expected to lead to an increased efficiency in decision making during the drug development process and to a reduction in drug failures during late-phase testing.

Quantitative disease-progression models

Robust neurodegenerative disease models can offer quantitative insights into disease progression and opportunities for advanced measures of pharmacodynamics. These models can increase

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efficiency in making drug development decisions because many variables that influence outcomes can be considered simultaneously through the use of simulations. Also, the weight of knowledge and data gaps may be more systematically ranked and prioritized.^{1,3} For additional references on modeling and simulation, please see the **Supplementary Material** online.

A large spectrum of modeling methods may be used, depending on many different factors. As described in **Figure 1**, these methods include (i) empirical models, often originating from a “top-down” approach (from patient population data to pathophysiological phenomena); (ii) semimechanistic models, with increasingly explicit representation of pathophysiological, cellular, molecular, or drug pharmacodynamics and pharmacokinetics; (iii) mechanistic, or “first-principle,” models, which often are built on a “bottom-up” approach (from molecular pathways to pathophysiology and clinical end points); (iv) search and inference algorithms, which may be applied across different scales, aimed at establishing links among variables of interest for which measurements are available; and (v) an integration thereof to generate systems biology models that incorporate highly complex interrelationships between parameters and analyze data from multiple experimental sources.³

Efficacy and safety biomarkers, as explained below, are fundamental components of evolving disease models and should be considered during all stages of development. For neurodegenerative diseases in particular, models should

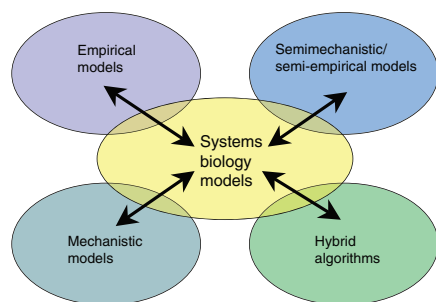


Figure 1 Quantitative disease models. Interrelations between disease progression models.

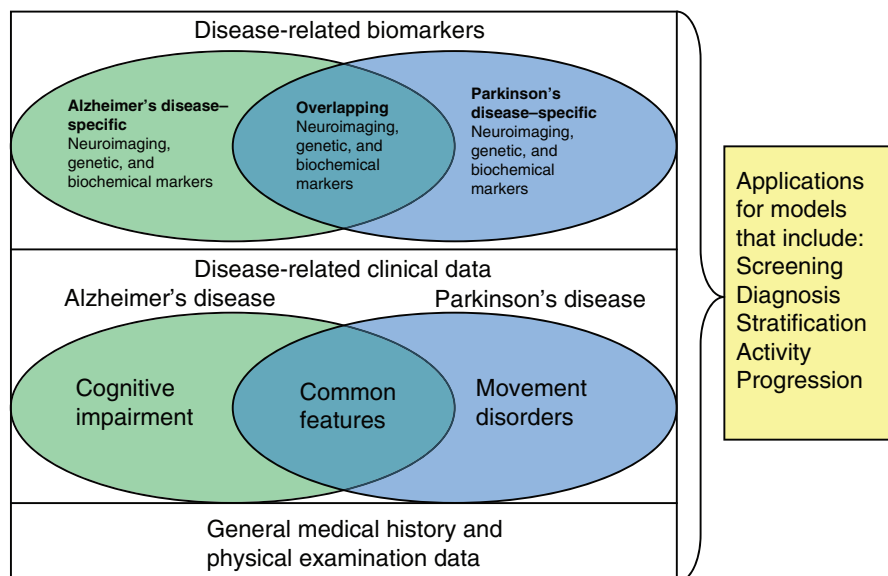


Figure 2 Integrated models of neurodegenerative diseases.

predict both response to drug and rates of disease progression in defined patient subpopulations.

As described above, different methods may be used to create disease models. In the specific case of Parkinson's and Alzheimer's diseases, given the incomplete understanding of the molecular and physiological chains that govern disease progression, a top-down approach may be preferred initially. Satellite modeling efforts (e.g., models borrowing from *in vitro* or *in vivo* studies and scaling up to human, molecular-marker kinetic models in various body compartments, and model-based imaging scaling from animals to patients) may be used to indirectly support the top-down approach.^{1,3}

Such an approach should start by considering existing empirical models based on clinically observed phenomena, which are included in each disease's clinical score metrics (the Unified Parkinson's Disease Rating Scale and the Alzheimer's Disease Assessment Scale), followed by an attempt to incorporate key pathophysiological functions that feed into clinical score subcomponents. For additional references on clinical rating scales, please see the **Supplementary Material** online. In this downwardly integrative attempt, the role of certain biomarkers may be ascertained more

fully, thereby providing a basis for their possible future qualification for use by regulatory agencies.

Biomarkers

Based on the successful framework from C-Path's Predictive Safety Testing Consortium, the CAMD will establish a process and execute the plan for compiling and evaluating the scientific merit of potentially useful candidate biomarkers for drug or diagnostic test development for Parkinson's and Alzheimer's diseases. For additional references on biomarkers, please see the **Supplementary Material** online.

An initial list of potential biomarkers will be compiled from CAMD members. Publicly available data sources will be thoroughly and systematically reviewed and analyzed. Gap analysis will be performed, and programs will be implemented to address gaps. When biomarkers are determined by the CAMD to be adequately supported by evidence, these will move into the qualification process (see below).

A biomarker-evaluation subcommittee with members from all CAMD stakeholder groups will evaluate and prioritize candidate biomarkers for submission and qualification review by regulatory agencies (the FDA and the EMEA) based on (i) analysis of established

databases such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), (ii) incorporation into quantitative disease-progression models, (iii) internal data from CAMD member organizations, and (iv) published scientific articles. The subcommittee will establish and execute a systematic process for review of candidate biomarkers and evaluate the scientific strength of their evidence for disease detection, stratification, activity, progression, predisposition, prediction of treatment response, and/or safety.

Criteria for evaluation and methods of rating the degree of confidence in each biomarker will be defined according to established review methods.⁴ Biomarkers will be ranked, and evaluation of top-tier candidates will continue with agreement for the claim of specific use(s), review of evidence, and identification of gaps therein. The second phase will be the ongoing evaluation of evidence and selection of the most promising biomarkers for qualification. The subcommittee will evaluate external reports and data from members through literature and internal data presentations, with the participation of additional invited experts. Evidence will be thoroughly reviewed, including rigorous statistical analyses. A clinical evaluation program involving either *de novo* or re-mining of retrospective data will be designed to address gaps. Standardized templates will be developed that can be used as tools to uniformly guide the clinical program development.

Integration

Because biomarker qualification is context dependent, as provided by the integration of drug and disease models, their qualification is intimately linked. Another important component of the integration process is the collaboration with other initiatives focusing on the dissemination of quantitative models such as the one described at <http://www.opendiseasemodels.org>.

Although Parkinson's and Alzheimer's diseases are, according to the available evidence, two different medical conditions, areas of pathophysiological and clinical similarity and overlap exist.⁵ To better understand the mechanistic implications of these similarities, scientists

focusing on each disease will have constant interaction. This continual process of information sharing will provide useful insights for scientists working on both diseases (Figure 2).

Data needs and standards

Because the process for constructing disease models and qualifying biomarkers is iterative, each new development will build on previous ones.^{1,3} As the complexity of the models increases, the scope of contributing data will also increase. Various sources of data will build on previous ones as data are incorporated from NIH clinical studies and consortia (e.g., the ADNI), available biomarker data, and electronic health record data. For additional references on data standards, please see the **Supplementary Material** online.

Conversion and remapping of data from disparate sources will be a necessary part of the effort. The CAMD will submit models and biomarkers to the FDA and the EMEA for qualification, and by using Clinical Data Interchange Standards Consortium (CDISC) data element standards the CAMD can ensure that regulatory authorities will be able to readily receive and work with the submissions.

Vision

The CAMD will address the need for tools and methods that can result in a more reliable and predictable process of drug development for Parkinson's and Alzheimer's diseases. The combination of qualified biomarkers and quantitative disease progression models will provide tools for the pharmaceutical industry and other clinical investigators to more rapidly and reliably identify potential new therapies. For references on Alzheimer's/Parkinson's disease burden and the need for new therapies, see **Supplementary Material** online.

The CAMD's working goal is to submit biomarkers and disease progression models for Parkinson's and Alzheimer's diseases for FDA and EMEA review and consideration of qualification within the first year. As additional data become available, further applications and updates will be submitted.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at <http://www.nature.com/clpt>

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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