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Crowdsourcing Proposal Supporting Patient Engagement in Parkinson's Disease: A Digital Research Environment (DRE)-Enabled, Patient Swarm Approach to Develop QSP Models

The Journal of Clinical Pharmacology
2025, 0(0) 1–13

DOI: 10.1002/jcph.70028

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Abstract

Seeking to incorporate the patient voice into a collaborative effort to develop a quantitative system pharmacology (QSP) model for Parkinson's disease (PD) we propose the creation of a "patient swarm" in conjunction with a digital research environment (DRE) connecting various academic centers of excellence and their compute environments to promote data sharing and model collaboration with patient engagement. Patients, their advocates, and other stakeholders are welcome to join the crowdsourcing effort with the intention of reading the relevant source literature and contributing thoughts on model priors and model development while sharing their personal disease trajectories. Training materials are provided from experienced modelers and clinical stakeholders and maintained on the DRE as a resource for the "Swarm." While a number of prominent modelers and clinical stakeholders are part of the initial effort to date, there is an open invitation to the global PD research community to join this effort and help contribute to a solution.

Keywords

crowdsourcing, patient engagement, Parkinson's disease (PD), quantitative systems pharmacology (QSP)

Introduction

Parkinson's disease (PD) affects nearly a million Americans, a number that will increase over the coming decades as the population ages.[1,2] While available medical therapies are usually effective for controlling motor symptoms in the initial years following diagnosis, higher doses of multiple agents are required over time, with increasing side effects and incomplete control of symptoms. Despite the investment in PD research and development by academic, for-profit, and nonprofit stakeholders, many gaps exist in our collective knowledge regarding disease heterogeneity and progression as well as the mechanism of action of common therapeutic strategies used as part of the current standard of PD care. Likewise, many approved drugs still cite "mechanism of action unknown" in their drug monograph/label. Indeed, mechanism of action as a drug attribute is still perceived as a "nice to have" as opposed to a "need to have" entity.

Parkinson's disease itself represents a challenging target since describing the myriad of conditions and disease states as a single etiology is most assuredly an oversimplification and a mistake in guiding treatment strategies.[3,4] Most preclinical pharmacology efforts are focused on generating a meaningful proof-of-concept (POC) but lack sufficient data to definitively characterize the mechanism of action. The absence of definitive mechanism of action can lead to unanticipated side effects, off-target effects, pharmacodynamic drug interactions, and poor patient response in general. The lack of knowledge in this area has contributed to examples

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Submitted for publication 3 December 2024; accepted 18 March 2025.

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where drugs have been removed from the marketplace (e.g., Seldane, Vioxx, and Accutane).[5,6]

The current understanding of the pathophysiology of PD has evolved significantly based on advances in human molecular genetics. Such findings are now elucidating specific molecularly defined therapeutic targets for intervention and common pathways amongst distinct candidate genes.[7] Such advances are now leading to refining the traditional syndromic definition of PD to enable precision medicine therapeutic strategies.[8] Of course, these knowledge gaps in disease understanding are linked to drug development gaps principally in the area of target indication, patient selection, and both biomarker and clinical endpoint strategies and recommendations. Quantitative systems pharmacology (QSP) modeling has the potential to fill in some of these knowledge gaps particularly in the areas of mechanism of action rationale, biomarker strategy and selection, patient selection, and clinical endpoint requirements.[8] Part of the challenge for QSP model development is the time and cost required to develop a credible model. Interestingly, proposals to reduce these factors involve more expedited ways to acquire, review and evaluate source literature from which QSP model parameter priors are often abstracted.[9] QSP models are often established on the basis of preclinical and limited clinical data which cover only small snapshots of the overall disease trajectory of this chronic, progressive disease. A key challenge then is determining how we can translate finite, short-term data into longer-term clinical outcomes. Given the disease progression time scale, clinical signs and symptoms associated with a certain pathways may develop well after that pathway has been impacted, so translating population level QSP models into subgroups of patients or even individual patients requires real-world patient trajectories. Not coincidentally, this (expedited, less costly, and more patient-centric QSP development for PD) are the primary driving forces behind our proposed patient-led crowdsourcing effort proposed herein. It is hopefully appreciated that the QSP use case is merely a starting point and POC for a collaborative, patient-centric approach to developing tools that support drug development. One could (and hopefully will) envision a family of models, tools, and solutions that inform Parkinson's disease drug development.

Methods

Representing Patients and Mobilizing the Patient Swarm

Patient-powered registries and research networks developed by patient organizations are rapidly evolving and leading to significant improvements in patient engagement, in research, care, and health[10]; Trial Finder, https://www.michaeljfox.org/trial-finder. These patient-powered registries are creating tools and resources to provide more sophisticated ways to tailor patient group engagement in the research process, but few of these engage patients to work with drug development scientists to develop decision-making tools in any meaningful way. Likewise, there is little interaction or feedback from drug development scientists and patients. The notion of including what patients feel, experience, say, and do in the construction of decision-making tools represents a real-world opportunity to develop therapies tailored to improving patient needs.

For example, the Parkinson Disease Patient Report of Problems (PD-PROP) is an innovative approach to capture the problems and functional impact that patients report in their own words in response to open-ended questions: (1) What is the most bothersome problem for you due to your Parkinson's disease? and (2) In what way does this problem bother you by affecting your everyday functioning or ability to accomplish what needs to be done? Verbatim replies are analyzed by natural language processing (NLP), human-in-the-loop clinical curation, and machine learning to classify and enumerate symptoms according to priorities and seriousness assigned by respondents. These clinically meaningful symptoms have been tracked longitudinally on the Michael J. Fox Foundation Fox Insight platform in >25,000 PD research participant to create a patient-reported natural history of PD that can be used as predictors of milestone events (e.g., onset and progression of postural instability and cognition symptoms) as well as clinically meaningful correlates of digital measures. Such unfiltered reporting in patients own words is expected to improve prediction of falls and cognitive impairment, particularly when compared with traditional clinician-reported measures.[11–13] In a further effort to integrate the patient voice more actively into the prioritization of clinical endpoints to be used in prospective clinical trials with systematic review of patients' recommendations on clinical endpoints and attribute weighting, recent work by FDA and Michael J. Fox Foundation scientists[14] provide a roadmap for patient engagement and refinement which we have adapted into our proposal herein.

QSP models take significant time and effort to create when compared to statistical or classical data-driven models; mostly because of the length of time to identify, evaluate, and populate credible model priors. Our intention is to construct a platform that both integrates available mechanistic data for new treatment modalities under development and receives data from a community-centric crowdsourcing approach that includes patients (patient swarm) so that model priors from the published scientific literature can be more efficiently catalogued and evaluated by data curators and QSP modelers. Crowdsourcing efforts will be evaluated

as the model is being constructed and the patient swarm will be engaged to comment on both the structure and its predictive potential to explain disease progression and evaluate historical and current development candidates in real time. In addition, patient-generated disease trajectories will be used as a real-world data source to validate the model. Upon completion, the patient swarm will serve to verify that the model is able to generate synthetic data that more closely mimics their own situation and coincidentally the heterogeneity of the family of disease etiologies currently classified as Parkinson's disease. It may also be possible to identify patient subgroups within the broader population with distinct risk–benefit profiles. Patient research participants will describe their illness in quantitative terms with the help of an experienced QSP modeling team, some of whom will construct a model based on priors collected from all available sources (public and private sector) using an AI/ML-driven text mining approach to identify source data from the literature. One of the more exciting potential uses of the QSP model is the support of digital twins.[15,16] Digital twins can be tailored to individual patients, allowing for precise modeling of their unique progression of Parkinson's disease. This helps in creating personalized treatment plans based on the patient's genetic, environmental, and lifestyle factors, leading to more effective outcomes. Digital twins can act as virtual control groups, minimizing the need for real patients to participate in placebo arms. This helps address ethical concerns, particularly in progressive diseases like Parkinson's, where patients may be reluctant to forgo potentially beneficial treatments for the purpose of the study. In addition, with the use of digital twins it is possible to simulate long-term disease progression without the need for extended trial durations, allowing researchers to observe potential long-term effects of treatments on Parkinson's disease over a shorter time frame. This is particularly useful in neurodegenerative diseases, where long-term data is critical.

Coordination of the proposed patient swarm crowdsourcing network includes the formation of a QSP Expert Committee (including those effected by PD and clinical experts) working seamlessly with QSP Modeling Core teams at several universities, and the identification of PD patients willing and interested to provide input and data to the QSP modeling effort. Patients contribute to the "Swarm" in a variety of ways. Patient contributions include one or more of the following tasks: contribution of individual patient roadmaps, review and curation of source data/literature, and guidance and review of the model development and validation effort. The QSP Expert Committee also provides guidance to patient research participants in each of these tasks and specific guidance regarding the extraction of model priors from the filtered literature by generating training materials (video and other content) to explain the approach and solicit the assistance of qualified members to join in the activity. The initial network of QSP experts includes Valvanera Vozmediano Esteban (CTI Clinical Trial and Consulting) as well as Professors Benedetto Piccoli (Rutgers University) and Stephan Schmidt (University of Florida). These experts are also intended to be joined by the modeling and simulation working group of the Critical Path for Parkinson's (CPP) Consortium of the Critical Path Institute (https://c-path.org/programs/cpp/) which adds significant industry-based scientific oversight to the project. It should be clear that there is an open invitation to the global PD research community to join this effort and help contribute to a solution both from a modeling and clinical pharmacology perspective.

Leveraging Existing Technologies and Data

The current integrated dataset available through the CPP includes 18 studies with 12,462 individual anonymized patient records; these are fully aggregated as of September 2020 though, at present, these data are not available for data sharing beyond CPATH/CPP. Recent reviews by McFarthing[17] and Prakash[18] attest to the myriad of clinical trials recently completed in Parkinson's patients. The list comprises both repurposed drugs and novel drug candidates and includes drugs targeted for symptomatic relief as well as potential disease modifying agents. While clinical data is important from the standpoint of establishing the safety and activity of various classes of approved agents and agents under investigation, they are typically lacking in mechanistic context. Emerging new evidence shows that α-synuclein seed amplification assays (SAAs) have the potential to differentiate people with Parkinson's disease from healthy controls. Recently, investigators from the Parkinson's Progression Markers Initiative (PPMI) used the cohort to assess the diagnostic performance of the α-synuclein SAA and to examine whether the assay identifies heterogeneity among patients and enables the early identification of at-risk groups.[19,20] A happy coincidence of this recent finding is that the α-synuclein pathway was the chosen emphasis of one of the QSP models in development proposed herein.

An important aspect of the modeling effort will be to construct an initial model framework with pathophysiologic mechanisms based on literature data summarizing mostly preclinical experiments. These data summaries will come from in vitro and ex vivo pharmacology trials, toxicology and toxicokinetic trials, in silico and in vitro absorption, distribution, metabolism, elimination (ADME) experiments as well as the

physiochemical properties of target species themselves derived from either the scientific literature or patents.

Diversity in Planned and Completed Clinical Trials

There is a growing understanding that PD is not just "heterogeneous" or "complex" but a syndrome[21] belonging to a wide range of complex multifactorial and polygenic disorders influenced both by genetic and environmental factors and are very likely a combination of both in a large proportion of PD patients. Likewise, the landscape of Parkinson's disease targets generated from the portfolios of the collective pharmaceutical stakeholder community spans many targets and includes agents targeted for symptomatic relief in addition to those that may offer the potential to delay or shift disease progression. The problem for patients is the myriad of etiologies currently classified as Parkinson's disease. The lack of MOA clarity promotes enrollment of patients unlikely to respond to therapy and thus low overall response rates, ill-defined clinical endpoints with no mechanistic underpinning, and sampling schemes that may be inappropriate as they do not adequately reflect nuances in patient status and disease progression. The end result is poor benefit: risk and low expectations for patients. This situation highlights the need for a holistic systems biology platform, encompassing both a QSP framework and more broadly a data science strategy that prescribes a hub of mechanism-based data streams spanning pan-omic and pathway level data.

Necessary data requirements for constructing this platform include a diverse array of physiologic, kinetic, and dynamic data as well as genomic, pathway, and bioinformatic data. The origin of these data types is equally diverse and scattered which is part of the challenge in getting started. Key data elements for QSP models are often found embedded in the scientific literature, patent literature, or shared preclinical data stores viewed as "pre-competitive space." Other data is found in consortium or public databases for biomarkers, systems biology, and pathway data, for example, Kyoto Encyclopedia of Genes and Genomes (KEGG), Reactome, or The Human Protein Atlas. It takes significant effort, from a human resource, as well as technological algorithms, to catalogue and integrate these wide array of data streams into a comprehensive alignment of tangible multi-scale data specific to the PD syndrome systems biology platform.

The planned environment can accommodate a variety of model types and it should be clear that models focused on data entirely in the precompetitive space that recapture past performance of historical agents as well those that might incorporate more proprietary data inputs can co-exist without issue as the underlying DRE can accommodate complex sharing heuristics.

Prototype Data Environment and the DRE Future Home

A POC, QSP data input platform has been created to allow collaborator access and data input (QSP model priors) as well as catalogue of filtered publications. This approach provided source data from which the initial conceptual model was created but has been modified, enhanced, and automated in the digital research environment (DRE) crowdsourcing platform.

With the advent of transformers,[22] language models (LMs) have been shown to perform at or above human ability on many NLP tasks. Applying LMs to scientific literature could help alleviate the problem of reading and extracting the information in an ever-growing body of literature. Besides being able to rapidly scan millions of articles, the models need to be very accurate. The precision of the document ranking directly affects the quality of the search results and impacts all the downstream tasks. Even though the NLP field advanced significantly since the emergence of transformers and transfer learning, information retrieval (IR) remains one of the most challenging problems in NLP. The goal of document ranking is to return the best set of results for the user based on their underlying intent.

There is a vast variety of approaches to document ranking, such as DeepCT, ColBERT,[23] and RepBERT. Number of approaches are very accurate, but computationally heavy, requiring deep neural networks that consist of tens or even hundreds of billions of parameters. Other approaches are very light, fast, and easy to implement, but their results are inferior. Our method presents the best tradeoff between quality and cost efficiency. A cascade method that utilizes the fast Okapi BM25 as the first step to choose 1000 topmost relevant documents. At the next step a mono-relevancy estimator is utilized, followed by a duo-relevancy estimator. To better comprehend scientific articles of biomedical domain, in addition to the general English language, the models were pretrained on biomedical corpus, BREATHE[24] and exert a specialized healthcare vocabulary.

The initial R/Shiny-based prototype was developed to help conceptualize the platform (https://kylebarrett.shinyapps.io/QSP_Builder). The initial prototype only provided the scaffolding, with the intent of show stakeholders an idea of potential functionality and navigation. The platform in development provides a mechanism for the swarm and modeling ecosystem to interact and collaborate. The Aridhia DRE provides a mechanism for organizations seeking to establish value creation via data, models, tools and other solutions stored in a secure, cloud-based environment.[25,26] The DRE as a secure end-to-end biomedical research facilitation platform, connects data owners to researchers in a controlled and audited manner, ensuring data owners

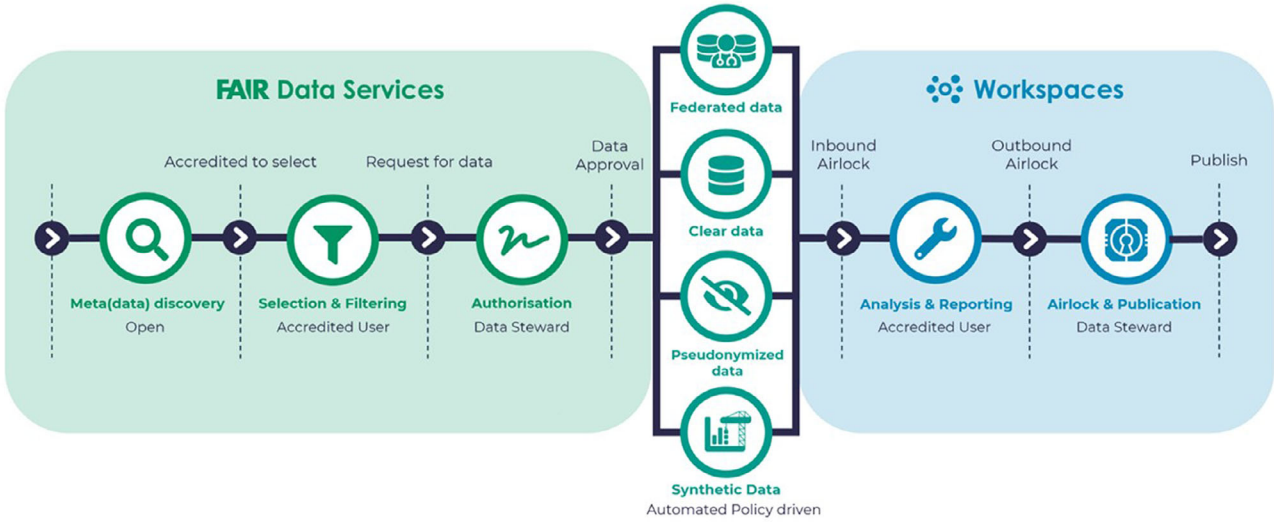

Figure 1. Underlying functionality of the digital research environment (DRE) used to support the patient swarm and connect the PD QSP modeling community—interplay between FAIR data and workspace services with data curation, quality assessment, and governance.

are always in control of how their data is used, who it can be used by and what it can be used for (see Figure 1).

Given the implicit goal of many DRE implementations is to establish high quality data stores and solutions constructed from data that can be used with high fidelity, value is easy to establish. Recouping costs can be managed in a variety of ways including fee for service, access membership, and/or consortia models based on collective and shared research interests. Many existing customers implementing the DRE are already doing this with more considering such options. The Critical Path Institute (c-path.org) in particular has benefitted greatly from implementing the DRE as the backbone of their RDCA-DAP platform (https://c-path.org/program/rare-disease-cures-accelerators-data-and-analytics-platform/). Similar value proposition can be shown for other DRE implementations including the Alzheimer's Disease Data Network—AD Workbench (alzheimersdata.org) and International Covid-19 Data Alliance—ICODA Workbench (icoda-research.org).

Engaging the Swarm

A critical component of the crowdsourcing approach is the necessity of engaging patients to contribute to the research in a meaningful way. There are several levels envisioned for this project including communication to obtain feedback at regular intervals and provision of updates on project milestones. Transparency of progress and decision making is not assumed, and the patient voice is represented on the modeling core team as well as the Steering Committee providing oversight and governance of the project. Quarterly meetings with the patient swarm members will be held to provide updates on the project and secure input on project milestones.

Engagement levels are both content and task specific and performed via periodic roundtable discussion and videotaped lectures viewable at the convenience of the patients. Some of the specific components already being planned include the following topics: Abstracting QSP model priors from the literature: what to look for and where to find it, what does a QSP model look like and how can it be used to understand Parkinson's disease, and how does my data inform a QSP model. Several of these topics are also addressed in text-based FAQ sheets and incorporated into the DRE's splash page content. The patient-focused engagement materials will likely be video/lecture based on content stored and indexed in the DRE as well.

Real-World Patient Level Data

Traditionally, the data used to construct, qualify, and validate QSP models includes mechanistic preclinical data that supports the preclinical POC, ADME data, physiochemical properties of biologically active entities of interest (drug and metabolites, biomarkers, etc.), and complimentary clinical data optimally in the target patient population. While such data must be obtained from publications, from shared preclinical and clinical data sources from pharmaceutical sponsors, and/or derived from chemical structures, it seldom comes from patients themselves. A novel component of this project is the intention to collect, curate, and integrate patient contributed real-world contemporary reports of what they feel and experience describing the roadmap of their illness from time of diagnosis through their current clinical status.

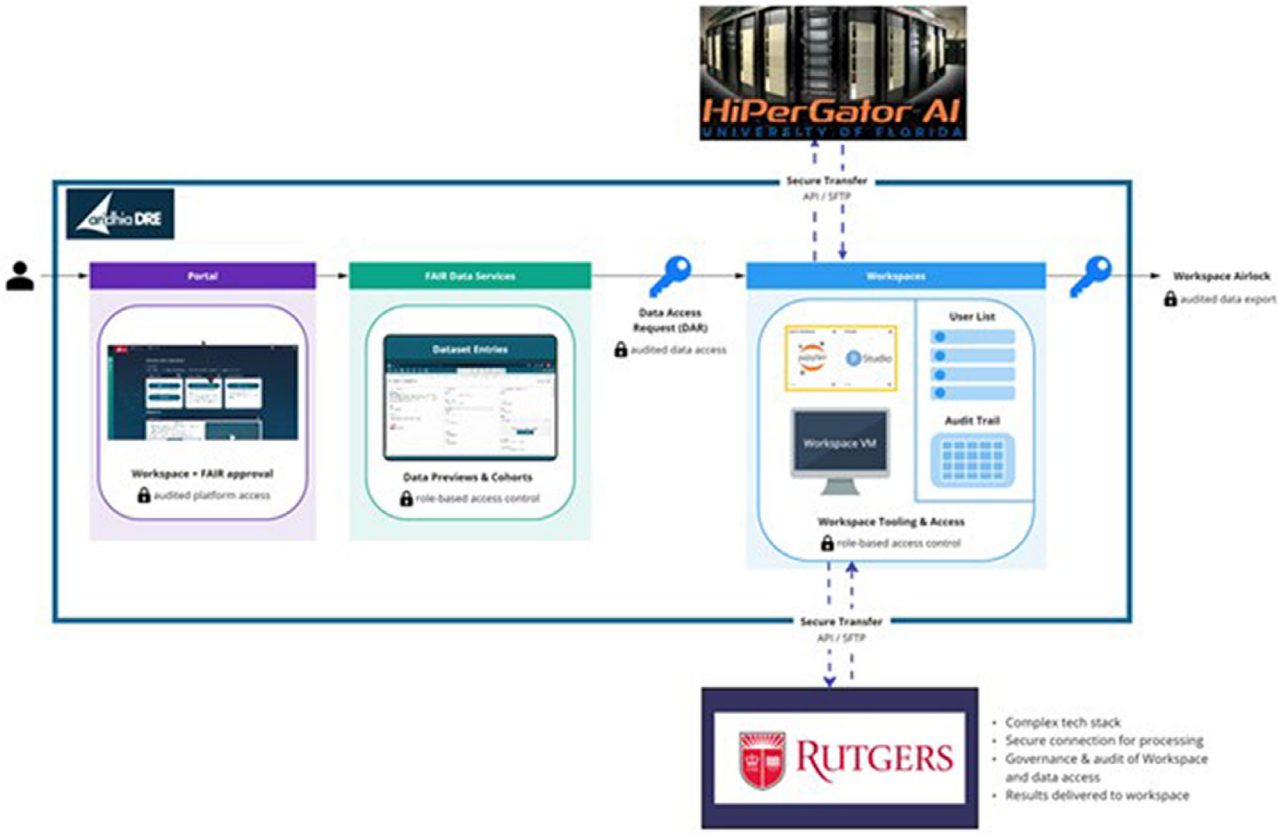

Figure 2. Schematic showing the linkage of the DRE infrastructure and functionality to academic compute environments supporting the QSP model development.

The proposed DRE will serve many purposes on the receipt and assembly of QSP model priors, but it will also be a portal for the assembly of longitudinal patient data that describes the time course of their illness progression including the treatments they have received throughout and an assessment of their and symptoms. The platform will also benefit from similar efforts to collect such PD patient level data such as the PROP (Patient Report of Problems) app.[27] The app and complimentary research effort ask patients open-ended questions about their most bothersome problems and how these problems affect their daily functioning to gather broader data and better understand how patients talk about their disease. More than 25,000 people with Parkinson's in the Michael J. Fox Foundation-sponsored Fox Insight online study have replied to the PD-PROP questions. A team of clinical experts (curators) review verbatim reports and classify them into 56 clinically meaningful symptoms, representing four motor and six non-motor domains to ultimately generate a profile of symptoms that portrays the clinical features and course of Parkinson's as reported directly by patients. Such data in addition to what this effort will generate will be extremely useful to validate the QSP model and assess the assignment of phenotype as determined from clinical assessments alone.[1]

On the compute functionality aspect the DRE workspace will be connected to the Rutgers University and University of Florida's High Performance Computing (HPC) environments (see Figure 2) and also incorporate r-based QSP model coding and development capabilities through collaboration with ESQ Labs (https://esqlabs.com/) and the PK-Sim/MOBI open-source solution.[28,29] The Rutgers HPC environment (Amarel, https://oarc.rutgers.edu/resources/amarel/) contains 700 compute nodes (with over 20,000 CPU cores) and 190 GPUs. Current compute nodes are based on 2x Intel Xeon Processors, 256GB DIMMS, and an on-board 480GB SSD. The University of Florida's HPC environment (HiPerGator, https://www.rc.ufl.edu/about/hipergator/) contains a total of 70,320 cores, 140 NVIDIA DGX A100 nodes, 17,920 AMD Rome cores, 1,120 NVIDIA Ampere A100 GPUs, 2.5 PB All-Flash storage, and over 200 HDR Infiniband and various Ethernet switches for connectivity.

QSP Modeling Approach

The goal of the modeling component of this project is to develop a quantitative systems pharmacology

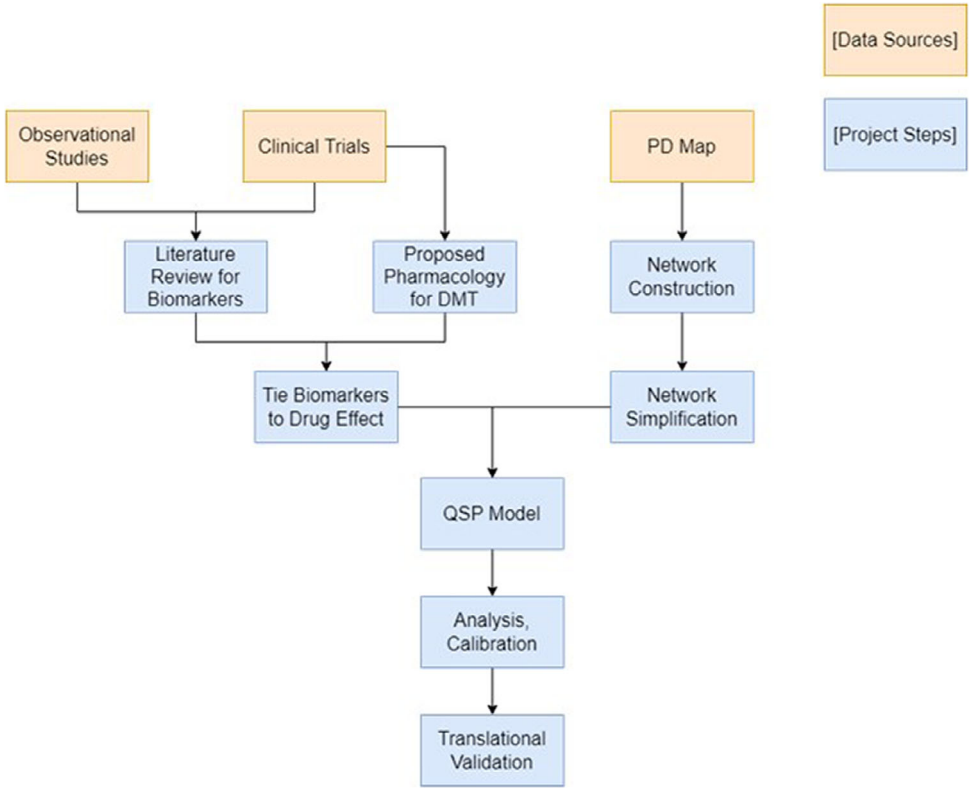

Figure 3. Generalized Parkinson's disease QSP model development workflow; data sources show in orange and project steps in blue.

(QSP) model to identify novel biomarkers with the intention of aiding and enhancing industry's ability to have confidence in proof of mechanism for gene-based targets. The initial modeling effort will develop specific biological network representations and ODE systems implementation for the QSP model.[30] While this [modeling effort] is the initial goal, the future goal is to link models with outcome data derived from patients for ultimate clinical utility. In this preliminary activity, an initial model based on data harnessed from the literature will be developed and harmonized as the first iteration toward operationalizing a comprehensive QSP platform. Figure 3 illustrates the QSP model development flow in a schematic representation. The LIFE approach developed by Rutgers' group in collaboration with previous collaborators[31–34] will provide a means of assessing the disease states achievable by the model structure and identifying model-driven ways of compensating for gaps in the biological networks. With this approach the model is simulated to study the drug action on targeted metabolic networks. This has been done for other human metabolic pathways, such as cholesterol metabolism. The graphs constructed for simulations are more representative of biological network topology than simplified network diagrams, as they can incorporate hyperedge representations that connect multiple reactants to multiple products. This modeling choice provides a way to maintain stoichiometric properties among reactants implicit in the network structure. Drug action is modeled as a so-called "uberedge" that connects a drug molecule to edges in the network. This approach models the ability of the drug to inhibit or enhance a reaction by targeting the corresponding enzyme.

Initial QSP models for Parkinson's disease[35] and Alzheimer's disease[36,37] have been developed but most of these are application specific (e.g., differentiating symptomatic vs more curative type of mechanistic expressions) by design. Nonetheless, they provide a starting point from which the relevant pathophysiology has been quantitatively defined thus far. The Roberts effort provides a QSP platform of the closed cortico-striatal-thalamic-cortical basal ganglia loop of the dorsal motor circuit.[37] A mechanism-based approach was based on known neuroanatomy and neurophysiology of the basal ganglia and explicitly incorporated domain expertise. Model qualification was examined as well and the correlation between the outcome of the QSP model and the reported changes in UPDRS III Motor Part for 22 placebo-normalized drug–dose combinations was $R^2 = 0.84$ showing an excellent POC for QSP to explain clini-

cally relevant endpoints generated from historical trials.

There also exists models in adjacent areas. A translational model for the disposition of antibodies through the blood–brain barrier and in the brain[38] captures relevant physiological data in mouse, rat, monkey, and human systems and shows promising alignment with experimental data. While the results of the model are promising, the fine-detail that the model examines causes longer runtimes than more coarse-grain models. This work has been expanded on recently[39] aiming to alleviate the computational concerns. This is done by coarse graining several of the compartments in the original model from over 100 equations down to 16. Bloomingdale[39] shows that the minimal physiologically-based pharmacokinetics (PBPK) model performs similarly with a reduction in computational cost of around 10 times. This work highlights the importance of integrability and fit for purpose design in model development and shows that extremely detailed modeling in the compartments not directly related to disease pathology may not be required.

While the space of modeling in CNS diseases is expanding, there is a lack of models that capture the genetic component of Parkinson's disease. α-synuclein, LRRK2, and refers to the enzyme glucocerebrosidase (GCase), crucial for breaking down glucocerebroside, a lipid molecule are several of the genetic components that are implicated in disease progression for monogenic Parkinson's disease. With the expansion of clinical trials that are targeting genes associated with disease progression,[40] there is a need for a model that captures the relevant physiology associated with α-synuclein, LRRK2, and GBA, along with their relevant pathways and potential use for patient segments under the broad umbrella of PD. An additional goal of the QSP model will be to provide insights into disease state and progression through the identification of high-quality biomarkers and the use of longitudinal observational study data, clinical trial data, and translational preclinical data that helps to bridge the gap between pathophysiological processes and long-term clinical outcome.

Patient Engagement and Model Refinement with the Voice of the Patient

The CPP community includes patients some of whom have had careers in the pharmaceutical or life sciences industry or academia (https://c-path.org/programs/cpp/overview/people-with-parkinsons/). They are regular participants in current meetings and consortium planning. An expectation of the quarterly meetings with the patient community will be that the QSP modeling team present updates on model development progress to both the Steering Committee and the patient community. The intention for these meetings is not only to provide transparency of the effort and progress but also to solicit the input from the patient community on the model structure, verification of associations between symptoms and clinical outcomes. Patients are expected to weigh in on the extent to which they feel the QSP model addresses their patient experience as well as suggest correlations or events they feel are not adequately captured or defined. In addition to the feedback collected from each meeting, periodic surveys will be administered to patients to provide a quantitative assessment of the benefit of the engagement experience and the value derived by patients as well as the modeling community.

An adage often used in the PD community is, "when you see one Parkinsons' patient, you've seen one Parkinsons' patient." While this phrase has created an appreciation of the diversity of the PD population, this heterogeneity poses challenges not only for those in drug development but also for the patients who volunteer for clinical trials. The recruitment of adequate numbers and diverse groups of patient volunteers for clinical trials is a well-known issue. The Parkinson's patient community highly supports scientific tools and research platforms that directly incorporate the patient voice in ways that improve clinical protocol design, the odds of development success, decrease the time and cost of clinical trials, and more rapidly expand a pipeline of successful interventions. In neurology, investigational drugs that often show promise in early trials sometimes fail or show mixed results in larger registrational efforts, resulting in frustration and disappointment to the sponsor, the collaborating investigators, and in particular the patients who dedicate valuable time and personal risk to participate in these trials.

As an example, a phase 3 program in the development of an investigational drug for neurogenic orthostatic hypotension (nOH) recently issued a series of corporate communications on its mixed result.[41] In previous phase 2 studies, the investigational drug, ampreloxetine provided the sponsor a positive efficacy signal in a mixed group of Parkinsonism nOH patients (PD, MSA, and PAF) to advance the IND into a complex registrational program involving two phase 3 studies and a long-term open label extension study. In September 2021, the sponsor announced the first phase 3 trial missed its primary endpoint in all Parkinsonism patients, and the company made the corporate decision to terminate the second phase 3 study (partially recruited) and ended the nOH development program. Seven months later after termination, a subset analysis of the partially completed second phase 3 study showed that MSA-treated patients, but not PD or PAF study

Table 1. Current Databases with PD Biomarker and Genetic Data for Quantifying Disease Progression and Mechanistic QSP Modeling

Database	Type of Data	Reference
PPMI	Clinical, biomarkers, genetics	[42]
AMPPD	Clinical, genetics, biomarkers	[43]
GP2	Clinical, genetics	[44]
PDBP	Clinical, biomarkers	[45]
OPDC	Clinical, biomarkers, genetics	[46]
MDSGene	Genetics	[47]

Luxembourg PD database molecular signaling networks, https://parkinson.lu/research-participation/luxembourg-parkinsons-study

participants, had improved clinical nOH symptoms as compared to placebo.

In retrospect, could QSP and the development of mathematical biology and pharmacology models have predicted this outcome or redirected the future development focus with greater predictability? Could patient swarming and directly speaking to patients help prioritize the severity and priority of symptoms in a heterogeneous group of patients and predicted a difference between Parkinsonisms? The authors of this paper believe QSP and systems biology more broadly holds promise in improving clinical trial outcomes and create greater confidence in the patient community. Moreover, would the use of QSP improve the odds of drug development success giving patients a better level of confidence in selecting which future trials are fully vetted using the best research platforms? The collaborators on this project believe the answer to these questions is yes and have made inroads to establishing a framework by which the effort can be advanced.

Current Progress

A listing of the available contributed clinical data managed by the CPP consortium is shown in Table 1. These data are extremely rich with respect to the sampling in the context of a clinical trial but there are limitations in the utility of the data on several fronts. First, they represent (for the most part but not entirely) successful trials on compounds that were eventually approved for one or more PD indications, mostly focused on symptomatic relief and not disease modification. Second, in the context of a clinical trial, observations and data collection are typically of short duration and reflect only agreed-upon clinical endpoints that reflected the current (at the time of the trial) negotiated statistical criteria as the basis for an approval or at least favorable regulatory opinion. In this context they are also dated to the then-current scientific and regulatory thinking. Hence, these trial designs were typically not exploratory-based, learning trials, and instead favored more confirmatory-based approaches based on both endpoint selection and design construct. Finally, the patient selection criteria were based on disease stage but not necessarily tailored to the expected mechanistic response of the proposed treatment. Despite these limitations, the collective clinical data provide a clinical response to therapeutic intervention and often considered dose–response considerations thus providing an important anchor for mechanistic PK/PD characterization. The current QTIPS prototype is based on a simple R/Shiny construct and does not reflect the full functionality of production platform to be made operational by the time the initial QSP model structure is defined.

In order to identify source data for the QSP modeling effort, we utilize state-of-the-art machine learning techniques to identify latent insights from literature and deep neural network-based model for language understanding. Based on emerging language architectures (BERT, T5) to achieve these insights and compute infrastructure running on the Google Cloud Platform, we can take advantage of the massive compute power available via the TensorFlow Research Cloud. By utilizing the compute, storage, and networking along with standard open-source platforms and tools such as TensorFlow, we can train, refine, and iterate models with great performance.

An initial trusted research environment (TRE) has been set up to host the educational training materials (video content for the swarm) and for the existing QSP centers of excellence (Rutgers and University of Florida) to share data, code, and models of common interest.

Successful implementation and sustainability of the crowdsourcing effort will require financial support and grant funding from one or more sources. While there are a diversity of funding avenues including the American Parkinson's' Disease association, the Michael J. Fox Foundation (MJJF), NINDS/NIH, Cure Parkinson's Association, the Parkinsons Alliance, and others. Funding proposals are highly competitive and there is no guarantee of funding. More importantly, typical funding opportunities and grants are typically structured over finite time windows without much consideration for sustainability beyond a few years. In addition, applying for a grant can be a time-consuming and complex process and grant offers often contain numerous conditions and non-compliance could mean further funding being refused and sums already paid being taken back. A long-term solution will certainly require an expanded ecosystem of funders likely including Pharma. A multi-institutional investment would be equitable and productive assuming one get around concerns over intellectual property (IP). An advantage of the TRE is the ability to selectively share only agreed-upon content (data, code, or models) while still working in your own secure workspace environment.

QSP Modeling Progress: Rutgers Group

An extensive literature search has been completed from which model development has been initiated. Since the hallmark symptom of Parkinson's disease is the presence of α-synuclein fibrils in the Lewy body, we choose to include metabolic pathways and processes that surround the formation and handling of proteins. Given the abundance of such pathways, we define model features from three possible scales:

1. Macroscopic extracellular to incorporate clinical data with the goal of identifying biomarkers and fulfill by the need of detecting drug-target engagement in clinical trials. The model includes some key compartments as: blood, CSF, and brain.
2. Extracellular scale to capture cell–cell interaction and signaling.
3. Intracellular to capture the cellular processes implicated in disease progression in Parkinson's involving the key genes of interest: SNCA, GBA, and LRRK2.

In order to calibrate and validate our model, we will utilize the data available from: Parkinson's Progression Marker Initiative (PPMI),[48] Parkinson's Disease Biomarkers Program (PDBP),[49] Accelerating Medicines Partnership Parkinson's Disease (AMP PD),[41] and Global Parkinson's Genetic Program (GP2).[50] Each of these databases includes a variety of data types and scales—including but not limited to: dopamine transporter scan (DaTSCAN) imaging, diffusion tensor imaging (DTI), magnetic response imaging (MRI), plasma metabolomics, proteomic analysis, genome-wide-association studies (GWAS), blood/plasma biomarkers, and blood RNA biomarkers. We hope to use imaging data to inform the macroscopic scale of our model, while also using the metabolomic and RNA biomarker data to inform the extracellular and intracellular scales. In order to facilitate rapid development of the model, we will build on existing works, including the Parkinson's Disease Map built in collaboration with the University of Luxembourg and the Systems Biology Institute, Tokyo.[51] This "map" of PD provides a highly detailed description of the metabolic and genetic processes implicated by PD pathophysiology. We have also been carefully considering previous models developed for PD modeling. Bloomingdale et al provides a description of commonalities within neurodegenerative diseases that includes a categorization of existing PD models.[52] Of particular interest to our mechanism-focused biomarker-identifying model are: a biochemical systems theoretic model applied to α-synuclein,[53] two models involving dopamine metabolism and dopamine within neurons,[54,55] and an insulin-resistance model, specific to PD.[56,57] We plan to expand on these existing models, during the ongoing model development to provide insight into potential biomarkers for PD.[58]

QSP Modeling Progress: University of Florida Group

Many QSP models face difficulties with translating processes on the cellular or the tissue level to long-term clinical outcome. This is due to the fact that processes on the cellular or tissue level are typically (relatively) fast, whereas it takes years for clinical signs and symptoms to establish. As a result, there is often a purported lack of correlation between cell- or tissue-based biomarker data (e.g., brain imaging biomarkers) and Unified Parkinson's Disease Rating Scale developed by the Movement Disorder Society (MDS-UPDRS) scores. Instead, simple (e.g., monotonic) functions are used either alone or in combination with advanced statistical algorithms (e.g., item response theory, IRT) to characterize and predict the patients' disease progression over time, which limits the predictive performance of these algorithms, particularly for individual patients.

To overcome this challenge, the University of Florida group developed biomarker-directed clinical endpoint model that links non-invasive dopamine active transporter (DAT) scan data in putamen and caudate to MDS-UPDRS data for Parts I, II, and III in early stage PD patients using an IRT-modeling approach.[58] Compared to conventional correlational analyses, where at best a weak correlation (∼12%–14%) between DAT scan data, expressed as striatal binding ratio (SBR) has been reported,[59] our analysis identified a much stronger linear correlation between the two (∼50%–55%) once interindividual differences in the onset of disease progression and onset of symptoms as well as interindividual variability in the relationship between SBR and clinical scores were taken into consideration. The results of the analysis further suggest that a stratification according to the degree of damage in a patient's striatum (both putamen and caudate) rather than stratification into left and right hemispheres may provide some additional benefits. This algorithm further allows to categorize early stage PD patients into three groups: fast progressors, average progressors, and slow progressors based on their age and MDS-UPDRS score at diagnosis. It also allows us to create priors for virtual twins, which can be informed by swarm data to enrich clinical trial populations, define early stop criteria, and serve as virtual placebo arm for clinical efficacy trials, where withholding of medication over an extended period of time is unethical.

Discussion: Delivering for Patients

Parkinson's disease drug development remains challenging for a variety of reasons, not the least of which is more mechanistic biomarkers more closely related

to the mechanism of action that also correlate with indices of well-being and quality of life that are more clearly aligned with patient benefit. While recent efforts to engage patients to participate in various aspects of drug development are encouraging and represent key progress in ensuring alignment with both drug targets and drug candidates, there are no examples where a crowdsourcing effort has been brought to bear on the construction of tools that will specifically address gaps in understanding and at least have the potential to influence drug development. We strongly believe that while success cannot be guaranteed from the standpoint of the development of a fully functional QSP model that will immediately impact PD drug development, there will be significant lessons learned regarding the mechanism of a patient-contributed crowdsourcing effort. Likewise, we fully expect that the open science approach to QSP model development for PD will engage a broad array of stakeholders to invest and collaborate in a meaningful way.

The proposed crowdsourcing project will sponsor the creation of a platform that will serve as a conduit for patient data integration, clinical data, and other real-world data sources. An initial model framework will be generated from an extensive literature review which will be harmonized and completed to build a comprehensive QSP model. Specific software tools (Matlab, Python, or other language as needed) for the simulation of the comprehensive QSP model will also incorporated as needed into the future DRE. An initial R/Shiny-based prototype platform has been developed as a demonstration POC tool to facilitate patient understanding of the project and approach. The final version of this platform will be based on a DRE model that provides secure but open access to the PD ecosystem so that the initial QPS model can evolve and be joined with other model assets that facilitate PD drug development. Patients will participate in this effort both from the standpoint of oversight provision on the modeling effort as well as hands on contribution toward the assembly of literature-based model priors which will be integrated with data that has already or soon will be contributed to this crowdsourcing effort. The progress from this effort will be shared within the Critical Path Institute's CPP consortium, training materials will be shared as among the Parkinson's disease ecosystem, made available through the MJFF and model development and all codes will be shared in GitHub[57] via the DRE workspace environment.[60]

Acknowledgments

This manuscript is dedicated to our friend and mentor, Dr. Ira Shoulson.

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

No funding was received to support this work.

Data Availability Statement

Data generated herein for this analysis is based on literature and web review; links to open-source solutions, works in progress, and DRE use cases are provided in the text.

Principal Investigator's Statement

The authors confirm that Jeffrey S. Barrett, PhD, FCP is the PI responsible for this research and analysis.

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