Scoping Review Protocol
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Translational Research on Polygenic Risk Scores in Common Neurodegenerative Diseases - A Scoping Review Protocol*

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Abstract

Objective. The purpose of this protocol is to clearly describe the process for the scoping review we plan to conduct on the topic of polygenic risk scores (PRS) in common neurodegenerative diseases. We will present the review's objective, the strategy for evidence search, the data extraction and analysis procedure, and how the results will be presented. **Methods.** The inclusion criteria for the planned scoping review will focus on evidence sources that involve PRS applied to neurogenerative diseases such as Multiple sclerosis, Parkinson's disease, Alzheimer's disease, and Amyotrophic lateral sclerosis in any phase of translational research, from early development to clinical implementation. This includes its use in risk prediction, early diagnosis, prognosis, and treatment decision-making. The research questions were created based on the population, context, and concept framework. We will consider both peer-reviewed papers and grey literature published in English or German for inclusion. Two independent reviewers will search for information. **Conclusion.** The findings from the scoping review will be presented descriptively and summarized according to the research questions to illustrate the current status of translational research on PRS in common neurodegenerative diseases.

Key Words: Evidence Gaps ▪ Genetic Risk Score ▪ Nervous System Diseases.

Introduction

Neurodegenerative diseases such as multiple sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS), are complex disorders characterized by progressive deterioration of nervous system function. These conditions pose a substantial and growing global health burden due to their chronic nature, the lack of curative treatments, and the aging population, which increases the prevalence of these diseases (1). Despite different aetiologies, a common feature of neurodegenerative diseases is chronic activation of innate immune cells within the central nervous system, and in diseases like MS, the influx of peripheral immune cells across the blood-brain barrier (2).

Even with significant progress in understanding the pathophysiology of these diseases, much remains unknown about the genetic and environmental factors that contribute to their onset and progression. Genetic predisposition plays a crucial role in many neurological disorders. Advances in genome-wide association studies have led to the identification of numerous genetic loci associated with increased risk for common neurodegenerative diseases (3-7). However, the individual effects of most genetic variants are small, and the underlying genetic architecture is highly polygenic. To address this complexity, polygenic risk scores

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(PRS) have emerged as a method for estimating an individual's overall genetic risk by combining the effects of multiple genetic variants (8). As a result, PRS offers the potential for improving risk prediction, early diagnosis, and personalized treatment by integrating genetic information into clinical decision-making.

Despite the promise of PRS, translational research in the field of neurodegenerative diseases faces several challenges that must be addressed to move from research to clinical practice. One significant challenge is the need for large, diverse datasets to ensure that PRS calculations are accurate and applicable across different populations. Most PRS models are currently based on data from individuals of European ancestry, which limits their generalizability and clinical utility for other populations (9). Moreover, PRS needs to be integrated with other risk factors, such as environmental exposures and lifestyle factors, to provide a more comprehensive risk assessment and guide more effective interventions (10). Addressing these challenges is critical for translating PRS into routine clinical tools that can improve outcomes in neurodegenerative diseases.

To assess the current state of translational research on PRS in common neurodegenerative diseases, specifically MS, PD, AD, and ALS, we are aiming to conduct a scoping review. The objective of the planned review will be to map existing literature on the clinical applicability of PRS, explore its potential benefits and limitations, and identify knowledge gaps that need to be addressed to advance the integration of PRS into routine clinical practice. By utilizing a scoping review approach, we will seek a wide range of information, including peer-reviewed articles and various forms of grey literature.

Methods and Analysis

This scoping review protocol has been registered via the Open Science Framework. The public registration is uniquely identified with the following DOI: https://doi.org/10.17605/OSF.IO/2NRGQ. The protocol was developed based on the Joanna Briggs Institute (JBI) Protocol Template (11) and in accordance with JBI methodology (12). The proposed scoping review will be conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) (13) and the guidelines set by the JBI (14). Any modifications in the protocol during the scoping review procedure will be reported and documented in the final manuscript.

A preliminary search was conducted on MEDLINE (via PubMed), the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis, with no time restrictions applied. The search used the initial terms "genetic risk score," "polygenic risk," "neurodegenerative disease," "neurodegenerative disorder," and "review." No current or ongoing systematic reviews or scoping reviews on this topic were found.

Review Question

We formulated the following research questions:

1) What is the current state of translational research on PRS?
2) What is the evidence base for clinical implementation of PRS?
3) What is the predictive power/value/performance/accuracy of PRS?
4) What are the contexts of use of PRS?
   a. Healthcare clinical setting / laboratory / commercial entity
   b. Screening / diagnosis / prognosis / therapy

for the common neurodegenerative diseases, such as MS, PD, AD, and ALS.

Eligibility Criteria

Population

The scoping review will encompass studies involving patients with one of four common neurodegenerative diseases: MS, PD, AD, or ALS. It will also cover public opinion studies regarding the clinical use of PRS in these neurodegenerative diseases. Additionally, we will include methodological papers describing the development of PRS for the aforementioned diseases.

Concept

In the scoping review, we will be examining different concepts. The first will be related to translational research on PRS. The information will be organized according to a four-tier framework established by Khoury et al. (15). The first category, T1 studies, will encompass observational studies and clinical trials that focus on the health applications of the polygenic score. The T2 category will involve studies that evaluate the clinical utility of PRS. The T3 category will cover studies related to dissemination and implementation research of PRS, while the T4 category will address research on the population-level health impact of PRS.

Additionally, we will extract descriptive information from the evidence sources regarding the clinical implementation and predictive power of PRS in four studied neurodegenerative diseases. This information will be maped according to the type of disease and context of use.

Context

The scoping review will focus on evidence sources related to genetic testing providers, including healthcare clinical settings, laboratories, and commercial entities. The review will specifically consider the PRS test category, which encompasses risk prediction, early diagnosis, prognosis, and treatment decision-making.

Types of Evidence Sources

The scoping review will consider a wide range of peer-reviewed scientific literature, as well as grey literature. The types of eligible sources will therefore be:

- Systematic reviews or reviews of other types (16); meta-analyses
- Primary studies according to T1-T4 translation research phases (15); e.g., randomized controlled trials, non-randomized controlled studies, observational studies, dissemination and implementation research studies, outcome research studies
- Grey literature, such as guidelines, policy documents, registers, and websites

Primary sources will be excluded if already incorporated into an included evidence synthesis unless the data they contain are not otherwise reported in the evidence synthesis.

Evidence sources in English or German language will be included to broaden the search scope. This approach allows for the identification of relevant non-English papers, particularly grey literature. No time period restrictions will be applied.

Inclusion and exclusion criteria based on the population, context, and concept (PCC) framework and types of evidence sources are summarized in Table 1.

Table 1. Inclusion and Exclusion Criteria Based on Study PCC* Framework and Types of Evidence Sources

Criteria	Inclusion	Exclusion
Population	Evidence sources involving PRS† in patients with ‡MS, §PD, ‖AD, or ¶ALS	Studies presenting evidence on any related disease other than ‡MS, §PD, ‖AD, or ¶ALS
Concept	Evidence sources on PRS† according to the T1-T4 translation research phases framework established by Khoury et al. (15)	Purely methodological papers on PRS* without reference to any of the previously mentioned diseases
Context	Evidence sources related to genetic testing providers (healthcare clinical setting, laboratories, commercial entities)	-
	Evidence sources related to contexts of use of PRS† (screening, diagnosis, prognosis, therapy)	-
Types of evidence sources	Primary studies, reviews, meta-analyses, grey literature	Primary sources if already incorporated into an included review or meta-analysis
	Evidence sources in English or German	Studies not available in full form
	No time period restrictions	-

*Population, Concept, and Context; †Polygenic risk score; ‡Multiple sclerosis; §Parkinson's disease; ‖Alzheimer's disease; ¶Amyotrophic lateral sclerosis;.

Search Strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of MEDLINE was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for MEDLINE via PubMed (see Table 2). The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The reference list of all included sources of evidence will be screened for additional studies.

Sources of Information

The electronic databases to be searched include:
- Cochrane Database of Systematic Reviews
- MEDLINE via PubMed
- Google Scholar
- JBI Evidence Synthesis
- JBI Evidence Implementation

Sources of Unpublished Studies/Grey Literature to Be Searched Include:

- ClinicalTrials.gov
- PHG Foundation
- Precision Health Database

Source of Evidence Selection

Evidence sources related to PCC criteria (Table 1) will be selected by two independent reviewers. Through each phase of the review, that is, screening, eligibility, and inclusion, discrepancies in study selection between the reviewers will be evaluated by calculating the inter-rater kappa coefficient. The points of disagreements will be discussed and solved to reach the acceptable level

Table 2. Search String for MEDLINE via PubMed

	Search String String
Concept 1: Neurodegenerative disease	(("Multiple Sclerosis"[Mesh] OR "Demyelinating Autoimmune Disease*"[tiab] OR MS[tiab] OR "Disseminated Sclerosis"[tiab]))
	OR
	("Parkinson Disease"[Mesh] OR "Parkinson Disease*"[tiab] OR "Paralysis Agitans"[tiab] OR "Parkinson's Disease*"[tiab] OR "Primary Parkinsonism*"[tiab])
	OR
	("Alzheimer Disease"[Mesh] OR "Alzheimer Disease*"[tiab] OR "Alzheimer Syndrome*"[tiab] OR "Alzheimer-Type Dementia*"[tiab] OR "Alzheimer Type Dementia*"[tiab] OR "Alzheimer's Disease*"[tiab] OR "Alzheimer Dementia*"[tiab] OR "Alzheimer's Disease*"[tiab] OR "Senile Dementia*"[tiab] OR "Alzheimer Type Dementia*"[tiab] OR "Alzheimer Type Senile Dementia*"[tiab] OR "Primary Senile Degenerative Dementia*"[tiab] OR "Alzheimer Sclerosis"[tiab] OR "Presenile Dementia"[tiab])
	OR
	("Amyotrophic Lateral Sclerosis"[Mesh] OR "Amyotrophic Lateral Sclerosis"[tiab] OR "ALS"[tiab] OR "Gehrig's Disease*"[tiab] OR "Gehrig Disease*"[tiab] OR "Gehrigs Disease*"[tiab] OR "Lou-Gehrigs Disease*"[tiab] OR "Charcot Disease*"[tiab] OR "Guam Disease*"[tiab])
	OR
	("Dementia"[Mesh] OR "Dementia"[tiab] OR "Amentia*"[tiab]))
	AND
Concept 2: Polygenic risk score	("Genetic Risk Score"[Mesh] OR "Genetic Risk Score*"[tiab] OR "Polygenic Risk Score*"[tiab] OR "Genetic Predisposition to Disease*"[tiab] OR "Genetic Predisposition*"[tiab] OR "Genetic Susceptibility"[tiab] OR "Genetic Susceptibilities"[tiab])

of agreement of 90% or higher (17). Following the search, all identified citations will be collated and uploaded into reference manager and duplicates removed. Titles and abstracts will then be screened for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full and assessed in detail against the inclusion criteria. Reasons for exclusion of sources of evidence at full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram (13).

Data Extraction

Data extraction process will be conducted in accordance with JBI recommendations (18). Data will be extracted from papers and other evidence sources by two independent reviewers using a data extraction tool developed by the reviewers. Any disagreements between the reviewers will be resolved through discussion or with the involvement of an additional reviewer. The data extracted will include specific details about the population, concept, context, study methods and key findings relevant to the review questions. A draft extraction form is provided (see Table 3). The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included evidence source. Any modifications will be detailed in the scoping review. In addition to the data extraction form, an extraction guidance form will be developed, detailing each item to be extracted, and shared with each scoping reviewer.

Data Analysis and Presentation

The data will be analyzed and the results presented following the JBI recommendations (18). The analysis will be descriptive, and the findings will be visualized in tables and graphs. The evidence collected will be presented in accordance with the PCC framework based on the research questions. The results will be summarized using a narrative approach. Research gaps will be identified, and potential implications for future research will be discussed.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Table 3. Draft Data Extraction Form

Type of evidence*	Year	Author	Title	Aim	Disease†
Ancestry of polygenic score	Translational phase‡	Type of research, methodology§	Setting‖	Context of use¶	Key findings

*Peer-reviewed papers / grey literature; †Multiple sclerosis, Parkinson's disease, Alzheimer's disease, Amyotrophic lateral sclerosis; ‡T1-T4 according to Khoury et al. (15); §Type of research: primary research, evidence synthesis, grey literature; ‖Healthcare clinical setting, laboratory, commercial entity; ¶Screening, diagnosis, prognosis, therapy

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